Attention Deficit Hyperactivity Disorder: an overview of current advances in the field

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Outline of presentation

1. ADHD: definitional issues
2. ADHD: comorbid conditions
3. ADHD: developmental stages
4. ADHD: aetiological issues
5. ADHD: treatment issues
"Hello, Emily. This is Gladys Murphy up the street. Fine, thanks... Say, could you go to your window and describe what's in my front yard?"
1. **ADHD: definition**

Diagnostic nosology-some comments:

DSM-IV definition of a mental disorder-
A mental disorder is conceptualized as

a clinically significant
*behavioural pattern* that occurs
in an individual
and
is associated with *impairment* in
one or more areas of functioning

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1. ADHD: definition

Diagnostic nosology-some comments

in children and adolescents-

impairment is developmentally inappropriate, judged relative to children of the same age, gender and IQ in social, academic, occupational or other important areas of functioning

multi-informant reports required

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1. **ADHD: definition**

   multi-informant reports required:
   
   parent,
   
   teacher
   
   child

   
   low concordance repeatedly shown

   
   varys between externalising and internalising disorders

   
   externalising: parent-teacher: increased agreement

   
   internalising: child-teacher: increased agreement

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1. **ADHD: definition**

   assessment within a developmental context:

   symptom patterns and associated with impairment in social, academic, occupational or other important areas of functioning

   need to be monitored longitudinally so the clinician can accurately assess the child

   [1] within their current developmental phase and
   [2] across developmental phases as each child develops
1. **ADHD: definition**

Attention Deficit Hyperactivity Disorder (ADHD)

DSM-IV CRITERIA

- six or more symptoms, at least six months duration, maladaptive/inconsistent with developmental level
- inattention dimension and/or hyperactivity-impulsivity dimension
- evident in at least two settings
- onset before seven years of age
- impairment in social, academic, occupational functioning
- symptoms not due to a PDD, Psychotic, Mood, or Anxiety Disorder

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1. ADHD: definition

TYPES of ADHD

- combined type
- predominantly inattentive type
- predominantly hyperactive-impulsive type
2. **ADHD: key comorbid conditions:**

- oppositional defiant disorder/conduct disorder
- anxiety and/or depressive disorders
- tic disorders
- language learning disorders (spelling/reading/arithmetic/writing)
- speech and language disorders (articulation/grammar)
- developmental coordination disorder
3. ADHD: developmental stages

Common possible developmental pathways: all associated with educational, social, occupational under-achievement, alcohol/substance abuse/dependence disorders, altered adult personality

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<thead>
<tr>
<th>Childhood</th>
<th>Adolescence</th>
<th>Adulthood</th>
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<tbody>
<tr>
<td>ADHD-CT</td>
<td>ADHD-IA</td>
<td>ADHD-IA</td>
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<td>ADHD-CT</td>
<td>Depressive d</td>
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<td>ADHD-CT</td>
<td>Conduct d</td>
<td>ASPD</td>
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4. ADHD: Key biological risk factors

\[ d = 1.0 \]

\[ d = 0.5 \]

Biological risk factors

Psychosocial risk factors

Healthy

ADHD

ADHD

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4. ADHD: Key biological risk factors

Neuropsychology of ADHD
4. ADHD: Key biological risk factors

Cognitive neuroscience
response inhibition tasks (eg STOP tasks)
working memory tasks (eg n-back; VSWM tasks)
deficits in both implicating PFC-striatal and
PFC-striatal-parietal neural networks
comorbid conditions: association unclear
investigated as markers for medication response
in children with ADHD
Spatial working memory task - CANTAB
Between Search Errors (mean)

Level of Difficulty

- ADHD-CT(um)
- ADHD-CT(m)
- Controls
Delayed Matching to Sample task - CANTAB
Effect sizes before and after additional comorbid conditions.
4. ADHD: Key biological risk factors

Cognitive neuroscience

working memory (Mehta et al., 2000)

PET VSWM task 10 healthy adult males 2 sessions 2W apart
MPD 40mg or placebo with scanning 90+ minutes later
↓ rCBF -left DLPFC, left SMA, left PPC
associated with improved VSWM performance

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4. ADHD: Key biological risk factors

Cognitive neuroscience

selective attention/working memory
(Bush et al., 2008)

fMRI MSIT 21 adults ADHD RCT 6 weeks
OROs-MPD or placebo
↑ daMCC associated with improved performance
4. ADHD: Key biological risk factors

Composite z-scores
ADHD children in the low dose and high dose Condition (dex. 2.5mg/7.5mg)
(Mollica et al., Human Psychopharmacology 2004)
4. ADHD: Key biological risk factors

Neuroimaging of ADHD
4. ADHD: Key biological risk factors

Neuroimaging
- structural MRI:
  ↓ prefrontal cortex, basal ganglia, medial temporal and inferior parietal lobes (global 3% decrease)

primarily white matter (d=.45 cf .28 gray matter)

developmental trajectories independent of medication treatment

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Castellanos et al., JAMA 2002

Controls > ADHD

$p < .003$
4. ADHD: Key biological risk factors

Neuroimaging
- functional MRI:
  - prefrontal cortex, basal ganglia, medial temporal
  - and inferior parietal lobes

  bilateral task dependent decrease in activation

  post-puberty - midline activation - compensatory?
  pre-puberty - not evident

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N=14, CBCL inattention subscale T score: 72.23 (10.72)
<table>
<thead>
<tr>
<th>Region of activation</th>
<th>BA</th>
<th>C (mm)</th>
<th>Z</th>
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<tbody>
<tr>
<td>Control Group greater than ADHD-CT Group</td>
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<tr>
<td>Parieto-Occipital</td>
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<tr>
<td>R Precuneus</td>
<td>19</td>
<td>24 -70 32</td>
<td>3.53</td>
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<tr>
<td>R Cuneus</td>
<td>19</td>
<td>32 -90 28</td>
<td>2.82</td>
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<tr>
<td>Posterior Parietal</td>
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<tr>
<td>R Inf. Parietal</td>
<td>40</td>
<td>36 -40 50</td>
<td>2.82</td>
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<tr>
<td>Frontal/Subcortical</td>
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<tr>
<td>R Caudate Nucleus, Body</td>
<td>18</td>
<td>18 -12 22</td>
<td>2.82</td>
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N=24, CBCL inattention subscale T score: 72.14 (9.43)
Greater Activation for Control than Dysthymic Disorder

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<thead>
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<th>Region</th>
<th>BA</th>
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<td><strong>Right Frontal Lobe</strong></td>
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<td>Inferior Frontal Gyrus</td>
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<td>10</td>
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<td>Middle Frontal Gyrus</td>
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<td>44</td>
<td>42</td>
<td>14</td>
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<tr>
<td>Middle Frontal Gyrus</td>
<td>46</td>
<td>40</td>
<td>18</td>
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<tr>
<td>Middle Frontal Gyrus</td>
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<td>34</td>
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<tr>
<td>Inferior Frontal Gyrus</td>
<td>44</td>
<td>50</td>
<td>14</td>
<td>14</td>
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<tr>
<td><strong>Right Parietal Lobe</strong></td>
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<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>40</td>
<td>-58</td>
<td>44</td>
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<tr>
<td>Superior Parietal Lobule</td>
<td>7</td>
<td>36</td>
<td>-74</td>
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<tr>
<td>Inferior Parietal Lobule</td>
<td>39</td>
<td>48</td>
<td>-62</td>
<td>40</td>
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<tr>
<td>Superior Parietal Lobule</td>
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<td>-74</td>
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<td>Precuneus</td>
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<td>Inferior Parietal Lobule</td>
<td>40</td>
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<td>-44</td>
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N=14, CBCL inattention subscale T score: 70.88 (9.75)

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4. ADHD: Key biological risk factors

Molecular genetics of ADHD
4. ADHD: Key biological risk factors

Genetics:

- heritability estimates 65%-90% phenotypic variance in population

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
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<tbody>
<tr>
<td>DAT1 10-repeat allele,</td>
<td>1.13</td>
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<tr>
<td>DRD4 7-repeat allele,</td>
<td>1.45</td>
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<tr>
<td>Taq1 polymorphism DBH,</td>
<td>1.33</td>
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<tr>
<td>SNAP-25 gene</td>
<td>1.19</td>
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<tr>
<td>5HT1B</td>
<td>1.44</td>
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4. ADHD: Key biological risk factors

- Cognitive deficits in ADHD are associated with these key candidate genes:

Healthy children:

DAT1 3’ VNTR 10-repeat allele
DAT1 intron 8 VNTR 3-repeat allele → R spatial inattention
DAT1 3’ UTR VNTR 10-repeat allele (η² = .07/.08/.08)

- this 10/3DAT1 haplotype – ADHD (OR 2.58)
Epigenetics has arrived....
The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
RNA polymerase
transcription factors
acetylated histones

DNA methyltransferase
Histone deacetylase

methylated DNA

Chromatin remodelling proteins

deacetylated histones
They Are What She Ate

Scientists have found that certain nutrients consumed during pregnancy can change the way genes are activated in the offspring of laboratory mice, without affecting their underlying DNA.

NORMAL DIET

One strain of mice tends to have fat, yellow pups that are prone to cancer, diabetes and other diseases.

Most pups are fat and yellow because the “agouti” gene that determines coat color and appetite control goes into overdrive when an adjacent segment of genetic material interferes with it.

The segment, called a transposon, is the remnant of a past viral infection. Transposons act like on or off switches for genes.

MODIFIED DIET

(Adding vitamin B12, folic acid, choline and betaine)

Transposons are powered by compounds, called methyl groups, from food.

When pregnant mice were fed extra methyl groups found in supplements like folic acid, both the transposon and agouti gene were silenced. Most of their pups were brown and had normal appetites.

Source: Dr. Randy L. Jirtle, Department of Radiation Oncology, Duke University
Epigenetics

-Gene functional activity not structure (DNA sequence) changed

-parental care affects stability genes: stress responsiveness, neural development, neural reproduction

-tactile stimulation/nurture (week 1)

\[
\begin{align*}
\text{GH} & \uparrow \\
\text{IGF} & \uparrow \\
\text{glucocorticoids} & \downarrow
\end{align*}
\]
-tactile stimulation/nurture

CRF gene

CRF mRNA

glucocorticoid receptors – eg hippocampus

serotonin protective effects blocked by

absence of NGF1-A mRNA

NGF1-A a transcription factor – binds to exon 1 GR and increases GR expression

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The structure of a typical human protein coding mRNA including the untranslated regions (UTRs)
-regulatory regions turn on/off coding areas

Exon 7 binding site for NGF1-A

Exon 7  3’   5’

- maternal care

demethylation 5’ and histone deacetylation

open up chromatin and increase binding translational factors
high stimulation ↓ low stimulation 1\textsuperscript{st} 24 hours

NGF1-A Exon 7 5’ methylation and histone acetylation

CRF

Glucocorticoid receptors – eg hippocampus

-this process can be reversed by dietary methionine (a histone deacetylase inhibitor) in adult rats
4. ADHD: Key biological risk factors

Summary

- biological factors important
- large effect: CogNS constructs
- brain structural/functional changes
  developmental stage-independent deficits
  compensatory changes post-puberty
- small effect: candidate genes - symptoms
- medium effect: candidate genes - CogNS measures;
- medication changes non-specific currently
- epigenetics emphasizing importance of biological and psychosocial factors being in synergy
4. ADHD: Key psychological risk factors

**Summary**

- parental psychopathology: alcohol/depressive/anxiety disorders
- marital functioning:
- family functioning:
- peer group functioning:

“empathy/attunement/sensitivity/responsiveness”

“flexibility/adaptiveness/regulation of affect/problem solving”

sociocultural context affects the character of these aspects and their detection

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Seminal research study

Conclusion: Protective factors can make a more profound impact on the life course than a specific risk factor

Individual coping styles
- Social Competence
- Problem Solving Skills
- Autonomy
- Sense of purpose, belief in a bright future

Environmental factors
- Caring Relationships
- High Expectations
- Opportunities for participation

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<table>
<thead>
<tr>
<th>Risk factors</th>
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<tr>
<td><strong>Child factors</strong></td>
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<tr>
<td>Low self esteem</td>
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<td>Poor social skills</td>
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<td>Poor problem solving</td>
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<td>Difficult temperament</td>
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<td>Lack of empathy</td>
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<td>Homelessness</td>
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<td>Early school leaving</td>
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<tr>
<td><strong>Family factors</strong></td>
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<tr>
<td>Family violence</td>
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<tr>
<td>Poor supervision</td>
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<tr>
<td>Harsh or inconsistent discipline</td>
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<tr>
<td>Lack of warmth and affection</td>
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<tr>
<td>Abuse and neglect</td>
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<tr>
<td><strong>School context</strong></td>
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<tr>
<td>School failure</td>
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<tr>
<td>Bullying</td>
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<td>Peer rejection</td>
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<tr>
<td>Poor attachment to school</td>
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<tr>
<td>Deviant peer group</td>
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<tr>
<td><strong>Life events</strong></td>
</tr>
<tr>
<td>Divorce and family breakup</td>
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<tr>
<td>Death of a family member</td>
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<tr>
<td><strong>Community and cultural factors</strong></td>
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<tr>
<td>Neighbourhood violence and crime</td>
</tr>
<tr>
<td>Lack of support services</td>
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<tr>
<td>Social or cultural discrimination</td>
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<tr>
<td>Community norms concerning violence</td>
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<table>
<thead>
<tr>
<th>Protective factors</th>
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<tbody>
<tr>
<td><strong>Child factors</strong></td>
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<tr>
<td>Social competence</td>
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<tr>
<td>Attachment to family</td>
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<td>Empathy</td>
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<td>Problem solving</td>
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<tr>
<td>Optimism</td>
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<td>School achievement</td>
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<tr>
<td>Easy temperament</td>
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<td>Good coping style</td>
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<tr>
<td><strong>Family factors</strong></td>
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<tr>
<td>Supportive caring parents</td>
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<tr>
<td>Family harmony</td>
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<tr>
<td>Secure and stable family</td>
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<tr>
<td>Supportive relationship with other adult</td>
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<td>Strong family norms and morality</td>
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<tr>
<td><strong>School context</strong></td>
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<tr>
<td>Positive school climate</td>
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<tr>
<td>Prosocial peer group</td>
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<tr>
<td>Sense of belonging</td>
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<tr>
<td>Opportunities for some success at school and recognition of achievement</td>
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<tr>
<td>School norms re violence</td>
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<td><strong>Life events</strong></td>
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<tr>
<td>Meeting significant person</td>
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<tr>
<td>Moving to new area</td>
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<tr>
<td>Opportunities at critical turning points or major life transitions</td>
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<tr>
<td><strong>Community and cultural factors</strong></td>
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<td>Access to support services</td>
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<td>Community networking</td>
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<tr>
<td>Attachment to the community</td>
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<tr>
<td>Participation in community group</td>
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<tr>
<td>Community/cultural norms against violence</td>
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<tr>
<td>Strong cultural identity/ethnic pride</td>
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</table>
"Our psychopharmacologist is a genius."
I worry about the decreased polarization of our society.
"All right, Billy, you just go right ahead! ... I've warned you enough times about playing under the anvil tree!"
"Rub his belly, Ernie! Rub his belly!"
5. A model for intervention

-assessment and treatment focuses on delineation of risk factors and resilience factors—biologically (eg, executive function deficits; good arousal regulation) psychologically (eg, externalise blame; balanced critical self-reflection) and socially (eg, hostile critical interpersonal environment; confiding, nurturing consistent interpersonal environment)

-monitoring of these risk and resilience factors and their response to treatment through developmental phases

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5. **A model for intervention**
-a practical approach

[A] psychological and social treatment approach implemented for 4-6 weeks (may take 6 months of new habit formation before sustained behavioural change)

*key elements are the interpersonal and the intra-individual milieu*

**interpersonal:** positive reinforcement, response cost, token economy, contingency planning (turn taking, active listening, active ignoring, empathy skills, etc), making and keeping friends

**intra-individual:** controlled breathing, muscle biofeedback, guided visual imagery

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5. **A model for intervention**

- a practical approach

[B] key other vulnerabilities addressed – vision, hearing, specific verbal and/or visuospatial learning difficulties, developmental coordination difficulties, speech and language difficulties

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5. A model for intervention

A practical approach

[C] medication use to facilitate availability of the young person to learn from the psychological and social interventions through

- better arousal regulation
- better mood regulation
- better executive functioning

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5. A model for intervention

**Summary**
- medication can aid a child’s ability to invest in a psychosocial treatment program and learn from this program
- can take 6 months of practice before new habits are formed
- biological and psychosocial treatments maximize resilience and minimize risk factors through shared effects on the brain and the mind
5. A medication approach (Australian perspective)

- stimulant medication is the first line treatment

short-acting forms: methylphenidate, dexamphetamine
long-acting forms: OROS-methylphenidate, LA-methylphenidate

clear and substantial evidence for methylphenidate efficacy up to a dose of 60mg daily for treatments periods of approximately 12 months

methylphenidate and dexamphetamine similar efficacy and adverse effects profile although individual preferences manifest
5. A medication approach (Australian perspective)

- **Stimulant medication benefits**
  
  decrease core symptoms of ADHD  
  decrease aggression  
  increase quality of social interactions  
  increase compliance  

- **Stimulant medication indications**

  ADHD diagnosis and psychosocial interventions insufficient

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5. A medication approach (Australian perspective)

- Stimulant medication adverse effects

  initial insomnia,
  appetite suppression

  nervousness, restlessness, dysphoria,
  easy crying, agitation, depressive symptoms, stomach ache
  headache, dizziness, rash, motor tics, mannerisms

  in overdose: delirium, sweating, tremor, twitching, vomiting

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5. A medication approach (Australian perspective)

- Stimulant medication adverse effects

  growth retardation (MTA 3y f/u: 2cm ↓/2.7kg ↓)
  weight loss

  epileptic seizures
  psychotic episodes
  abuse potential

  not adverse effects but careful monitoring needed in vulnerable patients

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5. A medication approach (Australian perspective)

- Atomoxetine is the second line treatment

  specific potent noradrenaline re-uptake inhibitor indicated when stimulant medication ineffective, associated with significant adverse effects

  common adverse effects: nausea, drowsiness, initial insomnia, appetite suppression

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5. **A medication approach (Australian perspective)**

- **Imipramine** is a third line treatment tricyclic compound similar to atomoxetine (a phenylpropanolamine derivative) but with less specific noradrenaline effect and significant cardiac adverse effects.

- **Clonidine** is a third line treatment central $\alpha$-2 noradrenergic agonist with significant effect; primarily hyperactivity/impulsiveness, significant drowsiness, hypotensive and cardiac adverse effects. Gradual withdrawal because of rebound hypertension and tics.

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5. **A medication approach (Australian perspective)**

- **Neuroleptic medication is a third line treatment**
  atypical neuroleptic medication: eg risperidone / aripiprazole
  low doses (up to risperidone 1.5mg daily equivalent)
  severe aggression, affective lability, PDD, ID

  typical neuroleptic medication: eg pericyazine - thioridazine
  equivalent (now withdrawn)

  third line treatments only used with careful monitoring
  and involvement in a treatment-resistant unit

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5. A medication approach (Australian perspective)

Conclusion

- start low, go slow, finish slow, although ensure optimal doses are used

- medication facilitates each child’s ability to learn in the classroom, playground and home environment: new habits can take 6 months to evolve

- Comprehensively assess and treat with approved medication and/or psychosocial treatments all comorbid conditions

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5. We need an adequate evidence base for medication treatment, psychosocial treatment and their combination.
In the context of careful systematic comprehensive training…
TRANSLATIONAL CLINICAL SCIENTISTS

From laboratory bench, social/cultural factors to clinical practice
Tools for Translation: 2009

WGAS
Sequencing
Transgenics
Epigenetics
Databases

Electrode
Arrays
Zebrafish
PET
fMRI
DTI
Databases

Web 2.0
Knowledge management

Repositories – Data Sharing - Integration