INTRODUCTION

Ivan Pavlov was a Russian scientist and he was doing research on the process of digestion. For this purpose he designed an experiment to collect saliva from a live dog’s mouth by placing tubes in the cheeks of the dog. The dog first used to salivate at the sight of food offered to it. After a few days Pavlov observed that the dog started salivating when listening to the foot steps of the person bringing food. This was relatively a simple observation but based on that Pavlov developed the learning theory of conditioning. He became so interested in this psychological work that he gave up his research on digestion for which he already won a Nobel Prize. According to Pavlov the reflux of salivation at the sight of food was a natural or unconditional reflux but salivation after listening to the foot steps of the experimenter was conditional reflux because, in natural circumstances, the dog doesn’t salivate after listening to a sound of foot steps.

Even in the case of human beings the subjective feelings like getting angry or irritated by certain kinds of noise are conditional responses.
Have you ever seen a pound of anger, a quart of hate, or an ounce of joy? Of course the question is ridiculous, yet we talk about emotions as if they were 'real' things. Rage, grief, ecstasy, joy, sadness, boredom and we use these terms so freely. The emotions are often inferred from the actions of others; they cannot be directly observed. We encounter regularly the persons who may mistake anger for fear, guilt for depression, or lust for love. For such reasons the study of emotion is difficult, however, the emotions separate us from machines, plants and computers and add deeper meaning to life.

Most people closely identify a pounding heart, sweating palms and 'butterflies' in the stomach with the experience of emotion. This observation is valid since psychological changes taking place in the body are the core of fear, anger, joy and other emotions. These changes include alterations in heart rate, perspirations and other bodily stirrings. Most of these reactions are caused by actions of the nervous system.

Psychopathology may be defined as the inability to behave in ways that foster the well being of the individual and ultimately of society and any behavior that interferes with personal growth and self fulfillment. The prevalence of psychiatric disorders occurring in people is that, one out of every ten children will experience either a major or a minor mental disorder and that may be inherited. One out of every hundred persons will become so severely disturbed as to require to consult a psychiatrist at some point of his/her life time. Every year over 2 million people are admitted or readmitted to psychiatric treatment in general hospitals.

Psychotic disorders are the most severe type of psychopathology often requiring hospitalization. In psychosis, there is a retreat from reality and the person can no longer tell what is fantasy and hallucination, and what is real. In addition there is usually a major loss of ability to control thoughts and actions. Anxiety disorders may take the form of phobias (irrational fear of objects, activities, or situations), panic (in which the patient suffers sudden unexplainable feelings of total panic), or chronic and persistent anxiety.
In the 20th century, the miraculous achievement of medicine was that lot of life threatening diseases had been eradicated from the world. Discovery of vaccine for polio is an excellent milestone. Small pox vaccine invention has completely washed away the viral disease from nook and corner of the universe. By using modern scientific advancements such as genetic modification of the genes or insertion of healthy genes or transfer of genes may be useful in treating diseases like AIDS, Alzheimer disease, Parkinson's disease and even diabetes and other life long life threatening diseases. The majority of the diseases can be completely cured and eradicated by these advancements at least by the middle of 21st century except only mental illnesses if we don't follow proper life style with fast growing changes in life. The stress, depression, anxiety and psychoses are those illnesses that are impossible to avoid. In developed and developing countries among the total population 15% are affected by any one of these illnesses. There is no complete cure of these diseases and one should continue the medication if the environments triggering these kinds of diseases are not avoided. Compulsions in life, fear of defeat, business competition, unclear mind and unusual thinking makes the people inactive and subsequently the loss of induction takes them to surrender to psychiatric illness.

There is continuous increase in the number of psychiatric patients world wide. Loss of clear thinking and loss of conscience in approaching one's own problems makes a person depress himself to spend months to years for meaningless thoughts and the restlessness makes him unhappy. In coming 50 years there will be lot of reasons for triggering these kinds of illnesses due to technological developments and sophisticated life and the people will loose the mental strength for even small defeats in life. There is lot of mechanism proposed for these kinds of diseases. Altered secretion of adrenaline, serotonin, dopamine, GABA and other neurotransmitters may be responsible for this. Majority of drugs now available in the market possess many side effects and that may result in neuro degeneration. So as a growing concern, we must take immediate steps to
curb these diseases and find more useful drugs with lesser side effects to combat the situation in the near future.
AN OVERVIEW OF EPILEPSY AND ANTIEPILEPTIC DRUGS:

Epilepsy, the word derived from the Greek *epilepsia*, meaning “to come upon, to be grabbed hold of or thrown down, to attack, to seize hold of.” In 1861 Hughlings Jackson\(^1\) first developed the theory that seizures were caused by an excessive discharge of gray matter of the brain. Epilepsy is a general term given to the wide range of symptoms that reflect many functions of the brain in a pathologically disturbed manner. It is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence, and management.

Epilepsy implies a periodic recurrence of seizures with or without convulsions\(^2\). The seizures that are prolonged or repetitive can be life threatening. At least 8% of the general population will have at least one seizure in their lifetime. However it is possible to have seizure and not have epilepsy\(^3\). Recurrence of first unprovoked seizure within 5 years ranges between 23% and 80%. Children with an idiopathic first seizure and a normal electroencephalogram (EEG) have a particularly favorable prognosis\(^4\). Epilepsy is a chronic disorder characterized by recurrent seizures.\(^1\) Every year about 125,000 new epilepsy cases occur; of these, 30% are in people under the age of 18 at the time of diagnosis. The relatively high frequency of epilepsy in the elderly is now being recognized. At least 10% of patients in long-term care facilities are taking at least one antiepileptic drug (AED). At this time, it is unknown if these AEDs are used for seizures or other conditions\(^1\). The type and the cause of the seizure change with the age.\(^5\)

ETIOLOGY OF EPILEPSY:

Seizures occur because small numbers of neurons discharge abnormally. Anything that disrupts the normal homeostasis of the neuron and disturbs its stability may trigger abnormal activity and seizures. The causes of seizures in the elderly may be multifactorial and include cerebrovascular disease (both ischemic and hemorrhagic stroke), neurodegenerative disorders, tumor, trauma, metabolic disorders, and CNS infections\(^5\). Many factors have been shown to precipitate seizures in susceptible individuals\(^2\). Hyperventilation may precipitate absence seizures.
Sleep, sleep deprivation, sensory stimuli, and emotional stress may initiate seizures. Hormonal changes occurring at the time of menses, puberty, or pregnancy have been associated with the onset of or an increased frequency of seizures. A history for theophylline, alcohol, phenothiazine, antidepressant (especially maprotiline), and street drug use should be obtained from the patients presenting with seizures. In certain cases, the anti epileptic drugs (AEDs) in toxic concentrations may precipitate seizures. Perinatal factors and subsequent events have been identified as risk factors for the later development of epilepsy. The most clearly established risk factors in all age groups are head trauma, especially in cases where the dura mater has been breached and where there is evidence of loss of consciousness, CNS infections, and stroke. Some seizures may occur as single events resulting from withdrawal of CNS depressants (e.g., alcohol, barbiturates, and other drugs) or during acute illness (e.g., meningitis or encephalitis) or toxic conditions (e.g., uremia and eclampsia). Some cases will have seizures only associated with fever. These febrile cases do not fall under class of epilepsy.

**PATHOPHYSIOLOGY OF EPILEPSY:**

Seizure activity is characterized by paroxysmal discharges occurring synchronously in a large population of cortical neurons. This is characterized on the EEG as a sharp wave or spike. The basic physiology of a seizure episode is traceable to an unstable cell membrane or its surrounding supporting cells. The seizures originate from gray matter of any cortical or perhaps subcortical area. Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic currents breakdown and excess excitability spreads, either locally to produce a focal seizure or more widely to produce a generalized seizure.

The clinical manifestations depend on the site of focus, the degree of irritability of the surrounding area of brain, and the intensity of the impulse. An abnormality of potassium conductance, a defect in the voltage sensitive ion channels, or a deficiency in the membrane ATPases linked to ion transport may result in neuronal membrane instability and a seizure.
Selected neurotransmitters (e.g., glutamate, aspartate, acetylcholine, nor-epinephrine, histamine, corticotrophin RF, purines, peptides, cytokines, and steroid hormones) enhance the excitability and propagation of neuronal activities. Whereas, \( \gamma \)-amino butyric acid (GABA) and dopamine inhibit neuronal activity and propagation. A relative deficiency of inhibitory neurotransmitters such as GABA or an increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity. Normal neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, chloride, calcium, and amino acids. Systemic pH is also a factor in precipitating seizures.

Control of abnormal neuronal activity with AEDs is accomplished by elevating the threshold of neurons to electrical or chemical stimuli or by limiting the propagation of the seizure discharge from its origin. Raising the threshold most likely involves stabilization of neuronal membranes, whereas limiting the propagation involves depression of synaptic transmission and reduction of nerve conduction. During a seizure, there is large increase in the demand for blood flow to the brain to carry off \( \text{CO}_2 \) and to bring substrates for neuronal metabolic activity. The brain has a limited capacity to increase blood flow, and during a seizure, the brain may use more energy than it can manufacture. The more prolonged the seizure, the more likely the brain to suffer ischemia that may result in neuronal destruction and brain damage, the developing brain is more vulnerable to damage. Although individual seizures as such do not cause a significant decrease in intelligence, it has been suggested that individuals suffering a large number of generalized tonic-clonic seizures (GTC) or who have multiple episodes of status epilepticus, may be at risk for eventual cognitive declines.
Genetics of epilepsy and Epileptogenesis:

A hereditary component to epilepsy has been suspected since the time of Hippocrates. Sushrutha too in Indian system of medicine-Ayurveda, emphasizes the role of hereditary influences in epilepsy. It is now known that the genetic factors have greater influences in idiopathic than symptomatic epilepsies. There are over 200 individually rare mendelian disorders in which epilepsy forms part of their phenotype. These disorders, however, are few and account for only 1% of all epilepsy. These include neuro cutaneous, neuro degenerative, inherited metabolic disorders and inherited malformation of cortical development. These have helped but not contributed much towards understanding the basic mechanism of human epileptogenesis. On the other hand, epilepsies with predominantly complex genetic disposition are common and account for about 50% of all genetically based epilepsies.

The vast evidence in favor of the existence of mutant “epilepsy genes” has been derived from studies of family with a clustering of specific forms of epilepsy. In all the studies, individuals with epilepsy with in the family have been correlated with the inheritance of a specific DNA marker or a mutant gene. In other words it involves the matching of a specific genotype (mutant gene) or a specific phenotype (epilepsy type). A variety of such candidate genes and specific genetic markers have now been identified that can be assayed in small blood samples. The other is defining specific epileptic syndromes that follow a hereditary pattern in the population. The study of families with common phenotypes by modern molecular biology techniques is essential to such progress. One approach for identifying potential gene mutation believed to cause human epilepsies is Restriction Fragment Length Polymerization (RFLP) analysis. In this method probes are used to analyze the DNA from families in which epilepsy is inherited. The other approach is to identify candidate epilepsy genes in animals and search for their homologous counter parts in human.
The epileptogenesis refers to the transformation of the brain to a long lasting state in which recurrent spontaneous seizures occurs. It may involve a focal area of the brain (partial epilepsy) or the entire brain (generalized epilepsy). Epileptogenesis must be distinguished from seizure expression, which is concerned with processes that trigger and generate seizures, because seizures can arise in non-epileptic brain exposed to acute insults.

Knowledge of the mechanisms underlying epileptogenesis has considerable clinical relevance. The Anti epileptic drugs (AEDs) currently used to treat patients with epilepsy affect seizure expression but a better approach in the future would be to develop agents that prevent epileptogenesis that is anti epiletogenic drugs.

Epileptogenesis occurs in a variety of ways, in general, these processes can be divide in to genetic acquired mechanisms. Acquired mechanisms may be of acute or chronic. In the last decade, remarkable progress has been made in understanding the genetics of epilepsy. Over thirteen genes associated with human epilepsy have been identified so far and at least 33 single gene mutations in mice have been linked to an epileptic phenotype.

The mutant genes for three idiopathic syndromes – Benign Familial Neonatal Convulsion (BFNC), Generalized Epilepsy with Febrile Seizure Plus (GEFSP) and Autosomal Dominant Nocturnal Frontal Lope Epilepsy (ADNFLE) are known. The common theme is that all the three are due to mutations in gene coding for voltage gated or ligand gated channels suggesting that these epilepsies are channelopathies.

BFNC is inherited in an autosomal dominant manner. Patients develop clonic and apneic seizures on the second or third day of life. Seizures typically stop with in a week although they may recur in life of 10-15 % of patients. By linkage analysis loci were initially found on chromosome 20q13.3 and later on chromosome 8q24 in different families. The mutations were identified in genes for previously unknown Potassium channels, which are named KCNQ2 and KCNQ3. A similar gene expressed in the heart and mutated in the long QT syndrome, termed as
KCNQ1. The KCNQ potassium channels, that is different from the K channels that are involved in the repolarising action potentials. They are activated by small depolarization and because of their slow rates of opening and closing, allow firing of single action potentials but oppose sustained depolarization and repetitive firing. Mutations that cause BFNC are associated with loss of function of KCNQ channels leading to decrease in the size of the potassium current. It has been suggested that even a moderate reduction (20-25%) of function may be associated with epilepsy.

For GEFS+ is characterized by the occurrence of the seizures with fever beyond the age of 6 years. Two loci have been described, GEFS1 on chromosome 19q and GEFS2 on chromosome 2q. A point mutation in the gene coding for the β-subunit of a voltage gated sodium channel (SCN1B) was identified for GEFS1 in 1998 and more recently another mutation was found in the α-subunit of the sodium channel (SCNA-1A) gene.

ADNFLE begins clinically in childhood and the patients have brief nocturnal seizures with motor features. Two mutations have been identified in a ligand-gated channel- the α4 subunit of the neuronal nicotinic acetylcholine receptor (CHRNA4) on chromosome 20q13.2. A second locus has been mapped to chromosome 15q24, which also contains subunits of nicotinic cholinergic receptors.

The common idiopathic generalized epileptic syndromes such as absence epilepsies and juvenile myoclonic epilepsies have complex inheritance patterns. In some of the symptomatic epilepsies such as progressive myoclonal epilepsy, seizures occur as part of neuro degenerative disease. PME is a group of rare single gene epilepsies characterized by myoclonus, generalized tonic-clonic seizures and progressive neurological dysfunction mainly in the form of dementia and ataxia. Among five major causes of PME, the gene and gene product have been identified in two diseases a) Unverricht- Lund Borg disease (ULD), an autosomal recessive disorder characterized by prominent myoclonus, generalized tonic-clonic seizures, ataxia and mild dementia b) Lafora
Acquired mechanisms, most studies on acquired epileptogenesis have focused on chronic mechanisms but in the last decade it has been recognized that epileptogenesis can also be an acute process. Acute epileptogenesis develops within minutes to hours and can be reversible whereas chronic epileptogenesis takes weeks, months or years to develop and is usually irreversible.

Cellular mechanisms of epilepsy and neurotransmitters:

The intracellular correlate of an intracortical spike on the EEG is the synchronized occurrence of a paroxysmal depolarizing shift (PDS) in a group of neurons. Thonston and Brown showed that PDS is a network-driven phenomenon resulting from an imbalance between excitation and inhibition. The synchronizing potential is a giant excitatory postsynaptic potential (EPSP), which is mediated by glutamate. The NMDA and AMPA types of ionotropic glutamate receptors largely mediate PDS, although metabotropic receptors also play a role by modulating the frequency of PDS discharges. In hippocampal slices and cultures, NMDA receptor activation by lowering extracellular mechanism, which normally blocks the receptor leads to seizures.

In normal brains and hippocampal slices, NMDA receptor do not participate in low frequency synaptic transmission, but in epileptic brains they may be recruited in to synaptic transmission. This increased activation of NMDA receptors may be due to expression of novel receptors or altered regulation by calmodulin dependent phosphorylase, Calcineurin.

In addition to excitatory connections reduction of inhibition is necessary synchronization of bursts. GABA-mediated inhibition normally holds the membrane potential below the action potential threshold and prevent recruitment of bursts. It also prevents synchronization of intrinsic burst discharges in pyramidal neurons by decreasing the connectivity of their divergent polysynaptic excitatory pathways. In epileptic brains decreased inhibition increases the probability of firing action potentials in response to an EPSP and allows synchronization of burst discharges.
Recently it has been speculated that decreased inhibition of TLE may be due to alteration of the molecular structure of GABA-A receptors in the hippocampus. In epileptic brain, mossy fibers aberrantly innervate granule cells and release Zinc and this will alter the subunit composition of the GABA-A receptors, which determines its properties and lead to changes in the function and in normal brains the granule cells are not sensitive to Zinc.

INTERNATIONAL CLASSIFICATION OF EPILEPTIC SEIZURES\textsuperscript{6}

I. Partial seizures (Seizures begin locally)
   A. Simple (without the impairment of consciousness)
      a). With motor symptoms
      b). With special sensory or somatosensory symptoms
      c). With psychic symptoms
   B. Complex (with impairment of consciousness)
      a). Simple partial onset followed by impairment of consciousness- with or without automatism
      b). Impaired consciousness at onset- with or without automatism
   C. Secondarily generalized (Partial onset evolving to generalized tonic-clonic seizures

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II. Generalized seizures (bilaterally symmetrical and without local onset)
   a). Absence seizures
   b). Myoclonic seizures
   c). Clonic seizures
   d). Tonic seizures
   e). Tonic-clonic seizures
   f). Atonic seizures
   g). Infantile spasms

III. Unclassified Seizures

IV. Status Epilepticus
AN OVERVIEW OF ANTICONVULSANTS:

Currently, all available drugs are anticonvulsants (i.e. antiseizure) rather than antiepileptic. The term antiepileptic should be used only for drugs that prevent or treat epilepsy and not solely its symptoms. The goal of therapy with an anticonvulsant is to have the patient seizure free without interfering normal brain function. Thus, the selection of an anticonvulsant is based primarily on its efficacy for specific types of seizures and epilepsy. There is a growing need for new drugs with a greater benefit as related to side effects and tolerability, even at the expense of efficacy, when compared to the existing antiepileptic drugs.

The anticonvulsants may be conveniently grouped in the three general categories:

1. First generation or older agents as exemplified by Phenytoin, Carbamazepine, Valproate, Benzodiazepines, Ethosuximide, Phenobarbital, Primidone, Trimethadione; all of these were introduced during the period 1910-1970 (Fig 1).

2. Second generation or newer agents consisting of Vigabatrin, Gabapentin, Felbamate, Lamotrigine, Oxycarbazepine, Zonisamide, Tiagabine, Topiramate, and Levetriacetam (Fig 2).

3. The third generation agents are in Preclinical or Clinical development stages at present.
Fig 1: First Generation anticonvulsants
Vigabatrin  Gabapentin  Felbamate

Lamotrigine  Oxcarbazepine  Zonisamide

Levetriacetam

Fig 2: Second Generation anticonvulsants
Pharmacophore model for anticonvulsants\textsuperscript{7}:

There have been several attempts to postulate a general pharmacophore model for the different anticonvulsant classes, all of which are anti MES in animal studies and are, or have the potential to be effective in tonic-clonic seizures. These include Benzodiazepines, Barbiturates, Triazolines, and Semicarbazones.

Features of commonality include:

At least one aryl ring

One electron donor atom

A second donor atom in close proximity to NH group forming a hydrogen bond acceptor/donor

The Unverferth pharmacophore model for anticonvulsants acting at the voltage dependent sodium channels on the basis of molecular dynamitic simulations.

Phenytoin
Evaluation of antiepileptic drugs:

There is an increasing need to screen novel molecules as AEDs and to subsequently evaluate them. There are certain difficulties in evaluating AEDs because of multiple types of epilepsies, heterogeneous pathophysiology of the disorder, validation of the model required, as imitation of clinical types is not always so trustworthy. Thus the basic aim is to evaluate potential efficacy of agent but along with, the procedure must also point towards the possible mechanism of action.

CLASSIFICATION OF EXPERIMENTAL SEIZURE MODELS:

1. Electrically induced
   a. Maximal Electro Shock Seizures (MES)
   b. Threshold
   c. Kindling

2. Chemically induced
   a. Pentylene tetrazole (PTZ) or Metrazole (MMS)
   b. Biculline
   c. Strychnine
   d. Picrotoxin

3. Genetic Models
   a. Spontaneous
   b. Semi spontaneous
AN OVERVIEW OF ANXIETY AND ANXIOLYtics:

Anxiety is an integral part of human life and is a normal emotion that all people experience to some extent, indeed, anxiety is an essential part of the adaptive response to stressful or threatening stimuli. The anxious state is somewhat very difficult to define. It may be described as a sense of unpleasant anticipation and excessive mental tension. A significant number experience anxiety that is uncontrollable and completely out of proportion to the generating stimulus. In such cases anxiety is pathological and such individuals suffer from an anxiety disorder. The psychological symptoms include overwhelming worry and apprehension, coupled with feelings of helplessness and inability to cope. These are frequently accompanied by somatic symptoms such as tachycardia, palpitations, sweating, dizziness, nausea, insomnia, irritability and impaired concentration. The anxiety associated with certain every day activities can result in avoidance behaviors that cause extensive disruption of life and serious impairment of productivity and social functioning

Recent epidemiological studies show that anxiety is second only to depression in causing workplace absenteeism and reduced productivity. Anxiety disorders, as a group, are among the most common psychiatric conditions with lifetime incidence rates ranging between 16% and 25%. Anxiety is not a single disorder but rather a group of conditions with their own epidemiology and symptoms. The American Psychiatric Association in 1994 published the Diagnostic and Statistical manual of Mental disorders –IV (DSM-IV), in that the anxiety has been classified according to characteristic clustering of symptoms.
DSM-IV: CLASSIFICATION OF ANXIETY DISORDERS.

Generalized Anxiety Disorder (GAD)

Panic Disorder (PD)
   a) With agoraphobia
   b) Without agoraphobia

Agoraphobia without a history of Panic Disorder

Social Anxiety Disorder (SAD) or Social Phobia

Obsessive Compulsive Disorder (OCD)

Post-Traumatic Stress Disorder (PTSD)

Acute Stress Disorder

Specific Phobias
Generalized anxiety disorders are defined as excessive anxiety and worry occurring more days than not for a period of at least six months\textsuperscript{16}. The anxiety is accomplished by at least three of the following symptoms: 1) Restlessness 2) Fatigue 3) Impaired concentration 4) Irritability 5) Muscle tension 6) Sleep disturbance. GAD has the lifetime prevalence of 6-10\%\textsuperscript{17}. The NCS study indicates a high co-morbidity with other psychiatric disorders, especially depression and panic disorder\textsuperscript{13}.

Social phobia is characterized by significant and persistent fear of social situations from which embarrassment may result or situation where one is being observed or scrutinized by others\textsuperscript{18-20}. Exposure to the feared situation induces pronounced anxiety and the situation is either totally avoided or is endured only with extreme stress. The avoidance behavior and associated anxiety cause significant disruption of the patient’s normal social and occupational functioning. It can be classified into Specific phobia and Generalized social phobia\textsuperscript{21}. The epidemiological studies reveal lifetime prevalence rates around 10\%, making social phobia one of the most common anxiety disorders\textsuperscript{22}.

The panic disorder\textsuperscript{23} is the occurrence of repeated and unexpected panic attacks. There is a marked worry about the consequences of the attack and the possibility of having a future attack. The persistent anxiety evoked by the panic attack causes major behavioral changes and intrusion into normal life. Around 50\% of panic disorder patients also suffer from agoraphobia. A lifetime prevalence of 3.5\% has been estimated\textsuperscript{13} and a high co-morbidity with depression and other anxiety disorder is observed.

Obsessive-compulsive disorder involves recurrent obsessions and compulsions, which are severe enough to cause marked distress and major functional impairment. The sufferer is aware that the obsessions and compulsions are unreasonable, but is powerless to control it. Obsessions are recurrent, unwanted thoughts or images, whereas compulsions are repetitive acts or rituals. The individual typically feels compelled to perform compulsions to alleviate the anxiety
associated with an obsession or to prevent the occurrence of some dreaded event. The lifetime prevalence of 2.3% is estimated.  

Posttraumatic stress disorder (PTSD) is a characteristic set of symptoms and develops following exposure to an event that induces extreme fear or terror. These symptoms include a persistent and intrusive re-experiencing of the event through flashbacks and nightmares, and an intense distress to exposure to cues that are reminiscent of the event. The sufferer deliberately avoids such stimuli and may become detached, withdrawn and emotionally numb. Additional symptoms include insomnia, impaired concentration and unprovoked anger. Prevalence rates of 9-13% in the general population have been reported, but this can increase to over 70% in high-risk populations.  

Specific phobias are perhaps the most familiar of the anxiety disorders, and are characterized by a disproportionate fear of an object or situation. When the stimulus is confronted, it elicits an intense anxiety reaction, which the sufferer recognizes to be excessive but is unstable to moderate. Prophylactic use of anxiolytics for predictably stressful situations is helpful, but in the long term medication is less successful than behavioral therapy in the treatment of specific phobia.

An ideal anxiolytic would be orally efficacious with a rapid onset of action, and be devoid of side effects such as tolerance, withdrawal complications, dependency, sedation, motor and cognitive impairment, interaction with CNS depressants and toxicity in overdose. Despite the progress made in anxiolytic research, the current available anti-anxiety agents fall some way short of this profile. This fact coupled with the prevalence of the anxiety disorders, their impact on society and consequent market size ensures a continued intense interest within the profession of drug research in the development of new anxiolytics with an ideal profile.

Currently there are more biological mechanisms under investigation as potential targets than ever before. The most advanced of these approaches are those involving the γ-Amino butyric
Biological Basis of Anxiety:

The anxiety disorders are primarily biologic illnesses associated with an underlying genetic vulnerability. Anxiety may not reflect an imbalance in a single neurotransmitter system, but may be the result of multiple interactions among various neurotransmitters including Nor-epinephrine (NE), γ-Amino butyric acid (GABA), and 5-Hydroxy tryptamine (5HT).

Noradrenergic model:

The basic premise of the noradrenergic theory is that, the Autonomic Nervous System (ANS) of anxious patients in hypersensitive conditions clearly displays symptoms of peripheral autonomic hyperactivity, hyperventilation, palpitation and tremulousness. The midbrain nucleus locus coeruleus (LC), mid brain nucleus may play a major role in regulating the anxiety. The LC contains neurons that supply 50-70% of brain’s Nor-epinephrine (NE) with widespread projections to many areas. In response to anxiety or fearful situations, the LC serves as an alarm center activating NE release and stimulating the sympathetic nervous system. The presynaptic α2 adrenergic autoreceptor plays a significant role in controlling the release of NE from the synapse. Chronic central noradrenergic overactivity down regulates α2 adrenergic autoreceptor in GAD patients. This receptor may also be abnormal in some patients with panic disorders. Drugs with anxiolytic or antipanic effects inhibit LC firing, decrease noradrenergic activity and block the effects of anxiogenic substances.

Benzodiazepine (BZ) Receptor Model:

The BZ receptor is functionally linked to GABA\textsubscript{A} receptor and a chloride ion channel. This is referred to as supramolecular receptor complex. GABA is the major inhibitory neurotransmitter in the CNS and has strong regulatory and inhibitory effects on the 5HT and NE systems. When GABA binds to its receptor, the adjacent chloride ion channels open and permit
the influence of negatively charged chloride ions. This results in hyperpolarization of the cell membrane and causes a decrease in nerve cell excitability when BZs bind to their receptor. The inhibitory effects of GABA are potentiated via an increase in the frequency of chloride ion channel openings. Benzodiazepines in the absence of GABA have little effect on the nerve cell excitability. The therapeutic effects of benzodiazepines are mediated through the GABA<sub>\alpha</sub> receptor and they also enhance GABA effects.

**Serotonin (5HT) Model:**

In general, pharmacological manipulations that enhance serotonin also enhance anxiety; whereas reduced serotonin may also reduce anxiety. Anxiety is essentially the opposite of depression. 5HT is an inhibitory neurotransmitter; its origin is in the raphe nuclei of the brain stem. Eight different receptor subtypes regulate the 5HT functions. Azapirone and buspirone are selective 5HT<sub>1A</sub> partial agonists that are effective in controlling GAD but ineffective in panic disorder. The 5HT<sub>1A</sub> partial agonists reduce serotonergic activity; 5HT reuptake inhibitors are effective in panic disorders<sup>1</sup>.

**CLASSIFICATION OF ANXIOLYTICS BASED ON TYPES OF DSM-IV DISORDERS<sup>14</sup>:**

**Generalized Anxiety Disorder (GAD):**

Benzodiazepines, tricyclic antidepressants, buspirone, trazadone, ß blockers.

**Panic Disorder (PD)**

Tricyclic antidepressants (TCA), selective serotonin reuptake inhibitor (SSRI), Monoamine oxidase Inhibitors (MAOI), benzodiazepines,

**Obsessive Compulsive Disorder (OCD):**

Clomipramine, MAOI, buspirone, clonazepam, fenfluramine

**Post-Traumatic Stress Disorder (PTSD):**
TCA, SSRI, trazadone, MAOI, lithium, carbamazepine, valproic acid, alprazolam, clonidine, β-blockers.

**Phobic disorders:**

β-Blockers, benzodiazepines, SSRI, buspirone, MAOI.
AN OVERVIEW OF PSYCHOSES AND ANTIPSYCHOTIC AGENTS:

Antipsychotics constitute a diverse class of drugs that are effective in the treatment of major psychoses, including those associated with schizophrenia. These agents were originally known as “Neuroleptics” because of their ability to lessen the reactivity to emotional and physical stimuli in highly agitated and in psychotics with little or no effect on consciousness. It had been widely believed that the occurrence of acute extrapyramidal symptoms (EPS), including pseudo-parkinsonism, dystonias, and akathisia, was an expected consequence of antipsychotic drug therapy. The positive correlation between neuroleptic-induced EPS and the emergence of the biochemically very different and long-lasting syndrome of tardive dyskinesia (TD) reinforced the belief that motor system side effects were necessary correlates of antipsychotic efficacy.

Schizophrenia is a severe, lifelong, idiopathic psychiatric disorder with a polygenic component. It is composed of severe thought disorders termed psychoses and are characterized by illogical, delusional, or paranoid thoughts. Schizophrenia typically has its onset in early adulthood with remissions and exacerbations throughout life. The expression of these symptoms varies across the patients and over time, but the cumulative effect of the illness is always severe and usually long lasting.

The etiological process or processes by which a casual agent creates the pathophysiology of schizophrenia is not known. However, a good deal is known about the risk factors for developing schizophrenia, which leads to direct interferences, regarding possible etiopatho physiologies. The principal hypotheses regarding causation include genetic factors, environmental, neuro immuno virological factors, childbirth and pregnancy, and complications such as hypoxic neurotoxic damage. 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 of biological relatives.
The antipsychotics used in schizophrenic conditions are conveniently classified under following classes:

Typical antipsychotics: Chlorpromazine, loxapine, penfluridol, haloperidol, trifluperidol, fluphenazine, triflupromazine, thioridazine, trifluperazine, pimozide, zuclopenthixol, prochlorperazine, and flupenthixol.

Atypical antipsychotics: Clozapine, olanzapine, resperidone, ziprasidone, and quetiapine.

Depot preparations: Fluphenazine decanoate, haloperidol decanoate, flupenthixol decanoate, zuclopenthixol decanoate, penfluridol, and pimozide.

Animal models of efficacy:

Because of its genetic complexity and uncertain etiology, schizophrenia, like so many neuropsychiatric disorders, has resisted the development of suitable animal models. Early progress in the field was hampered because of the prevailing belief that schizophrenia was a social or psychological disorder rather than a neuro-developmental brain disorder.

Behavioral Effects of psycho stimulants:

The psychoses-inducing properties of the psychostimulants amphetamine and phencyclidine (PCP) in human are well known. Both drugs also exacerbate psychotic symptoms in schizophrenic patients. However, the constellation of symptoms elicited by the two psycho stimulants differs significantly. Amphetamine induces predominantly positive symptoms such as paranoia in normal subjects and tends to worsen such symptoms in schizophrenics. Certain negative symptoms may actually be improved by amphetamine. PCP induces positive and negative psychotic symptoms in normal subjects and worsens a broad spectrum of psychotic symptoms in schizophrenics. Because of psychomimetic effects of amphetamine and...
phencyclidine, both drugs have been used for evaluating antipsychotic activity of new chemical
entities in animal models.

**Behavioral models for evaluating antipsychotic activity:**

These models are based on the dopamine theory of schizophrenia\(^42\). The antagonism of
increased locomotor activity and stereotypic behaviors induced by dopamine stimulants like
apomorphine and amphetamine, the induction of catalepsy and the disruption of the conditioned
avoidance response, each result from the blockade of D2/D3 dopaminergic receptors\(^43\),\(^44\). The
prepulse inhibition is the reduction in the startle reflex response produced by a weak sensory
stimulus given just before the startling stimulus and is a measure of sensory motor gating and
information processing and is reliably impaired in schizophrenic patients.

The latent inhibition (LI) is a retarded acquisition of a conditioned response that occurs
when a subject is exposed to the conditioning stimulus before the conditioning trials. Deficits in
LI reflect the inability of the subject to ignore irrelevant stimuli. Amphetamine disrupts the LI
response in rats and this is reversed by haloperidol and clozapine\(^45\),\(^46\). Prepulse inhibition is a
sensory motor gating process that does not require conditioning and relies on mechanisms that
filter exteroceptive stimuli for their physiological or cognitive significance. Latent inhibition is
cognitive process requiring preconditioning and reflects a subjects ability to adjust behavior to
changing conditions. In contrast to PPI, LI is not disrupted by phencyclidine.

In conditioned avoidance response (CAR) model, the experimental animals are trained to
avoid a mild shock. Trained avoidance responses may be active (climbing a pole, jumping out of
box) or passive (remaining in the darker of two compartments). Classical antipsychotics reduce
avoidance responding at doses that do not impair natural escape responding. CAR is inhibited by a
wide variety of structurally different D2 antagonists. There is a positive and significant correlation
between anti avoidance activities of various antipsychotic drugs in rats and their D2 receptor
blockade\(^47\). The complexity of CAR test is evident from the variety of drugs that either suppress
or enhance responses. Wadenberg and Hicks\textsuperscript{48} conclude that CAR is sensitive test for potential antipsychotic drugs that act by various receptors, particularly those in the \textit{nucleus accumbens} shell.

Catalepsy is a state of tonic immobility in experimental animals. In this test, rats or mice are placed in an unusual position and the time required for the animal to correct this unusual position is determined. The induction of catalepsy reflects the potential of the drug to cause extrapyramidal side effects.