Attention Deficit and Hyperactivity Disorder:
The disorder of many faces

S. Tyano MD FRCPsych. FAPA HFWPA
Professor Emeritus in Child and Adolescent Psychiatry
School of Medicine
Tel Aviv University
Israel
Is there any difference?

Disruptive behaviors

ADHD

“ADD”

CD

ODD
ADHD
No-ADHD
Etiology
ADHD is a highly heritable disorder. Heritability rate: 0.8

Hartman, Jensen This disorder has an evolutionary advantage

It is highly probable to find more than one patient in a family
Environmental influences that affect ADHD

- Though the genetic factor is highly important, environmental factors tend to have an effect, too
- **Prenatal factors**: miscarriage symptoms, premature delivery symptoms, maternal respiratory viral infection, moderate to severe physical illness in the mother during gestation, prenatal cigarette and alcohol exposure
Environmental influences that affect ADHD (2)

- Neonatal factors: neonatal seizures, asphyxia or anoxia, severe neonatal illness, LBW
- Early childhood: mild speech retardation, moderate brain injury, febrile seizures, delayed physical growth and motor development
- Environmental factors: lead poisoning, etc.
Fetal alcohol syndrome and drugs neuroimpairment

- High frequency of ADHD among children who had:
  Fetal alcohol syndrome
  Exposure to street drugs during pregnancy

Heredity or environment?

Genetics

- Family twin and adoption studies converge with molecular genetic studies in showing that genes influence susceptibility to ADHD.
- The genetic mechanisms that predispose individuals to ADHD are complex.
- It seems likely that the disorder is caused by the combined actions of several genes.
- It is equally clear that aberrant genes create a vulnerability to the disorder that is not expressed in all environments.
Anatomy

- Smaller frontal lobes, especially the Right prefrontal lobe
- Smaller basal ganglia, especially the right
- Cerebellar changes
- Thinner Corpus Callosum, especially the dorsal parts
Four elements of lateralized brain function were measured: LH specialized, RH specialized, LH with interhemispheric processing (LH/IH), and RH with interhemispheric processing (RH/IH).

These elements’ association with cognitive ability, psychiatric comorbidity, and sibling correlations were tested in 79 children with ADHD.

RH/IH processing was uniquely associated with other outcome measures. There were no associations for independent RH or LH function alone.

Interhemispherically networked RH processing is critical in ADHD. In addition, lack of association between LH specialized processing and cognitive ability (especially for verbal cognitive tasks) supports increased RH mediation of task processing.
Physiology

Disruptive executive functions (Barkley):

- Attention
- Inhibition
- Working memory

Decrease of oxygen and glucose consumption in specific brain areas (right prefrontal lobe) in attention-demanding situations
PET for dopamine transporters in the brain

Higher density as seen with more yellow to white color

ADHD

Normal

Krause et al., Neuroscience Letters 285 (2000); 107-110
DAT1 gene, expressed predominantly in the basal ganglia, preferentially influences caudate volume, whereas the DRD4 gene, a gene expressed predominantly in the prefrontal cortex, preferentially influences prefrontal gray matter volume (Durstston et al, 2005)

The homozygosity of the 10-repeat allele at DAT1 seems to be associated with a poor response to MPH. Significantly higher regional cerebral blood flows assessed by SPECT were detected in medial frontal and left basal ganglia areas in children with homozygosity for the 10-repeat allele at DAT1 gene (Rohde et al, 2003)
Biochemistry

- The most important neurotransmitter involved is dopamine.
- There is also serotonergic and noradrenergic involvement.
- It is suggested that there are also differences according to the specific type of diagnosis (ADHD, ADD, ADHD + CD).
Classification
ICD-10 versus DSM IV

- Hyperkinetic Syndrome (F90)
  - Inattentiveness
    - Inattentive Type 314.00
  - Impulsivity
    - Hyperactive impulsive Type 314.01
  - Disturbed activity (Hyperactivity)
    - Combined Type 314.01
DSM-IV-TR Criteria: obligatory

- Some symptoms begin before the age of 7
- There must be clear evidence of clearly significant impairment in Academic, Occupational or Social functioning
- Some impairment from the symptoms is present in at least two settings
The symptoms do not occur exclusively during the course of Pervasive Developmental Disorder, Schizophrenia or other Psychotic disorder, and are not better accounted for by another mental illness.
DSM-IV-TR criteria: possible

A: 6+/9

H: 6+/9

ADHD, predominantly inattentive

ADHD, mixed

ADHD, predominantly hyperactive
Inattention

- Often fails to give close attention to details/makes careless mistakes
- Often has difficulty sustaining attention in tasks
- Often does not seem to listen when spoken to directly
- Often does not follow through instructions and fails to finish schoolwork, chores or duties in the workplace
- Often has difficulty organizing tasks and activities
Inattention (cont’)

- Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort
- Often loses things necessary for tasks and activities
- Is often easily distracted
- Is often forgetful in daily activities
Hyperactivity

- Often fidgets with hands or feet
- Often leaves seat in classroom or in other situations in which remaining seated is expected
- Often runs about or climbs excessively in situations in which it is inappropriate or risky
- Often has difficulty playing or engaging in leisure activities quietly
- Is often “on the go”
- Often talks excessively
Impulsivity

- Often blurts out answers before questions have been completed
- Often has difficulty awaiting turns
- Often interrupts or intrudes on others
Children and adolescents:
- Around 10% of the population
- New studies from Europe and U.S.A. report: 5 - 17%

Adults:
- Estimated as 4-7% of the population
A general population of Northern Finland Birth Cohort 1986 was studied.

9,432 children followed prospectively from the early fetal period was surveyed at adolescence (ages 16-18) for ADHD behaviors.

A subset of 457 likely cases and controls were evaluated for ADHD and other psychiatric disorders.

The estimated prevalence of ADHD: 8.5%

Male/female ratio of 5.7:1.

The distribution of ADHD subtypes: 28% Combined, 64% Inattentive, and 8% Hyperactive-Impulsive.

A lifetime diagnosis of a broadly defined ADHD (probable or definite) had a prevalence of 18.2% with a male/female odds ratio (OR) of 3.2.

Comorbidity: anxiety (OR 2.4), mood (OR 2.9), and disruptive behavioral disorders (OR 17.3)
Prevalence of ADHD in adults

- Estimated around 2-6% of all population
- No large-scale epidemiological studies, hence estimation based on childhood prevalence and persistence of 50% (1)

National comorbidity survey replication (2):
- 4.4% among US adults suffer from ADHD.
- Only 11% are treated (Kessler et al.)

Gender Difference

- Much more boys than girls:
  - Factor 4 epidemiologically
  - Factor 9 clinically

- Adults: Equal numbers men and women

- There are much more girls suffering from ADHD than diagnosed.

Clinical characteristics:
Important issues
The Clinical Course

- From infancy to old age
- The prognosis differs according to characteristics, treatment and life events
Most Important Features

- Age
- Dependent
- High comorbidity
- Sociability
- Response to medication
Self esteem

- From a population-based group of 10-11-year-old children in a Swedish municipality those with ADHD/subthreshold ADHD (n = 30) and those with milder attention and/or learning problems (n = 64) were targeted for the study.

- Significant gender differences were found, girls reporting lower self-esteem concerning mental well-being and poorer relationships with parents and peers.

- However, children with ADHD/subthreshold ADHD did not report significantly lower global self-esteem when compared to a reference population.

The importance of gender

- There are much more girls suffering from ADHD than diagnosed.
- Girls with ADHD are 5.4 times more likely to be diagnosed with major depression and three times more likely to be treated for depression before their ADHD is diagnosed.
- Girls with ADHD are also more likely to be diagnosed with Borderline PD.
- Eating disorders, particularly binge eating and bulimia, have been recently linked to ADHD in girls and women.

ADHD through the ages

Specific ages, specific problems
Early Age ADHD

The first symptoms may appear as soon as the youngling hatches.
Early Age ADHD

The first symptoms include:

1. Unregulated sleep and appetite
2. Early motor development
3. Tendency to inattention, a need of parents’ attention and holding
Early Age ADHD

- The most prominent feature: the hyperactivity – impulsivity
- Attention is sometimes very difficult to measure
- Young children with ADHD exhibit more problematic behavior and are less socially skilled than normal counterparts
Preschoolers’ ADHD: the multisite Preschool ADHD Treatment Study (PATS)

- Describes the clinical presentation of preschoolers diagnosed with moderate to severe ADHD
- 303 preschoolers (3-5.5 years) were diagnosed with moderate to severe ADHD Hyperactive/Impulsive or Combined type.
- The majority of participants (n = 211, 69.6%) experienced co-morbid disorders
- The most common: ODD, communication disorders, and anxiety disorders.
- Participants with co-morbid communication disorders were found to be more anxious and depressed.
- ADHD severity was found to correlate with more internalizing difficulties and lower functioning.
- Boys and girls had similar symptom presentations
- Younger children had significantly higher ADHD severity.

Differential Diagnosis

- Difficult temperament
- Children who have been given no clear limits.
- Behavioral disorder or ODD
- Deviations in IQ (talented / retarded).
- Spasms of Petit Mal type.
- Pervasive Developmental Disorders
- Psychosis
- Post Traumatic Stress Disorder (PTSD) of Infancy.
- Others
Early Age ADHD: Treatment

- Preschool children with ADHD respond to psychostimulants but need close monitoring because of frequent side effects compared to older children.
- Psychostimulants are not a necessary component of effective treatment for many children with preschool ADHD.
- Constructive training in parenting strategies is an important element.
Childhood ADHD

Most children are diagnosed in the age of elementary school
Childhood ADHD

- The **time factor** begins to be critical (before adolescence)
- There is high frequency of comorbidity, which increases with age.
Impact of ADHD on Patients and Family

- **Patients**
  - Poor academic achievement
  - Social impairment
  - Low occupational status
  - Increased risk of substance abuse
  - Increased risk of injury

- **Family**
  - Increased stress levels
  - Increased depression
  - Increased marital discord
  - Changed work status
Impact of ADHD on school performance

- Poor classroom behaviour
- Poor academic achievement
- Special education requirements (tutoring and special educational programmes)
- School exclusion (either suspension or expulsion)
- Repetition of grades
- Failure to graduate from high school
Adolescent ADHD

The clinical features of adolescent ADHD are comprised from the clinical features of ADHD as well as those of adolescence.
Adolescent ADHD

- Which means that these adolescents tend to be oppositional, defiant, and have a need to be exactly like their peers.

- They are also highly interested in their body and its perfection.
Adolescent ADHD

Hence, they reject being diagnosed and being treated, especially by medications.
Comorbidity
Dysregulation

- Dysregulation is highly frequent in ADHD patients in all age groups
- It affects: sleep, appetite, mood, sensory regulation, transfer between states and more
For example: Sleep

- Sleep is reported to be affected in ADHD patients.
- The sleep disorders tend to be non-specific, although some specific disorders, such as restless leg syndrome were described.
- The frequent complaints: difficulty falling asleep, difficulty waking up, restlessness, night terrors, enuresis nocturna.
Early Age ADHD: Comorbidity

- Preschool children with ADHD are likely to exhibit ODD, anxiety, or mood disorders
Comorbidity during Childhood (Zametkin et al, 1999)

- ADHD alone: 31%
- Conduct Disorder: 14%
- Anxiety Disorder: 34%
- Oppositional Defiant Disorder: 40%
- Tics: 11%
- Mood Disorders: 4%

MTA Cooperative Group. Arch Gen Psychiatry 1999; 56:1088–1096
Comorbidity in adolescents

Some comorbid states are accentuated during adolescence:

1. Sleep disorders
2. Eating disorders
3. Suicide
4. Substance Abuse Disorders (SAD)
5. Delinquency
Specific Comorbid Disorders

Through all age groups
Learning Disorders

- 30% of all children diagnosed as LD suffer from ADHD
- Hence, as part of each diagnosis: Rule out LD.
- On the other hand, there is a risk of over-diagnosis of LD instead of ADHD
Other disruptive behaviors

ODD: most undiagnosed children above the age of 10 years show ODD features.

CD: perhaps a separate entity, even genetically.

ADHD + CD: The most dangerous diagnosis.
Bullying (Holmberg et Hjero, 2008)

- The association of ADHD with bullying in the peer group in school was studied in an entire population of 516 children (252 females, 264 males), who were fourth graders (10-year-olds) in one municipality in Stockholm, Sweden.

- The schoolchildren were screened for ADHD (CRS-P, -T) and information about bullying was collected from the children themselves in a classroom questionnaire.

- Pervasive ADHD was diagnosed in 9.5% (95% confidence interval [CI] 5.6-12.8) of the males and 1.6% (CI 0.1-3.1) of the females.

ADHD was associated with bullying other students (adjusted OR 3.8 [CI 2.0-7.2]) as well as being bullied often, OR 10.8 [CI 4.0-29.0]; sometimes, OR 2.9 [CI 1.5-5.7]).

Bullying other students was associated with high scores in parental reports of behavioral problems at entry into first grade, suggesting a causal link to the ADHD syndrome.

Being bullied, on the other hand, was not linked to behavioral problems at school entry.
Suicide

- Only few studies discuss the correlation between ADHD and suicidal behavior
- Usually there is another factor involved, such as delinquency or SAD
- We will introduce two studies
ADHD and Suicide in Irish population (Lynch et al, 2005)

- This study evaluated prevalence rates of psychiatric disorders, suicidal ideation and intent, and parasuicide in a population (N=723) of Irish adolescents aged 12-15 years in a defined geographical area.
- **19.4%** were identified as being 'at risk'.
- This 'at risk' group was interviewed along with a comparison sample.

15.6% of the total study population met the criteria for a current psychiatric disorder: 4.5% an affective disorder, 3.7% an anxiety disorder, and 3.7% ADHD.

Significant past suicidal ideation was experienced by 1.9%, and 1.5% had a history of parasuicide.

Binge drinking was associated with both affective and behaviour disorders.
Dr. Archibald was known for his very thorough Proctology exams...
The diagnostic process

1. Clinical interview (H & E)

2. Rating scales (P & T)

3. Neuro-cognitive tests as C.P.T.
Interview

- A thorough interview with the family (parents and child), including full history from pregnancy onwards.
- Assessment of ADHD criteria, according to DSM-IV
- Assessment of comorbid disorders, such as CD, LD, mood disorders
Clinical Examination

- Full Clinical psychiatric examination of the child, including the mental part (SNS, domination, reading, writing, and arithmetic skills, etc.)
- Again, it is necessary to assess every possible comorbid disorder.
Rating Scales

The Child Behavior Checklist (CBCL) of Achenbach and Edelbrock. A profile of Externalizing, Internalizing and the “in-between” problems. It is given to parents and teachers, as well as to youths.

The Strengths and Difficulties Questionnaire (SDQ) of Goodman R. A five-factor structure (emotional, conduct, hyperactivity-inattention, peer, prosocial) gathering to Internalizing and Externalizing scales. Can be completed by parents, teachers, or youths.

Conners Rating Scales of Conners K. There is a full as well as an abbreviated form. Can be completed by parents and teachers.

Others
Cognitive tests

- Special cognitive tests or tests for executive function.
- Include parts from the Wechsler, memory tests, inhibitory control, etc.
- The most popular in the clinic is the Continuous Performance Test.
The CPT is a widely used measure of sustained attention, which may rely on the efficiency of cognitive inhibition.

The Test of Variables of Attention (T.O.V.A.) is a computer-administered, visual continuous performance test that provides measures of attention and of inhibitory control.
Results before and after ritalin challenge:

Ritalin is efficient
Results before and after ritalin challenge:

Ritalin is inefficient
Treatment

"These drugs will effect your short term memory, so you better pay me now."
“Pure” ADHD: Integrative Treatment

- Pharmacotherapy
- Parents’ education and behavioral therapy
- School instruction (in children)
Childhood ADHD: Treatment

The Triangle principle:

- Pharmacotherapy
- School Instruction
- Parents Education and BT
The onion model

- Treatment of ADHD children, as well as adults is many times like an onion
- With each therapy (medications, psychotherapy) another layer is exposed
- Time is also a therapeutic factor
Comorbidity Algorithm

ADHD

No comorbidity
According to response

Comorbidity

Behavioral axis
Long term stimulant
Add drug (risperdal)

Affective axis
Not a stimulant?
Add drug (antidepressant)
ADHD and Comorbidity

Behavioral comorbidity:
- Behavioral pharmacotherapy
- Behavioral psychotherapy

Affective comorbidity:
- Antidepressants/antianxiolytics with and without psychostimulants
- Atomoxetine?
- Psychotherapy (cognitive, behavioral, dynamic, etc.)
ADHD and Aggression algorithm

Texas CMAP treatment algorithm for children with ADHD and aggression. *J Am Acad Child Adolesc Psychiatry*

**Stage 0**
Diagnostic Assessment and Family Consultation Regarding Treatment Alternatives

Any stage(s) can be skipped depending on the clinical picture

**Stage 1**
Begin ADHD Algorithm

Partial response or nonresponse of aggression

Improvement of ADHD and aggression

Continuation

**Stage 2**
Add behavioral intervention*

Partial response or nonresponse of aggression

Improvement of ADHD and aggression

Continuation

**Stage 3**
Add atypical antipsychotic to stimulant**

Partial response or nonresponse of aggression

Improvement of ADHD and aggression

Continuation

**Stage 4**
Add lithium or divalproex sodium to stimulant

Partial response or nonresponse of aggression

Improvement of ADHD and aggression

Continuation

**Stage 5**
Add agent not used in stage 4

Imagery of ADHD and aggression

Continuation

Clinical consultation

Maintenance

* Evaluate adequacy of behavior treatment after inadequate response at any stage.
** If the patient is an imminent threat to self or others, atypical antipsychotic may be started with behavioral treatment.
ADHD and CD treatment algorithm

Assess whether patient poses significant risk to self or others

- If specialist unavailable
- If specialist available
- Refer to specialist

Psychosocial interventions such as: parent training, classroom intervention, family therapy, social skills therapy, cognitive behavior therapy

&

Psychostimulant medication: Begin at minimal recommended dose

- If insufficient response at 2-4 weeks
  - Titrate psychostimulant ensuring full-day coverage (use thrice-daily dosing or long-acting agents). Allow sufficient time between dose increments to observe effects on target symptom(s)
    - If insufficient response at maximum recommended dose
      - Add risperidone at minimal recommended dose and continue psychosocial interventions
        - If insufficient reduction in aggression at 4-6 weeks
          - Titrate dose allowing sufficient time between increments to determine therapeutic response. Do not exceed maximal recommended dose. Continue/increase psychosocial interventions
            - If insufficient reduction in aggression at 4-6 weeks at maximum doses of both medications
              - Hospitalize or consider residential treatment

Risk

No risk
### Medications approved by the FDA

<table>
<thead>
<tr>
<th>Generic Class/ Brand Name</th>
<th>Dose Form</th>
<th>Typical Starting Dose</th>
<th>FDA Max/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylphenidate preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focalin</td>
<td>2.5, 5, 10 mg cap</td>
<td>2.5 mg b.i.d.</td>
<td>20 mg</td>
</tr>
<tr>
<td>Methylin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 10, 20 mg tab</td>
<td>5 mg b.i.d.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ritalin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 10, 20 mg</td>
<td>5 mg b.i.d.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metadate ER</td>
<td>10, 20 mg cap</td>
<td>10 mg q.a.m.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Methylin ER</td>
<td>10, 20 mg cap</td>
<td>10 mg q.a.m.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ritalin SR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20 mg</td>
<td>10 mg q.a.m.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>10, 20, 30, 40, 50, 60 mg</td>
<td>20 mg q.a.m.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>10, 20, 30, 40 mg</td>
<td>20 mg q.a.m.</td>
<td>60 mg</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerta</td>
<td>18, 27, 36, 54 mg cap</td>
<td>18 mg q.a.m.</td>
<td>72 mg</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>10, 15, 20, 30 mg patches</td>
<td>Begin with 10 mg patch q.d., then titrate up by patch strength</td>
<td>30 mg</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>5, 10, 15, 20 mg cap</td>
<td>5 mg q.a.m.</td>
<td>30 mg</td>
</tr>
<tr>
<td><strong>Amphetamine preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adderall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 7.5, 10, 12.5, 15, 20, 30 mg tab</td>
<td>3–5 y: 2.5 mg q.d.; ≥6 y: 5 mg q.d.–b.i.d.</td>
<td>40 mg</td>
</tr>
<tr>
<td>Dexedrine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 mg cap</td>
<td>3–5 y: 2.5 mg q.d.</td>
<td></td>
</tr>
<tr>
<td>DextroStart&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 10 mg cap</td>
<td>≥6 y: 5 mg q.d.–b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine Spansule</td>
<td>5, 10, 15 mg cap</td>
<td>≥6 y: 5–10 mg q.d.–b.i.d.</td>
<td>40 mg</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>5, 10, 15, 20, 25, 30 mg cap</td>
<td>≥6 y: 10 mg q.d.</td>
<td>30 mg</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>30, 50, 70 mg cap</td>
<td>30 mg q.d.</td>
<td>70 mg</td>
</tr>
<tr>
<td><strong>Selective norepinephrine reuptake inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>10, 18, 25, 40, 60, 80, 100 mg cap</td>
<td>Children and adolescents</td>
<td>Lesser of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;70 kg: 0.5 mg/kg/day</td>
<td>1.4 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 4 days; then 1 mg/kg/day</td>
<td>or 100 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 4 days; then 1.2 mg/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

*Note: FDA = U.S. Food and Drug Administration; ADHD = attention-deficit/hyperactivity disorder.*

<sup>a</sup> Generic formulation available.
## Dosage Conversion (ritalin)

<table>
<thead>
<tr>
<th></th>
<th>Regular Ritalin</th>
<th>Ritalin SR</th>
<th>Ritalin LA</th>
<th>Concerta</th>
<th>Daytrana</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influence time</strong></td>
<td>4 hrs.</td>
<td>6-8 hrs.</td>
<td>8-9 hrs.</td>
<td>12 hrs.</td>
<td>9-10 hrs.</td>
</tr>
<tr>
<td><strong>“Real” Dosage</strong></td>
<td>10 mg</td>
<td>8 mg</td>
<td>20mg=8mg, 30mg=12mg, 40mg=16mg</td>
<td>18mg=5mg, 27mg=7.5mg, 36mg=10mg, 54mg=15mg</td>
<td>27.5mg=10mg, 41.3mg=15mg, 55mg=20mg, 82.5mg=30mg</td>
</tr>
</tbody>
</table>
## Dosage Conversion (Focalin)

<table>
<thead>
<tr>
<th>Influence time</th>
<th>Regular Ritalin</th>
<th>Focalin</th>
<th>Focalin XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hrs.</td>
<td>4 hrs.</td>
<td>8 hrs.</td>
<td></td>
</tr>
</tbody>
</table>

**“Real” Dosage**

<table>
<thead>
<tr>
<th>Regular Ritalin</th>
<th>Focalin</th>
<th>Focalin XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>Half of ritalin: 5mg 10mg</td>
<td>Half of ritalin LA 20mg=10mg F 20mg=40mg LA *Max dosage approved: 20mg</td>
</tr>
</tbody>
</table>

*Max dosage approved: 20mg*
## Dosage Conversion (Adderall)

<table>
<thead>
<tr>
<th>Influence time</th>
<th>Regular Ritalin</th>
<th>Adderall</th>
<th>Adderall XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hrs.</td>
<td>6 hrs.</td>
<td>12 hrs.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Real” Dosage</th>
<th>10 mg</th>
<th>5, 7.5, 10, 20, 30mg</th>
<th>10, 20, 30mg</th>
</tr>
</thead>
</table>

**Dosage Influence Time**

- Regular Ritalin: 4 hours
- Adderall: 6 hours
- Adderall XR: 12 hours

**Real Dosage**

- Regular Ritalin: 10 mg
- Adderall: 5, 7.5, 10, 20, 30 mg
- Adderall XR: 10, 20, 30 mg
What are these medications?
Psychostimulants

- Improve Attention
- Improve inhibition
- Short-term (up to 12 hours)
- Efficacy: 85-95% (all group)

- Very efficient for ADHD.
MPH (Ritalin): how does it work?

- MPH chiefly affects the prefrontal cortex and striatum, the mechanism of action being modulation of catecholaminergic tone.
- MPH treatment produces an increase in dopamine (DA) signaling through multiple actions, including:
  1. Blockade of the DA reuptake transporter
  2. Amplification of DA response duration
  3. Disinhibition of DA D2 autoreceptors
  4. Amplification of DA tone
  5. Activation of D1 receptors on the postsynaptic neuron.
- The actions of MPH may also be mediated by stimulation of the noradrenergic alpha2 receptor and DA D1 receptor in the cortex.
- The role of other neurotransmitters such as histamine, acetylcholine, serotonin, and alpha-agonists in modulating catecholamine pathophysiology in ADHD and ADHD treatment needs to be elucidated.

Ritalin’s side effects

- Inhibits appetite
- Inhibits sleep
- 15%: apathy and decrease in attention.
- Rebound
- Aggravates underlying depression
- Psychosis. Might indicate wrong diagnosis
Therapeutic doses of oral MPH significantly increase extracellular dopamine in the human brain (Volkow et al, 2001)

- Oral MPH significantly increased extracellular DA in brain in striatum
- This result coupled with recent findings of increased dopamine transporters in ADHD patients provides a mechanistic framework for the therapeutic efficacy of MPH.
MPH down-regulates the dopamine receptor and transporter system in children with ADHD. (Vles et al, 2003)

- Brain dopamine transporter and receptor activity in 6 boys with ADHD was studied by SPECT.

  3 months after initiation of treatment:
  - Down-regulation of the post-synaptic dopamine receptor with a maximum of 20 %
  - Down-regulation of the dopamine transporter with a maximum of 74.7 % in the striatal system.
"Many people believe that laughter is the best medicine, so the government has declared a ban on all laughing until further studies can be done."
An overview on growth (Poulton, 2005)

- 29 studies were reviewed following a Medline search.
- Children: 11 studies gave results consistent with height attenuation on stimulant medication: eight were longitudinal, one was cross-sectional, and two showed growth rebound on ceasing medication.
- Studies with negative findings were inadequately powered (n = 3), lacked controls or statistical analysis (n = 3), measured height velocity without reference to treatment duration (n = 2), or used inappropriate growth parameters (n = 1), controls (n = 1), or normative data (n = 1).

CTD

- Late adolescents/adults (treated as children): 2 studies associated childhood gastrointestinal side effects with attenuated late adolescent or adult height; all 6 cross-sectional studies had negative findings.

- The height deficit amounted to approximately 1 cm/year during the first 1-3 years of treatment.
Children receiving > or = 1.5 mg/kg/day MPH will show diminished weight gain after 1 year; those receiving > or = 2.5 mg/kg/day MPH will show diminished gains in height after 4 years.

Long-term use of high doses of stimulants during a period of 1 to 5 years is likely to have measurable effects on the rate of growth in school-age children with attention-deficit/hyperactivity disorder.
Specific medications
Ritalin® LA - Objectives

- Fast onset of action in the morning, with a high morning dose
- Double peak pharmacokinetic with raising plasma levels over the day
- Duration of action about 8 – 10 h to cover schoolday, but not to interfere with sleep at night
- Easy to swallow, no food interaction
- Easy switch from standard medication
- Individualized dosing
The CONCERTA® Formulation

MPH Overcoat

Tablet Shell

Laser-Drilled Hole

MPH Compartment #1

MPH Compartment #2

Push Compartment
Atomoxetine/ Strattera

- A non-stimulant medication.
- Blocks the NE transporter
- Does not have abuse potential
- Max. plasma concentrations: 1-2 hours after dosing
- Metabolized via the hepatic cytochrome P450 2D6 pathway, and excreted primarily in the urine
- Half-life: ~ 5 hours
- Observed duration of action with once-daily dosing suggests:
  - Therapeutic effects may persist after drug is cleared and/or
  - Brain concentration may differ from plasma concentration
Mechanism of Action
Highly Selective Norepinephrine Reuptake Inhibitor
Behavioral therapy
Tools Used in Behavioural Treatment

- Specific strategies
  - Reward system
  - Time out
  - Social reinforcement
  - Behaviour modelling

- Support for parents

- Family and patient education
  - Group problem-solving
  - Sports skills
  - Social skills training
Behavioural Treatment at Home

- Identify problem situations and the precipitating factors
- Enhance positive parent–child interactions
- Limit negative parent–child interactions
- Use cost systems to reduce problem behaviours
- Use time outs as punishment for serious problem behaviours
Behavioural Treatment in the Classroom

- Behavioural treatment in school setting similar to the approach used in home with parents
- Goal: Reduce inattention and disruptive behaviour
- Specific school accommodations:
  - Ensure structure and predictable routines
  - Employ cost–response token economy systems
  - Use daily report cards
  - Teach organisational and work/study skills
Hence

- A long way to go
- An unknown land to discover
- Collaborations are vital

- The longest journey begins in one step
  (Mao Tse Tong)
The end

Thank you