"Let me see if Philip can
Be a little gentleman;
Let me see if he is able
To sit still for once at
table."

The Story of Fidgety Philip
by Dr. Heinrich Hoffmann
1845
As he trudged along to school,
It was always Johnny's rule
To be looking at the sky
And the clouds that floated by;
But what just before him lay,
In his way,
Johnny never thought about;
So that everyone cried out,
"Look at little Johnny there,
Little Johnny Head-in-Air!"

The Story of Johnny Head-in-the-Air
by Dr. Heinrich Hoffmann
1845
Defining adult ADHD (DSM-5)

● **Criteria A**: 5 or more symptoms of inattention or hyperactivity-impulsivity

● **Criteria B**: Several symptoms present by the age of 12

● **Criteria C**: Several symptoms present in two or more settings

● **Criteria D**: Symptoms interfere with or reduce quality of social, educational or occupational functioning

● **Criteria E**: Symptoms are not better explained by another condition, such as mood disorder

American Psychiatric Association. Diagnostic and Statistical Manual (DSM) of Mental Disorders. 5th Edition 2013
Tax Issues & Relationship Problems

Substance use problems

Teenage Pregnancy and aggressive behaviour

Several Issues!

Several High Profile Business Failures
Inter rater Reliability of Diagnoses From the Initial DSM-5 Field Trials

Kappa

Major Neurocognitive disorder
Autism
PTSD
ADHD
Bipolar 1
Schizophrenia
Conduct Disorder
ODD
Major Depressive Disorder
Disruptive Mood Dysregulation Disorder
Generalised Anxiety Disorder

Am J Psych 2013
ADHD is common

Prevalence of ADHD in China (Shanghai)

- Two stage assessment
  - ADHD-RS-IV parent reported questionnaire
  - KIDDIE SADS diagnostic interview

- Questionnaires
  - 15,412 distributed
  - 12,954 returned
  - 9,900 valid (64.2%)
  - 5,648 eligible for interview stage (several schools opted out of this stage)

- Interviews
  - 1187 were interviewed
  - **Overall prevalence 4.6%**

- Gender ratio 2.5 : 1
  - Boys 6.6%,
  - Girls 2.7%

- Type
  - Combined type 1.8%
  - Inattentive type 2.4%
  - Hyperactive/Impulsive type 0.4%

- Age
  - 5-6 years 5.2%
  - 7 – 10 years 6.3%
  - 11 – 15 years 2.4%

Polanczyk et al 2007

Coghill, Du, Su in preparation
There is considerable cross national variability in prescribing for ADHD.
ADHD IS IMPAIRING
Pre-treatment mean domain T-scores for HRQoL in three ADHD study populations and controls

<table>
<thead>
<tr>
<th>Domain</th>
<th>Study SPD498-326</th>
<th>ADORE study</th>
<th>Pooled ATX studies</th>
<th>Diabetes mellitus</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achievement</td>
<td>30.2</td>
<td>30.2</td>
<td>30.5</td>
<td>49.7</td>
<td>48.6</td>
</tr>
<tr>
<td>Risk Avoidance</td>
<td>32.3</td>
<td>29.9</td>
<td>30.2</td>
<td>50.0</td>
<td>50.5</td>
</tr>
<tr>
<td>Resilience</td>
<td>36.8</td>
<td>36.0</td>
<td>36.0</td>
<td>45.3</td>
<td>44.6</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>35.5</td>
<td>32.8</td>
<td>34.4</td>
<td>45.5</td>
<td>42.8</td>
</tr>
<tr>
<td>Comfort</td>
<td>44.5</td>
<td>42.5</td>
<td>43.7</td>
<td>50.8</td>
<td>53.5</td>
</tr>
</tbody>
</table>

CHIP CE Domains

Dundee Data
The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime

Faraone, S. V. et al. (2015) Attention-deficit/hyperactivity disorder
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.20
Adult outcomes of ADHD

- Grade point average
- Class rank (%)
- Suspended during high school
- Special education during high school
- Retained in grade
- Graduated high school
- Enrolled in college
- Currently full-time student
- Total years of education

- Number of full-time jobs
- Ever fired from employment
- Number of lifetime moves
- Close friends now
- Social problems
- Dating partners since high school
- Age at first sexual intercourse
- Total no. of sex partners
- No. of sex partners in past year
- Time spent watching TV
- High rates of crime
- High rates of substance misuse
- High rates of psychiatric disorder
- Have trouble saving to pay bills
- Driving offences and accidents
- Ever had a credit card
- Have a savings account
- High rates of crime
- High rates of substance misuse
- High rates of psychiatric disorder
What works for ADHD
Which treatments work for ADHD?

- **Restrictive elimination diets**
- **Artificial food colourings**
- **Omega 3 fatty acids (fish oils)**
- **Cognitive Training**
- **Neurofeedback**
- **Stimulant Medications** (e.g. Ritalin)

**Effect Size**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrictive elimination diets</td>
<td>0.51</td>
</tr>
<tr>
<td>Artificial food colourings</td>
<td>0.42</td>
</tr>
<tr>
<td>Omega 3 fatty acids (fish oils)</td>
<td>0.16</td>
</tr>
<tr>
<td>Cognitive Training</td>
<td>0.24</td>
</tr>
<tr>
<td>Neurofeedback</td>
<td>0.29</td>
</tr>
<tr>
<td>Parent training</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Parent Training Does improve parenting and conduct problems

**Negative parenting**

- SMD 0.43
- Overall SMD = 0.43; 95% CI = 0.24 - 0.62

**Positive parenting**

- SMD 0.63
- Overall SMD = 0.63; 95% CI = 0.47 - 0.7

**Conduct Problems**

- SMD 0.31
- Overall SMD = 0.31; 95% CI = 0.05 - 0.57
Which treatments work for ADHD?

- Restrictive elimination diets
- Artificial food colourings
- Omega 3 fatty acids (fish oils)
- Cognitive Training
- Neurofeedback
- Parent training
- Stimulant Medications (e.g. Ritalin)

Effect Sizes:
- Restrictive elimination diets: 0.51
- Artificial food colourings: 0.42
- Omega 3 fatty acids (fish oils): 0.16
- Cognitive Training: 0.24
- Neurofeedback: 0.29
- Parent training: 0.02
- Stimulant Medications (e.g. Ritalin): 1.00

Note: The treatments marked with a checkmark have shown statistically significant effects.
Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis

Samuele Cortese, Nicoletta Adamo, Cinzia Del Giavone, Christina Mohr-Jensen, Adrian J Haynes, Sara Carucci, Lauren Z Atkinson, Luca Tessari, Tobias Banaschewski, David Coghill, Chris Hollis, Emily Simonoff, Alessandro Zuddas, Corrado Barbui, Marianna Purgato, Hans-Christoph Steinhausen, Farhad Shokraneh, Jun Xia, Andrea Cipriani

Summary

Background The benefits and safety of medications for attention-deficit hyperactivity disorder (ADHD) remain controversial, and guidelines are inconsistent on which medications are preferred across different age groups. We aimed to estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.

Methods We did a literature search for published and unpublished double-blind randomised controlled trials comparing amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo. We systematically contacted study authors and drug manufacturers for additional information. Primary outcomes were efficacy (change in severity of ADHD core symptoms based on teachers’ and clinicians’ ratings) and tolerability (proportion of patients who dropped out of studies because of side-effects) at timepoints closest to 12 weeks, 26 weeks, and 52 weeks. We estimated summary odds ratios (ORs) and standardised mean differences (SMDs) using pairwise and network meta-analysis with random effects. We assessed the risk of bias of individual studies with the Cochrane risk of bias tool and confidence of estimates with the Grading of Recommendations Assessment, Development, and Evaluation approach for network meta-analyses. This study is registered with PROSPERO, number CRD42014008976.
133 double-blind RCTs, >24,500 participants
## Mean change in ADHD symptoms

### CHILDREN & ADOLESCENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>SMD [95% CI]</th>
<th>Favors</th>
<th>SMD [95% CI]</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>-1.02 [-1.19, -0.85]</td>
<td>drug</td>
<td>-0.79 [-0.99, -0.58]</td>
<td>placebo</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>-0.56 [-0.66, -0.45]</td>
<td>drug</td>
<td>-0.45 [-0.58, -0.32]</td>
<td>placebo</td>
</tr>
<tr>
<td>Bupropion</td>
<td>-0.96 [-1.69, -0.22]</td>
<td>drug</td>
<td>-0.46 [-0.85, -0.07]</td>
<td>placebo</td>
</tr>
<tr>
<td>Clonidine</td>
<td>-0.71 [-1.17, -0.24]</td>
<td>drug</td>
<td>no data</td>
<td>placebo</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>-0.67 [-0.85, -0.50]</td>
<td>drug</td>
<td>no data</td>
<td>placebo</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>-0.78 [-0.93, -0.62]</td>
<td>drug</td>
<td>-0.49 [-0.64, -0.35]</td>
<td>placebo</td>
</tr>
<tr>
<td>Modafinil</td>
<td>-0.62 [-0.84, -0.41]</td>
<td>drug</td>
<td>0.16 [-0.28, 0.59]</td>
<td>placebo</td>
</tr>
</tbody>
</table>

### ADULTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>SMD [95% CI]</th>
<th>Favors</th>
<th>SMD [95% CI]</th>
<th>Favors</th>
</tr>
</thead>
</table>

---

**Drugs vs placebo - Efficacy**

Methylphenidate in C&A only and amphetamines in adults only were significantly better than placebo (OR 0.69 and 0.68, respectively)
Drugs vs placebo - Tolerability

### Dropouts due to adverse events

<table>
<thead>
<tr>
<th>Drug</th>
<th>CHILDREN &amp; ADOLESCENTS</th>
<th>ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95% CI]</td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td>2.30 [1.36, 3.89]</td>
<td>3.26 [1.54, 6.92]</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>1.49 [0.84, 2.64]</td>
<td>2.33 [1.28, 4.25]</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.51 [0.17, 13.27]</td>
<td>2.55 [0.33, 19.93]</td>
</tr>
<tr>
<td>Clonidine</td>
<td>4.52 [0.75, 27.03]</td>
<td>no data</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>2.64 [1.20, 5.81]</td>
<td>no data</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>1.44 [0.90, 2.31]</td>
<td>2.39 [1.40, 4.08]</td>
</tr>
<tr>
<td>Modafinil</td>
<td>1.34 [0.57, 3.18]</td>
<td>4.01 [1.42, 11.33]</td>
</tr>
</tbody>
</table>

- **Weight decreased** by AMPH and MPH in C&A + adults.
- **Systolic blood pressure increased** by AMPH in C&A only, and MPH in adults only
- **Diastolic blood pressure increased** by AMPH in C&A only, and MPH in C&A + adults.
Is there consistent evidence of genetic, environmental or neurobiological risk factors associated with ADHD?

Causal pathways to ADHD
"Single cause" model of ADHD

Genetic factors

Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways

1° Behavioural Inhibition deficits

2° Broader Executive Dysfunctions e.g. Working memory, planning

ADHD Symptoms

Biological

Cognitive

Behaviour
Causal heterogeneity in ADHD

Multiple Environmental Factors ↔ Multiple Genetic Factors

Mesolimbic reward circuits

Fronto cerebellar circuits

Dopaminergic and noradrenergic abnormalities in fronto/striatal pathways

Temporal lobe, amygdalo/hippocampal circuits

? Acetylcholine

Delay aversion

Timing deficits

Behavioural Inhibition deficits

Working Memory Deficits

Non-Working Memory Deficits

ADHD Symptoms

Coghill, Seth and Matthews, 2014
A direct comparison of neuropsychological functioning across the six key domains in ADHD

<table>
<thead>
<tr>
<th>Factor</th>
<th>ADHD Mean (SD)</th>
<th>TYP Mean (SD)</th>
<th>p</th>
<th>Effect Size (δ)</th>
<th>% with deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>-0.43 (1.00)</td>
<td>0.54 (1.04)</td>
<td>&lt; .001</td>
<td>0.95</td>
<td>30.1</td>
</tr>
<tr>
<td>Inhibition</td>
<td>-0.12 (0.44)</td>
<td>0.15 (0.44)</td>
<td>&lt; .001</td>
<td>0.61</td>
<td>22.9</td>
</tr>
<tr>
<td>Delay Aversion</td>
<td>-0.37 (0.96)</td>
<td>0.47 (1.10)</td>
<td>&lt; .001</td>
<td>0.82</td>
<td>36.1</td>
</tr>
<tr>
<td>Decision Making</td>
<td>-0.20 (0.85)</td>
<td>0.25 (0.79)</td>
<td>&lt; .001</td>
<td>0.55</td>
<td>20.5</td>
</tr>
<tr>
<td>Timing</td>
<td>-0.36 (1.16)</td>
<td>0.43 (1.07)</td>
<td>&lt; .001</td>
<td>0.71</td>
<td>31.3</td>
</tr>
<tr>
<td>Variability</td>
<td>-0.10 (0.79)</td>
<td>0.13 (0.40)</td>
<td>.029</td>
<td>0.37</td>
<td>18.1</td>
</tr>
</tbody>
</table>

Coghill, Seth and Matthews, 2014
A direct comparison of neuropsychological functioning across the six key domains in ADHD

Coghill, Seth and Matthews, 2014
<table>
<thead>
<tr>
<th>Task/Measure</th>
<th>Hyperkinetic disorder vs controls effect size (d)</th>
<th>Proportion ADHD cases with deficit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Working Memory</td>
<td>0.75</td>
<td>24</td>
</tr>
<tr>
<td>• BSE</td>
<td>0.70</td>
<td>15</td>
</tr>
<tr>
<td>• Strategy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tower of London (Planning, working memory)</td>
<td>0.38</td>
<td>13</td>
</tr>
<tr>
<td>ID/ED Attentional Set Shifting</td>
<td>0.46</td>
<td>11</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>0.60</td>
<td>11</td>
</tr>
<tr>
<td>Delayed Matching to Sample</td>
<td>0.92</td>
<td>39</td>
</tr>
<tr>
<td>Pattern Recognition</td>
<td>0.89</td>
<td>30</td>
</tr>
<tr>
<td>Spatial Recognition</td>
<td>0.72</td>
<td>28</td>
</tr>
<tr>
<td>PAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tot errors</td>
<td>0.47</td>
<td>19</td>
</tr>
<tr>
<td>• Tot trials</td>
<td>0.58</td>
<td>21</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>0.71</td>
<td>8</td>
</tr>
</tbody>
</table>

Rhodes et al 2005
ADHD is associated with significant deficits in both executive and non-executive aspects of working memory. However these deficits were not associated with altered response latencies or inhibitory control. Neither were deficits in any of the other executive functions measured (data not shown). These data present a strong challenge to the primacy of inhibition deficits in ADHD.
These deficits in non working memory are restored by an acute challenge with methylphenidate.

However acute methylphenidate fails to restore executive memory planning or set shifting deficits.

Chronic challenge with methylphenidate also results in improvement of non-executive memory functioning.

There is however evidence that a degree of tolerance may develop with chronic exposure.

Chronic exposure still does not impact on executive deficits.

Despite clear evidence for clinical response in these subjects there was no association between clinical and neuropsychological response.

Genes & Environment

Brain Structure and Function

Cognition

Symptoms

Methylphenidate

Coghill et al 2007 Biological Psychiatry

Improves Cognition

Improves Symptoms

X

Improves Cognition

X

Methylphenidate
Genes & Environment

Brain Structure and Function

Cognition

Symptoms

Development

Cognition Improve

Symptoms Improve

Improves Cognition

Improves Symptoms

Methylphenidate

Coghill et al 2007 Biological Psychiatry

Potential Impacts

• Can explain why cognitive training approaches (e.g. working memory training) does not impact on symptoms but may still improve functioning
• A need to measure both symptom and cognitive outcomes
• Presents and opportunity to provide more concrete evidence as to why the regulators should consider cognitive outcomes when licensing medications

AADPA Annual Conference 27th and 28th of July 2019 in Brisbane.
## Cohort Summary for GWAS studies

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cases</th>
<th>Controls</th>
<th>Design</th>
<th>PGC Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>262</td>
<td>262</td>
<td>Trios</td>
<td>PGC ADHD1</td>
</tr>
<tr>
<td>IMAGE-I</td>
<td>700</td>
<td>700</td>
<td>Trios</td>
<td>PGC ADHD1</td>
</tr>
<tr>
<td>IMAGE-II</td>
<td>624</td>
<td>1755</td>
<td>Case/control</td>
<td>PGC ADHD1</td>
</tr>
<tr>
<td>PUWMa</td>
<td>635</td>
<td>635</td>
<td>Trios</td>
<td>PGC ADHD1</td>
</tr>
<tr>
<td>Toronto, Canada</td>
<td>109</td>
<td>109</td>
<td>Trios</td>
<td>PGC CDG</td>
</tr>
<tr>
<td>Barcelona, Spain</td>
<td>572</td>
<td>425</td>
<td>Case/control</td>
<td>PGC CDG</td>
</tr>
<tr>
<td>Cardiff, UK</td>
<td>721</td>
<td>5081</td>
<td>Case/control</td>
<td>PGC CDG</td>
</tr>
<tr>
<td>Germany</td>
<td>487</td>
<td>1290</td>
<td>Case/control</td>
<td>PGC CDG</td>
</tr>
<tr>
<td>Beijing, China</td>
<td>1012</td>
<td>925</td>
<td>Case/control</td>
<td>Solo (Yang et al. 2013)</td>
</tr>
<tr>
<td>Bergen, Norway</td>
<td>295</td>
<td>202</td>
<td>Case/control</td>
<td>New (Zayas et al. 2015)</td>
</tr>
<tr>
<td>Yale-Penn</td>
<td>182</td>
<td>1315</td>
<td>Case/control</td>
<td>New</td>
</tr>
<tr>
<td>Denmark iPSYCH</td>
<td>14584</td>
<td>22492</td>
<td>Case/control</td>
<td>New</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20183</strong></td>
<td><strong>35191</strong></td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
PGC + iPSYCH Meta-Analysis
Is there consistent evidence of genetic, environmental or neurobiological risk factors associated with ADHD?

Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (Left) and the prefrontal cortex (Right).

Shaw P et al. PNAS 2007;104:19649-19654
Effects of age and stimulants

Meta-analysis, Nakao et al., 2011
Patients with ADHD had significantly reduced grey matter in the putamen (P) and cerebellum (C) and significantly reduced white matter in the brainstem (B) and cerebellum (C).

Using Feature Selection with a Gaussian SVM resulted in individual scan predictive accuracies of 91% using grey matter alone and 97% using grey and white matter data (p<0.001).

Johnston et al., 2014