2.1. Introduction

Mental, behavioral and neurological disorders occurs frequently in general population. Persons suffering from these disorders are often isolated from society because of poor quality of life and increased mortality rate. These disorders also lead to social and economical burden of an individual or a family (Thirupathy et al., 2011).

Mental disorder is the state of mental illness based on the psychological pattern which is reflected in behavior and generally linked with disability. Mental affects a person’s feeling that is associated with brain and nervous system. According to World Health Organization (WHO) about 450 million people worldwide suffer from behavioral or mental disorders (WHO, 2001).

2.2. Mental Disorder - Classification

Classification of mental disorder is essential for diagnostic and therapeutic purposes (APA, 2000). Currently there are two widely established systems for classifying mental disorders-Chapter V of the International Classification of Diseases (ICD-10) published by World Health Organization (WHO) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by American Psychiatric Association (APA), they are mainly used for operational definitions (Dalal et al., 2009).

2.3. Anxiety

Anxiety is an emotional response of an individual to different circumstances. It is triggered by genetic and stress factors. Moreover, the emotion which is inappropriate, excessive and persistent leads to pathological condition of anxiety disorder. According to DSM-IV, anxiety disorders may be classified as Generalized
Anxiety Disorder (GAD), Panic disorder, Phobias, Agrophobia, Seasonal Anxiety Disorder (SAD), Obsessive and Compulsive Disorder (OCD) and Post Traumatic Stress Disorder (PTSD).

2.3.1. Classification of anxiety disorders

Table 2.1. Classification and characteristics of anxiety disorders

<table>
<thead>
<tr>
<th>S.No</th>
<th>Anxiety disorders</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Generalized Anxiety Disorder (GAD)</td>
<td>It is a common persistent disorder and the excessive fear is oriented with everyday matters (Arnold et al., 2006).</td>
</tr>
<tr>
<td>2.</td>
<td>Panic Disorder</td>
<td>This condition is caused by intense fear and apprehension and also associated with cardiac and CNS symptoms (Rollman et al., 2006).</td>
</tr>
<tr>
<td>3.</td>
<td>Phobias</td>
<td>This is the single largest category of anxiety disorders caused by specific stimulus (Markowitz et al., 1995).</td>
</tr>
<tr>
<td>4.</td>
<td>Agrophobia</td>
<td>This specific excessive fear is caused by difficult or inescapable situation (Schweizer et al., 1995).</td>
</tr>
<tr>
<td>5.</td>
<td>Seasonal Anxiety Disorder (SAD)</td>
<td>This is described as severe fear of negative public scrutiny or of public embarrassment or humiliation (Arborelius et al., 1999).</td>
</tr>
<tr>
<td>6.</td>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>Symptoms include repetitive obsession (distressing, persistent, and intrusive thoughts or images) and compulsions (urges to perform specific acts or rituals) (Phil Barker, 2003).</td>
</tr>
<tr>
<td>7.</td>
<td>Post Traumatic Stress Disorder (PTSD)</td>
<td>This trauma occurs during extreme situation like storm, flood, combat and etc., (Phil Barker, 2003).</td>
</tr>
</tbody>
</table>
2.3.2. Causes of anxiety

The main factors that cause anxiety are genetic, social, environmental and biological.

2.3.2.1. Genetic

Anxiety as any recognized genes can directly be associated to their function within the cell and the neural circuits. The familial aggregation is well established in all types of anxiety disorders especially in panic disorders that showed higher incidence in twin subjects (Gorwood et al., 1999). With respect to co-morbidity in panic disorder, GAD and depression are also liable with familial aggregation (Maier et al., 1995; Kendler et al., 1996). Moreover the risk of onset of anxiety is high in monozygotic (MZ) twins than dizygotic (DZ) twins (Skre et al., 1993). Quantitative trait locus mapping is mainly used to identify the genes of cross species and human phenotypic in anxiety disorders. Glutamic acid decarboxylase 2 (Gad2), Regulator of G-protein signaling 2 (Rgs2), Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (Ppargc1a), Gabra 2, Oprm1 and TrkB in PTSD are well studied genes in anxiety. GAD 2 is an enzyme involved in the synthesis of GABA and the intriguing effect of GAD 2 is observed in abnormalities of anxiety disorders.

2.3.2.2. Social and environmental factors

Gender and cultural activities also play important role in anxiety disorders. As expected the predominant level of anxiety is high in women than men. Social issues that are associated with unexpected experiences in life would definitely cause anxiety and the solid factors that include parental rejection, drug abuse, child abuse and high hostility (Connell et al., 2009). Some of the intoxicants from other stimulants are also linked with panic attacks. Likewise, chronic exposure to organic solvents like varnishing, painting and carpet laying also cause anxiety (Morrow et al., 2000).
2.3.2.3. Biological

Some of the imbalances in chemistry of neurotransmitters in brain are associated with anxiety. People with OCD have increased grey matter volume (Radua et al., 2009; Radua et al., 2010) and these are in contrast with other anxiety disorders, where they have decreased grey matter volume (Radua et al., 2010). The amygdala plays central role in dealing fear and anxiety, and its activity may be affected in anxiety disorders. Usually sensory information enters the amygdala through the nuclei of the basolateral complex are also involved in sensory-related fear memories and continued with the medial prefrontal cortex and sensory cortices of brain.

2.3.2.4. Pathophysiology of anxiety

So far, the pathophysiological mechanism in anxiety is not fully elucidated. Many biological theories including neurochemistry, genetic, psychological and behavioral factors have been proposed. GABA (Gamma amino butyric acid), serotonin (5-hydroxy tryptamine-5HT), nor-epinephrine (nor aderenaline-monoaminergic neurotransmitters) and glutamate are the main neurotransmitters involved in anxiety. Corticotropin releasing factors and cholecytokinin also contributes to anxiety.

The GABA circuits are mainly involved in anxiety and it is the major inhibitory neurotransmitter of brain. Among the three GABA receptors (GABA_A, GABA_B and GABA_C) in post synaptic vesicles, GABA_A receptor dysfunction leads to pathophysiology of anxiety (Lydiyard, 2003). They act as gatekeepers for chloride channels and it has multidisciplinary site for anxiolytic drugs like benzodiazepine (BZD). Thus the mechanism of action of BZD facilitates to combine with GABA_A receptor and increase the chloride channel opening and further the hyperpolarization of cell. This action prevents the cellular excitability (Nemroff, 2003).
Fig. 2.1. GABA$_A$ receptor (source: Google images)

GABA$_A$ receptors is a glycoprotein containing oligomeric transmembrane (Fig.2.1) and it is known as super family of ligand gated ion channel receptors. GABA$_A$ receptor combined with five major units and 18 subunits and chloride channel is centered one (Ninan, 1999).

Serotonin is one of the neurotransmitters found in amygdala and frontal cortex of brain and its abnormalities are also involved in anxiety (Kent et al., 2002). So far 14 subunits of 5-HT receptors has been identified through selective serotonin reuptake inhibitors which are considered to be therapeutic target (Roth et al., 2000; Hoyer et al., 2002). The amygdale is located in anterior part of medial front lobe and is considered as the key structure in fear response coordination (Davis, 1992).

2.3.2.5. Epidemiology of anxiety disorders

Anxiety disorder is characterized as persistent, disabling mental illness, worry and excessive fear that are difficult to control and always interfere with day to day activities. Approximately anxiety disorders occur in 30% of mood cases (Young et al., 2004 ) and the lifetime prevalence rate is about 16.6%.
Anxiety disorders are common during the perinatal period, with reported rates of OCD and GAD being higher in postpartum women than in the general population (Rossi et al., 2006). Social anxiety disorder (SAD) is among the most common of all psychiatric disorders with lifetime prevalence estimates of 7 to 13%. Co-morbidity cases of anxiety and major depression is also highly prevalent. About 47.5% of patients with major depressive disorder, met criteria for anxiety disorders, and at the same time, 26.1% patients with anxiety disorders also met criteria for major depressive disorder (Beekman et al., 2000). Moreover 8% of patients consulting professionals at primary care have GAD. Primary complaints of anxiety appear at age of 20-35 years that is also predominant in women.

Generally, the panic disorders commonly coexist with other diseases like primary hypertension and postural tachycardia syndrome (Roy–Boyrne, 2006). The current prevalence of panic disorder is around 1-2% in adult population. Panic disorder is commonly accompanied with gender inequalities, socioeconomic factors in childhood temperament. The prevalence of panic disorder is high in European continent (Goodwin et al., 2005).

2.3.3. Antianxiety agents

Anxiolytics are the antianxiety agents that are involved in the inhibition of anxiety includes benzodiazepine, busipirone, β- blockers, antidepressants including monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors. The anxiolytics with their advantages and disadvantages are described in table 2.2.
<table>
<thead>
<tr>
<th>S.NO</th>
<th>Anxiolytics</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| 1.   | **Benzodiazepines** | • Alprazolam (Xanax)  
• Chlordiazepoxide (Librium)  
• Diazepam  
• Lorazepam  
• Oxazepam | Psychoactive drug-containing the fusion structure of benzene and diazepine, used to enhance the level of GABA. BZD’s are also categorized as short, intermediate and long term. In short term, they are used for the treatment of insomnia and long term treatments are applicable for anxiety (Shorte, 2005; Page et al., 2002; Olkkola and Ahonen, 2008; Dikeos et al., 2008). | Drowsiness, dizziness, decreased alertness and concentration, lack of coordination in elderly patients, depression, hypotension and difficulties in breathing (Tasman and Lieberman, 2006; Stone et al., 2008; Rapoport et al., 2009) |
| 2.   | **Buspirone**     | Anxiolytic psychotropic drug categorized under azapirone chemical class (NAMI, 2014). Mainly used in the treatment of GAD. | Dizziness, headache and sleepiness, insomnia, nervousness, nausea, dry mouth (common) and jitteriness (Pecknold, 1997) |
| 3.   | **β-blockers**    | **Propranolol**  | Used in the treatment of somatic symptoms associated with anxiety, acute stress reactions, adjustment disorders, panic disorder and agrophobia | Dizziness, fatigue, hypotension and brachycardia |

(Tab. 2.2: Advantages and disadvantages of anxiolytics)
<table>
<thead>
<tr>
<th>4.</th>
<th>Monoamine oxidase inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phencelzine</td>
</tr>
<tr>
<td></td>
<td>Tranylcypromine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.</th>
<th>Tricyclic antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clomipramine</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6.</th>
<th>Selective Serotonin Reuptake Inhibitors (SSRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Citalopram</td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
</tr>
</tbody>
</table>

(Emilien et al., 1998).

Used in the treatment of agrophobia, social phobia and PTSD (Liebowitz et al., 1990).

Weight gain, severe hypertension, headache, nausea, vomiting and dietary compliance (Lippman et al., 1990; Gardner et al., 1996; Walker et al., 1996)

Particularly imipiramine used in the treatment of GAD with or without co-morbid depression (Fricchione, 2004)

Hypersensitivity, weight gain or loss, tachycardia, hallucinations, twitching (Gelder et al., 2005)

Used in the treatment of GAD and OCD

Nausea, diarrhea, body tiredness, headache, insomnia, nervousness and sexual dysfunction (Andreatini et al., 2001).

2.4. Depression

Major depressive disorder (MDD) is a mental disorder that is defined as a pervasive and persistent low mood which is associated with low self-esteem and loss of self interest or happiness in normal life. Thus this disabling condition adversely affects person’s family, work life, sleeping and eating habits and general health (NIMH, 2012).
2.4.1. Classification and subtypes of depression

The DSM IV-TR (Diagnostic Statistical Manual-4th Text Revision) divided the depression in to five subtypes and it is described in table.2.3.

Table.2.3. Classification and characteristics of depression

<table>
<thead>
<tr>
<th>S.No</th>
<th>Depression types</th>
<th>Characteristics features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melancholic depression</td>
<td>Characterized by loss of happiness in all activities, increased quality of depressed mood and the symptoms include excessive guilt, weight loss and psychomotor retardation (APA, 2000).</td>
</tr>
<tr>
<td>2</td>
<td>Atypical depression</td>
<td>Characterized by paradoxical anhedonia (mood reactivity) and positivity, increased weight gain and sleeping habits (hypersomnia), symptoms include body heaviness and in limbs to leaden paralysis, social impairment (APA, 2000)</td>
</tr>
<tr>
<td>3</td>
<td>Catatonic depression</td>
<td>Designated as severe form of MDD and it is associated with motor dysfunction and muscular impairment, mainly occurred in schizophrenic and manic episodes (APA, 2000)</td>
</tr>
<tr>
<td>4</td>
<td>Postpartum depression</td>
<td>This form of depression occurs in new mothers who develop a major depressive episode (MDD) within one month of delivering their baby (Henshaw, 2003)</td>
</tr>
<tr>
<td>5</td>
<td>Seasonal affective disorder (SAD)</td>
<td>Seasonal oriented depressive episode which occurred in autumn or winter and resolve in spring season (Raymond, 2000)</td>
</tr>
</tbody>
</table>
2.4.2. Causes of depression

The biopsychosocial (biological, psychological and social factors) models have proposed the causes of depression (Santrock, 2007). Even the stressful events in life play crucial role in depressive disorder.

2.4.2.1. Genetic

Genetic susceptibility also plays crucial role in development of MDD. Specifically about 7% of panic disorder and 8% of MDD is related with family history and alcohol dependence respectively. Weissman et al (1984) and Akiskal and Weller (1989) have suggested the role of genetic component in etiology of depression. Nobile et al (1999) has confirmed that the human platelet 5-hydroxy tryptamine uptake is differentially influenced in childhood with or without depressive disorder by a common genetic variant of the gene 5-HT. These findings could lead to identification of a trait marker for depression in children (Birmaher et al., 1997).

The genetic factors did not show any specific role in late-onset of depression (Blazer, 2003). A family history of depression is less common among older adults than younger adults. However, certain genetic markers have been, although inconsistently, associated with late-onset of depression, including polymorphisms of the brain derived neurotrophic factor (BDNF), apolipoprotein E and 5-HT transporter genes. At the same time, these markers are also associated with hippocampal volume, cognitive impairment and antidepressant response respectively.
2.4.2 Biological

2.4.2.1 Pathophysiology of depression

Among the 30 neurotransmitters identified so far, serotonin, nor-adrenaline and dopamine found to play a pivotal role in depression. In affected individuals, they required antidepressant course, which influence the deficient neurotransmitters that describes the mechanism of action of drugs (Nutt et al., 2008).

![Fig. 2.2. Monoamine hypothesis of depression (source: Google images)](image)

The monoamine theory of depression proposed that the pathophysiology of depression is widely accepted. In this theory, three monoamines are involved and the deficient level of serotonin is found to affect nor-adrenaline, thereby it reduces another monoamine dopamine. Thus the antidepressant drugs targets the serotonin, and thereby increases the level of serotonin and in turn increased the level of nor-adrenaline and dopamine (Shah et al., 1999). So the monoamine hypothesis is also known as permissive hypothesis and this chemical imbalance conditions coincide with depressive events (Lacasse and Leo, 2005).

Generally nor-adrenaline is related to energy, alertness, attention, as well as interest in life but deficit in serotonin lead to anxiety and OCD complications. Likewise, dopamine is related to alertness, enthusiasm, happiness, and reward, and interest in life (Nutt et al., 2008). Therefore the monoamine theory aid in identifying the specific target molecule for treatment of depression. Depression coupled with anxiety are also treated with SSRI drugs (Nutt et al., 2008)
2.4.2.2. b. Other facts about depression

Recent studies on neuroimaging have proposed that there are differences between normal brain and depressed brain. Depression complications increased the volume of adrenal gland and lateral ventricles and reduced the volumes of basal ganglia, hippocampus, thalamus and frontal lobe extending the orbitofrontal cortex and gyrus rectus (Kempton et al., 2011; Arnone et al., 2011).

Decreased neurons or neurogenesis in hippocampus (Arnone et al., 2011) (centre for mood and memory) of depression individuals leads to dysthymic effect and memory impairment. The therapeutic drugs may increase both the level and total mass of hippocampus and aid in increasing the memory and restoring the mood effect (Mayberg, 2007; Herrmann et al., 2008). The anterior cingulated cortex of brain also implicated the modulation of behavior emotions (Sheline et al., 2003). Brain-derived neurotrophic factor (BDNF) is one of the neurotrophins where their level is decreased in blood plasma among depressed patients. Therefore, BDNF serves as one of the target molecule for antidepressant agents.

The hyper activity of Hypothalamic-Pituitary-Adrenal axis (HPA) also causes major depression. Previous studies have confirmed that increased level of cortisol play vital role in pathogenesis of depression (Monteleone, 2002). In addition, low levels of estrogen hormone also leads to depression in women and variations is seen in all stages of life (Cutter et al; 2003; Douma et al., 2005; Lasiuk et al., 2007).

2.4.2.3. Psychological

The persistence of depression is based on the integral role of personality and development with negative emotion (Raphael, 2000). Depression is also associated with the adverse events. Mood and self esteem also plays an important role in depression (Warman, 2003).
Social

Mental health problems are usually linked with extreme poverty and social isolation in general (Raphael, 2000). Emotional, physical, sexual negligence and child abuse are also linked with increased risk of depression in later part of their life (Heim et al., 2008).

Problems in family life, depression mood during delivery and unsatisfactory in marital life or divorce, death of closed ones, or other conflicts in parenting are additional risk factors of depression (Hopko et al., 2008. The stressful events in life cause MDD which is more prevalent than other causes (Mashman, 1997; Panksepp et al., 2002; Carey et al., 2005). In this context, life events connected to social rejection appear to be particularly related to depression (Sloman et al., 2003; Tooby, et al., 2005).

Epidemiology of depression

Globally, depression is the main cause of morbidity (WHO, 2001). The lifetime prevalence of depression varied from 3% in Japan to 17% in US. During this decade, the number of people who would suffer from depression in their life falls within a range of 8–12%. In one of the surveillance studies conducted in North America among particular group of people have confirmed that the probability of having a major depressive episode within any year-long period is anywhere between 3–5% for males and between 8–10% for females (Andrade and Caraveo, 2003).

Previous studies have shown that major depression is about twice common in women as in men; even it is unclear why it's happening, and whether factors unaccounted are contributing to this type of depression. The relative increase in occurrence is related to pubertal development rather than the chronological age (15 and 18) thereby psycho social factors play main role than hormonal factors (Acta Psychiatrica Scandinavica, 2003) MDD is more common in African and Mexican Americans than European Americans (Stephanie and Riolo, 2005).
The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death and it is adopted by WHO from 1996 (WHO, 2002). DALY measures depression rates per 100,000 individuals in worldwide were published by WHO. Moreover, it has confirmed that India ranks fifth in major depression among individuals (WHO, 2004).

Chronic physical illness increases the risk of depression: in which 23% of people with two or more chronic physical problems were rated as depressed versus 3.2% of healthy controls (Depression, Clinical Knowledge Summaries, February 2010). NICE recently issued specific guidelines regarding the depression in adults with a chronic physical health problem (NICE, 2009)

2.4.4. Antidepressant agents

The drugs that are used to treat depression are referred as antidepressants. Antidepressant drugs, their action and their side effects are presented in table. 2.2.

2.5. Dementia

Dementia is one of the broad category of neurodegenerative disorders that specifically causes gradual decrease in thinking ability and memory performance; moreover it affects the person’s day-to-day activities (WHO, 2012). The symptoms include language problems, emotional and motivational decrease (Burns and Iliffe, 2009).

2.5.1. Classification of Dementia

Memory, language, visual-spatial, attention to the situation and problem solving skills are most commonly affected in dementia. In dementia, changes in brain have been happening for a long period of time. Even the prevalence of mixed dementia is about 10% in general population, which is usually a combined form of Alzheimer's disease with another type of dementia known as vascular dementia.
or frontal temporal dementia (Lee, 2011). According to DSM-IV TR and ICD-10, the classification of dementia and their characteristics are presented in table 2.4.

**Table 2.4. Classification and characteristics of dementia**

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Dementia types</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Reversible Dementia</td>
<td>Vitamin B$_{12}$ deficiency, hypothyroidism, neurosyphilis and lyme disease causes dementia and this type is reversible one.</td>
</tr>
<tr>
<td>2.</td>
<td>Alzheimer’s disease</td>
<td>Alzheimer’s disease is one of the common forms of dementia (Thompson, 2006). The main symptoms include short term memory loss and difficulties in word finding. The major part of brain affected is hippocampus and brain shrinkage also occurred in temporal and parietal lobes (Solomon, 2011)</td>
</tr>
<tr>
<td>3.</td>
<td>Vascular dementia</td>
<td>It is the second most cause of dementia in which about 20 % are affected by this dementia and mainly occurred due to stroke (Iadecola et al., 2012)</td>
</tr>
<tr>
<td>4.</td>
<td>Dementia with Lewy bodies (DLB)</td>
<td>This type of dementia includes hallucinations and Parkinsonian symptoms (Solomon, 2011).</td>
</tr>
<tr>
<td>5.</td>
<td>Frontal temporal dementia (FTD)</td>
<td>FTD occurred during drastic change of personality with language skill difficulties (Solomon, 2011).</td>
</tr>
<tr>
<td>6.</td>
<td>Progressive supranuclear palsy (PSP)</td>
<td>The main symptoms include problems with eye lid movement and it is misdiagnosed with Parkinson symptoms (ICD 10, 2000)</td>
</tr>
</tbody>
</table>
The other types of dementia includes corticobasal degeneration, rapidly progressive, mild cognitive impairment, fixed cognitive impairment and slowly progressive.

2.5.2. Causes of dementia

Dementia is also an inherited disorder and it may pass from parents to children. Some of the Alzheimer's tend to cluster within particular families, sometimes several generations affected in the same family are called as familial disease. In few cases, early onset of AD is caused by mutations in one of three particular genes. The three main genes that are responsible for AD are the amyloid precursor protein gene (APP), and two presenilin genes (PSEN-1 and PSEN-2) (Andrew et al., 2011).

Recent studies have suggested that vascular factors, such as midlife hypertension, diabetes, and cerebrovascular disease, contribute significantly to the development of dementia and Alzheimer's disease, and their active engagement in mental, physical, and social activities may postpone the onset of dementia by providing cognitive reserve (Qiu et al., 2007).

2.5.3. Pathophysiology of dementia

In brain, the metabolic pathways have confirmed that acetylcholine (Ach) is synthesised from acetyl-coA in the cytoplasmic terminals of autonomic nerve. The final step in the synthesis is catalysed by the enzyme choline acetyl transferase (CAT). In Alzheimer’s disease, CAT is less active than non-Alzheimer’s brain resulting in a reduction in the synthesis of Ach. As CAT activity declines, less ACH is packaged into the synaptic vesicles and released at the nerve terminal. This deficit in Ach and increased acetylcholine esterase activity leads to decreased neurotransmission that is implicated in the pathogenesis of Alzheimer’s disease (Katzung, 2001)
2.5.4. Epidemiology of dementia

In 2007, approximately 24 million people suffered from dementia globally, and it is expected to double by every 20 years. At the same time, about 60% of dementia is diagnosed in developing countries, with the proportion being raised to more than 70% by 2040 (Qiu et al., 2007). In the year 2010, it is estimated that 35.6 million people have been affected by dementia worldwide. The prevalence rate increased with the age for example 5% in 60 years and 20-40% in 85 years (WHO, 2010).

Incidentally, the prevalence of dementia is high in low and middle income countries. In the year 2013, death reports due to dementia were about 1.7 million whereas in 1990 only 0.8 million deaths have been reported (Larson et al., 2013).

2.5.5. Drugs used in the treatment of dementia

The drugs used in the treatment of dementia include acetylcholine esterase inhibitors, N-methyl-D-aspartate (NMDA) receptor blockers, antidepressants, and benzodiazepine is presented in table 2.5. The antidepressants and benzodiazepine action and their adverse effects are previously described in the table. 2.2.
Table 2.5. Advantages and disadvantages of antiamnesic agents

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drugs</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acetylcholine esterase inhibitors (AChE)</td>
<td>Used in the treatment of Alzheimer’s disease, dementia with Parkinson, vascular dementia</td>
<td>Bradycardia and Syncope (Jayeb et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>• Donepezil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>N-methyl-D-aspartate (NMDA) receptor blockers</td>
<td>Used in the treatment of various type of dementia but activity is considerably slighter than AChE</td>
<td>Common side effects include dizziness, drowsiness, insomnia and hallucination (Rossi, 2006)</td>
</tr>
<tr>
<td></td>
<td>• Memantine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Piracetam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.6. Parkinson’s Disease (PD)

Parkinson's disease (PD) is a neurodegenerative disorder that results due to the death of dopaminergic neuronal cells in the basal ganglia (substantia nigra compacta and pedunculopontine nucleus) of brain. The brain loses 50-70% of dopaminergic neurons over the course of neurodegeneration (Davie, 2008). Neuropathological effect of PD includes degeneration in dopaminergic nigrostriatal pathway, increased effect of glutathione depletion, Fe deposition, increased LPO, oxidative DNA damage, mitochondrial dysfunction, excitotoxicity and alterations in antioxidant (Gerlach et al., 2003; Chaturvedi et al., 2006; Hritcu et al., 2008; Zhou et al., 2008; Ciobica et al., 2009).
2.6.1. Classification of Parkinson’s Disease (PD)

Basically, PD is classified into primary Parkinson, secondary Parkinson, hereditary Parkinsonism, and Parkinson plus symptoms (Jankovic, 2006). The classification of Parkinson’s disease (Pradeep et al., 2012) is presented in Table 2.6.

Table 2.6. Classification and characteristics of PD

<table>
<thead>
<tr>
<th>S.No</th>
<th>Classification</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Primary Parkinson (or) Idiopathic PD</td>
<td>Neuro degeneration of dopaminergic neurons in Substantia Nigra portion of brain (SN) with the remaining Lewy bodies in the brain due to aged condition</td>
</tr>
<tr>
<td>2</td>
<td>Secondary Parkinson (or) Drug induced</td>
<td>Reserpine, haloperidol, phenothiazines, Alpha methyl dopa, Butyrophenones, Metoclopramide</td>
</tr>
<tr>
<td></td>
<td>Infections induced</td>
<td>Post encephalitic, Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic (hypoxia, parathyroid dysfunction, hepatocerebral degeneration)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Structural (trauma, brain fever, hydrocephalus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxin (carbon monoxide, rotenone (or) MPTP, carbon disulphide, cyanide)</td>
</tr>
<tr>
<td>3</td>
<td>Hereditary Parkinsonism</td>
<td>Autosomal-dominant cerebellar ataxias, Wilson’s disease</td>
</tr>
<tr>
<td>4</td>
<td>Parkinson plus syndromes</td>
<td>Cortical-basal ganglionic degeneration, Progressive supranuclear palsy</td>
</tr>
</tbody>
</table>
2.6.2. Causes of PD

Parkinson’s disease is usually idiopathic (there is no specific cause for this disease). Genes play a main role in developing PD along with some other factors.

2.6.2.1. Genetic

Generally PD is considered as non-genetic disorder and approximately 15% of individuals with PD have a first-degree relative who have already suffered by PD. Even 5% of individuals have this disease due to mutation of several specific genes (Lesage et al., 2009). Genes play minor role in developing PD along with other factors.

2.6.2.2. Environmental

Environmental factors play a dominant role in causing PD. Several environmental factors have been linked with the increased risk of PD which includes exposure to pesticides, farming culture, head injuries by accidents (Noyce et al., 2012; Van Maele-Fabry et al., 2012). Some of the insecticides like chlorpyrifos and organo chlorines are also primarily involved in PD (Freire et al., 2012). Likewise, the pesticides like rotenone or paraquat and Agent Orange herbicide are also implicated in PD (De Lau and Breteler, 2006; Tanner et al., 2011). Additionally exposure to heavy metal affected the substantia nigra in PD (De Lau and Breteler, 2006).

2.6.2.3. Pathophysiology of PD

The major pathophysiology of Parkinson's is the loss of dopamine producing neurons in the substantia nigra (SN) portion of the brain. During aging process, these neurons gradually degenerate and die. Dopamine is basically a neurotransmitter or chemical messenger, normally passes the signals to the corpus striatum, and it is involved in the smooth voluntary movement. Also the death of dopamine producing neurons leads to depletion of dopamine in the corpus striatum. Following which an imbalance between dopamine (inhibitory neurotransmitter) and
an acetylcholine (excitatory neurotransmitter) occurs that results in motor dysfunction of PD. When the motor symptoms of PD first appear, more than 50% of dopamine producing cells in the substantia nigra has already been lost and further there is a 50-70% decline in striatal dopamine (Mesbah et al., 2011)

In PD, Lewy bodies (named by Friedrich Lewy who first described, 1912) develop in the remaining neurons in the SN portion and also in other regions of the brain. Lewy bodies contains alpha-synuclein (unusual deposits of protein) which is the hallmark of pathophysiology of PD (Mycek et al, 1999).

It is believed that the pathological changes of PD does not begin in SN portion of brain. Initially, slight changes occurs in olfactory bulb of brain (involved in the sense of smelling) followed by lower brainstem and ascending brainstem which is next to the basal forebrain and amygdala, substantia nigra, and finally extending the changes in thalamus and cortex. These process explains that the Parkinson's disease first starts with non-motor symptoms, like loss of sensation in smell, problems in sleep, mood oriented disorders or constipation then motor symptoms.

![Comparison between neurons in normal and Parkinson’s disease](image)

**Fig.2.4. Comparison between neurons in normal and Parkinson’s disease**

(Source: Google images)
2.6.3. Epidemiology of PD

Globally PD is listed as second most neurorodegenerative disease after Alzheimer’s disease. Worldwide, approximately 7 million people have been affected by this disease and majorities are in United States (Yao et al., 2013). In industrialized countries, about 0.3% of people were affected by PD (De Lau and Breteler, 2006).

The prevalence of PD is increased by 1% for 60 years and above and 4% for above 80 years of age. This indicates that onset of PD is 60 years of age. Some time, the onset of PD also occurs even in the age group of 20 and 50 years (5-10 %). Some of the studies have reported that PD is highly prevalent in men than women, finally the incidence of PD is approximately between 8 and 18/100,000 individual years (De Lau and Breteler, 2006).

2.7. Phytochemicals used in the treatment of neurological and neurodegenerative disorders

Phytoconstituents, the derivatives of primary metabolites from medicinal plants play a significant role in maintaining the brain's chemical balance by influencing the activities of receptors for major inhibitory neurotransmitters. In traditional medicine, several herbs have been used to treat neurological disorders. It was found that herbal medicines that are used in Ayurvedha and Chinese medicines contain multiple compounds and phytochemicals that possess neuroprotective effect. They are highly useful and beneficial in treating different neuropsychiatric and neurodegenerative disorders (Kumar and Khanum, 2012)

In the last decade, we have witnessed an intense increase in herbal medicines in which phytochemical constituents have long-term health benefits. In contrast, many medicinal plants exert specific medicinal actions without serving a nutritional role in the human diet and may be used in response to specific health problems over short- or long-term intervals. Phytochemicals are believed to reduce the risk of several major diseases including cardiovascular diseases, cancers as well as
neurodegenerative disorders. Therefore people who consume high amount of vegetables and fruits may be at reduced risk for some of the diseases caused by neuronal dysfunction (Selvam et al., 2008; Lobo et al., 2010)

2.8. Role of phytochemicals as antioxidants in neurodegeneration

Brain has a large potential oxidative capacity but its ability is limited due to imbalances caused by oxidative stress (Weiss and Fintelmann, 2000). Oxidative stress are mainly implicated in neurodegenerative disorders. Although the brain accounts for less than 2% of the body weight, it consumes about 20% of the oxygen available through respiration. Because of its high oxygen demand, brain is the most susceptible organ to oxidative damage (Weiss and Fintelmann, 2000). Phytopharmaceuticals show promising effects in modern medicine as well as in traditional system of medicine owing to their therapeuitic efficacy. Novel antioxidants may offer an effective and safe means of bolstering body's defense against free radicals. CNS neurons are able to combat oxidative stress using some limited resources like, vitamins, bioactive molecules, lipoic acid, antioxidant enzymes and redox sensitive protein transcriptional factors. Even, this defense mechanism can be activated/ modulated by nutritional antioxidants such as polyphenols, flavonoids, terpenoids, fatty acids and other phytochemicals.

The plant derived alternative antioxidants (AOX) are regarded as effective in controlling the effects of oxidative damage, and hence they had influence in what people eat and drink. (Viana et al., 1996; Pinder and Sandler, 2004). There is increased scientific and empirical evidence supporting the use of antioxidants for the control of neurological disorders. As the focus of medicine shifts from treatment of manifest disease to prevention, herbal medicine (with its four pillars of phytochemistry, phytopharmacy, phytopharmacology and phytotherapy) is coming in to human consideration.
An increasing number of herbal medicines have been introduced into neuropsychopharmacology profile in the last decade. In this area of research, a large number of phytopharmaceuticals whose therapeutic potential has been assessed in a variety of preclinical animal models and mechanisms of their actions have been investigated through neurobiochemical approaches. These experiments have provided useful information for the development of novel pharmacotherapies from medicinal plants for use in clinical neuropsychopharmacology.

2.9. Flavonoids and their neuroprotective effects

2.9.1. Flavonoids in cognitive and memory improvement

Flavonoids are polyphenolic compounds which exerts a multidimensional neuroprotective effect. Flavonoids protect neurons from injury caused by neurotoxins, thereby reducing the neuroinflammation. These are one of the potential candidates that promote learning memory and also reduce cognitive impairment.

Due to these mechanisms exhibited by flavonoid, consumption of flavonoid enriched food is now gaining importance in daily life. Flavonoid rich extract from Blueberry improved the spatial recognition memory and showed remarkable improvement in motor function (Casadesus et al., 2004; Barros et al., 2006; Williams et al., 2008) moreover it is also involved in ‘objects recognition memory’ of rodents (Goyarzu et al., 2004). Blue berry extracts are also involved in the inhibitory effect of fear conditioning learning (Barros et al., 2006). Blue berry extracts have been proved to effective in short-term memory (Ramirez et al., 2005) and also in improving long-term reference memory (Casadesus et al., 2004). Overall, the flavonoid enriched food and beverages improves the motor performance (Shukitt-Hale et al., 1999; Shukitt-Hale et al., 2006). Neuroprotective and spatial recognition memory of quercetin and rutin has been reported in radial arm maze rat model (Pu et al., 2007)

Similarly, flavonoid-enriched extract of Ginkgo biloba showed remarkable improvement in memory and learning (Clostre, 1999; Cohen-Salmon et al., 1997).
The effects of flavonoid-enriched extract on cognitive function are due to the strong interaction of flavonoid with cellular and molecular architecture (Spencer, 2008a; Spencer, 2008b).

2.9. Effects of flavonoids on the blood brain barrier

Flavonoids have the ability to cross the Blood Brain Barrier (BBB) in order to reach the Central Nervous System (CNS). The BBB is organized by brain capillary endothelial cells firmly controlling the activation of very small polar molecules and macromolecules into the brain. Youdim et al (2002) reported that most of the tested flavonoids, their derivatives and their representative metabolites are able to cross the BBB along with the uptake of several flavonoids at picogram and nanogram concentration respectively.

2.9.3. Direct and indirect antioxidant activities

Basically flavonoids have high reactive hydroxyl group (OH) that gets oxidized by donation of electrons to free radicals thus, leading to stabilization of free radical to a less reactive molecule. This reaction is the direct scavenging effect of flavonoids with the superoxide anions, singlet oxygen and lipid peroxyl radicals. These considerable evidences confirmed that flavonoids efficiently attenuate the deleterious effects of free radicals and ROS/RNS. Quercetin is one of the basic flavonoid which shows direct antioxidant activity (Dajas et al., 2003). Hodnick et al (1994) compared hydroxylation and methoxylation patterns of flavonoids referring to their NADH-oxidase inhibition ability. In this event, flavonoids showed increased level of endogenous antioxidants in the body.

2.9.4. In vivo effects of flavonoids

Flavonoid enriched extract from Monodora tenuifolia seeds exhibited remarkable antidepressant effect in forced swim test among stress induced mice (Ekeanyanwu and Njoku, 2015). Synergistic antidepressant effects of quercetin and Hypericum perforatum extract has been reported by Liu et al (2013). Likewise,
high flavonid content of *Hibiscus esculentus* extracts also possessed antidepressant effect (Ebrahimzadeh et al., 2013)

### 2.9.5. Flavonoids as GABA<sub>A</sub>-benzodiazepine receptor

Like benzodiazepine molecules, many flavonoids were able to bind with GABA<sub>A</sub> receptors with significant affinity (Wang et al., 2002; Wasowski et al., 2002; De Feo and Faro, 2003; Goutman et al., 2003; Marder et al., 2003). Therefore, flavonoids seem to exert their behavioral effects through the binding affinity with GABA<sub>A</sub> receptor complex (Dajas et al., 2003).

### 2.9.6. Flavonoids as Monoamine oxidase inhibitors

Majority of the flavonids are identified as MAO –A and B inhibitors. Some of the examples are, glycosidic flavonoid quercetin and other flavonoids isolated from *Ginkgo biloba* extract exhibited monoamine oxidase inhibition. Quercetin isolated from *Calluna vulgaris* also inhibited MAO A and B activity (Saaby et al., 2009). Quercetrin, rutin and other flavonoid isolated from *Melastoma candidum* were shown to inhibit MAO-B activity.

### 2.10. *Hypericum hookerianum*

*Hypericum hookerianum* is a small woody shrub and native of Bangladesh, China, Bhutan, India (specifically in high altitudes), Nepal, Myanmar and Northern Thailand. *H.hookerianum* belongs to the family of *Hyperiaceae* (Fyson, 1974) which grows in edges of the forest and high altitudes. The name of the plant is originated from Greek “hyper” means over and “eikon” means image of unclear reference and whole name of this species is honored to the English botanist William Jackson Hooker (1785-1865). Therefore the common name of this species is Hooker’s St. John’s wort.

Approximately 20 different species of *Hypericum* occur in India, some are cultivated in gardens (The Wealth of India, 1962). All species of the genus *Hypericum* are widely used in folk medicine and are ethnopharmacologically
important. In India *H.hookerianum* is mostly found in Khari, Sikkim, Jaintia hills, Nilgiris of Tamil Nadu (The Wealth of India, 1962; Fyson, 1974). *H.hookerianum* has a round topped small woody shrub with yellow flowers, inflorescent period in summer season with weakly spreading, non-erect branches.

### 2.10.1. Classification of *Hypericum hookerianum*

**Common Name**  
Golden lotus of St. John’s Wort (*H. perforatum*)

**Classification**

<table>
<thead>
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<td>Species</td>
<td><em>Hypericum hookerianum</em></td>
</tr>
</tbody>
</table>

**Figure 2.5. Hypericum hookerianum**

### 2.10.2. Medicinal uses

*H.hookerianum* is a well known plant used in folklore medicine for its different therapeutic potentials including antidepressant, spasmolytic, stimulant, hypotensive and antimicrobial activities. The tribal communities of the Shola forest in Tamil Nadu, India used the aerial parts of *H.hookerianum* for treating wounds and burns (Asolkar et al., 1992).
2.10.3. Antitumour activity

The antitumour activity of methanolic leaf extract of *H. hookerianum* has been reported by Dongre et al (2007). The HPLC standardized methanolic extract of *H. hookerianum* was tested against Ehrlich ascites carcinoma (EAC) tumor induced mice. The study results confirmed the potent antitumour nature of leaf extract of *H. hookerianum*.

2.10.4. Antioxidant activity

The total antioxidant capacity of leaf, flower, root and aerial parts extracts of *H. hookerianum* were tested and found that leaf and flower extracts of *H. hookerianum* exhibited higher antioxidant activity. The leaf extract of *H. hookerianum* also exhibited better *in vivo* antioxidant potential against carbon tetra chloride induced hepatotoxicity in rats (Chandrashekar et al., 2009).

2.10.5. Wound healing activity

The wound healing potential of leaf and stem methanolic extracts of *H. hookerianum* was studied against incision and excision model in rat. This study strongly confirmed that leaf extract exhibited high wound healing potential than stem extract of *H. hookerianum* (Mukherjee and Suresh, 2000)

2.10.6. Antimicrobial activity

The acetone, methanol and chloroform extracts of *H. hookerianum* was tested against six different gram negative and gram positive bacteria. Among the extracts, methanolic extract of *H. hookerianum* exhibited potent antibacterial activity than others (Mukherjee et al., 2001). Antiviral activity of *H. hookerianum* against Herpes Simplex Virus (HSV) has been reported (Vijayan et al., 2004)

2.10.7. CNS activity

The CNS potential of hydro alcoholic extract of *H. hookerianum* and *H. patulum* in rat model is tested by spontaneous, exploratory behavior and
antipyretic activity. The study confirmed that *H. hookerianum* exhibited strong CNS active and whereas *H. patulum* did not exhibit any significant effect (Mukherjee et al., 2002).

### 2.10.8. Cytotoxicity

The xanthones and cinnamate esters identified in *H. hookerianum* exhibited cytotoxic effect in human tumour cell lines (Vijayan et al., 2003).