CHAPTER 1

General Introduction & Review of Literature
1.1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood [APA, 1994]. It is characterised by developmentally inappropriate levels of inattention, hyperactivity and impulsivity, which often gives rise to serious impairments in academic performance, social adaptive and behavioural functioning, both inside and outside the home [Greene et al., 1996; Stein et al., 1995]. Prevalence rate of ADHD is 4 -12% in school aged children [APA, 2000]. ADHD probands primarily face problems in school, and most of the time they display poor academic performance. They may also have problems mixing with other children. These difficulties can persist till adulthood [Borrill, 2000]. Children with ADHD are also easily distracted by irrelevant things; being impulsive, these children find it very hard to carry out tasks which involve waiting. They have trouble focusing or concentrating on a problem or a task and thus it is hard for them to learn new skills because of their inability to focus. They also have trouble completing what they start. Some children have significant problems in concentration and attention, but are not necessarily overactive or impulsive. These children are sometimes described as having Attention Deficit Disorder (ADD) rather than ADHD. ADD can easily be missed because the child is quiet and dreamy rather than disruptive. ADHD is not related to intelligence. Children with all levels of ability can have ADHD.

We know that young children have lots of energy and like to be active. Young children also tend to have a short attention span they soon get tired of an activity and want to move on to something new. So to a certain extent the diagnoses is mainly based on the matter of degree and it is done by the mental health professionals (child psychiatrist and child psychologist) according to Diagnostic and Statistical Manual for Mental Disorders [APA, 1994; APA, 2000].
1.2. Historical perspective

Analysis of historical literature suggests that children with the symptoms of inattention, hyperactivity, and impulsivity have previously been described by several authors during the last 200 years. The clinical characterizations, underlying concepts, and nomenclature of the described dysfunctions have changed over the time. Many of the historical descriptions are, however, consistent with the modern diagnostic criteria for ADHD. Details of the historical perspectives of modern day ADHD are as follows:

First descriptions of children with ADHD symptoms are made as early as 1902 by Sir George Frederick Still, an English physician and were thought to have a 'defect of moral control' [Still, 1902]. During 1917-1918, children from North America suffered from encephalitis epidemics and survivors had many behavioral problems resembling contemporary ADHD [Ebaugh, 1923; Hohman, 1922]. From 1930s to 1950s the behavioral problems, e.g. hyperactivity, restlessness, distractibility were identified as "Brain Damage Syndrome" [Berder, 1942; Goldstein, 1936]. By the time 1950s-1970s, behaviour of hyperactivity and poor impulse control of children was described as "hyperkinetic impulse disorder" or "hyperactive child syndrome" [Burks, 1960; Chess, 1960]. After that C. Keith Conners published a study on the effects of methylphenidate in 'emotionally disturbed children' in 1963 [Conners, 1963]. The second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) was published by the American psychiatric association (APA) in 1968 where all childhood disorders were described as "reactions," and the hyperactive child syndrome became "hyperkinetic reaction of childhood" [APA, 1968]. In 1983, Douglas renamed the disorder as Attention Deficit Disorder (ADD), giving importance mainly to the attentional problems [Douglas, 1983]. The DSM-III-R (revised edition), published in 1987, again changed the name, this time to Attention Deficit Hyperactivity Disorder (ADHD), but did not include any subtypes [APA, 1987]. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was published by the APA in 1994 and described three types of Attention Deficit Hyperactivity Disorder.
(ADHD), including combined, predominantly inattentive and predominantly hyperactive-impulsive types [APA, 1994]. In the year 2000, the DSM-IV was revised for text [APA, 2000]. Finally the development and publication of DSM-5 was arrived in 2013 where a variety of new classifications were included [APA, 2013].

1.3. Diagnosis

Diagnosis of ADHD is made primarily by reviewing one’s history; there is no fullproof test for ADHD. It is mainly based on criteria outlined by the Diagnostic and Statistical Manual of the American Psychiatric Association [APA, 1994] which were further revised in the year 2000 [DSM-IV-TR; APA, 2000]. Sometimes diagnosis is also performed based on the International Classification of Diseases-10 (ICD-10) formulated by the WHO, which identifies symptoms of inattention and hyperactivity together as Hyperkinetic Disorder [WHO, 1992].

As per the DSM-IV-TR, probands must exhibit the following symptoms of inattention, hyperactivity and impulsivity before the age of 7 years in two or more settings (eg, at school or work and at home).

1.3.1. DSM-IV Diagnostic criteria for attention-deficit hyperactivity disorder

Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a disruptive level:

**Symptoms of inattention**

(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
(b) Often has difficulty sustaining attention in tasks or play activities
(c) Often does not seem to listen when spoken to directly
(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
(e) Often has difficulty organizing tasks and activities
(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) Often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)
(h) Is often easily distracted by extraneous stimuli
(i) Is often forgetful in daily activities

Six (or more) of the following symptoms of hyperactivity and impulsivity have persisted for at least 6 months to a disruptive level:

**Symptoms of Hyperactivity:**
- a) Often fidgets with hands or feet or squirms in seat
- b) Often leaves seat in places where remaining seated is expected
- c) Often runs about or climbs when & where it is not appropriate
- d) Often has trouble playing or enjoying leisure activities quietly
- e) Is often “on the go” or act as if “driven by a motor”
- f) Often Talks excessively

**Symptoms of impulsivity**
- (g) Often blurts out answers before questions have been completed
- (h) Often has difficulty awaiting turn
- (i) Often interrupts or intrudes on others

- There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
- The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder.
Some other scales are also used to evaluate the ADHD probands:

- **Conners’ Parents and Teachers Rating Scale**- To measure hyperactivity level [Conners et al., 1998].
- **Wechsler’s Intelligence Scale for children**- To assess the intelligence/developmental quotient for children above five years [Wechsler, 1991]
- **Developmental Screening Test**- To assess Developmental Quotient of children below 5 years [Bharat Raj, 1971].

### 1.4. ADHD Subtypes

According to the DSM-IV-TR, ADHD is classified into three subtypes [APA, 2000]:

1. **Predominantly hyperactive-impulsive** – In this group most symptoms (six or more) are in the hyperactivity-impulsivity category. Although inattention may be present to some degree, fewer than six symptoms are detected.

2. **Predominantly inattentive** – Here majority of the symptoms (six or more) belong to the inattention category and fewer than six symptoms of hyperactivity-impulsivity are present, although hyperactivity-impulsivity may still be present to some degree. Children with this subtype are less likely to act out or have difficulties getting along with other children. They may sit quietly, but fail to pay focussed attention. Therefore, these children may be overlooked, and parents and teachers may not notice that he or she has ADHD.

3. **Combined (hyperactive-impulsive and inattentive)**– Children of this category have six or more symptoms of both inattention and hyperactivity-impulsivity. Most of the ADHD children belong to the combined subtype.
1.5. Epidemiology

Worldwide prevalence of ADHD among school children and adolescents varies broadly; some investigators reporting 8-12% while others have reported as low as 4-5% [Brown et al., 2001; Faraone et al., 2003]. Mean worldwide prevalence of ADHD was reported to be between 5.29% and 7.1% in children and adolescents (<18 years) [Polanczyk et al., 2007; Willcutt et al., 2012]. Prevalence of ADHD in Europe was estimated at below 5%, however, there are still few global or European data on rates of incidence, prevalence or epidemiology of ADHD [Polanczyk et al., 2007]. Estimation of the prevalence of ADHD may be complicated by a range of factors such as methodological and cultural differences, variability in identification and medical classification systems used for diagnosis.

1.5.1. Prevalence factors

ADHD prevalence rates may vary depending on several factors:

- **Age** – ADHD is one of the most common childhood- onset psychiatric disorders affecting mainly preschool or school aged children but can persist till adolescence and adulthood [Kessler et al., 2006; Schlack et al., 2007; Lara et al., 2009; Wichstrøm et al., 2012].

- **Variations in rating scales** – Diagnostic criteria or rating scale used to assess symptoms contribute to a large extent in the variations in prevalence rates [WHO, 1992; APA, 2000].

- **Source of Information** – Prevalence rates may also vary depending on the source of information on a patient’s condition (e.g. parent, patients, teacher or specialist) [Polanczyk et al., 2007, Skounti et al., 2007].

- **Gender** – A higher prevalence is often reported in males [Biederman et al., 2004; Novik et al., 2006].

- **Subtype of ADHD** – Combined-type ADHD is generally considered most prevalent in all age-groups [Wilens et al., 2009].
1.6. ADHD associated co-morbid conditions

When one or more disorders occur at the same time with the primary disease or disorder, the term co-morbidity comes into the picture. Individuals diagnosed with ADHD are often found to have a number of different comorbid disorders thus complicating the clinical picture [Barkley 2006a; Brown 2009]. A survey conducted by the National Survey of Children Health involving over 60,000 children aged 6-17 years, including over 5,000 with ADHD, showed that co-morbidities were very common in children with ADHD [Larson et al., 2011]. Since co-morbid conditions are associated with greater cognitive, social, and psychological impairments, proper diagnosis of co-morbid conditions during psychometric evaluation, recognition and treatment become crucial for disease management and early vigorous intervention is warranted. Most commonly occurring co-morbidity in ADHD children includes oppositional defiant disorder (ODD), conduct disorder (CD), learning disability (LD), anxiety disorder (AD) and mood disorder (MD) [Biederman et al., 1991]. Another important co-morbid condition Substance use disorder (SUD) which is mainly detected in ADHD proband during adolescence or early adulthood [Timothy et al., 2011]. Beside these, there are some other co-morbid conditions, such as suicidality, tic disorder, obsessive compulsive disorder, etc. associated with ADHD. Some of these important ADHD associated co-morbid disorders are described as follows:

- **Oppositional defiant disorder (ODD)** – ODD is the most commonly found co-morbid conditions associated with ADHD. ODD symptoms occur in as many as 21% to 60% of children with ADHD [Serra-Pinheiro et al., 2004]. Evidence from twin studies indicates a shared or common genetic contribution between ADHD and ODD [Faraone et al., 2005]. The main characteristic features of ODD are aggressiveness, tendency to oppose to the other’s request
and purposefully bother and irritate others [Biederman et al., 1991]. Probands mainly meet the criteria for a diagnosis of ODD by 7-years or later. The most common reason for ODD is parental vulnerability resulting in insecurity of the child who responds with a need to control. This manifests by active confrontation of authority they perceive as being weak. So it is often noticed that ODD symptoms tend to occur more often with people whom the child is close to or knows well such as family or care givers. Children with ODD have recurring negativistic, defiant, hostile and disobedient behaviour, especially toward authority figures. Studies suggest that most of the ADHD children with co-morbid ODD will develop CD also however many children with ADHD and ODD do not evolve into CD [Loeber et al., 2000]. As the onset of ODD is usually prepubertal, early identification, diagnosis, and treatment are crucial.

➤ **Conduct disorder (CD)** – About 40% of children with ADHD also meet criteria for conduct disorder [Biederman et al., 1991] while it is very low in children without ADHD. CD involves repeated aggression towards people or animals, property destruction, stealing, and violation of rules of society (i.e. missing school or running away from home). Co-occurrence of ADHD and CD in adolescents is often an indicator of antisocial behaviours, nicotine use, substance use or abuse, anxiety or depression, and development of antisocial personality disorder as adults [Wilens et al., 1997; Biederman et al., 1998]. ADHD children with these co-morbidities show the poorest outcome in educational and social aspects of life. Conduct problems are generally reduced by all effective ADHD treatments (stimulant and non-stimulant medication and psychosocial treatment). However, treatment for ADHD may not be sufficient to resolve all the symptoms.

➤ **Learning Disability (LDis)** – LDis is a disorder of cognition, manifested as difficulty in academic skills and needs cautious, methodical and complete evaluations. Over half of all children with ADHD also have learning problems. Though ADHD affects the ability to learn, it is not a true condition for learning disability. So treating the symptoms of ADHD will not correct the learning
disorders that a child may have. LDis is a specific disorder that affects one of the four primary steps needed for learning; the steps are- i) recording information (ex. input of a visual or auditory perception problem), ii) understanding information (integration: ex. Sequencing and organization problem), iii) storing information (placing information into memory), and iv) retrieving information (memory: ex. immediate recall of the recently learned information). Although ADHD may globally interfere with the success of these steps, it is the impulsivity, hyperactivity and distractibility that interfere with the learning process. ADHD does not specifically impact one of these four steps. Reading disorders are common in ADHD. About 25-40% with ADHD children may have major reading and writing difficulties [Shaywitz et al, 1992]. Disorders of written expression are characterized by significant impairment in writing grammatically correct sentences and paragraph organization and occasionally with dysgraphia. The overlay between ADHD and mathematic disorder, dyscalculia, is considerably more and is more frequently diagnosed in an inattentive type of ADHD. Although some ADHD symptoms are usually presented in infancy, it is not until the school age group that a full extent of symptoms becomes prevalent because of the highly structured school environment. Developmental dyslexia and dyscalculia become apparent when the child attends school and is required to read, write, and do calculations. Developmental dyslexia, especially reading and spelling disorders, is characterized by difficulty with reading comprehension, reading decoding and reading fluency and spelling. Impairment in multiple cognitive functions, such as executive functions, is common in ADHD and developmental dyslexia. The symptoms may negatively affect the developmental course of ADHD and will lead to stagnation of the process of learning to read. In some cases, ADHD and dyslexia may not share an etiological factor. A dyslexic child may be inattentive in some classes because he or she will be impaired due to generalized reading problems.

- **Mood disorder (MD)** – As per the DSM IV-TR classification, disturbance in mood is hypothesized to be the main underlying feature of MD and shows 10% to 40% occurrence in clinic-referred ADHD children averaging to about
25% [Biederman et al., 1991; Barkley 2006a; Schatz & Rostain, 2006]. Two types of MD are broadly recognized; the division is based on whether a manic or hypomanic episode has ever been present. Thus, there are depressive disorders, of which the best-known and most researched is major depressive disorder (MDD) and the other one is bipolar disorder (BD), formerly known as manic depression. Depression is the most common MD; a person with depression feels “very low.” Symptoms may include: feelings of hopelessness, changes in eating patterns, disturbed sleep, constant tiredness, an inability to have fun, and thoughts of death or suicide. Since these symptoms may attribute to normal childhood behaviour, diagnosis of depression may be missed for a long time. Family-based studies suggest there is some genetic link between depression and ADHD. People with mania or bipolar disorder often have periods of unusually “high” or elated feeling; they show strong emotional feelings, hyperactive behaviour, overbearing manner, and difficulty waking up in the morning. Children and adolescents with severe bipolar symptoms may have excessive and lengthy temper tantrums that are sometimes destructive in nature.

- **Anxiety disorder (AD)** – Anxiety disorder is another important co-morbid feature of ADHD with estimated rates of 20% to 40% [Spencer et al., 1999, Jensen et al., 2001]. Anxiety is defined as a psychological and physiological state characterized by emotional, somatic, cognitive and behavioural issues. It is a well thought out, normal response to stress, but if anxiety reaches its top level, it may disturb normal life of a person. Often general anxiety is thought to be the most prevalent disorder followed by social phobia and separation anxiety. Some children with ADHD may present with more than one AD [Souza et al., 2005]. Presence of anxiety in ADHD patients may inhibit impulsivity, so children with ADHD and co-morbid anxiety may have less impulsivity but more inattentive. It is very important to distinguish between the true AD and those children who are experiencing anxiety in response to ADHD because treatment is very different. Stimulants, while helpful for ADHD symptoms, may actually worsen the symptoms of a true AD.
➢ **Tic Disorder (TD)** – Tic disorders are defined in the DSM-IV-TR based on the type (motor or phonic) and duration of tics (sudden, rapid, nonrhythmic movements). The core symptoms of tic disorder are motor and vocal tics which wax and wane over time. The risk for co-morbid tics among children with ADHD is about 20% [Simpson *et al.*, 2011]. Most of the time TD goes unnoticed and resolve within a year of onset but in chronic conditions, including chronic motor or vocal TD (also known as Tourette syndrome), last more than a year and are less common [APA, 2000]. Tics can be found more frequently as co-morbidity to ADHD when there is a family history of TD and or there is an early onset of a TD of high severity of symptomatology. Patients with co-existing TD may occasionally need, beside treatment with a stimulant for ADHD, additional medication with a dopaminergic agonist, like Risperdal.

➢ **Obsessive compulsive disorder (OCD)** – Rate of OCD among children with ADHD is 8-11% [Arnold 2005]. It is characterized by recurrent intrusive thoughts and images or repetitive behaviours that aim to reduce anxiety or by a combination of such obsessions and compulsions. Symptoms of the disorder include excessive washing or cleaning, repeated checking, extreme hoarding, preoccupation with sexual, violent or religious thoughts, relationship-related obsessions, aversion to particular numbers such as opening and closing a door a certain number of times before entering or leaving a room. These symptoms can often cause severe emotional and financial distress. However, OCD sufferers generally recognize their obsessions and compulsions as irrational and may become further distressed by this realization. OCD affects children and adolescents, as well as adults. Patients with co-morbid OCD and ADHD symptoms seem to require special care and treatment because the longer these symptoms persist; the more they increase in severity.

➢ **Substance use disorder (SUD)** – In DSM-IV-TR, substance use disorders were diagnosed as substance abuse or substance dependence [APA, 2000]. However, in DSM-5 this is replaced with substance use disorder [APA, 2013]. Previous studies showed that half of the ADHD patients have a co-
morbid substance use disorder [Wilens et al., 2006a; Wilens and Morrison, 2011a]. Presence of ADHD increases the risk of smoking by at least 3 times as compared to the general population. Smoking usually begins at an earlier age and persists throughout life. It is more difficult to give up in ADHD cohort. Alcohol consumption is another common type of SUD in ADHD. In adolescents, alcohol abuse cases are seen most often with ADHD in clinical based studies. Children with ADHD who also have conduct and/or bipolar disorders co-occurring with ADHD seem to have the poorest outcome with respect to developing SUD [Brook et al., 2010]. Stimulant treatment was found to reduce the risk for SUD by 50% in ADHD [Farone, 2003]. This suggests that treatment for ADHD may itself reduce the long-term risk of developing SUD and thus highlights the importance of early recognition and treatment of ADHD.

1.7. Etiology of ADHD

Till date, no single etiological factor has been identified for ADHD and is consistent with the multifactorial hypothesis. The proposed etiological factors include brain damage, neurobiological, neurochemical, genetic and environmental factors which either singly or jointly may contribute to the pathophysiology of ADHD in different individuals.

1.7.1. Neurobiology of ADHD (Altered anatomy and function of the brain):

Though we still do not know the exact mechanisms underpinning ADHD, a variety of theories have been proposed. Brain damage was initially proposed as an initial and chief cause of ADHD symptoms [Still, 1902], either occurring as a result of known brain infections, trauma, or other injuries or complications occurring during pregnancy or at the time of delivery [Barkley, 2006a; Barkley & Peters, 2012]. Imaging studies have linked the condition with specific structures of the brain. Structural and functional imaging studies, involving functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), documented deficits in neural activity in the frontostriatal circuits in patients with ADHD [Dickstein et al., 2006]. There is also evidence that genes controlling dopamine (DA) pathway proteins are associated with
regional brain volume changes in the frontal lobe and caudate nucleus [Durston et al., 2005].

Fig. 1.1. Positron emission tomography (PET) scans showing differences in the nucleus accumbens, a part of the brain’s reward center, between ADHD and control subjects. [http://mybrainnotes.com/depression-adhd-ocd.html]

Several reports also suggest that ADHD children have reduced brain volume than the normal one [Castellanos et al., 1996b, 2001, 2002; Filipek et al., 1997; Kates et al., 2002; Mostofsky et al., 2002; Hill et al., 2003]; in ADHD patients the total cerebrum, particularly the right hemisphere is 3%–5% smaller. One study also reported reduced intracranial volume [Durston et al., 2004]. Smaller total gray and white matter in the brain has also been reported in ADHD probands as compared to control individuals [Castellanos et al., 2002; Mostofsky et al., 2002]. MRI reports of ADHD children identified smaller prefrontal volumes in areas corresponding to the dorsolateral prefrontal cortex (PFC), either in the right or left hemisphere, regions mainly involved in organization, planning, working memory, and attention processes [Castellanos et al., 1996b, 2001, 2002; Durston et al., 2004; Filipek et al., 1997; Hill et al., 2003; Hynd et al., 1990; Kates et al., 2002; Mostofsky et al., 2002]. A reduction in the right superior frontal gyrus volume was also reported [Overmeyer et al., 2001].
Automated, computational image analyses revealed reduced brain surface extent in the inferior portions of dorsolateral PFC bilaterally [Sowell et al., 2003]. Use of single-photon emission computed tomography (SPECT) and positron-emission tomography (PET), to estimate the blood flows in a child’s brain, showed lower than normal blood flow in brain areas already implicated in ADHD such as to the frontal area of the brain, particularly in the caudate nucleus- an important structure in the pathway between the most frontal portion of the brain and the structure in the middle of the brain known as limbic system [Barkley 2000]. This region is important in inhibiting behaviour and sustaining attention [Barkley 2000].

Neurotransmitters have been studied quite a bit in relation to psychology and human behaviour. There are several neurotransmitters which play a role in the way we behave, learn, the way we feel, and sleep etc. and, some play a role in mental illnesses. Dysregulation of different neurotransmitters are said to have a role in the etiology of ADHD. In the literature, dopamine (DA) and norepinephrine (NE) may be the most commonly studied neurotransmitters in regard to ADHD. Serotonin has also showed importance. These neurotransmitters affect signalling across the brain.
**Fig 1.3: 1.1** Diagram of the human brain showing the right hemisphere, and particularly the location of the caudate nucleus. (striatum), globus pallidus, and cerebellar vermis [Barkley, 1990].

**Fig 1.4:** Role of different neurotransmitters 

---

**Fig 1.4:** Role of different neurotransmitters 
Dopamine – Animal, genetic, as well as imaging studies suggest that dopamine plays an important role in regulating symptoms associated with ADHD [Konrad et al., 2003]. Altered function of DA neurons has been hypothesized as the main predisposing factor for ADHD [Oades et al., 2005]. The brain includes several distinct DA systems, one of which plays a major role in reward-motivated behaviour. Other DA systems are involved in motor control and in controlling the release of several important hormones. There are eight dopaminergic pathways, of which four are vital; these are:

(i) Mesolimbic pathway (ii) Mesocortical pathway (iii) Nigrostriatal pathway and (iv) Tuberoinfundibular pathway [Le Moal, 2013].

(i) **Mesolimbic pathway** – The mesolimbic pathway transmits DA from the ventral tegmental area (VTA) of the midbrain to the limbic system via the nucleus accumbens.

(ii) **Mesocortical pathway** – The mesocortical pathway transmits DA from the VTA to the frontal cortex.

(iii) **Nigrostriatal pathway** – The nigrostriatal pathway transmits DA from the substantia nigra to the striatum. This pathway is associated with motor control.

(iv) **Tuberoinfundibular pathway** – The tuberoinfundibular pathway transmits DA from the hypothalamus to the pituitary gland. This pathway influences the secretion of certain hormones, including prolactin.

DA can be synthesized from the essential amino acid phenylalanine or the non-essential amino acid tyrosine. These amino acids are found in nearly every protein and as such are provided from intake of protein-containing food, with tyrosine being the most common. Although DA itself is also found in many types of food, it is incapable of crossing the blood–brain barrier that surrounds and protects the brain. It must therefore be synthesized inside the brain in
order to perform its neural actions. In the first step L-Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase (TH), with tetrahydrobiopterin (THB) $O_2$, and ferrous iron ($Fe^{2+}$) as cofactors. L-DOPA is converted into DA by the enzyme aromatic L-amino acid decarboxylase (AAAD; also known as DOPA decarboxylase DDC), with pyridoxal phosphate (PLP) as the cofactor.

DA is formed in the dopaminergic neurons by the following pathway (Fig. 1.5):

$$
\text{L-Tyrosine} \xrightarrow{\text{Tyrosine hydroxylase}} \text{L-DOPA} \xrightarrow{\text{DOPA decarboxylase}} \text{Dopamine}
$$

**Fig. 1.5. Biosynthesis of DA from L-tyrosine.**

Existing evidences support a link between ADHD and the dopaminergic system which include:

1) **The neuropharmacology of stimulant medication used for treating ADHD**– For example, methylphenidate the most common psychostimulant used for treating ADHD mainly act on the dopaminergic system specifically by blocking the DA transporter [Amara and Kuhar 1993; Wender, 1998];

2) **Brain imaging studies** show changes in specific regions of the brain that are rich in dopaminergic innervations. In children with ADHD size of the PFC and basal ganglia are 5-10% smaller than in normal children [Zametkin and Liotta, 1998; Cheon et al., 2003];

3) **Studies using animal...**
model - Experiments on rats have shown lesions in the dopaminergic systems resulting in alterations in attention processing [Giros et al., 1996; Gainetdinov et al., 1999; Jaber et al., 1999; Russell 2000; Nieoullon, 2002]; 4) Molecular genetic studies - Molecular genetic studies support the involvement of the dopaminergic system genes. Most of these studies have been focused on the role of dopaminergic genes in clinical phenotypes and drug effects [Khan et al., 2006]. Together all these evidences implicate very strong role of DA and the dopaminergic system in the etiology of ADHD and thus this system is of immense importance to researchers for further exploration.

➢ Norepinephrine – Norepinephrine (NE) or noradrenaline is another important catecholamine with multiple roles including as a hormone and neurotransmitter which is released from the sympathetic neurons to affect the heart. As a stress hormone, NE affects parts of the brain, such as amygdala, where attention and responses are controlled [Tanaka et al., 2000]. Areas of the body that produce or are affected by NE are described as noradrenergic and the noradrenergic neurotransmitters exert their effect on alertness and influence the reward system. NE is synthesized from DA by the enzyme dopamine β-hydroxylase in the secretory granules of the medullary chromaffin cells (Fig. 1.6).

![Dopamine β-hydroxylase reaction](image)

**Fig 1.6. Synthesis pathway of NE from DA**

It is released from the adrenal medulla into the blood as a hormone, and is also a neurotransmitter in the central nervous system and sympathetic nervous
system, where it is released from noradrenergic neurons in the locus coeruleus. NE performs its action by being released into the synaptic cleft, where it acts on adrenergic receptors, followed by signal termination, either by degradation of NE or by uptake by surrounding cells. NE is released when a host of physiological changes are activated by a stressful event. NE, like DA, is recognized to have a role in the attention process [Berridge et al., 1993] and thus have also been proposed to play a key role in the pathophysiology and pharmacotherapy of ADHD [Zametkin and Rapoport 1987; Pliszka et al., 1996; Arnsten et al., 1996; Biederman and Spencer 1999]. The beneficial effects of NE may be especially relevant to medications used to treat ADHD to improve attentional, arousal, and cognitive processes. NE improves PFC function through actions at the post-synaptic alpha2A receptors. Amphetamine, a commonly prescribed medication used to treat ADHD, blocks NE transporters and thereby enhances catecholamine neurotransmission [Barkley, 1977]. For this reason, many molecular genetic studies have been focused on this system.

**Serotonin** – Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter primarily found in the gastrointestinal (GI) tract, platelets, and central nervous system (CNS) of animals including humans. It is thought to be a contributor to feelings of well-being and happiness [Young 2007]. In the CNS, 5-HT plays various functions including regulation of mood, appetite, cognitive functions including memory and learning as well as sleep. Modulation of 5-HT at synapses is thought to be a major action of several classes of pharmacological antidepressants. In the brain, 5-HT is mainly released from the neurons of the raphe nuclei, released into the space between neurons, and diffuses over a relatively wide gap (>20 μm) to activate 5-HT receptors located on the dendrites, cell bodies and presynaptic terminals of adjacent neurons. In humans, 5-HT is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC); TPH-mediated reaction being the rate-limiting step in the pathway (Fig.1.7) [Cote et al., 2003].
There is an abundance of evidence implicating a role for the serotonergic system in children with disruptive behavioural disorders such as ADHD, ODD and CD [Retz et al, 2004; Li et al, 2007]. Moreover an involvement of 5-HT and the serotonergic system in the pathophysiology of ADHD has also regained researchers’ interest, since there is an interaction between the dopaminergic and serotonergic neurotransmitter systems. It was suggested that 5-HT can modulate activity of DA and an alteration in serotonergic neurotransmission can also alter DA-mediated behaviour [Oades, 2008; Seo, 2008]. Further support for the 5-HT hypothesis come from the use of several 5-HT enhancing agents in the treatment of ADHD including selective serotonin reuptake inhibitor (SSRIs) [Barrickman et al., 1991; Quintana et al., 2007] and certain selective monoamine oxidase inhibitors [Ernst et al., 1997]. However, the relevance of 5-HT in ADHD needs to be further explored.
1.7.2. Genetic factors

Evidence for a genetic basis of ADHD stems from four sources: family studies of the aggregation of the disorder among biological relatives, adoption studies, twin studies, and, most recently, molecular genetic studies identifying individual candidate genes [Smith et al., 2009; Banaschewski et al., 2010; Wu et al., 2012]. Extensive family, twin and adoption studies suggest a strong genetic component associated with the disorder with a mean heritability estimate of 75-91%, however the exact cause of the disease still remains unknown [Levy et al., 1997; Faraone et al., 2005]. Family studies have also revealed that relatives of adopted children with ADHD are less likely to have the disorder [Alberts-Corush et al., 1986], while the biologic and first-degree relatives have a greater risk as compared to the controls [Biederman et al., 1990; Hudziak et al., 1998; Sprich et al., 2000]. Twin studies also provide evidence for a genetic contribution to ADHD. The most straightforward analysis of twin data involves a comparison of the rate of concordance for the disorder in pairs of monozygotic versus dizygotic twins; rate of concordance was significantly higher among monozygotic pairs (58% - 82%) than same-sex dizygotic pairs (31% - 38%) [Levy et al., 2001; Willcutt et al., 2000; Nikolas & Burt, 2010]. Another important source to establish the genetic influence in the disorder is the molecular genetic studies. The candidate gene approach investigates role of a specific gene in association with the disorder. Most of the medications used for the treatment of ADHD increase availability of catecholamines in the synaptic cleft, and therefore genetic association studies examining putative risk genes have mainly focused on genes of the catecholaminergic mainly DA and norepinephrine (NE) neurotransmitters systems. Published studies have tested for an association between ADHD and several different candidate genes such as the DA receptor 2 (DRD2), DA receptor 4 (DRD4), DA receptor 5 (DRD5) DA transporter (DAT), NE transporter (NET), DA β hydroxylase (DBH), Dopa decarboxylase (DDC), 5-HT transporter (5HTT), synaptosomal associated protein 25 (SNAP-25), catechol-o-methyl transferase (COMT) etc. [Comings et al., 2000; Faraone et al., 2005; Cheuk et al., 2006; Li et al., 2006; Smoller et al., 2006; Yang et al., 2007; Mick et al.,
2008a; Gizer et al., 2009; Das et al., 2011; Das Bhowmik et al., 2013] with promising results. Although the limited number of studies and inconsistency of results across samples preclude definitive conclusions at the present time, these studies clearly suggest that multiple genes are involved in the etiology of ADHD, and that few if any of these genes are necessary or sufficient to cause the disease.

1.7.3. Environmental factor

Many different environmental factors have been also reported to be associated with ADHD, but it has been difficult to identify which are definitely causal. Link between the mother’s exposure to different chemicals and occurrence of ADHD in their children have been observed [Jacobson et al., 2003; Ribas-Fito et al., 2007]. Smoking by pregnant women was reported to increase the risk of giving birth to an ADHD child [Langley et al., 2005a]. Similarly, maternal and paternal stress during pregnancy has also been found to be associated with ADHD in the offspring [Glover, 2011; Grizenko et al., 2008]. Although there are biologically plausible mechanisms through which these risks could lead to ADHD, it remains unclear whether or not the associations are causal [Thapar & Rutter, 2009]. In contrast to the risk of ADHD with prenatal nicotine exposure, the link between alcohol and ADHD is contradictory [Mick et al., 2002; Linnet et al., 2003]. Several other environmental factors, such as maternal pregnancy/birth complications, intrauterine growth retardation and low birth weight/prematurity etc. have also been identified as risk factors for ADHD [Pineda et al., 2007; Strang-Karlsson et al., 2008; Bhutta et al., 2002]. Beside the prenatal environmental factors, early postnatal environmental influences related to ADHD or ADHD core symptoms include neonatal anoxia and seizures, brain injury, exposure to lead [Aguirre et al., 2007; Nicolescu et al., 2010]. Some studies also suggest that psychosocial adversity and high levels of family conflict were associated with ADHD [Biederman et al., 1995; Ellis and Nigg 2009].
1.8. Treatment of ADHD

Pharmacotherapy as well as psychosocial interventions or a combination of these two are mentioned as a valid treatment option by all ADHD clinical guidelines [AAP, 2011; Taylor et al., 2004; Kutcher et al., 2004; NICE, 2009; CADDRA, 2011, Wilens 2011b]. A variety of psychosocial treatment interventions for ADHD may be beneficial, including behaviour modification, parent training, and social skills training. These interventions may be school or home-focused but should provide consistency throughout in their approach. In general, techniques that use reward systems and consequences for failure to meet goals appear most effective. Since most ADHD children have co-morbid disorders, combination of different treatment modalities is usually indicated [Taylor et al., 2004; AAP, 2011]. When drug treatment is considered appropriate for the patient, the central nervous system stimulants and non-stimulant medications are recommended [NICE, 2006; NICE, 2008], both being affective in improving the core symptoms.

- **Stimulants**- To control the behavioural symptoms of majority of children with ADHD, psychostimulants (methylphenidate (MPH), amphetamine (AMP), dextroamphetamine, pemoline) are the most common medications; in approximately 70% of the children with ADHD, treatment with stimulants improve symptoms of hyperactivity, impulsivity, and inattention [Spencer et al., 1996; Wilens and Spencer 2000]. In addition to improving core symptoms of ADHD, stimulants also improve associated behavioural problems, including on-task behaviour, academic performance and social functioning on a short term. Stimulants have been shown to increase intra synaptic concentrations of DA and NE [Solanto et al., 2001; Wilens 2008]. Therapeutic effects of MPH appear to be elicited primarily by blocking the reuptake of DA by binding to the DAT on the presynaptic membrane, with a minor influence on NET [Volkow et al., 2001; Volkow et al., 2002]. On the other hand AMP, another common stimulant, diminish presynaptic reuptake of DA, taken into the DA neuron and facilitate the release of DA from vesicles into the cytoplasm, prevent reuptake...
from the cytoplasm into the vesicles and are associated with the release of more DA from the presynaptic neuron [Wilens 2008]. Although different studies consistently demonstrate the response rate of ADHD children to stimulants of approximately 70%, it has been variable in adults [Spencer et al., 1995; Adler et al., 2009b]. The side effects of the stimulants in ADHD adults have been reported to be generally mild to moderate, such as dry mouth, insomnia, edginess, diminished appetite, weight loss, dysphoria, obsessiveness, tics and headaches. Stimulant-related psychosis at therapeutic doses has not been reported in adults during clinical trials [Timothy et al., 2011; Graham et al., 2011]. However, the cardiovascular effects of stimulants across the lifespan is also debated and the results are inconsistent [Nissen, 2006; Wilens et al., 2006b; Vetter et al., 2008; Perrin et al., 2008; Olfson et al., 2012].

- **Noradrenergic agents-** Atomoxetine (ATX) is a very common noradrenergic medication for treating ADHD and was the first medication approved by the US FDA for specifically treating adults [Michelson et al., 2003; Levin et al., 2006]. ATX specifically inhibits presynaptic NE reuptake, increasing synaptic NE and DA [Bymaster et al., 2002]. ATX is rapidly absorbed following oral administration and food does not appear to affect absorption. In addition to the treatment of both inattention and hyperactivity/impulsivity in adults with ADHD, ATX may be particularly useful when ADHD is associated with co-morbid anxiety, mood, substance abuse or tic disorder [Wilens et al., 2008; Adler et al., 2009a]. The most common side effects observed with the use of ATX include dry mouth, insomnia, nausea, decreased appetite, increase in heart rate, constipation, decreased libido, dizziness, abdominal pain, and sweating [Michelson et al., 2003].

- **α-agonists-** The FDA-approved α-adrenergic agonists clonidine and guanfacine have been used in childhood ADHD, particularly in those cases with a marked hyperactive or aggressive component [Connor et al., 1999]. Although forms of both clonidine and guanfacine ER are now FDA approved for the treatment of children with ADHD, they are not approved in the treatment of adults with ADHD. It has central actions on either pre- or postsynaptic alpha 2
receptors. The most common side effects are dry mouth, dizziness, constipation, sedation, hypotension, nervousness, nausea/vomiting.

*Antidepressants*- Bupropion is an antidepressant which has mixed catecholaminergic effects and has been reported to be moderately helpful in reducing the symptoms in children with ADHD [Casat et al., 1987]. Bupropion may be helpful in ADHD, particularly when associated with co-morbid depression [Daviss et al., 2001], substance abuse [Levin et al., 2002; Wilens et al., 2010] or bipolar disorder [Wilens et al., 2003]. The monoamine oxidase inhibitor (MAOI) is another antidepressant used for the treatment of ADHD which reduce the impulsivity and inattention seen in adults with ADHD [Wender et al., 1985].
1.9. Objective of the present study

ADHD is a common cognitive and behavioural disorder. Children with ADHD have elevated problems in many areas, including academic performance, behavioural problems etc. and if remain untreated, these symptoms are also found in adulthood and their social and family relationships are negatively affected [Currie and Stabile, 2006; Strine et al., 2006]. Studies also showed that in presence of different ADHD associated co-morbidities these functioning in social and educational domains become poorer [Bowen et al., 2008; Hurtig et al., 2007; Nijmeijer et al., 2008; Spencer, 2009]. So management of ADHD is very important and researchers have also found great interest to study on this disorder. As it is a complex disorder which typically results from multiple interacting genes and also is one of the most heritable psychiatric disorder [Faraone et al., 2005] there are several association studies on different genes (DRD2, DRD4, DRD5, DAT, NET, COMT, DBH, DDC, etc.) of catecholaminergic system in different population [Comings et al., 2000; Faraone et al., 2005; Cheuk et al., 2006; Li et al., 2006; Smoller et al., 2006; Yang et al., 2007; Mick et al., 2008; Gizer et al., 2009]. These previous studies suggest that many genes are involved in ADHD and that each of which have small but significant effects. This justifies the rationale for doing genetic studies on ADHD subjects.

Objective of the present study was to explore the association of the polymorphisms in the genes such as DRD2, DRD4, DAT, NET, COMT and DBH with ADHD as well as its associated co-morbid characteristics in the eastern Indian population. Successful outcome of the proposed study will lead to better understanding of the disease condition and therefore may lead to better management of the sufferers of the disorder.