Attention Deficit Hyperactivity Disorder

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Attention Deficit Hyperactivity Disorder

- Definition
- Current theoretical conceptualisation
- Epidemiology
- Assessment and diagnosis
- Associated problems
- Management
Definition

Developmentally inappropriate degrees of:
- impulsivity,
- inattention,
- and often hyperactivity
### Historical Conceptualisations

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1798</td>
<td>Alex Crighton “mental restlessness”</td>
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<tr>
<td>1902</td>
<td>George Still (RCP lectures)</td>
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<tr>
<td></td>
<td>n=43: “passionate”, “defect in moral control”</td>
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<tr>
<td>1920’s-30’s</td>
<td>Post-encephalitic behaviour disorder</td>
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<tr>
<td>1940’s</td>
<td>Brain injured child</td>
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<tr>
<td>1950’s</td>
<td>Minimal brain damage</td>
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<tr>
<td>1960’s</td>
<td>Minimal brain dysfunction</td>
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<tr>
<td>1960’s-70’s</td>
<td>Hyperactivity</td>
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<tr>
<td>1970’s</td>
<td>Hyperkinetic reaction of childhood</td>
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<tr>
<td>1980’s</td>
<td>Attention deficit disorder (Douglas)</td>
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<tr>
<td>1990’s</td>
<td>Motivational disorder, behavioural disinhibition</td>
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</tbody>
</table>
Subtypes

- Combined – Inattention + Hyperactive / Impulsive
- Predominantly Inattentive
- (Predominantly Hyperactive / Impulsive)
ADHD - DSM-IV criteria

Either 1 or 2
1. **INATTENTION**

   At least 6 of the following symptoms have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
   - Often fails to give close attention to details or makes careless mistakes in school work, work or other activities.
   - Often has difficulty sustaining attention in tasks or play activities
   - Often does not seem to listen to what is being said to him or her
   - Often does not follow through on instructions and fails to finish schoolwork chores or duties in the workplace
   - Often has difficulty organising tasks or activities
   - Often avoids or strongly dislikes tasks (such as schoolwork or homework) that require sustained mental effort
   - Often loses things necessary for tasks or activities
   - Often easily distracted by extraneous stimuli
   - Often forgetful in daily activities
ADHD - DSM-IV criteria

2. HYPERACTIVITY / IMPULSIVITY
   At least 6 of the following symptoms have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level

   HYPERACTIVITY
   • Often fidgets with hands or feet and squirms in seat
   • Often leaves seat in classroom
   • Often runs about or climbs excessively in situations where it is inappropriate
     (in adolescents or adults may be limited to feelings of restlessness)
   • Often has difficulty playing or engaging in leisure activities quietly
   • Often ‘on the go’ or acts as if ‘driven by a motor’
   • Often talks excessively

   IMPULSIVITY
   • Often blurts our answers to questions before they have been completed
   • Often has difficulty waiting in line or awaiting turn in group activities
   • Often interrupts or intrudes on others
Current theory

Executive function deficits (fronto-striatal)

(Barkley Psychol Bull 1997)

- Response disinhibition
- Working memory – auditory, visuo-spatial
- Self-regulation

How specific to ADHD? (cf lang dis/RD)
Brain structures involved

- Limbic system (amygdala, hippocampus, anterior cingulate)
  - emotions / desire; driver
- Prefrontal cortex
  - Cognition; servant of limbic system
- Deep grey matter
- Parietal cortex
- Others
  - Cerebellum, precuneus?
Imaging *(Castellanos JAMA 2002)*

- MRI - total cerebral volume and *cerebellar* vol. 3% reduced cf controls
  - Reduced cortical thickness
  - Caudate vol smaller school-age, no diff older
  - Holds when control for med history
- fMRI - activate more diffuse areas than controls during cognitive tasks

*fronto-striato-cerebellar* model *(Castellanos & Tannock Nature 2002)*
Core functional difficulties

- poor effort persistence
- unable to tolerate delays in gratification
- excessive behaviour or action
- great variability in behaviour and work performance
- diminished response to positive reinforcement
Co-morbidities

80% have one or more

- Specific learning disability 30-50%
- Other disruptive behaviour disorders
  - ODD conduct disorder 35-40%
- Emotional/mood disturbance
  - anxiety 25%, depression / dysthymia 20%
- Asperger
- Neurodevelopmental delays
  - short-term auditory memory
  - perception / motor planning (DAMP, DCD)
Co-morbidities

- Determine heterogeneity
  - i.e. different types of kids - same label
- Often dictate best interventions
...And his dad's never there and he watches a lot of telly and eats junk food...

All of which can be fixed with medication.
Aetiology - Genetics

- Heritability > 70%
  - 1st degree relatives - 4-8 X increased risk
  - MZ twins - 50-90% concordance
  - gender-dependent expression

- Neurotransmitters with candidate polymorphisms:
  - dopamine (DRD4, DAT1), NA, MAO, GABA, serotonin

- Genome-wide scan
  (Fisher Am J Human Gen 2002 126 affected sib pairs)
  - no stat signif peaks (linkage studies ? chrom 5p, 6q, 17p)
Aetiology - Environmental exposures

- **Toxins**
  - prenatal tobacco *(Thapar Am J Psychiatry 2003; Kahn J Peds 2003 - genetic modifier)*,
  - prenatal alcohol - inconclusive *(Linnet Am J Psychiatry 2003)*
  - lead

- **Diet**
  - salicylates, amines, colourings, preservatives
  - sugar, milk, wheat
  - allergy
Aetiology (cont.)

- Traumatic brain injury (*Herskivitz Radiology 1999*),
- CVA - putamen (*Max JAACAP 2002*)
- Early deprivation
- Psychosocial disadvantage (*Biederman 1995*)
- Television (*Christakis Pediatrics 2004 yes, Stevens Pediatrics 2006 no*)
Epidemiology

- Prevalence 3-5%
- All countries, all ethnic groups
- Little variation across social classes
  Males - 3X in community settings
  - 6-10X in clinic referrals
Assessment

- History
  - developmental
  - academic
  - behaviour

- Examination
  - incl. neurodevelopmental

Behaviour rating scales (parent & teacher)
  - broad band eg Achenbach
  - ADHD specific eg Conners

Psychometric testing
  - cognitive
  - academic achievement
Laboratory measures

- Psychological tests
  - ‘ACID’ profile on WISC-III
  - Neuropsych: “exec function“ eg TOVA
- Surface EEG - inc theta-beta ratio
- Quantitative EEG (brain mapping)
- fMRI
- PET, SPECT scanning

THERE IS NO DIAGNOSTIC TEST
Differential diagnosis

- Normal
- Specific learning disability
- Intellectual disability
- Emotional disturbance
  - attachment disorder
  - abuse
  - adjustment reaction
  - anxiety/depression
- Autistic spectrum disorder
Predom. Inattentive

- Heterogeneous group
- Processing (Input vs output)
- Often assoc lang/SLD, anxiety
- Sluggish Cognitive Tempo
  *(McBurnett J Abn Child Psychol 2001)*
  - daydreams, apathetic, sluggish, in a fog, underactive, “space cadets”
  - ? separable from purely inattentive
- “Psychiatrically benign” *(Taylor)*
- Response to stimulants less marked?
Parent counselling (Psychoeducation)

- Explanation
- Grief reaction
- Disability perspective
  - reasonable expectations
  - foster strengths
  - modify environment instead of child
- Support groups
SHOW
DISCIPLINE
Multi-modal management

- medication
- behaviour mod
- educational strategies
- individual therapy
  - eg. CBT
- group therapy
  - social skills, anger management
- family therapy
Behaviour modification

- Clarity
- Consistency
- Calmness
- Lack internal locus of control
  - Praise and reward good behaviour
  - Ignore minor irritating behaviour
  - Immediate consequences for unacceptable behaviour
    eg time out, removal of privileges
Classroom adaptations

- Position in classroom
- Routines
- Limit choices
- Instructions
- Allow time, help pacing
- Set achievable goals
- Breaks
- Frequent positive reinforcement
- Clear graded consequences
Medication in ADHD

- Stimulants
- “Non-stimulants”
- “Antidepressants”
  - SSRIs, SNRI’s, tricyclics, MAO inhibitors
- Clonidine
- “Antipsychotics”
Psychostimulants

- Dextroamphetamine Bradley 1937 (post-LP headache)
- methylphenidate (Ritalin) 1956
- ↑ CNS arousal & alertness
- sympathomimetic
  - block re-uptake, ↑ pre-synaptic release, inhibit MAO
  - ↑ DA and NA in synaptic cleft
Stimulants effects - general

- Reduced impulsivity
  - physical
  - verbal
- Improved vigilance / sustained attention
- Reduced motor activity
- Increased compliance
- Improved parenting style
- Improved peer interactions / social standing
Stimulants effects

Cognitive
- Working memory / task planning
- Attention span / task completion
  cognitive effects dissociated from behavioural effects

Academic
- Mental arithmetic
- Reading comprehension
- Handwriting
- Retention of new material
Stimulant side-effects - short-term

- Anorexia / nausea → poor weight gains
- Initial insomnia
- Irritability / tearfulness / withdrawn
- Anxiety
- Abdominal pain
- Headache
- Dizziness
- Tics
- Mild mean inc. HR, BP
Stimulants – risk sudden death?

- 2006 - alarm sans data *(Nissen NEJM)*
- Epidemiology – no incr. over background rate sudden unexplained death
- FDA recommendations:
  - History
    - child: syncope, dizziness, palpitations, SOB, chest pain
    - Family: CVS disease, premature sudden death
  - Examination
  - If H +/- or E raise concern, or child develops symptoms
    - ECG, ECHO +/- cardiol consult

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Stimulant side-effects
- long-term

- growth suppression
  - Possible small effect in sub-group
  - av 2cm less growth over 3 yrs
  (MTA: Swanson JAACAP 2007)

- substance abuse
  - protective
(Willens Pediatr 2003 meta-analysis)
Stimulants in pre-schoolers

- lower efficacy
- more adverse effects
  - irritability, appetite suppression
  - dexamphetamine > MPH
Stimulants (tablets – immediate-release) - pharmacokinetics

- absorbed small bowel, 1st pass liver

<table>
<thead>
<tr>
<th></th>
<th>Onset</th>
<th>Peak</th>
<th>Wear off</th>
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<tbody>
<tr>
<td>MPH</td>
<td>30-60 min</td>
<td>1-3 hrs</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Dex</td>
<td>30-60 min</td>
<td>1-3 hrs</td>
<td>4-6 hrs</td>
</tr>
</tbody>
</table>

(cf injected / inhaled – seconds)
Long-acting stimulants

Methylphenidate
- Ritalin-LA
- Concerta

Dexamphetamine
- Adderall

Modafinil (Provigil)
Ritalin LA

- caps with 50:50 immediate:delayed release MPH beads
- don’t crush or chew; can open into soft food
- 20 white / 30 yellow / 40 mg light brown caps
- Better than placebo by teacher and parent ratings
  (Biederman J et al Paediatric Drugs. 2006)
Ritalin LA – in practice

- some delayed onset
- usually no dip
- usually as effective as IR MPH BD
- often wears off after 5-6 hours
CONCERTA OROS Delivery System

Before operation

- Laser-drilled hole
- Methylphenidate overcoat
- Rate-controlled membrane
- Methylphenidate compartment #1
- Methylphenidate compartment #2
- Push compartment

During operation

- Water
- Water
Concerta (2003)

- Ascending profile ("acute tolerance"); 10-12 hrs
- 18 mg (5/5/5), 27mg(7.5), 36 mg (10), 54mg (15) (USA have 72mg)
- = MPH TDS > placebo by teacher and parent ratings

(Pelham W et al Pediatrics 2001)
Stimulants: Troubleshooting

- Early emotional lability - perseverere
- Rebound - 3.30 dose, clonidine
- Wearing off early - extra dose
- Weight loss - post-meals, W/E holidays, ↓ dose
- Insomnia - earlier, ↓ dose, pm dose, clonidine
- Dysphoria - alt. stimulant, depression, subst abuse
- Tics
- Seizures
Practical tips

- Start 7 days
- Don’t over-attribute
- Always assume non-compliance
- Document scripts written
  - calculate time tabs will last
Stimulants - rate of prescribing in Australia

Only NSW and WA collect comprehensive data. Rates vary by state, region:

- NSW: 1.1% aged 2-17 (Salmelainen 2002)
- WA: 2.4% age 3-17 (unpublished data)

Peaks in adolescence
“Non-stimulants” for ADHD

- Atomoxetine (Strattera)
  - SNRI: inhibits pre-synaptic NA transporter
- Anti-cholinesterases
  - Aricept (donepezil), Exelon (rivastigmine)
  - used with stimulants allowing lower stimulant dose
Atomoxetine (Strattera)

- “Highly-selective” noradrenaline reuptake inhibitor
- “Does not bind to receptors associated with abuse potential” (dopamine, GABA, opioid, etc.)
  - dogs prefer food; adols w SUD find it unpleasant
- t1/2 5 hours (brain kinetics vs plasma kinetics)
  - ? benefits still next am
- Better than plac core ADHD symptoms
  (Michelson D et al. Pediatrics 2001)
  - head-to-head with MPH – data debatable
  - dec anxiety, dysthymia symptoms (in pts with ADHD)
Atomoxetine – side-effects

- GI
  - nausea, abdo pain, anorexia, constipation
  - take with food
- CNS
  - somnolence (early) - ? nocte dosing
- CVS
  - HR inc 8/min, BP syst 2-3mmH
- growth
  - flat wt and ht z scores 12-18 mths
Atomoxetine - cont.

Dosing
- 0.5 - 1.2 mg/kg/day, daily or BD, with food
- build over 3-7 days
- caps: 10, 18, 25, 40, 60mg

CYP2D6 slow metabolisers (5-7% cauc’ns)
- no diff safety profile to date
Atomoxetine – in practice

- Smooth / steady state effect
  - May take some weeks
- Variable dose-response curve
  - 0.5 - 1.2 mg/kg/d (? 2 mg/kg)
- Less powerful effect than stimulants
- Can be very sedating
- USA - 20% combination with stims
Atomoxetine – in practice

- Which kids?
  - Anxiety?
  - Asperger syndrome?
Clonidine

- $\alpha_2$ adrenergic agonist
  - widely distributed in brain
  - implicated in pathophysiology of disruptive behaviour disorders

- psychoactive properties via NA, 5-HT and DA systems:
  - interest in application to many psych syndromes (Tourette, BAD, SCZ, PTSD, social phobias, panic disorder, BZD w/d)
Clonidine in ADHD

Meta-analysis (Connor D JAACAP 1999:38:1551-9)
- 11 “good enough” studies (8 controlled),
- 150 subjects - ADHD +/- comorbid Dx, mean age 10
- dose - mean 180 mcg/day, range 100 - 240
- clinician, parent and teacher ratings
  - overall moderate positive effect size (variable)
  - recommend 2nd line

Added to stimulants (Hazell JAACAP 2003)
- reduced ODD / CD symptoms
Clonidine side-effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No. (%) of Studies Reporting Effect</th>
</tr>
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<tbody>
<tr>
<td>Sedation</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Irritability</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Drop in blood pressure</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Skin irritation (patch/2 studies reporting)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>ECG changes (3 studies reporting)</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

*Note: Number (percent) of 10 studies reporting at least some patients in their sample with side effect. ECG = electrocardiographic.*
Clonidine + MPH toxicity
- postulated mechanisms

1. Clonidine peak + MPH rebound
   - sedation, bradycardia, ↓ BP

2. MPH peak + clonidine rebound
   - activation, tachycardia, ↑ BP
Clonidine: Recommendations for use

- **MIMS**
  - hypertension; migraine prophylaxis; menopausal flushing
  - no mention of use in children

- **RCH Pharmacopoea 13th Ed 2002**
  - ADHD, Tourette's disorder, ODD, Conduct disorder
  - Initially 1 microgram/kg at night increased every 3-7 days to max 10 microgram/kg/day in 2-3 doses.

- **Psychotropic Guidelines 6th Ed. 2008**
  - 1 microgram/kg orally, daily initially (maximum 50 micrograms), increasing by 25 to 50 micrograms every third day up to 3 to 4 micrograms/kg daily
Sensible use of clonidine

- HR, BP (incl postural drop)
  - baseline and monitor
- lowest possible dose - < 200mcg/d
- use BD in combination with MPH
- taper slowly (rebound hypertension)
Antidepressants

- **SSRIs**
  - for comorbid anxiety
- **Tricyclics** (imipramine, desipramine)
  - if comorbid anxiety, depression
  - baseline ECG if > 2mg/kg/day

**Moclobemide, SNRIs**
Long-term outcome

- Improvement with time, but continues to affect fabric of daily life in most cases
- 75% continue to have problems into adolescence, 50% into adulthood
- Health care costs double controls

Increased risk

- academic failure / school drop-out
- delinquency
- unemployment
- relationship difficulties
- injuries eg MCA
- substance abuse
- crime & incarceration
Predictors of adult outcome

- Aggression
- SES
- IQ
- Peer relationships
- Parental psychopathology
- Treatment