

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

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

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 out 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
ie. 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

(Hay & Levy 2002, Faraone 2000)

- 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**

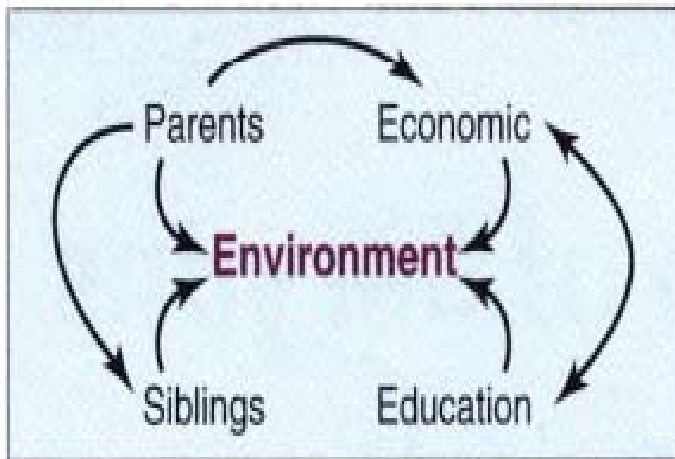
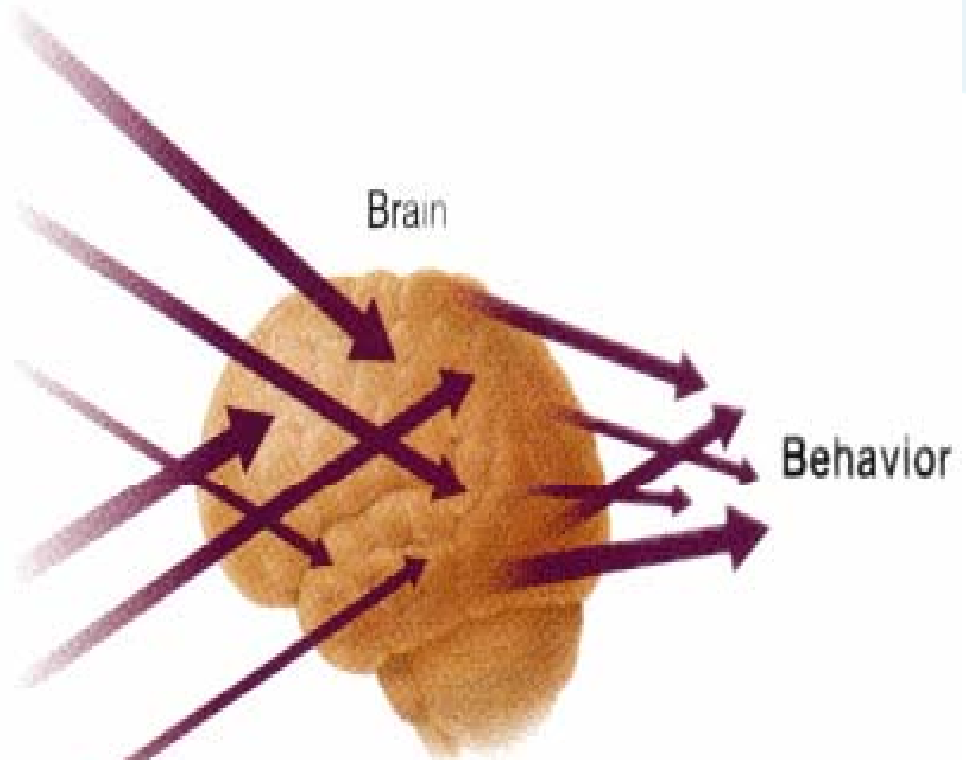
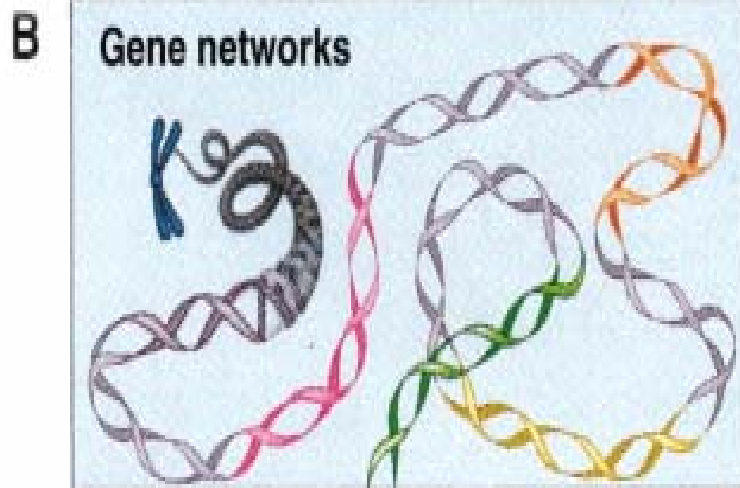
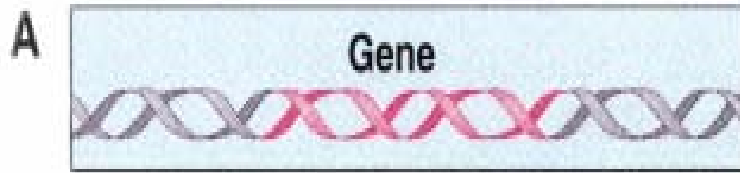
- prenatal tobacco (*Thapar Am J Psychiatry 2003; Kahn J Peds 2003 - genetic modifier*),
- prenatal alcohol - inconclusive (*Linnet Am J Psychiatry 2003*)
- lead

Diet

- salicylates, amines, colourings, preservatives
- sugar, milk, wheat
- allergy

Aetiology (cont.)

- Traumatic brain injury (*Herskivitz Radiology 1999*),
- CVA - putamen (*Max JAACAP 2002*)
- Early deprivation
(*Kreppner J Abnorm Child Psychol 2001 - adopted UK children*)
- Psychosocial disadvantage (*Biederman 1995*)
- Television (*Christakis Pediatrics 2004 yes, Stevens Pediatrics 2006 no*)



Hamer. Science, 2002

Genetics

Environment

ADHD

Developmental
stage

Functional impairments

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

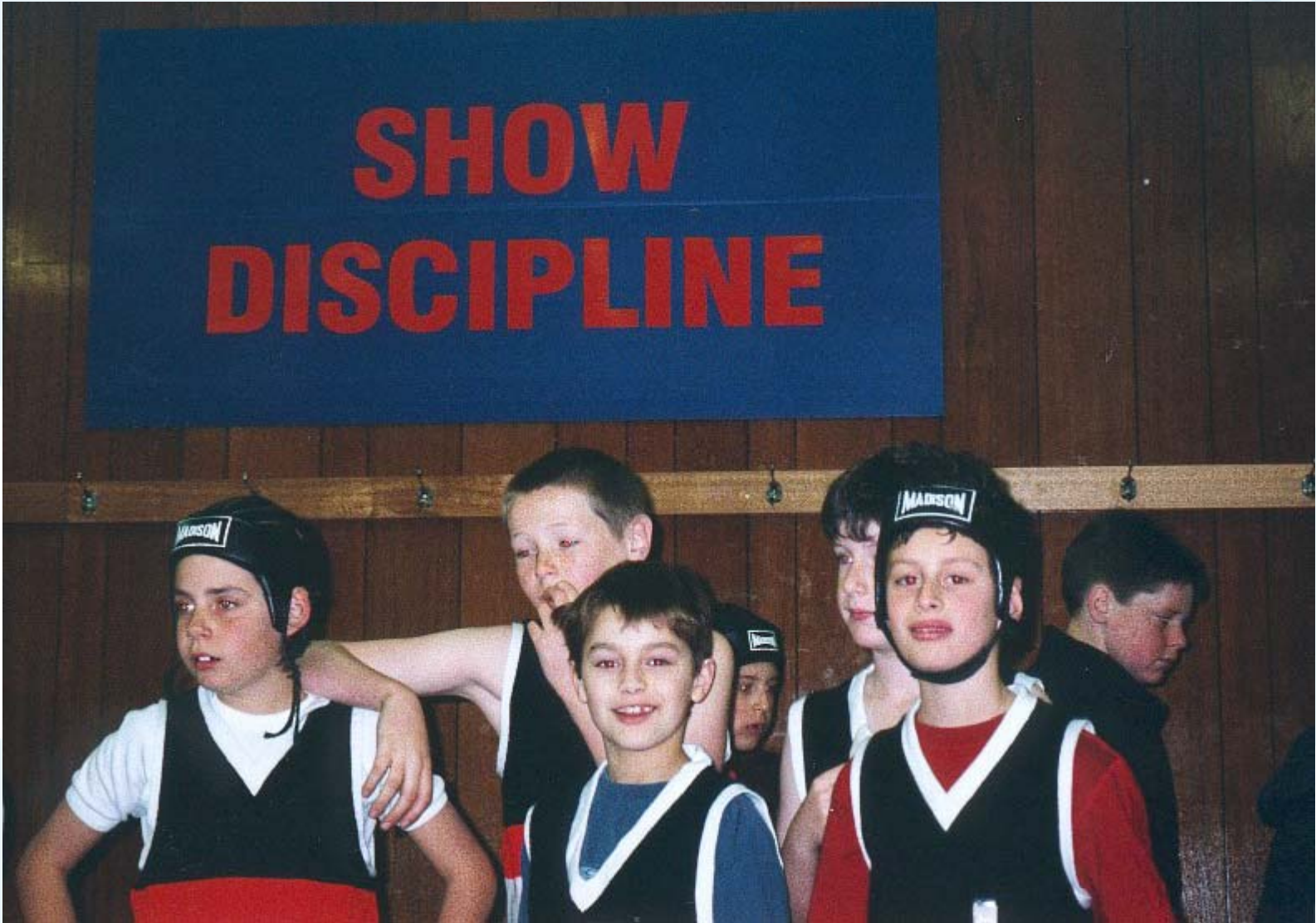
- Normal
- Specific learning disability
- Intellectual disability
- Emotional disturbance
 - attachment disorder
 - abuse
 - adjustment reaction
 - anxiety/depression
- Autistic spectrum disorder

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



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, inhib 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 +/- cardiologist consult

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

(Wilens 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

	<u>onset</u>	<u>peak</u>	<u>wear off</u>
MPH	30-60 min	1-3 hrs	3-5 hrs
Dex	30-60 min	1-3 hrs	4-6 hrs

(cf injected / inhaled – seconds)

Long-acting stimulants

Methylphenidate

- Ritalin-LA
- Concerta

Dexamphetamine

- Adderall

Modafinil (Provigil)

compounded
preparations



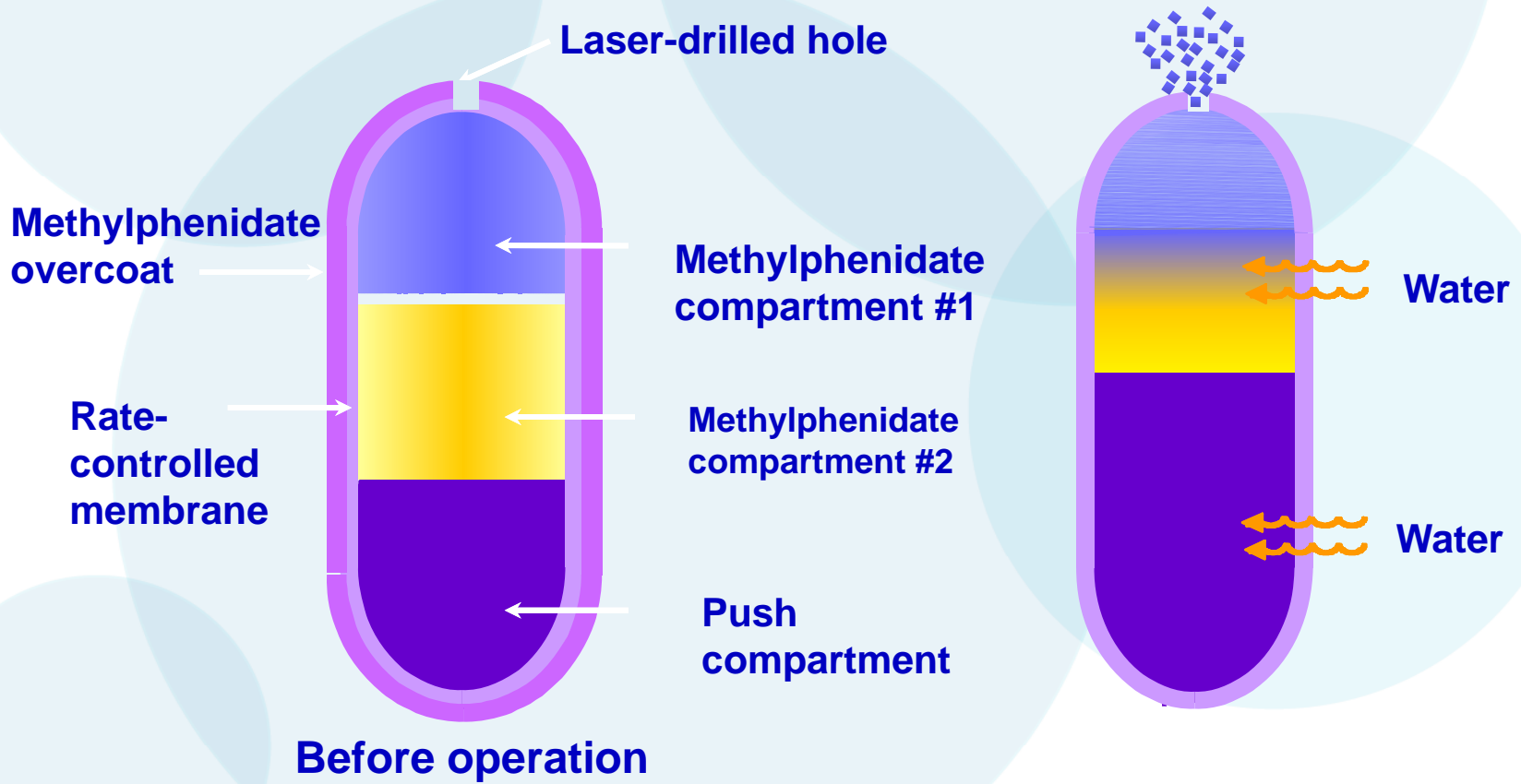
Ritalin LA

- caps with 50:50 immed: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



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 - persevere
- 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 v. sedating
- USA - 20% combination with stims

Atomoxetine – in practice

- Which kids?
 - Anxiety?
 - Asperger syndrome?

Clonidine

- α_2 adrenergic agonist
 - widely distributed in brain
 - implicated in pathophysiology of disruptive behaviour disorders
- psychoactive properties via NA, 5-HT and DA systems \therefore 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

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

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??