NEUROLOGICAL DISORDERS: AN OVERVIEW

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Summary

The Global Burden of Disease study, the ongoing international collaborative project between World Health Organization (WHO), the World Bank and the Harvard School of Public Health, has produced evidence, that neurological disorders as one of the greatest threats to public health. A clear message emerges that unless immediate action is taken globally, the neurological burden is expected to become an even more serious and unmanageable problem in all countries¹. According to a new report by the WHO, neurological disorders, affect up to 1 billion people worldwide and that number is destined to rise as population’s age. The report "Neurological Disorders: Public Health Challenges," by the U.N. agency says that neurological care should become part of basic health care so that under detected disabilities are diagnosed and treated. The WHO says unless immediate action is taken globally, the neurological burden is expected to become an even more serious and unmanageable threat to public health. Neurological disorders kill an estimated 6.8 million people each year, equating to 12 percent of global deaths².

Treatments are available, but nearly two-thirds of people with a known mental disorder never seek help from a health professional. Stigma, discrimination and neglect prevent care and treatment from reaching people with mental disorders. Where there is neglect, there is little or no understanding. Where there is no understanding there is neglect³.

There are more than 600 neurological diseases. Major types include:

- Behavioral/cognitive syndromes, migraine, seizure disorders.
- Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebrovascular disease, stroke.
- Cerebral palsy, encephalitis, meningitis, myelitis.
- Brain tumors, Parkinson's disease, Huntington's disease.
- Spinal cord disorders – tumors, infections, trauma, and malformations.
- Altered mental higher status, encephalopathy, stupor and coma⁴.

Out of these, the debilitating and most prevalent disorders include diseases such as Epilepsy and Psychosis.
Introduction

**Epilepsy:** Epilepsy is the most common of chronic neurological disorders and it imposes the biggest burden on health care systems. It varies greatly in its clinical features, aetiology, severity, and prognosis and its association with other neurological disabilities. In this modern era, epilepsy is the most frequent neurodegenerative disease after stroke. It afflicts more than 50 million people worldwide. Epilepsy usually begins in childhood, potentially impeding education, employment, social relationships and development of a sense of self-worth. Epilepsy is among the disorders that are strongly associated with significant psychological and social consequences for everyday living. People with hidden disabilities such as epilepsy are among the most vulnerable in any society. Stigmatization leads to discrimination and people with epilepsy experience prejudicial and discriminatory behavior in many spheres of life and across many cultures. People with epilepsy experience violations and restrictions of both their civil and human rights. Discrimination against people with epilepsy in the workplace and in respect of access to education is not uncommon for many people affected by the condition.

Epilepsy is defined by a state of recurrent, spontaneous seizures. Seizure is a period of abnormal, synchronous excitation of a neuronal population. The difference between seizures and epilepsy is commonly confused. The two are not the same. Epileptogenesis refers to the development of the state of epilepsy. It refers to the sequence of events that converts the normal brain into one that can support a seizure. Based on the Electroencephalographic seizure activity, seizures are divided into: Generalized seizures and Partial seizures.

**CLASSIFICATION OF SEIZURES**

- **Seizures**
  - **Partial**
    - **Simple**
    - **Complex**
  - **Generalized**
    - **Absence**
    - **Myoclonic**
    - **Tonic-clonic**
    - **Tonic**
    - **Atonic**

**Generalized Seizures:** Once initiated, it spreads quickly into the entire or at least the greater part of the brain. There are 5 types of generalized seizures.

1) **Absence seizures:** Loss or severe impairment of consciousness is considered to be the clinical hallmark of absences. EEG manifestations of typical absences, however, are frequently associated with mild, inconspicuous cognitive impairment. Absence seizures also known as minor seizures or petitmal seizures. It is reported to occur mainly in young children between the ages of 6 to 14. Seizures frequently disappear spontaneously after adolescence.
2) **Tonic-clonic seizure:** Also known as grandmal epilepsy. As the name indicates, initially there is a generalized tonic activity followed by clonic phase. It results due to potent cerebral excitation and is also known as major seizures. Its onset is pre-intimated to the patient by a warming sensation known as Aura. The total attack lasts for several minute. After the attack, sleeps prevails due to neuronal store-exhaustion. 

3) **Myoclonic seizures:** These seizures consist of short episodes of muscle contractions that may occur for several minutes. Myoclonic seizures are rare, occur at any age, and are often a result of permanent neurologic damage acquired as a result of hypoxia, uremia, encephalitis, or drug poisoning. 

4) **Tonic seizures** are characterized by stiffening of the muscles. 

5) **Atonic seizures** Atonic seizures consist of a sudden loss of postural tone, often resulting in falls, or, when milder, head nods or jaw drops. Consciousness is usually impaired and significant injury may occur. Duration is usually several seconds, rarely more than 1 minute. 

**Partial seizures:** Partial seizures are those in which the discharge begins locally, and often remains localized. The symptoms depend on the brain region or regions involved, include involuntary muscle contractions, abnormal sensory experiences or autonomic discharge, or effects on mood and behavior, often termed psychomotor epilepsy. These seizures are divided into simple, complex and those that evolve into secondary generalized seizures. The difference between simple and complex seizures is that during simple partial seizures, patients retain awareness, during complex partial seizures, they lose awareness. 

**Simple partial seizures** are further subdivided into four categories according to the nature of their symptoms: motor, autonomic, sensory or psychological. Motor symptoms include movements such as jerking and stiffening. Sensory symptoms caused by seizures involve unusual sensations affecting any of the five senses (vision, hearing, smell, taste or touch). Autonomic symptoms affect the autonomic nervous system. The only common autonomic symptom is a peculiar sensation in the stomach that is experienced by some patients with a type of epilepsy called temporal lobe epilepsy. Simple partial seizures with psychological symptoms are characterized by various experiences involving memory, emotions, or other complex psychological phenomena. 

**Complex partial seizures**, by definition, include impairment of awareness. Patients seem to be "out of touch," "out of it" or "staring into space" during these seizures. There may also be some "complex" symptoms called automatisms. Automatisms consist of involuntary but coordinated movements that tend to be purposeless and repetitive. Common automatisms include lip smacking, chewing, fidgeting and walking. The third kind of partial seizure is one that begins as a focal seizure and evolves into a generalized convulsive seizure. Most patients with partial seizures have simple partial, complex partial and secondarily generalized seizures. 

**Role of neurotransmitter in Epilepsy:** Various animal models of epilepsy helped for the study and understanding of the human epilepsies and showed evidence that the neurotransmitters glutamate and GABA (gamma-aminobutyric acid), are centrally involved in the development of epilepsy. GABA is the principal inhibitory transmitter in the mammalian brain. GABA maintains the inhibitory tone that counterbalances neuronal excitation.
When this balance is perturbed, seizures may ensue. GABA is formed within GABAergic axon terminals and released into the synapse, where it acts upon its receptors: GABA_A, to increase membrane chloride conductance and thereby stabilize or hyperpolarize the resting membrane potential\(^ {18} \), and GABA_B, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters. GABA_A-receptor binding influences the early portion of the GABA-mediated inhibitory postsynaptic potential, whereas GABA_B binding influences the late portion. GABA is rapidly removed by uptake into both glial and presynaptic nerve terminals and then catabolized by GABA transaminase. It has been found that: abnormalities of GABAergic function have been observed in genetic and acquired animal models of epilepsy, Reductions of GABA-mediated inhibition, activity of glutamate decarboxylase, binding to GABA_A and benzodiazepine sites, GABA in cerebrospinal fluid and brain tissue, and GABA detected during microdialysis studies have been reported in studies of human epileptic brain tissue, GABA agonists suppress seizures, and GABA antagonists produce seizures, Drugs that inhibit GABA synthesis cause seizures and Benzodiazepines and barbiturates work by enhancing GABA-mediated inhibition. Finally, drugs that increase synaptic GABA are potent anticonvulsants\(^ {19} \).

Excitatory glutamatergic neurotransmission is responsible for the initiation and spread of seizure activity, even if it is not necessarily the primary underlying pathogenic mechanism. Similarly, \( \gamma \)-aminobutyric acid (GABA)-mediated synaptic inhibition is known to be critical in regulating epileptic activity, as even a minor disinhibition can trigger hyperexcitability. Thus a dysfunction in either GABA or glutamate availability will have important consequences regarding seizure genesis. The duration of excitation during glutamatergic neurotransmission relies on specific transporters, which terminate the action of glutamate and control its extracellular level by clearing the synaptic cleft, thus preventing excitotoxicity and hyperexcitability\(^ {20} \).

### Targets for antiepileptic drug action

1) **Ion channels**

**Na\(^+\) channels:** The neuronal Na\(^+\) channel represents one of the most important targets for AED action. In the nervous system, voltage-dependent Na\(^+\) channels are responsible for the upstroke of the neuronal action potential, and ultimately control the intrinsic excitability of the nervous system. At normal membrane potentials, most Na\(^+\) channels exist in a closed, resting state. Upon depolarization, the channel activates, facilitating ion flux. Thereafter, the Na\(^+\) channel enters an inactivated state, from which it is not readily re-activated. Repolarisation of the neuronal membrane rapidly converts the channel back to a resting state, from which it can respond to subsequent depolarization.

**Ca\(^{2+}\) channels:** Voltage-sensitive Ca\(^{2+}\) channels can be broadly classified into low or high threshold. The low-threshold T-type Ca\(^{2+}\) channel is expressed predominantly in thalamocortical relay neurones, where it is believed to be instrumental in the generation of the rhythmic 3-Hz spike-and-wave discharge that is characteristic of generalized absence seizures. High threshold Ca\(^{2+}\) channels are sub classified by their pharmacological properties into L-, N-, P-, Q-, and R-types. The N-, P-, and Q-type channels, in particular, have been implicated in the control of neurotransmitter release at the synapse. Several AEDs have been reported to block voltage-sensitive Ca\(^{2+}\) channels in a subtype-specific manner, an effect that may contribute to their antiepileptic actions.
**K⁺ channel:** Neuronal K⁺ channels are responsible for the action potential down stroke or, more specifically, repolarisation of the plasma membrane in the aftermath of Na⁺ channel activation. Direct activation of voltage dependent K⁺ channels hyperpolarizes the neuronal membrane and limits action potential firing. Accordingly, K⁺ channel activators have anticonvulsant effects in some experimental seizure models, whereas K⁺ channel blockers precipitate seizures.

2. **γ-Aminobutyric acid-mediated inhibition:**
GABA is the predominant inhibitory neurotransmitter in the mammalian CNS, where it is released at up to 40% of all synapses. Impairment of GABA function is widely recognised to provoke seizures, whereas facilitation has an anticonvulsant effect.

3. **Glutamate-mediated excitation:**
Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Focal injection of glutamate induces seizures in animals, and over-activation of glutamatergic transmission or abnormal glutamate receptor properties are observed in certain experimental seizure models and human epilepsy syndromes. Inhibition of the neuronal release of glutamate and blockade of its receptors has received considerable attention in the search for novel AEDs. Glutamate is synthesised from glutamine by the action of the enzyme glutaminase in glutamatergic neurones. Following synaptic release, glutamate exerts its pharmacological effects on several receptors. Although none of the commonly used AEDs exert their pharmacological effects solely by an action on the glutamate system, blockade of glutamate receptors is believed to contribute to the antiepileptic activity of several compounds.

Commonly used anticonvulsants are:
- **Hydantoins:** Phenytoin
- **Dibenzapines:** Carbamazepine
- **Succinimides:** Ethosuximide
- **Barbiturates:** Phenobarbitone, Primidone
- **Benzodiazepines:** Diazepam, Clonazepam
- **Fatty acids:** Sodium Valproate
- **Newer anti-epileptic drugs:** Lamotrigine, Gabapentin, Topiramate, Tiagabine, Levetiracetam, Vigabatrin, Oxcarbazepine.

**Surgery:** Surgery is an option for a small number of patients whose epilepsy cannot be controlled with medication. A good candidate for surgery has seizures that always begin in the same cerebral location, which can be removed without creating deficits. There are two means by which a surgical operation can abolish epileptic seizures or reduce their frequency. The first is by treating focal brain pathology, which is not necessarily as easy as it seems because the pathology may be hard to demonstrate or it may be difficult to link such pathology directly with the patient's seizures. The second is to influence brain function in some way to prevent or restrict the propagation of the epileptic discharge. Many operations are hybrid in nature involving the application of both premises. The more successful and commoner surgery involves mostly the removal of pathology, although the removal of local brain tissue is also involved. By contrast operations employing the second premise are much rarer and on the whole less successful.
Non-medication therapy:

**Ketogenic diet:** When the body burns fat, it creates substances called ketones. The ketogenic diet tries to force the body to use more fat for energy instead of sugar by increasing fat and restricting carbohydrates. It is not yet clear how or why the ketogenic diet prevents or reduces seizures, but it has been shown to be effective in reducing epileptic seizures in some children\(^{24}\). It has been known since the time of Hippocrates that fasting is an effective treatment for seizures\(^{41}\), and the ketogenic diet was designed to mimic the anticonvulsant effects of fasting, which are known as suppressive seizures\(^{25,26}\).

**Psychosis**

Psychosis is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality." People suffering from it are said to be psychotic. Psychosis refers to a loss of contact with reality. When people can't tell the difference between what is real and what is not, it is called a psychotic episode.

The word *psychosis* was first used by Ernst von Feuchtersleben in 1845 as an alternative to insanity and mania. Kraepelin used the term 'manic depressive insanity' to describe the whole spectrum of mood disorders, in a far wider sense than it is usually used today. During the 1960s and 1970s, psychosis was of particular interest to counterculture critics of mainstream psychiatric practice, who argued that it may simply be another way of constructing reality and is not necessarily a sign of illness.
Since the 1970s, the introduction of a Recovery approach to mental health, which has been driven mainly by people who have experienced psychosis, or whatever name is used to describe their experiences, has led to a greater awareness that mental illness is not a lifelong disability, and that there is an expectation that recovery is possible, and probable with effective support\textsuperscript{27}. Psychotic disorders are serious and sometimes fatal illnesses which typically emerge during the sensitive developmental period of adolescence and emerging adulthood. For over a century, a corrosive blend of pessimism, stigma and neglect have confined therapeutic efforts to delay and inconsistent palliative care\textsuperscript{28}. Psychosis is a syndrome of psychiatric signs, symptoms, and behaviors that usually include hallucinations, delusions, disorganized speech and functioning, and impaired judgment. People with psychosis usually have an impaired ability to function in everyday life. Acute symptoms and aggressive or self-injurious behavior may call for emergency measures such as immediate medication, calling on personnel trained in emergency care, enactment of security measures, or hospitalization\textsuperscript{29}.

Psychotic symptoms can occur in an isolated episode or as part of an ongoing diagnosed illness such as schizophrenia, bipolar disorder, depression or schizoaffective disorder. Symptoms are generally described as either positive or negative. In addition to these symptoms, about 50 percent of people who experience psychosis will not recognize that there is anything wrong (lack of insight)\textsuperscript{30}. So, Psychosis is a symptom of mental illness, but it is not a mental illness in its own\textsuperscript{31}.

The causes of psychosis have three main classifications: Psychosis caused by psychological conditions, Psychosis caused by general medical conditions and Psychosis caused by substances, such as alcohol, or drugs\textsuperscript{32}.

Psychosis should be distinguished from:

- **Insanity**, which is a legal term denoting that a person is not criminally responsible for his or her actions. "Insanity is no longer considered a medical diagnosis"
- **Psychopathy**, a general term for a range of personality disorders characterized by lack of empathy, socially manipulative behavior, and occasionally criminality or violence\textsuperscript{33}. Despite both being abbreviated to the slang word "psycho", psychosis bears little similarity to the core features of psychopathy, particularly with regard to violence, which rarely occurs in psychosis, and distorted perception of reality, which rarely occurs in psychopathy.\textsuperscript{35}
- **Delirium**: a psychotic individual may be able to perform actions that require a high level of intellectual effort in clear consciousness, whereas a delirious individual will have impaired memory and cognitive function\textsuperscript{36}.

Patients with psychosis generally receive both pharmacologic and nonpharmacologic (psychological) treatments. The goal of pharmacologic treatment is to stabilize and control the acute symptoms and behaviors associated with psychosis. Nonpharmacologic treatment provides the patient and the family with support, education, and the work and social skills necessary to live and function in the community\textsuperscript{37}. 

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\textsuperscript{27} Singh et al.

\textsuperscript{28} Singh et al.

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\textsuperscript{36} Singh et al.

\textsuperscript{37} Singh et al.
Pharmacological treatment:

Antipsychotic drugs are useful for treating a range of severe psychiatric disorders. Applications include the short-term treatment of acute psychotic, manic and psychotic-depressive disorders as well as agitated states in delirium and dementia and the long-term treatment of chronic psychotic disorders including schizophrenia, schizoaffective disorder and delusional disorders.

Antipsychotics or neuroleptics were discovered in the late 1950's by the Company Rhone Poulenc in Paris. The first antipsychotic drug was called Chlorpromazine which was used as a 'tranquilizer'. There are two kinds of antipsychotic medications: classical and atypical. The classical medications are the original antipsychotic drugs that have been developed since the discovery of chlorpromazine. They work by blocking the dopamine receptors in the brain whereas the atypical drugs have other mechanisms of action.

Following are the class of drugs which are used as anti-psychotics

- Phenothiazine Compounds: Aliphatic derivatives (e.g. chlorpromazine), Piperidine derivatives (e.g. thioridazine): relatively less potent Piperazine derivatives (e.g. fluphenazine): relatively more potent
- Thioxanthen Compounds: Thiothixene
- Butyrophenones: Haloperidol-- most widely used butyrophenone
- Miscellaneous Chemical Structures: Pimozide, olanzapine, molindone, Quetiapine, clozapine, risperidone, loxapine

Non-pharmacological/psychological treatments: The need for psychological therapies for psychosis is increasingly recognised. In recent years, two psychological approaches, cognitive behavioural therapy (CBT) and family interventions (FI) have emerged from among a range of psychological approaches as effective therapies with the strongest evidence base. The need for psychological therapies for psychosis is increasingly acknowledged. There are a number of reasons for this. First, while antipsychotic medication has been the mainstay of psychiatric treatment and shows considerable benefits, it does not guarantee good outcome, being only partially effective or minimally effective in approximately 40% of cases.

1). Secondly, adherence to antipsychotic medication is frequently poor, with up to 70% of individuals failing to take medication as prescribed

2). thirdly, even when long-term antipsychotic medication is taken, a substantial proportion of patients will relapse.

3). the probability of which will be influenced by the social context, such as the nature of the family environment or the experience of life events

4). finally, although medication may improve certain symptoms, it typically does not impact on a wide range of individuals’ other concerns about their illness or experiences and often fails to remediate a number of other disabling problems, particularly of a social or cognitive nature.
Herbal drug in mental disorders: A number of indigenous plant products are listed in ayurvedic pharmacopoeia for the treatment of mental disorders. However, it is very difficult to ascertain pharmacological active principle of these plants from available phytochemical data. The indigenous tropical plant products have the potential of drug development, which may make the health care cheap and more acceptable; therefore there is a need to evaluate the psychopharmacological properties of the indigenous plant products. There is a global resurgence in the use of herbal medicines. An estimated one third of adults in the western world use alternative therapies, including herbs. In contrast to chemical drugs, herbs are generally claimed to be non toxic because of natural origin and long use as folk medicine.\(^\text{41}\).

Herbal preparations are most often recommended to treat mental disorders in Asian or African folk medicine practices. The herbal medicines which have beneficial effect on mental disorders include: *Ailanthus altissima*, *Artemisia vulgaris*, *Calotropis procera*, *Hypericum perforatum*, *Centella asiatica*, *Dictamnus albus*, *Senecio vulgaris*, *Taxus baccata*, *Valeriana officinalis*.\(^\text{42}\).

Herbal drugs are preferred over allopathic drugs because there are numbers of allopathic drugs which are already proved for their CNS effects.

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