1. INTRODUCTION

1.1. Epilepsy

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is one of the most common neurological conditions, occurring in about 1% of the global population. It is second most common disorder after stroke. Several new drugs have been licensed and many others are in various stages of development, e.g. remacemide, lamotrigine, flunarizine, loreclezole and levetiracetam. Despite optimal use of the 16 antiepileptic drugs marketed in the United States, many patients with epilepsy fail to express seizure control and others do so only at the expense of significant toxic side effects.

Phenytoin, Carbamazepine and Sulfamate topiramate (TPM) are antiepileptic drugs that have been clinically effective against different types of seizures. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients. The search for antiepileptic agents with more selectivity and lower toxicity continues to be an area of investigation in medicinal chemistry. The mechanisms of action of the antiepileptic drugs (AEDs) consist in the blockade of voltage-dependent Na\(^+\) channels or T-type Ca\(^{2+}\) channels, inhibition of glutamatergic transmission and facilitation of \(\gamma\)-aminobutyric acid (GABA) inhibitory neurotransmission.

1.1.1. Causes

All forms of epilepsy have their origin in the brain. The different types of epilepsies are not based on a single underlying mechanism, but are multifactorial in origin. Epilepsy results when many neurons in union, under a high excited stage, deliver massive discharges abolishing a finely organized pattern of the integrative activity of the brain. John Jackson proposed that these seizures are caused by occasional, sudden, excessive, rapid and local discharges of grey matter and once initiate by the abnormal focus, the seizures attack the neighboring normal brain resulting into generalized convulsions. This abnormal focus may originate as a result of local biochemical changes, ischemia or the loss of vulnerable cell inhibitory systems. However, certain physiological changes may trigger the focus and thus facilitate the spread of abnormal electrical activity to normal tissue. Such factors include

(a) Changes in blood glucose concentration
(b) Plasma pH
(c) Total osmotic pressure and electrolytes composition of extra cellular fluids
(d) Fatigue
(e) Emotional stress
(f) Nutritional deficiency
(g) Trauma, infection meningitis, brain tumors, cerebrovascular disease or metabolic abnormalities.

Epileptic seizures of unidentified cause are known as primary or idiopathic epilepsy while epileptic attacks of known causes are called as secondary or symptomatic epilepsy

1.1.2. Classification

[A] Generalized epilepsy: Once initiated, it spreads quickly into the entire or at least the greater part of the brain. It can be further classified into

(i) Tonic clonic seizures (grandmal type): It has a close resemblance with electrically induced convulsions where the mass stimulation of cortical neurons occurs. As the name indicates, initially there is a generalized tonic activity followed by clonic phase.

(ii) Absence or minor seizures (petitmal): It is reported to occur mainly in young children between the ages of 6 to 14 years. Seizures generally disappear spontaneously after adolescence.

(iii) Myoclonic seizures: The attack characterized by the jerky muscular movements of head, limbs or body as a whole. The etiology of attack is not known and is suppose to be due to brain damage.

(iv) Infantile spasms: The attack sometimes begins with a cry and is often associated with memory unconsciousness.

[B] Partial or focal epilepsy: In this type the initial neuronal discharge originates from a specific limited cortical area. It can further be classified as

(i) Complex partial seizures (psychomotor or lobe seizures); It usually originates in the anterior temporal lobe and is characterized by hallucinations, fear, hate or other emotional and behavioral abnormalities.

(ii) Motor epilepsy: Only one, entire side is affected, consciousness is not lost. Motor epilepsy is mainly witnessed in child hood and is due to more limited cortical abnormalities.
(iii) **Sensory epilepsy**: Similar to motor epilepsy except the fact that it arises in the sensory cortex area.

(iv) **Akinetic seizures**: Superficially no convulsions are seen. Patient may suddenly fall down on the ground without loss of consciousness.

[C] **Status epilepticus** (acute repetitive seizures): It is the condition in which one attack follows another without patient regaining consciousness. If it remains untreated it may be fatal.

1.1.3. Mechanisms

A) **Neuronal Sites of Action of antiepileptics**\(^2\) – Antiepileptic drugs acting upon neuronal site have been shown by Fig.1.

B) **Sites of Action of antiepileptics in GABAergic Synapse**\(^2\) - Antiepileptic drugs acting through GABAergic Synapse have been shown by Fig.2.
1.1.4. Targets and treatment approaches for anti-epileptic drugs

There are few targets for the Anti-Epileptic drugs
A) Inhibition of excitatory neurotransmitter, Glutamate
B) Enhancement of inhibitory neurotransmitter, GABA
C) Blockage of voltage-gated positive current, Na$^+$ and Ca$^{2+}$
D) Increase outward positive current, K$^+$

_Treatment Approaches_

The only effective means of treating epilepsy currently available are medication and, in a small proportion of patients in whom medication is not effective, surgery on the brain. Treating epilepsy by "natural" means alone (e.g. with herbal remedies) is ineffective and may be dangerous.

A. _Treatment by Medication/Drugs_

i) _Drugs acting through increasing inhibition_

Gabapentin and Pregabalin were the first drugs of this type to be developed. They are active against a wide spectrum of seizures. Vigabatrin appears to be a very useful medication in treating various forms of epilepsy that have not responded to other
drugs. Early reports of degenerative changes in neurons of animals treated with Vigabatrin led to the most stringent appraisal of its safety in humans, but no similar effect has so far been reported in man.

\textit{ii) Drugs Which Reduce Excitation of Neurons}

Lamotrigine partly blocks the release of the excitatory neurotransmitter glutamate from nerve endings, and reduces the influx of sodium in the recipient neuron (this influx of sodium is vital to nervous transmission). It too appears to have a wide range of anti-epileptic activity. Allergic reactions, especially skin rashes, are relatively common. It is used as an additional treatment in patients with partial seizures with or without secondary generalization, where seizures have not been controlled by other anticonvulsant drugs. Topiramate has been shown to significantly reduce the frequency of epileptic seizures, including refractory partial seizures. It appears to help balance electrical activity in the brain while blocking other substances that increase activity.

\textit{iii) Drugs that affect the availability of gamma aminobutyric acid (GABA)}

Gabitril (tiagabine hydrochloride) is one of a new class of compounds that affects the availability in the brain of gamma aminobutyric acid (GABA), a naturally occurring chemical that is thought to suppress the abnormal, repetitive pattern of central nervous system activity that can lead to seizures. Gabitril appears to work by inhibiting neuronal reuptake of GABA, thereby prolonging the amount of time it is available at receptor sites.

\textbf{B. Surgery for Epilepsy}

The idea of treating epilepsy by surgery is not new; the first operation for epilepsy was carried out in 1886. Interest in surgery has been revived in recent years, for it is now realized that it does have an important part to play in a small minority of patients, namely those who have a single solitary epilepsy-producing abnormality of the brain, situated in an area where removal does not leave any significant defect in the brain's function. Even in these patients, operation is contemplated only when satisfactory control cannot be achieved with medication.

To determine that a patient does indeed have only one area of the brain giving rise to epilepsy, new nuclear medical techniques (SPECT and PET scanning) are used to
supplement information from special EEG techniques including EEG telemetry, sleep studies, and recording from pharyngeal or sphenoidal electrodes as appropriate.

1.1.5. Established & Newer Antiepileptic Drugs

The currently used therapy of epilepsy includes various drugs that act through different mechanisms. There are several classes of antiepileptic drugs (AEDs) that have been divided on the basis of their chemical structure. Different established AEDs and newer antiepileptic drugs along with the drugs in pipeline are summarized in Table 1 and 2.

Table-1: General Description of Established Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Clinical Uses</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (Dilantin)</td>
<td><img src="image" alt="Phenytoin Structure" /></td>
<td>Partial and tonic-clonic</td>
<td>Prolongs closing of inactivating gate of sodium channels of excitatory NT receptors in the CNS</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td><img src="image" alt="Carbamazepine Structure" /></td>
<td>Partial and tonic-clonic</td>
<td>Prolongs closing of inactivating gate of sodium channels of excitatory NT receptors in the CNS</td>
</tr>
<tr>
<td>Phenobarbital (Luminal®)</td>
<td><img src="image" alt="Phenobarbital Structure" /></td>
<td>Partial and tonic-clonic</td>
<td>Facilitates the inhibitory action of GABA, increases the duration of chloride channel opening at GABA-A receptors</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin®)</td>
<td><img src="image" alt="Ethosuximide Structure" /></td>
<td>Absence seizures</td>
<td>Inhibits low-threshold T-type calcium currents in thalamic neurons</td>
</tr>
<tr>
<td>Valproic acid (Depakene®) Divalproex Na (Depakote®)</td>
<td><img src="image" alt="Valproic acid Structure" /></td>
<td>Partial and tonic-clonic and absence seizures</td>
<td>Prolongs inactivation of sodium channels of excitatory NT receptors in CNS Inhibits low-threshold T-type calcium</td>
</tr>
<tr>
<td><strong>Ph. D. thesis</strong></td>
<td><strong>Jamia Hamdard</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chapter 1</strong></td>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Structure</strong></th>
<th><strong>Effect</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin®)</td>
<td><img src="image" alt="Clonazepam Structure" /></td>
<td>Absence and myoclonic</td>
</tr>
<tr>
<td>Diazepam (Valium®)</td>
<td><img src="image" alt="Diazepam Structure" /></td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>Lorazapam (Ativan®)</td>
<td><img src="image" alt="Lorazapam Structure" /></td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>Chlorazepate (Tranxene®)</td>
<td><img src="image" alt="Chlorazepate Structure" /></td>
<td>Partial myoclonic, absence.</td>
</tr>
<tr>
<td>Trimethadione</td>
<td><img src="image" alt="Trimethadione Structure" /></td>
<td>Absence</td>
</tr>
<tr>
<td>Bromide</td>
<td><img src="image" alt="Bromide" /></td>
<td>Epilepsy in porphyrias.</td>
</tr>
</tbody>
</table>

- Currents in thalamic neurons. Increases the amount of GABA in CNS. Increases GAD activity. Decreases GABA-T and succinic semialdehyde dehydrogenase activity.
- Facilitates the inhibitory actions of GABA.
- Increases the frequency of opening of chloride channel of GABA-A receptor.
- Increases the frequency of opening of chloride channel of GABA-A receptor.
- Inhibits low-threshold T-type calcium currents in thalamic neurons.
- Not known.
Table-2: General Description of Newer Anticonvulsants

A) Marketed Drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STRUCTURE</th>
<th>MECHANISM</th>
<th>CLINICAL USES</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eslicarbazepine</td>
<td><img src="image1" alt="Structure" /></td>
<td>Novel voltage gated Na⁺-channel blocker</td>
<td>As adjunct in Partial onset seizures; also in bipolar disorder and trigeminal neuralgia</td>
<td></td>
</tr>
<tr>
<td>(Zebinix; Exalief)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td><img src="image2" alt="Structure" /></td>
<td>Possible blockade of NMDA receptor</td>
<td>Partial seizures. Lennox-Gastaut syndrome</td>
<td>Severe hepatitis Aplastic anemia</td>
</tr>
<tr>
<td>(Felbatrol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td><img src="image3" alt="Structure" /></td>
<td>Ca²⁺- channel blocker with Calmodulin binding property and Histamine blocking activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Sibelium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td><img src="image4" alt="Structure" /></td>
<td>Increases the release of GABA</td>
<td>Adjunct drug for partial and generalized tonicoclonic seizures</td>
<td>Somnolence Dizziness Ataxia Headache</td>
</tr>
<tr>
<td>(Neurontin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td><img src="image5" alt="Structure" /></td>
<td>Enhances slow activation of voltage gated Na⁺-channel</td>
<td></td>
<td>Dizziness Headache Diplopia Somnolence Skin Rash</td>
</tr>
<tr>
<td>(Vimpat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td><img src="image6" alt="Structure" /></td>
<td>Prolongs closing of inactivating gate of Na⁺ channel</td>
<td>Partial seizures</td>
<td></td>
</tr>
<tr>
<td>(Lamictal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Chapter 1

**Introduction**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical Structure</th>
<th>Action</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetan (Keppra)</td>
<td><img src="" alt="Levetiracetan" /></td>
<td>Binds to synaptic vesicle protein SV2A thereby impeding nerve conduction across synapse</td>
<td>Adjunct for partial seizures with or without secondary generalization</td>
<td>Minimal drowsiness, Anxiety, Amnesia</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
<td><img src="" alt="Oxcarbazepine" /></td>
<td>Blockade of voltage sensitive sodium channels</td>
<td>Partial seizures with or without generalization</td>
<td>CNS side effects, hematological abnormalities and effects on drug metabolizing enzymes are less than carbamazepine</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td><img src="" alt="Pregabalin" /></td>
<td>Not known</td>
<td>For neuropathic pain and adjunct therapy for partial seizure</td>
<td>Nervousness, Dizziness, Tremor, Depression</td>
</tr>
<tr>
<td>Tiagabine (Gabatril)</td>
<td><img src="" alt="Tiagabine" /></td>
<td>Inhibition of GABA uptake</td>
<td>Adjunct for partial seizures</td>
<td>Somnolence, Fatigue, Paresthesia, Confusion</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td><img src="" alt="Topiramate" /></td>
<td>Prolongs closing of inactivating gate of Na+ channel, potentiates the GABA effect and blocks AMPA receptors</td>
<td>Partial and generalized tonic-clonic seizures</td>
<td>Drowsiness, Dizziness, Paresthesia, Confusion</td>
</tr>
<tr>
<td>Vigabatrin (Sabril)</td>
<td><img src="" alt="Vigabatrin" /></td>
<td>Irreversible inhibitor of GABA aminotransferase (GABA-T)</td>
<td>Partial seizures</td>
<td>Drowsiness, Dizziness, Weight gain, Psychosis</td>
</tr>
</tbody>
</table>
Zonisamide (Zonegran)

- Inactivation of Na+ and Ca++ channels
- Partial and generalized tonic-clonic seizures
- Drowsiness, Cognitive impairment

Perampanel (E2007)

- Selective antagonist for the AMPA subtype of ionotropic glutamate receptors
- Drug suggests efficacy and safety in refractory epilepsy
- Dizziness, drowsiness, irritability, headache, falls, ataxia

B) Drugs under Clinical Trials

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STRUCTURE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| Safinamide | ![Safinamide structure](image1) | - Monoamine oxidase B inhibitor  
- Glutamate release inhibitor  
- Inhibit Dopamine reuptake |
| Denzimol   | ![Denzimol structure](image2) | - Imidazole derivative |
| Soretolide | ![Soretolide structure](image3) | - Does not interact with Glutamate or GABA receptors nor affects Na+ or Ca++ channel  
- Effective in MES test in rodents |
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Properties</th>
</tr>
</thead>
</table>
| Carabersat | ![Carabersat](image) | - Does not bind to ion channels, purinergic, aminergic, opioid and other peptidergic receptors  
- No effect on sodium channel, GABAergic or Glutamate pathway  
- Active against MES induced seizures and sc PTZ induced clonic seizures in rodents |
| Retigabine | ![Retigabine](image) | - Activates M-type potassium current and reduces excitability of neurons  
- Effective against MES induced seizures and sc PTZ induced clonic seizures in mice and rats |
| Talampanel | ![Talampanel](image) | - Blocks AMPA receptors in a stereoselective and non-competitive fashion via an allosteric site |
| Valrocehide | ![Valrocehide](image) | - N-valproyl derivative of GABA and Glycine  
- Effective against MES induced seizures and sc PTZ-induced seizures  
- Also used in corneal and hippocampal |
<table>
<thead>
<tr>
<th>Drug/Compound</th>
<th>Molecular Structure</th>
<th>Key Properties</th>
</tr>
</thead>
</table>
| Brivaracetam  | ![Molecular Structure](image1.png) | - 4-n-propyl analog of levetiracetam in a racetam derivative  
- Binds to ubiquitous synaptic vesicle protein SV2 |
| Ganaxolone   | ![Molecular Structure](image2.png) | - A steroid drug related to pregnanolone which has sedative, anxiolytic and anticonvulsant effects  
- Potent and selective positive allosteric modulator of GABA receptor  
- Well tolerated in case of partial seizures |
| Losigamone   | ![Molecular Structure](image3.png) | - Potential GABA dependent Chloride influx |
| Remacemide   | ![Molecular Structure](image4.png) | - Low affinity NMDA antagonist with Na⁺-channel blocking property |
| Loreclezole  | ![Molecular Structure](image5.png) | - A sedative and anticonvulsant which acts as a GABA agonist |
1.1.6. Pharmacophore model for new anticonvulsant agents

A suggested pharmacophore model of Pandeya et al.\textsuperscript{3,4} showed that four pharmacophoric elements are necessary for good anticonvulsant activity. These are (a) hydrophobic domain, A (b) Hydrogen bonding domain, HBD (c) distal hydrophobic domain, D (d) electron donor moiety, C. Dimmock et al.\textsuperscript{5,6} proposed that the pharmacophoric elements were thought to be a lipophilic aryl ring and hydrogen bonding moiety. The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring is to increase the van der waal’s bonding at the binding site and to increase potency. Substitutions in the aryl ring by halogens have been found to increase potency in the MES screen\textsuperscript{5,7}

1.2. Depression

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year. Depression is the leading cause of disability as measured by YLDs (Years Lived with Disability) and the 4\textsuperscript{th} leading contributor to the global burden of disease (DALYs - Disability Adjusted Life Years) in 2000. By the year 2020, depression is projected to reach 2\textsuperscript{nd} place of the ranking of DALYs calculated for all ages, both sexes. Today, depression is already the 2\textsuperscript{nd} cause of DALYs in the age category 15-44 years for both sexes combined. Depression occurs in persons of all genders, ages, and backgrounds.

1.2.1. Diagnosis

Currently, no laboratory test can be used to diagnose depression. Depression is diagnosed based on your reported symptoms, signs that your doctor observes while interviewing you, your medical history and your family's medical history. Criteria outlined in a handbook called the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is used in making the diagnosis. According to the DSM-IV, a person who suffers from major depressive disorder must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two week period. This mood must represent a change from the person's normal mood;
social, occupational, educational or other important functioning must also be negatively impaired by the change in mood. A depressed mood caused by substances (such as drugs, alcohol, medications) or which is part of a general medical condition is not considered to be major depressive disorder.

Major depressive disorder cannot be diagnosed if a person has a history of manic, hypomanic, or mixed episodes (e.g., a bipolar disorder) or if the depressed mood is better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder or psychotic disorder.

1.2.2. Symptoms and signs

The symptoms should not be accounted for by another illness, drugs of abuse or prescription medications. Common symptoms of depression are as follows:

A. Depressed Mood: A person may report feeling "sad" or "empty" or may cry frequently. Children and adolescents may exhibit irritability.

B. Decreased Interest or Pleasure: A person may show markedly diminished interest or pleasure in all, or almost all, daily activities.

C. Weight Changes: Significant changes in weight when not attempting to gain or lose (a gain or loss of 5% or more in a month) may be indicative of depression. In children, this may also present as a failure to make expected weight gains.

D. Sleep Disturbances: Insomnia or sleeping too much may be a symptom of depression.

E. Psychomotor Agitation or Retardation: The person may be observed to be either agitated or restless or physically slowed down in their movements.

F. Fatigue: Deep fatigue or a loss of energy is a symptom of depression.

G. Feelings of Worthlessness or Guilt: A depressed person may feel that they have no value or they may feel inappropriately guilty about things they have no control over.

H. Brain Fog: A depressed person may have a diminished ability to think, concentrate or make decisions.

I. Thoughts of Death: A depressed person may have recurring thoughts of death, especially thoughts of suicide, with or without a specific plan.

1.2.3. Causes of Depression
The causes of depression are complex. Genetic, biological, and environmental factors can contribute to its development. In some people, depression can be traced to a single cause, while in others; a number of causes are at play. For many, the causes are never known. Currently, it appears that there are biochemical causes for depression, occurring as a result of abnormalities in the levels of certain chemicals in the brain. While we still don't know exactly how levels of these neurotransmitters affect mood, we do know that the levels can be affected by a number of factors. Monoamine hypothesis of depression has been shown in Fig. 3.

**Fig. 3. Monoamine hypothesis of depression**

**Heredity:** Certain types of depression seem to run in some families. Research is ongoing as to exactly which genes are involved in depression. Just because someone in your family has depression, however, doesn't mean you will. Sometimes, family members who were known to abuse alcohol or other drugs were unwittingly trying to improve their mood (often called "self-medication" by professionals).

**Personality:** People with certain personality traits are more likely to become depressed. These include negative thinking, pessimism, excess worry, low self-esteem, a hypersensitivity to perceived rejection, overdependence on others, a sense of superiority or alienation from others, and ineffective responses to stress.

**Situations:** Difficult life events, loss, change, or persistent stress can cause levels of neurotransmitters to become unbalanced, leading to depression. Even major happy
events, such as childbirth, can cause changes in hormone levels, be stressful and cause clinical depression, as in postpartum depression.

**Medical conditions:** Depression is more likely to occur with certain medical illnesses. These "co-occurring" conditions include heart disease, stroke, diabetes, cancer, hormonal disorders (especially perimenopause or hypothyroidism, known as "low thyroid"), Parkinson's disease, and Alzheimer's disease.

**Medications:** Some medications used for long periods, such as prednisone, certain blood pressure medicines, sleeping pills, antibiotics and even birth control pills in some cases, can cause depression or make an existing depression worse. Some antiseizure medications, like Lamictal (lamotrigine), Topamax (topiramate), and Neurontin (gabapentin), may be associated with a higher risk of suicide.

**Substance abuse:** While it has long been believed that depression caused people to misuse alcohol and drugs in an attempt to make themselves feel better (self-medication), it is now thought that the reverse can also be the case; substance abuse can actually cause depression.

### 1.2.4. Types of Depression

There are several different types of clinical depression (mood disorders that include depressive symptoms):

**A. Major depression:** It is an episode of change in mood that lasts for weeks or months. It is one of the most severe types of depression. It usually involves a low or irritable mood and/or a loss of interest or pleasure in usual activities. It interferes with one's normal functioning and often includes physical symptoms. A person may experience only one episode of major depression, but often there are repeated episodes over an individual's lifetime.

**B. Dysthymia:** It is less severe than major depression but usually goes on for a longer period, often several years. There are usually periods of feeling fairly normal between episodes of low mood. The symptoms usually do not completely disrupt one's normal activities.
C. Bipolar disorder: It involves episodes of depression, usually severe, alternating with episodes of extreme elation called mania. This condition is sometimes called by its older name, manic depression. The depression that is associated with bipolar disorder is often referred to as bipolar depression. When depression is not associated with bipolar disorder, it is called unipolar depression.

D. Seasonal depression: Which medical professionals call seasonal affective disorder, or SAD, is depression that occurs only at a certain time of the year, usually winter, when the number of daylight hours is lower. It is sometimes called "winter blues." Although it is predictable, it can be very severe.

E. Psychotic depression: It refers to the situation when depression and hallucinations or delusions are experienced at the same time (co-occur). This may be the result of depression that becomes so severe that it results in the sufferer losing touch with reality. Individuals who primarily suffer from a loss of touch with reality (for example, schizophrenia) are thought to suffer from an imbalance of dopamine activity in the brain and to be at risk of subsequently becoming depressed.

1.2.5. Antidepressants- Management

There are several treatments available. Medications and psychotherapy either alone or in combination--are the most common forms of depression treatment. ECT and VNS are generally only administered when other treatments have failed or when medication might endanger the patient's health. Your doctor can help you select the best depression treatment for you. The terms "refractory depression" and "treatment-resistant depression" are used to describe cases that do not respond to adequate courses of at least two antidepressants.

Medications: The first-line treatment for depression is an antidepressant, as studies show these drugs help a significant number of people experience complete remission, or at least significant improvement, in their symptoms. The most-studied form of psychotherapy for depression is CBT, which teaches clients to challenge self-defeating, but enduring ways of thinking (cognitions) and change counter-productive behaviors. Research beginning in the mid-1990s suggested that CBT could perform as well or better than antidepressants in patients with moderate to severe depression. CBT may be effective in depressed adolescents, although its effects on severe
episodes are not definitively known.\textsuperscript{11} Combining fluoxetine with CBT appeared to bring no additional benefit or, at the most, only marginal benefit.\textsuperscript{12} Several variables predict success for cognitive behavioral therapy in adolescents: higher levels of rational thoughts, less hopelessness, fewer negative thoughts, and fewer cognitive distortions.\textsuperscript{13}

**Counseling and Psychotherapy:** Psychotherapy is a process in which a trained professional enters a relationship with a patient for the purpose of helping her with mental illness, behavioral problems, or personal growth. The process involves the patient and therapist sitting in a room talking, which is why it is often called "talk therapy." Psychotherapy is thought to be most effective for depression when used in conjunction with medication. "Psychotherapy" and "counseling" are often used interchangeably. However, in the context of mental health, counseling generally refers to a relatively brief treatment that is focused mostly upon behavior.

**Electroconvulsive Therapy:** Electroconvulsive therapy, also known as ECT, is a form of treatment for depression that involves the application of a brief electrical pulse to the scalp in order to produce a seizure. ECT might be administered when medications have not been effective, when medications might endanger the patient, or when a rapid response is needed.

**Vagus Nerve Stimulation:** Vagus nerve stimulation, or VNS, involves the use of an implanted device to provide periodic stimulation to the vagus nerve. The device was originally developed as a treatment for epilepsy. It has since been approved in the U.S., Canada and the European Union for treatment-resistant depression in both unipolar depression and bipolar disorder.

**Mothers and Their Children:** Mothers and children will face special treatment issues, especially regarding the safety and effectiveness of particular treatments. Pregnant and breast-feeding women must balance their own mental well-being against the needs of their baby. Mothers also have concerns about whether antidepressants are safe for their older child to use.

1.3. Pain
There are numerous different definitions for pain. The most widely accepted definition of pain is the one used by The International Association for the Study of Pain. It defines pain as “An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage”. The American Academy of Pain Medicine defines pain as – “An unpleasant sensation and emotional response to that sensation”. Pain has the dubious distinction of being the commonest symptom for which a person approaches medical care. The definition of pain that is most appropriate for use in clinical practice was given by Margo McCaffrey in 1968. He defined pain as “whatever the experiencing person says it is, existing whenever he says it does.”

Most pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body; and sometimes pain arises in the absence of any detectable stimulus, damage or pathology. Social support, cultural values, hypnotic suggestion, excitement in sport or war, distraction, and appraisal can all significantly modulate pain's intensity and unpleasantness.

The International Association for the Study of Pain (IASP) classification system describes pain according to five categories: duration and severity, anatomical location, body system involved, cause, and temporal characteristics (intermittent, constant, etc.). This system has been criticized by Woolf and others as inadequate for guiding research and treatment, and an additional category based on neurochemical mechanism has been proposed.
1.3.1. Cause of Pain

We may experience pain as a prick, tingle, sting, burn, or ache. Receptors on the skin trigger a series of events, beginning with an electrical impulse that travels from the skin to the spinal cord. The spinal cord acts as a sort of relay center where the pain signal can be blocked, enhanced, or otherwise modified before it is relayed to the brain. One area of the spinal cord in particular, called the dorsal, is important in the reception of pain signals.

The most common destination in the brain for pain signals is the thalamus and from there to the cortex, the headquarters for complex thoughts. The thalamus also serves as the brain's storage area for images of the body and plays a key role in relaying messages between the brain and various parts of the body. In people who undergo an amputation, the representation of the amputated limb is stored in the thalamus.

Pain is a complicated process that involves an intricate interplay between a number of important chemicals found naturally in the brain and spinal cord. In general, these chemicals, called neurotransmitters, transmit nerve impulses from one cell to another. There are many different neurotransmitters in the human body; some play a role in human disease and, in the case of pain, act in various combinations to produce painful sensations in the body. Some chemicals govern mild pain sensations; others control intense or severe pain.

Fig. 4. Pathways for pain mechanism

We may experience pain as a prick, tingle, sting, burn, or ache. Receptors on the skin trigger a series of events, beginning with an electrical impulse that travels from the skin to the spinal cord. The spinal cord acts as a sort of relay center where the pain signal can be blocked, enhanced, or otherwise modified before it is relayed to the brain. One area of the spinal cord in particular, called the dorsal, is important in the reception of pain signals.

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1.3.2. Classification of Pain

**Acute pain** - this can be intense and short-lived, in which case we call it acute pain. Acute pain may be an indication of an injury. When the injury heals the pain usually goes away.

**Chronic pain** - this sensation lasts much longer than acute pain. Chronic pain can be mild or intense (severe). Pain can be nociceptive, non-nociceptive, somatic, visceral, neuropathic, or sympathetic. Look at the table below.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Nociceptive</th>
<th>Non-Nociceptive</th>
</tr>
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<tbody>
<tr>
<td>Somatic</td>
<td>Visceral</td>
<td>Neuropathic</td>
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<tr>
<td>Sympathetic</td>
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**Nociceptive Pain** - specific pain receptors are stimulated. These receptors sense temperature (hot/cold), vibration, stretch, and chemicals released from damaged cells.

**Somatic Pain** - a type of nociceptive pain. Pain felt on the skin, muscle, joints, bones and ligaments is called somatic pain. The term musculo-skeletal pain means somatic pain. The pain receptors are sensitive to temperature (hot/cold), vibration, and stretch (in the muscles). They are also sensitive to inflammation, as would happen if you cut yourself, sprain something that causes tissue damage. Pain as a result of lack of oxygen, as in ischemic muscle cramps, are a type of nociceptive pain. Somatic pain is generally sharp and well localized - if you touch it or move the affected area the pain will worsen.

**Visceral Pain** - a type of nociceptive pain. It is felt in the internal organs and main body cavities. The cavities are divided into the thorax (lungs and heart), abdomen (bowels, spleen, liver and kidneys), and the pelvis (ovaries, bladder, and the womb). The pain receptors - nociceptors - sense inflammation, stretch and ischemia (oxygen starvation).
Nerve Pain or Neuropathic Pain- Nerve pain is also known as neuropathic pain. It is a type of non-nociceptive pain. It comes from within the nervous system itself. People often refer to it as pinched nerve, or trapped nerve. The pain can originate from the nerves between the tissues and the spinal cord (peripheral nervous system) and the nerves between the spinal cord and the brain (central nervous system, or CNS). Neuropathic pain can be caused by nerve degeneration, as might be the case in a stroke, multiple-sclerosis, or oxygen starvation.

Sympathetic Pain- The sympathetic nervous system controls our blood flow to our skin and muscles, perspiration (sweating) by the skin, and how quickly the peripheral nervous system works. Sympathetic pain occurs generally after a fracture or a soft tissue injury of the limbs. This pain is non-nociceptive - there are no specific pain receptors. As with neuropathic pain, the nerve is injured, becomes unstable and fires off random, chaotic, abnormal signals to the brain, which interprets them as pain.

1.3.3. Medications to neuropathic pain

Patients suffering from painful conditions need options to help treat their symptoms. The best pain control can be achieved by trying to target appropriate medications for the underlying problem, and trying to minimize pain with different medication and non-pharmaceutical treatments. Learn about different types of medications used to control pain.

Acetaminophen: Tylenol (Acetaminophen) is used to treat pain. Unlike some medications for pain, Tylenol does not have anti-inflammatory effects. Often, however, in cases of chronic pain, no inflammation is at the site of the pain, and thus Tylenol may be an appropriate treatment choice. Tylenol is safe when used appropriately, but can be dangerous when used excessively. Patients should be aware of Tylenol that is mixed in with prescriptions such as Percocet or Darvocet, and not take these medications as well as regular Tylenol.

Non-Steroidal Anti-Inflammatory Medications (NSAIDs): The NSAIDs (such as Ibuprofen, Motrin, Aleve, etc.) are most beneficial in cases of acute pain, or flare-ups in patients with chronic pain. NSAIDs are excellent at treating inflammatory conditions including tendonitis, bursitis, and arthritis. In general, NSAID use is limited for patients with chronic pain because of concerns about the development to
stomach problems. While the newer, so-called COX-2 inhibitors, such as Celebrex, were designed to avoid this complication, caution should still be used when using these medications for long periods of time.

**Corticosteroids:** As with NSAIDs, corticosteroids are powerful anti-inflammatory medications, and best used for acute pain or for flare-ups of a chronic inflammatory problem. Corticosteroids can either be taken orally (such as Medrol, Prednisone), or injected into the soft tissues or joints (cortisone injections).

**Narcotics:** Narcotics should be considered if pain cannot be otherwise controlled. Although these medications can be dangerous and addicting, they can also be extremely effective. While narcotic medications are useful for acute pain, they also have significant side effects. The short-acting types of these medications can lead to overuse and the development of tolerance. Long-acting options have fewer side effects, and better control of chronic pain. Narcotics can become addictive when they are used for lengthy times without gradual reduction in the dose, or if the medications are taken for reasons other than pain.

**Anti-Convulsants:** Anti-convulsant medications are the category of medications that work to relieve nerve pain. These medications alter the function of the nerve and the signals that are sent to the brain. The most commonly prescribed anticonvulsant medication for nerve pain is called Neurontin (Gabapentin). Another option that has more recently emerged, specifically for the treatment of fibromyalgia, is called Lyrica (Pregabalin).

**Local Anesthetics:** Local anesthetics can provide temporary pain relief to an area. When used in the setting of chronic pain, local anesthetics are often applied as a topical patch to the area of pain. Lidoderm comes in a patch that is applied to the skin and decreases the sensitivity of this area.

**Bottom Line:** Chronic pain is a problem that is seldom resolved quickly, or with one treatment. The best way to treat chronic pain is by working with your doctor and trying to attack the pain with different types of treatments. Other treatments effective for chronic pain include acupuncture, ice and heat application, massage, and other alternative treatments.
1.4. References
