



# **Review of Attention Deficit Hyperactivity Disorder (AD/HD) and the Medications Used for AD/HD**

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# **ATTENTION DEFICIT/HYPERACTIVITY DISORDER**

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## **Lecture Outline**

- 1. Historical Note**
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  - c. History of Treatment Studies
  
- 2. Clinical Description of Disorder**
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Neurologic or Medical Disorders  
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- 11. Psychiatric Status**
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## **Use of Medications for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) by H. Quintana, M.D.**

### **Introduction and Background--The body of knowledge or what we know about Attention Deficit Hyperactivity Disorder**

Hyperactive children have been described in the medical literature for many years—its first medical description was in 1902 (Ross & Ross, 1982). However, its appearance in children's literature it can be found even earlier for example a child with hyperactivity is described in the nursery rhyme about Fidgety Phil (who couldn't sit still). Children with this disorder have been labeled as hyperkinetic, hyperactive, Minimal Brain Damage, Minimum Brain Dysfunctional, attention deficit disorder (ADD) and now, according to most recent diagnostic terminology as Attention Deficit/Hyperactivity Disorder. Despite the various names, mental health professionals are in agreement about that regardless of the name or label you give this problem, this disorder has a group of key symptoms—hyperactivity, short attention span, distractibility, impulsivity, defiance, and learning problems. Although these various problems may vary in degree of severity, children with this set of problems have significant difficulties at school, with peers and at home.

In the 1960's, many researchers became particularly preoccupied with hyperactivity, however, during this time, the terminology of this disorder and mental health disorders in general were so confused and chaotic. Therefore, there was some major effort made to develop a unified diagnostic manual. However, it was not until 1980 when the Diagnostic Statistical Manual of mental disorders III came out that some semblance of order and general consensus. The more recent DSM--- DSM IV, released in 1994 has further improved on diagnostic criteria and our overall knowledge of this and other mental health disorders (APA, 1994). There maybe a genetic basis or strong family pattern in at least some children with the hyperactivity syndrome. There are many attempts to find a biochemical basis but a unifying theory has not been emerged. Biochemical bases (genetic, food hypersensitivity, environmental toxicity) have been suggested. Gross structural diseases of the cerebrum or cerebellum, as well as structural alterations of the brain by trauma, epilepsy, or infections like encephalitis can lead to the hyperactive syndrome as complication.

According to the current Diagnostic and Statistical Manual of Mental Disorders, version IV, the Disruptive Disorder category includes Attention Deficit/Hyperactivity Disorder (ADHD) which is divided into Inattentive type, hyperactive-impulsive type, and the combined (or mixed type), Oppositional Defiant Disorder and Conduct Disorders. In this chapter, we will focus our discussion to ADHD.

Attention Deficit/Hyperactivity Disorder is known to occur in various cultures, with some variations reported in prevalence among Western countries probably arising more from different diagnostic practices than from different clinical presentation (APA, 1994). The prevalence in the United States of ADHD is estimated at 5% - 8% in children. The data on the prevalence of in preschool-age, adolescent and adults are limited.

Therefore according to DSM-IV, the key defining symptoms of the disorder are hyperactivity, inattention, and impulsivity. It is a disorder that can present itself at any age, most of the research done has been on elementary school children-6-10 years of age (Barkley, 1991; McGee et al., 1991). It is a disorder that most have its onset before the age of 7 and have lasted for at least 6 months. This disorder usually peaks between the ages of 7-9 years. ADHD almost always begins in infancy as early as when the child begins to walk—the severely hyperactive child will usually be easily identifiable. This disorder is considered to be life-long with a number of children and adolescents continuing with some of the symptoms of this disorder into adulthood. The differences in presentation between preschoolers and high school children with ADHD may vary quite markedly. The syndrome is most difficult to define in infancy-preschool age group and in adolescents. Studies have reported that in general often referred to as hard to manage preschoolers (Campbell et al., 1986), at least one third have no difficulties in school whereas the remainder have ADHD, conduct disorder or other disorders. Therefore, sometimes the problem of over diagnosis may be a problem in the preschool group.

Most parents first observe high levels or excessive motor activity when the children are toddlers, frequently children with hyperactivity will exhibit this with the development of independent locomotion. However, despite these high activity levels many overactive preschoolers will not go on to develop Attention Deficit/Hyperactivity Disorder. More typically the disorder is first diagnosed during elementary school years, when school adjustment becomes affected. Generally, the disorder remains fairly stable through early adolescence. In most individuals, the symptoms of ADHD may become modified in adolescence and adulthood. Usually the hyperactivity may lessen and the inattention problems persist or the impulsiveness causes numerous problems for the adolescent and his/her parents. Current reports inform us that 65% of children who ADHD in childhood will exhibit ADHD symptoms in adolescence and that 60% of adolescence will go on to exhibit symptoms of ADHD in adulthood. In other words, this means that approximately 1/3 (or more exactly 35-39%) of children with ADHD will have symptoms in adulthood which are consistent with ADHD.

Unlike the potential danger for over diagnosis in the preschool group, in adolescents we sometimes have the opposite problem. For many years, it was believed that the disorder was gone by the time the child reached adolescence. More recent studies and reports consistently show that many clinic children with ADHD still have significant symptoms of ADHD adolescence. The interesting fact is that the Adolescents ADHD symptoms must be looked for specifically because the face of adolescent has changed from that of the child with ADHD. For example, symptoms move away from the hyperactivity symptom to more attentional and impulsive type problems. Furthermore, adolescents may have a number of associated problems such as poor motivation, demoralization, risk-taking behavior, and involvement in delinquent activities. Certainly these associated features may make it hard to recognize the potential long-term effects and presence of ADHD in this group. Also, other influences may relegate the possible recognition of ADHD as an underlying problems in adolescents because violence,

sexual, and drug problems may take the forefront. Nevertheless, ADHD persists or occurs in adolescence, however, it is more likely to be masked in adolescence.

Whereas hyperactivity, inattention, and impulsivity form the core or essential symptoms, others are found often enough to be part of the usual clinical picture. These include conflict with authority, antisocial, delinquent and substance abuse, learning problems, poor peer relations, lack of persistence and motivation. In preschoolers, particularly in those whose problems continue, is the conflict between primary caretaker (usually the mother) and child in which each seems to provoke negative responses from the other (Barkley, et al., 1990; Campbell, et al., 1985; Campbell, Ewing, 1990). This pattern may continue into childhood, though as with normal children, the level of compliance does improve with increasing age (Barkley, 1985). In adolescence the pattern may continue but takes the form of oppositional defiant disorder. As the child grows from child to adolescent, the range of authority figures in his life widen to include others such as teachers and other adults.

Let me elaborate on ADHD associated symptoms of learning problems, peer relations and lack of persistence and motivation. Learning problems are a common complaint in ADHD (Barkley, Anastopoulos, et al., 1991; Schachar, 1991) and may exacerbate the symptoms of ADHD. In early childhood, you may see developmental problems such as language delay and some other general delays that make the child look as less advanced than his/her siblings or other same-age peers. The problem that may at first be considered as part of the child's poor or short attention span, in late childhood and adolescence this may result in repetitive complaints of motivation and underachievement. Generally, the group of children with ADHD and learning problems by late adolescence are experiencing repeating grades, suspension, truancy and dropping out as common problems.

At least 50% of hyperactive have problems with their peers (Barkley, Fischer, Edelbrock et al., 1990). These problems include not understanding or following rules, monopolizing the game, changing activities, over-controlling behaviors and boisterousness (Weiss, Hechtman, 1986). Whatever the cause rejection by peers may be rapid and is often the result. The child with ADHD may have developmentally immature behavior and therefore the child may resort to making friends with younger or developmentally disabled children. By adolescents, these peer problems may have become compounded by years of difficulty with peers to frank outsider status (Barkley, Fischer, Edelbrock, et al., 1990). It is important to mention that not all children with ADHD have peer relationship difficulties and if they do these are of varying degrees—from minimal or mild to moderate to severe. It is likely that the parent-child conflict, family break-up, and parental psychiatric problems will add to ADHD related interpersonal skill difficulties.

Children and adolescents with ADHD are often found and reported to experience a lack in motivation or giving up easily, and this trait has been well demonstrated (Milich et al., 1991; Milich, Okazaki, 1991). It is not clear that to what extent this behavior is due to

ADHD or to the effects of chronic demoralizing or learned helplessness as a result of many years of academic failure/frustration.

An additional problem that we have become increasingly aware of is the fact that an uncomplicated ADHD is many times the exception rather than the rule. In recent years, evidence has accumulated of high levels of co-morbidity between attention deficit/hyperactivity disorder (ADHD) and a number of disorders including mood and anxiety disorders as well as conduct disorders (Biederman et al., 1991). For example, anxiety can occur in up to 32% of cases of ADHD, depressive disorders can occur in up to 18% of cases with ADHD, and conduct disorder can occur in 5-7% of patients with ADHD. The causes of comorbid disorders in children with ADHD remains unknown. If not recognized or attended to, the Comorbidity that they are manifesting may not be benign and may in fact jeopardize a successful treatment outcome. If not recognized and attended to, the combination of comorbid symptoms and ADHD may lead to high morbidity and disability with poor long-term prognosis.

In summary, ADHD changes shape and presentation from preschool through adolescence as the growing child develops. With increase development the trends are toward more self-control, more internal reflective behavior, and a diminution of motor behavior. The face of these children with ADHD maybe effected by the changing expectations of the family and the educational and social environment. Like most early onset disorders ADHD has a tendency toward spontaneous improvement. The spontaneous improvement may occur in those areas ordinarily subject to considerable developmental improvement such as activity level and impulsivity. Consequently, attention-cognition is a skill that grows with age, and these problems can persist as the fundamental effect in ADHD which will cause long term negative effects on academic achievement, work and even peer relations. Therefore, the core symptoms usually evolve with predictably with development, but along the way they may cause demoralization, poor self-image, and rejection by caretakers and peers. Although, the core symptoms are characteristic, their severity and their pattern are highly variable across individuals. The associated symptoms also vary greatly. Therefore, because of all these factors, the evolution of the syndrome from infancy to adolescence takes on more and more individualized shape—or many faces. Many children with ADHD have comorbid disorders, notably anxiety, depression or conduct disorder or learning disorder. Much of what passes for the evolution of symptoms of ADHD into adolescence is in fact contributed to these overlooked disorders.

## Historical Overview of Childhood and Adolescent Psychopharmacology

- 1930 - Use of psychoactive medication for the treatment of childhood psychiatric disorders began with Benzedrine during the 1930s.
- 1950s - Little was added until the onset of the “Biological revolution” in psychiatry beginning in the 1950s.
- 1950s/1960s Progressively increasing reports of efficacy for antipsychotic, antidepressant, minor tranquilizers, and stimulant medication for a wide variety of childhood disorders. \*

\* Almost without exemption the interpretation of the results reported in these studies is compromised by methodological limitations. These included diagnostic heterogeneity, the absence of a standardized diagnostic classification system, inadequate attention to control groups, absence of double-blind procedures, the unavailability of standardized assessment instruments, and variable dosage schedules.

*Evidence was accumulated for the efficacy of drugs in certain childhood disorders:*  
 -- Stimulants for hyperactive children  
 --antidepressants imipramine for enuresis  
 --antipsychotic medication for psychosis and aggressive behaviors in children and adolescents, and early reports on depression in children.

- 1970s - During the 1970s several major changes occurred to dramatically affect the field of the childhood psychopharmacology:
- Development of a number of reliable assessment instruments.
  - Increase knowledge of pharmacokinetics of psychoactive medications
  - Growing attention to and concern about immediate and longer term adverse effects of medications.
- 1980s - Introduction and gradual acceptance by 1980 of agreed upon by diagnostic criteria for psychiatric disorders (RDC and DSM-III:
- 1980s/1990s Midways into the 1980s, the field of childhood psychopharmacology is actively exploring the indications, contraindications, efficacy, pharmacokinetics, and adverse effects of several groups of drugs: stimulants, antidepressants, antipsychotics, lithium, anticonvulsants (carbamazepine), and benzodiazepines. Dosage and plasma/levels relationships.
- Since 1998 FDA determination that any medications that can be used in children and adolescents must be tested/studied in order to demonstrate for their safety and effectiveness in children and adolescents.
- 2000s Demonstration of safety and effectiveness of a number of medications shown to be effective in adult psychiatric disorders to child and adolescent age group. Concurrently studies are underway in refining the reliability and validity of diagnostic criteria, assessment instruments, the genetics of childhood and adolescent disorders and the comparative efficacy of different treatment approaches.

For the coming decade new drugs will be developed for the treatment of psychiatric conditions and existing drugs will be studied in order to determine their safety and effectiveness for child and adolescent psychiatric disorders.

## Use of Medications in ADHD

**Background:** Prevalence of ADHD in Child and Adolescents varies according to diagnostic criteria used and the population sampled. However, according to DSM IV the prevalence of ADHD is as follows:

**Prevalence:** **ADHD in general US population: 3% to 5%**  
**(Other estimates vary from 1.7% to 16%)**

**Risk Factors:**

**Boys compared to girls—ratio 3:1 to 4:1**  
**DSM IV widened diagnostic groups to include patients with inattention.**

**Prognosis:**

**More than 65% of children may continue to meet criteria for ADHD in adolescents**

**Up to 65% of adolescents may continue to meet criteria for ADHD in adulthood. Therefore, approximately 42% of adolescents will continue to have symptoms of ADHD in adulthood.**

**ADHD outcomes**

- **9 fold increase in antisocial behavior)**
- **4 fold increase in substance misuse disorder)**

## ADHD Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common child behavioral disorders treated by pediatricians, family practice physicians, pediatric neurologist, psychiatrist, and child and adolescent psychiatrist. It is among the most commonly written about disorders— as many as 400 journal articles are written per year on ADHD.

ADHD appears to affect from 4% to 12% of school-age children in the United States and is 3-5 times more common in males than females. A significant number of children diagnosed with ADHD will carry symptoms into adulthood and may be at increased risk for developing conditions such as antisocial and drug abuse disorders.

Complicating matters even more is that fact that we now know that rather occurring alone, ADHD often is accompanied by a number of associated diagnosis. Therefore, our increasing recognition of the associated comorbidities seen with ADHD often makes the diagnosis and treatment of ADHD more complicated.

There are three subtypes:

- Predominantly hyperactive/impulsive
- Predominantly inattentive; and
- Combined.

The core symptoms of ADHD are inattentiveness, hyperactivity, impulsivity, and distractibility. In addition meeting diagnostic symptom criteria for ADHD disorder requires:

- ✓ Onset before the age of 7.
- ✓ Symptoms evident in at least two settings (example, home, school or environment).
- ✓ Symptoms present for at least 6 months.
- ✓ Significant impairment in social, academic, or occupational functioning.

The American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry have developed clinical practice guidelines for the diagnosis and treatment of childhood ADHD, including evaluation by a physician, use of diagnostic criteria from DSM IV, collection of information from parents and teachers, and assessment of co-existing conditions.

There current evidence that ADHD can have a strong negative impact on the child's family and future development. These children have greater behavioral, social, family, and academic difficulties, when compared with those without ADHD. In addition, there is increased risk that their siblings will develop mood and behavior disorders.

The National Institute of Mental Health Collaborative Multi-site Multimodal Treatment Study of Children demonstrated that comprehensive medication management , was the most effective treatment for symptom reduction in these children. Since pharmacotherapy can be such a useful intervention for young patients, it is important that clinicians become familiar with the new developments in the field.

**General symptoms of ADHD**

1. Being fidgety or restless.
2. Unable to sit still for a long time—always on the go.
3. Easily distracted, cannot concentrate well on work.
4. Acting before thinking (impulsivity).
5. Forgetting what was said or not listening.
6. Difficulty finishing work on time.
7. Often losing personal things.
8. Difficulty waiting in lines—jumping ahead of others.

**ADHD According to DSM IV:**

- ADHD HI type requires that six out of nine items related to hyperactivity and impulsivity
- ADHD-C requires that patient score above cutoff on both inattention and hyperactivity impulsivity.
- DSM IV has had a profound influence on practice in the last 5 years, resulting in an increase in prevalence, a broadening of the disorder to include more girls, preschoolers, and adults, influencing pattern of comorbidity.
- It increased the prevalence of ADHD by more than 50%.

**ADHD inattentive type—more specific symptoms.**

1. Six or more of the symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.
  - a. Fails to give close attention to details or makes careless mistakes in school work.
  - b. Difficulty sustaining attention in tasks and play activities
  - c. Does not seem to listen when spoken to directly
  - d. Does not follow instructions and fails to finish school work.
  - e. Often has difficulty organizing tasks and activities
  - f. Avoids or is reluctant to engage in activities that require sustained mental effort
  - g. Losses things necessary for task
  - h. Is often easily distracted by extraneous stimuli
  - i. Often forgetful in daily activities
2. Six or more of the following symptoms of ADHD hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.
  - a. Often fidgets with hands or feet or squirms in seat.
  - b. Often leaves seat in classroom or in other situations in which remaining seated is expected.
  - c. Often runs about or climbs excessively in situations in which it is inappropriate
  - d. Often fidgets with hands or feet or squirms in seat.
  - e. Often leaves seat in classroom or in other situations in which remaining seated is expected.
  - f. Often runs about or climbs excessively in situations in which it is inappropriate
  - g. Has difficulty playing or engaging in leisure activities quietly
  - h. Is often “on the go” or often act as if driven by a motor
  - i. Often talks excessively

**ADHD Impulsivity**

- k. Often blurts out answers before questions have been completed
- l. Often has difficulty awaiting their turn
- m. Often interrupts or intrudes on others

**Associated features of ADHD-- Cognitive, Emotional & Social problems:**

- 65 % of children go into adolescents with persistent symptoms of ADHD (usually hyperactivity has decreased).
- 60-65% of adolescents go into adulthood with symptoms of ADHD.
- 

**It Ain't All ADHD: Differential Diagnosis—key clinical issues to be taken into consideration:**

- Physical causes, Sleep disorders, Excessive anxiety, & depression
- Specific learning or language disorder
- Child Abuse and or chaotic home
- Oppositional defiant disorder or Conduct disorder

**Table 1 List of Class of Drugs and Drugs used to Treat Attention Deficit/Hyperactivity Disorder**

<b>Chemical Class</b>	<b>Agent</b>	
<b>Psychostimulants</b>	<b>Amphetamine and related drugs Dexmethylphenidate</b>	<b>Dexedrine Dexedrine Spanules Adderal Adderal XR</b>
	<b>Methylphenidate related drugs</b>	<b>Methylphenidate (MPH) generic Ritalin Ritalin SR Ritalin LA Concerta Methadate Focalin</b>
	<b>Other Psychostimulants Magnesium Pemoline</b>	
<b>Selective norepinephrine Reuptake inhibitor</b>	<b>Atomoxetine HCL</b>	
<b>Adrenergic Agent</b>	<b>Clonidine Guanfacine (Tenex)</b>	
<b>Antidepressant</b>	<b>Bupropion (Wellbutrin)</b>	
	<b>Tricyclic agents Imipramine Nortriptyline</b>	
<b>Dopaminergic Agents</b>	<b>Modafinil</b>	

## Clarification of Dosing of Medication—Table 1 and Table 2

1. Treatment is started at low doses and gradually increased over several days; initial improvement noted may plateau after two to three weeks of continuous use—this does not imply tolerance. Patients should compare the plateau to their baseline, not to the peak effect seen in the first week, as otherwise there will be an urge to increase the dose.
2. Divided doses required with regular preparations of methylphenidate (dose every 2 to 6 hours).
3. Methylphenidate SR has a smoother onset, but no advantage in duration of efficacy over regular tabs.
4. Extended release, sustained release, or controlled release formulations may decrease inter-dose dysphoria or wearing off effects (rebound hyperactivity).
5. Combination of amphetamine and dextroamphetamine salts in Adderal provides a graded onset and duration of action; this may offer a smoother delivery of drug.
6. Recommendations regarding the Switching Formulations from a methylphenidate to amphetamine sulfate or visa versa.
  - MPH to MPH SR 10 mg bid= 20 mg SR
  - MPH to extended release MPH: 10 mg bid = 18-20 mg of extended release tablet or capsule in AM.
  - MPH to Dextroamphetamine: 5 mg bid = 2.5 mg bid dexmethylphenidate.
7. The core agent in most of the Psychostimulants, methylphenidate and amphetamine sulfate, have been in use over 50 years for the treatment of attention deficit/hyperactivity disorder. They have been repeatedly demonstrated to be safe, however, a number of side effects or adverse effects are commonly reported including: Insomnia, Appetite suppression, anxiety-agitation, dysphoria and rebound phenomenon. At high doses episodes of amphetamine induced psychosis and hypomanic/manic episodes have been reported.

**Table 2A: Comparison of Psychostimulant Medications Used for the Treatment of ADHD symptoms.**

<b>Stimulant Short-Acting Medications</b>			<b>Extended Release/Long Duration Stimulant Drugs</b>		
<b>Drug</b>	<b>Onset of Action/Peak Duration of Effects</b>	<b>Suggested Doses</b>	<b>Drug</b>	<b>Onset of Action/Peak/Duration of Effects</b>	<b>Suggested Doses</b>
<b>Immediate Release Preparations</b>	<b>Agents w/3-6 hr. duration</b>		<b>Second Generation Extended release</b>	<b>Agents w 8 hr. duration</b>	
Methylphenidate (Ritalin, Methylin, Metadate)	Onset: 20-30 min. Peak: .3-4hr Duration: 3-6 hrs.	10 mg bid/tid to increase 10 mg q week to 1-2 mg/kg/d	Methylphenidate Metadate CD,	Onset: 30 min-2 hr Peak: Bimodal Duration: 4-6 hrs	20 mg qd, increase wkly until target range of 1-2 mg/kg/d
D-amphetamine (Dexedrine, Dextrostat) Onset: 20-60 min.	Peak: 1-2hr Duration: 4-6 hrs	5 mg bid/tid increase 5 mg q week to 0.5 mg to 1.0 mg/kg/d	Ritalin LA)	Onset: 30min-2 hr Peak: Bimodal Duration: 4-6 hrs	< 6 years: 20 mg qd, increase by 10 mg at ≥ 1 wk to target of 1-2 mg/kg/d >6 20 mg qd w/increase by 10 mg at intervals ≥ 1 wk to target 1-2 mg/kg/d
D-L amphetamine (Adderal)	Onset: 30-60 min. Peak: 1-2hr Duration: 4-6 hrs	5-10 mg bid with increases 5-10 mg q week to 0.5 mg to 1.0 mg/kg/d			
<b>First-generation Sustained release Preparations</b>	<b>Agents w/5-8 hr. duration</b>	(older delivery Systems)	<b>Agents with a 10-12 hr Duration</b>		
Methylphenidate (Ritalin SR, Metadate ER, Methylin ER)	Onset: 60-90 min. Peak: 1.3-8.2 hr Duration: 5-8 hrs		Methylphenidate (Concerta)	Onset: 30 min.-2 hr Peak: Bimodal Duration: 12 hrs.	< 6 years: 18 mg qd, increase >1 wk until target range of 0.5-1mg/d. > 6 years: 36 mg qd, increase >1 week until target range 1-2mg/kg/day reached.
D-amphetamine (Dexedrine Spanules)	Onset: 30-90 min. Peak: N/A Duration: 6-8 hrs		D, L amphetamine (Adderal XR)	Onset: 1-2 hrs. Peak: Bimodal Duration: 10-12 hrs.	< 6 yrs. 18 mg/d > 6 yrs. 36 to target dose of 1-2 mg/kg/d

**Table 2B Approximate Dosage Strengths for Concerta and Adderal**

<b>Concerta</b>	<b>Adderal XR</b>
<b>27 mg</b>	<b>10 mg</b>
<b>54 mg</b>	<b>20 mg</b>
<b>72 mg</b>	<b>30 mg</b>
<b>108 mg</b>	<b>40 mg</b>
<b>144 mg</b>	<b>60 mg</b>

**Table 3 - Guidelines for monitoring of the Medication used to treat ADHD**

Stimulant Medication	Half-life	Pre-Med	Precautionary Lab. Tests	Dosage	Dose Range	Wkly/visit	Labs/other tests	Side Effects
<b>Methylphenidate (Ritalin reg. &amp; SR, Ethylene &amp; ER – sustained release.</b>	<b>Regular 4-6 hr</b>	<b>BP/HR-Wt./Ht.</b>	<b>ECG/ CBC * 60 mg. max.</b>	<b>5,10, 20 bid</b>	<b>0.3-1.5-2.0 mg/kg/dose</b>	<b>Wt/Ht &amp; BP/HR</b>	<b>BP/HR/wt/ht Dose Adjustments</b>	<b>↓ Appetite Insomnia</b>
Concerta (Osmotic controlled release tablets)	8-12 hrs.	BP/HR Wt./Ht.	ECG/ CBC *	18 -54 mg	0.3-1.5-2.0 mg/kg/dose	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia (Less dysphoria or rebound)
Metadate ER or Methylene ER (Sustained release)	8-12 hrs	BP/HR Wt./Ht.	ECG/ CBC *	10, 20 mg	0.3-1.5-2.0 mg/kg/dose	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia <dysphoria or rebound)
Metadate CD (extended release)	8-12 hrs	BP/HR Wt./Ht.	ECG/ CBC *	20, 30, 40 mg	0.3-1.5-2.0 mg/kg/dose	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia
Ritalin LA (extended release capsule)	8-10 hrs	BP/HR Wt./Ht.	ECG/ CBC *	20,30 & 40 mg.	0.3-1.5-2.0 mg/kg/dose	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia <dysphoria or rebound)
Dexmethylphenidate (Focalin-4-6 hr ½ life)	Regular 4-6 hr	BP/HR Wt./Ht.	ECG/ CBC *	2.5, 5, & 10 mg	0.3-1.5-2.0 mg/kg/dose	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia
<b>Dextroamphetamine (Dexedrine, Spanules &amp; Dextrostat,</b>	<b>Regular 4-6 hrs.</b>	<b>BP/HR-Wt./Ht</b>	<b>ECG/ CBC *</b>	<b>Age 3-5, 2.5mg qd/ 6 &gt; 5mg qd</b>	<b>.15-1.0 mg/kg/dose Max. 40mg</b>	<b>Wt/Ht &amp; BP/Pulse @ visit</b>	<b>BP/HR/wt/ht Dose Adjustments</b>	<b>↓ Appetite Insomnia</b>
Dextroamphetamine/ Amphetamine salt	Regular 4-6 hrs.	BP/HR Wt./Ht.	ECG/ CBC *	Same	Same	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia
Adderal	Regular 4-6 hrs.	BP/HR Wt./Ht.	ECG/ CBC *	Same	Same	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia
Adderal XR (Extended Release)	8-10 hrs	BP/HR Wt./Ht.	ECG/ CBC *	Same	Same	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia (Less
Methamphetamine (Desoxyn)	Regular 4-6 hrs.	BP/HR Wt./Ht.	ECG/ CBC *	Same	Same 5 mg tablets	Wt/Ht & BP/Pulse @ visit	BP/HR/wt/ht Dose Adjustments	↓ Appetite Insomnia
Magnesium Pemoline (Cylert) (Chewable tablet)	12-24 hours	BP/HR/ Wt./ CBC/LFT /ECG	Not used due to hepatotoxicity	37.5 mg qd: Max. 112.5 mg	0.5-2.0 mg/kg/dose	Wt/Ht & BP/Pulse @ visit	LFT :q3m & yrly CBC/WBC/L FT And ECG	↓ Appetite Insomnia Hepatotoxicity

*Note \*: For any of the Psychostimulants if there is a history of Cardiovascular problems or a history of Cardiovascular problems (i.e., heart murmur etc) an ECG is recommended before start of medications*

## Clarification of Dosing of Medication—Table 3 and Table 4

1. Treatment is started at low doses and gradually increased over several days; initial improvement noted may plateau after two to three weeks of continuous use—this does not imply tolerance. Patients should compare the plateau to their baseline, not to the peak effect seen in the first week, as otherwise there will be an urge to increase the dose.
2. Divided doses required with regular preparations of methylphenidate (dose every 2 to 6 hours).
3. Methylphenidate SR has a smoother onset, but no advantage in duration of efficacy over regular tabs.
4. Extended release, sustained release, or controlled release formulations may decrease inter-dose dysphoria or wearing off effects (rebound hyperactivity).
5. Combination of amphetamine and dextroamphetamine salts in Adderal provides a graded onset and duration of action; this may offer a smoother delivery of drug.
6. Recommendations regarding the Switching Formulations from a methylphenidate to amphetamine sulfate or visa versa.

MPH to MPH SR 10 mg bid= 20 mg SR

MPH to extended release MPH: 10 mg bid = 18-20 mg of extended release tablet or capsule in AM.

MPH to Dextroamphetamine: 5 mg bid = 2.5 mg bid dexmethylphenidate.

7. The core agent in most of the Psychostimulants, methylphenidate and amphetamine sulfate, have been in use over 50 years for the treatment of attention deficit/hyperactivity disorder. They have been repeatedly demonstrated to be safe, however, a number of side effects or adverse effects are commonly reported including: Insomnia, Appetite suppression, anxiety-agitation, dysphoria and rebound phenomenon. At high doses episodes of amphetamine induced psychosis and hypomanic/manic episodes have been reported.

**Table 4- Guidelines for monitoring of the Medication used to treat ADHD ---  
Non-psychostimulants.**

<b>Other medications Used in ADHD</b>	<b>Pre-Med Lab. Tests</b>	<b>Precautionary</b>	<b>Dosage</b>	<b>Dose Range</b>	<b>Wkly/visit labs</b>	<b>Other Tests</b>	<b>Side Effects</b>
<b>Atomoxetine HCL (Strattera)</b> --a norepinephrine uptake inhibitor	BP/HR- Wt./Ht.	ECG/CBC/ LFT	1.2 mg/kg/day	Max. 1.4mg/kg/ day	BP/HD Wt.	No MAOs Or in Narrow angle glaucoma	Headache Abd. Pain Decrease Appetite fatigue
<b>Clonidine (catapress)</b> -mod effectiveness for ADHD; Used in TD and CD	BP/HR	ECG if any CVD	0.05 – 0,3 mg per day (bid/tid)	0,05-0.9 mg/day	BP/HR		
<b>Clonidine patch</b>	BP/HR	ECG if any CVD (must taper off)	TTS 1 0.1 mg TTS 2 0.2 mg		BP/HR	EKG Yearly	Sedation Dizziness Hypotension
<b>Guanfacine (Tenex)</b>	BP/HR		0.5- 3mg/day given bid	0.5-3mg	BP/HR		Fatigue Mild sedation
<b>Bupropion (Wellbutrin)</b> --also, available in a sustained-release.	None	--Annual physical Exam  --Medical hx. Rule out Seizures	3– 6 mg/kg bid to tide	37.5-300 mg	None	None	Irritability Decreased Appetite Insomnia Worsening of Tics Drug induced seizures
<b>Tricyclic Antidepressants</b> Amitriptyline, Nortriptyline, & Imipramine	No longer recommended Replaced by Other agents.	BP/EKG					

**Table 5: Comparison of Medications Used for ADHD (Pharmacology, Dosing, and Pharmacokinetics).**

	<i>Methylphenidate</i>	<i>Dexamethylphenidate</i>	<i>Dextroamphetamine Amphetamine salts/ Methamphetamine</i>	<i>Atomoxetine (Strattera)</i>
<b>Pharmacology</b>	Selectively inhibits presynaptic transporter (i.e., reuptake) for dopamine and norepinephrine dependent on normal neuronal activity Mildly increases levels of synaptic dopamine & NE	Selectively inhibits presynaptic transport (i.e., reuptake) for dopamine and norepinephrine-dependent on normal neuronal activity. Mildly increases levels of synaptic dopamine & NE.	Causes release of dopamine, NE and 5-HT into the synapse – occurs independently of neuronal activity.  Inhibits MAO enzyme	Norepinephrine Re-uptake inhibitor—selectively blocks the reuptake of norepinephrine
<b>Dosing</b>	Start at 2.5-5 mg bid and increase by 2.5-5 mg/weekly Usual dose 5-60 mg/day or 0.3 to 1.0/1.5 mg/kg/day (up to 2.0-3.0 mg/kg has been used). Up to 120 mg in adult ADHD Extended release 10-20 mg qam; ↑ 10-20 mg weekly to a maximum of 60 mg/day.	Over age 6: start with 2.5 mg bid and can increase weekly to a maximum in divided doses. Usual dose: 5-20 mg daily given q4h.	Dextroamphetamine: Age 3-5 start with 2.5 mg and increase by 2.5-5.0 mg wkly. Usual dose dextroamphetamine 2.5-40 mg/day or 0.5-1.0 mg/kg in divided doses. (Spanules can be sprinkled ) Adderal 2.5-5.0 mg up to 40 mg/day (q4-7 h). Adderal XR: 10-30 qam. Dextroamphetamine-5-60 mg/d	Dosing is based on body weight. Children/adolescents Up to 70 kg start at 0.5 mg/kg/day, and increase every 3 days to a target dose of 1.2 (-1.4 mg/kg). Do not exceed 1.4 mg/kg/day. Max. 1.8-2.0 mg/kg/day.
<b>Pharmacokinetics</b> Bioavailability Peak Plasma level  Protein binding Onset of effects	> 90% Tab 0.3-4 h./\ SR= 1-8 h. Metadate CD =1.5h- pk 1 4.5h-pk 2 8-15% 0.5-2 h Absorption from GI tract is slow and incomplete.	? 1.0-1.5 h (fasting)  ? 0.5-2 h	Dextroamphetamine. > 90% Metamphet. > 65-70% Dextroamph. Tablets 1-4 h, Spanules 6-10 h. Adderal Tab. 1-2 h. Adderal XR 7 h. 12-15% 0.5- 2h Rapidly absorbed from GI tract.	Rapidly absorbed  1-2 h  Yes Between ½ h to 3 days Duration up to 24 hrs.

## **It Ain't all ADHD or -----Is it??**

### **When medications do not work in ADHD?**

- Co-Morbidity and Associated problems with ADHD
- Oppositional Defiant Disorder, Conduct Disorder, Anxiety, and Depression

### **ADHD Comorbidity**

- ADHD and Anxiety—18-32%
- ADHD and Learning Disorders
- ADHD and Mental Retardation
- ADHD and Tourette's Disorder
- Neurologic or Medical Disorders associated with ADHD
- ADHD plus ODD
- ADHD w/CD (worsens prognosis)
- ADHD and Depression--ADHD w/depression is common from 3-18%  
(Treatment of ADHD first is recommended before treatment of MDD)

### **ADHD and Bipolar Disorder**

- Manic illness is episodic with euphoric, and distinct periods of depression
- History of ADHD is chronic
  - *Some studies indicate that as many as 80% of patients with ADHD seem to go on to develop Bipolar Disorder*
  - *Similar studies indicate that as many as 90% of patients with Bipolar Disorder have had ADHD.*

### ***Similarities between ADHD and Bipolar disorder***

- *distractibility;*
- *talkative;*
- *hyperactive.*

**Jensen and colleagues proposed seven criteria that would define whether a comorbid condition exists in ADHD:**

- **Distinct clinical picture,**
- **demographics,**
- **psychosocial factors,**
- **biological factors/genetics,**
- **family environment,**
- **course and outcome,**
- **and response to specific treatment.**

**Brief insight into current theories of ADHD:**

- **Theoretical Concepts of ADHD**
- **Berkley's Theory—newer model.**
- **Other concepts**

**Assessment of ADHD:**

- a. **Parental Interview**
- b. **Evaluation of child in office**
- c. **Direct observation of child in school**
- d. **Information from school**
- e. **Psychoeducational assessment**
- f. **EEG and neurological evaluation**
- g. **Medical and other evaluations**
- h. **Rating Scales for ADHD**

**ADHD Rating Scales**

- **Connors Teacher and Parent Rating Scales**
- **Attention Deficit Hyperactivity Rating Scale-Revised (ADHD-RS)**
- **Child Behavior Checklist Rating Scale**

## **ADHD current treatments interventions**

- **Psycho education**
- **Parent training and contingency management**
- **Classroom Intervention**
- **Cognitive Behavior Therapy**
- **Social Skills Training**
- **Individual Psychotherapy/play therapy**

### **Summary of medication usage in ADHD**

- **Dramatic rise in use of psychostimulants, representing at least a doubling in the number of prescriptions every 5 years, or as many as 1.5 million children receiving medications for ADHD**
- **75% of children diagnosed with ADHD on medication.**
- **Large number still untreated**

### **Medication Treatments of ADHD**

- **Psychostimulants**
- **Short Acting**
  - **Methylphenidate agents**
  - **Dextroamphetamine agents**
- **New Longer acting agents**
  - **Methylphenidate agents**
  - **Dextroamphetamine agents**

### **Dexedrine vs. methylphenidate**

- **Similar benefits and similar side effects**
- **75% of children respond to first medication treatment**
- **For children that do not respond to the initial treatment, 90% will respond to alternation of dose or trial of different medication.**
- **Both medications are initiated at low dose and gradually increased.**
- **MPH: Up to 1 mg/kg/day for MPH or 60 mg**
- **Dexedrine: 0.5 mg/kg/day or 30 mg dextroamphetamine.**
- **Rebound phenomenon (more common with methylphenidate type agents)**
- **Outcome evaluated best with rating scales**

**MPH**

- onset 30-45 min
- max. effect seen in 1.5 to 2.5 hours
- last 3-4 hours
- complex racemic drug with two different isomers
- d-isomer harbors the bulk of clinical efficacy of the compound

**Dextroamphetamine**

- onset in 30-45 minutes
- max. effect in 5-6 hours
- 5 mg is equivalent to 10 mg MPH

**Comparison of Amphetamine Sulfate core agents versus Methylphenidate core agents**

<p><b>Amphetamine Sulfate core agents</b></p> <ul style="list-style-type: none"> <li>• ADDERAL</li> <li>• ADDERAL XR</li> </ul>	<p><b>MPH core agents</b></p> <ul style="list-style-type: none"> <li>• Concerta</li> <li>• Concerta XR</li> <li>• Metadate CD</li> <li>• Focalin</li> <li>• Ritalin LA</li> </ul>
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*Adderal is a mixture of dextroamphetamine/amphetamine salts, 5, 10, 15, 20, and 30 mg tablets. The mixture of salts is felt to prolong the duration of action, so it will last 6-8 hours.*

**Currently available Psychostimulants**

<p><b>Adderal XR</b> LOA-Up to 12 hours</p>	<p><b>Delivery system: Microtrol beads</b> --50% immediate release --50% time release</p>
<p><b>Concerta</b> LOA-up to 12 hours</p>	<p><b>Tri-layer core,</b> --22% immediate release --78% time release</p>
<p><b>Methadate CD</b> LOA-up to 8 hours</p>	<p><b>Multi-particular beads</b> --30% immediate release --70 % time release</p>
<p><b>Ritalin LA</b> Up to 9 hours</p>	<p><b>Mixture of beads</b> --50% immediate release --50% time release</p>
<p><b>Focalin</b> 3-4 hours</p>	<p><b>Immediate release</b></p>
<p><b>Strattera</b> Length of action up to 24 hours</p>	<p><b>Immediate release</b></p>

***Strattera approved by FDA (Nov. 2002) for the treatment of ADHD for children, adolescents and adults.***

- Atomoxetine HCl (Strattera)
- Approved in Nov. 2002
- NE uptake inhibitor
- Half life 5 hours, however increase in concentration at target site.
- Nonpsychostimulants, Low side effects
- Functional Improvements.

**Strattera:**

Clinical studies as of January 2003—> 4,000 and commercial use to present

- Advantages and disadvantages
- Dose titration
- Dosage—18, 25, 40 and 60 mg.
- Comparison with other psychostimulants

**Strattera Side effects**

	Strattera/Placebo
Appetite decrease	14.1%/5.5%
Dizziness	6.1%/2.4%
Dyspepsia	4.5%/1.4%
Dermatitis	4.5%/1.7%
Mood Swings	2.4%/ 1.5%

**Description of most common side effects and possible correction steps:**

**GI side effects**

- Are transient and usually subside within the first week.
- Dose should be taken with food'
- Food taken does not alter the effect of Strattera.

**Somnolence**

- Early onset effect & transient
- Options— adjust timing of QD dose, decrease dose, and some effects reduced when dosed with food.

**Psychostimulant Adverse Effects**

- Loss of appetite
- Headaches

- **Stomach problems**
- **Insomnia**
- **Issues of grow suppression and possible precipitating of tics.**
- **Psychiatric Side Effects--Social withdrawal, Appearing zombied, Rebound irritability and/or dyphoria.**

### *Other ADHD Medication Treatments--Second and third line*

#### **Second Line**

- **Tricyclic Antidepressants**

**Tricyclic Anti-depressants have been used for the following reasons:**

- 1. Patients unable to tolerate psychostimulants.**
- 2. Patients with ADHD with tics.**
- 3. Patients with depressive symptoms.**

*The tricyclics have fallen out of favor due to sedating symptoms and periodic cardiac effects (desipramine).*

- **Alpha Adrenergic agents  
clonidine and guanfacine)**
- **Bupropion (Wellbutrin)**

#### **Third Line agents**

**Used for severe ADHD, unresponsive to common treatments– (prior to their use one needs to review the diagnosis and consider comorbid diagnosis.**

- **Use of antipsychotics—risperidone, olanzapine, ziprasidone, or Abilify.**
- **(medication of last resort for short term use or stabilization**
- **Novel neuroleptics Agents—mostly with unproven safety and effectiveness**  
--For severe ADHD and for severe agitation and aggression associated with ADHD.  
--Risperidone, ziprasidone, olanzapine, and Abilify.

#### **New Agents**

- **MPH patch**
- **Other Strattera related compounds.**
- **Benefits and limitations**

#### **Multimodal Treatment Study of ADHD**

- **Medication Management**
- **Psychosocial intervention**
- **Medication and treatment**

- **When medications do not work--consider:**
  - **Inadequate or excessive dose**
  - **Expectation too high on part of parent or child**
  - **Poor compliance**
  - **Limited tolerance to side effects**
  - **Missed diagnosis/wrong diagnosis**
  - **Comorbid disorders**
  - **Other**

## ***ADHD vs. BPD***

### ***Current controversy about the relationship between ADHD vs. Bipolar Disorder:***

- **Bipolar I —children who had at least one manic episode.**
- **Bipolar II —children who have had at least one episode of major depression and hypomania.**
- **Bipolar disorder NOS –do not meet full criteria but suffer from symptoms of a mood disturbance and are functionally impaired. Severe irritability, chronic psychopathology, episodic cycling, and mixed or minimal symptoms of depression but may not manifest an elated mood or grandiosity.**
- **Bipolar I —children who had at least one manic episode.**
- **Bipolar II —children who have had at least one episode of major depression and hypomania.**
- **Bipolar disorder NOS –do not meet full criteria but suffer from symptoms of a mood disturbance and are functionally impaired. Severe irritability, chronic psychopathology, episodic cycling, and mixed or minimal symptoms of depression but may not manifest an elated mood or grandiosity.**

### **Core Features of Bipolar Disorder**

- **Mood symptoms: elevated, expansive or irritable mood.**
- **Associated Symptoms: 3 out of 7 (4 of 7 if irritable):**
  - **Inflated self-esteem/grandiosity**
  - **Decreased need for sleep**
  - **Flight of ideas/racing thoughts**
  - **Poor judgment or hypersexuality**
  - **Distractibility**
  - **Goal-directed activity**
  - **Talkative/pressured speech**

**Prepubertal versus Adolescent Onset Bipolar Disorder**

	<b>Prepubertal onset Bipolar Disorder</b>	<b>Adolescent onset BPD</b>	<b>Adult onset BPD</b>
<ul style="list-style-type: none"> <li>• Age of onset</li> <li>• Irritable mood</li> <li>• Elated Mood</li> <li>• Mixed Mood</li> <li>• Psychosis</li> <li>• Suicidal Behavior</li> <li>•</li> </ul>	Range 4-7.3 yrs.  77%-97.9% 75%- 89.3% 19.6-84% 16%-84% 25%	Age of onset 11-17 Yrs. Irritable Mood-14-22% Elated Mood 88.9% Mixed 19-26% Psychosis 28-75% Suicidal Behavior 20-44%	Age of Onset-30yrs. Irritable mood-100% Elated mood 90% Mixed 16-67% Psychosis 75% Suicidal Behavior 24-58%
Duration of episode Rapid Cycling	Duration of Episode 12-42 months Rapid Cycling 46-87%	Duration of Episode 1.5-4 months Rapid Cycling 10%	Duration of episode 4-13 months Rapid Cycling 20-25%

**Pre-pubertal Bipolar Disorder versus Adolescent Onset Bipolar Disorder**

<b>Puberty/Early Onset Adolescent Bipolar Disorder</b>	<b>Adolescent Onset Bipolar Disorder</b>
<b>Comorbidity:</b>  ADHD→75% ODD → 46-75% CD → 17.9-37% Anxiety– 12.5-56% Depression 15% Substance Abuse 0-17.6% PTSD - - - - IQ 92-115 Functioning CGAS 38-50	<b>Comorbidity:</b>  ADHD→12-53% ODD → 6% CD → 6% Anxiety– 33% Depression 55% Substance Abuse 22-40% PTSD - 27-48% IQ 83-138 Functioning CGAS 76

**Development and Outcome of Adolescent with ADHD**

- educational achievement
- Psychiatric status
- Antisocial personality and CD
- Increase car accidents
- family less stable, higher divorce rates

**Adult outcome statistics**

- 18-20 years full syndrome remission
- 27% have achieved symptomatic remission
- 10 % functional remission
- hyperactivity improves within 9-11 years
- impulsivity improves by 12-14 years
- attention problems persist

**Adult Outcome of patients with ADHD:**

- work history poor
- self esteem and social skill problems
- personality disorders
- Polysubstance abuse
- Earlier intercourse, use birth control less, and more sexual partners.
- more have been tested for HIV.

**Yes, perhaps it Ain't all ADHD after all.**