Are the effects of methylphenidate really uncertain?

Samuele Cortese, M.D., Ph.D.

Clinical Associate Professor & Honorary Consultant Child Psychiatrist
University of Southampton/Solent NHS Trust

Adjunct Associate Professor
New York University (NYU)
Conflicts of interest
(last 5 years)

• 2011-2013: Royalties for online educational activity on ADHD

• No other conflicts of interest
# Interpretation of Effect Size (ES)

<table>
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<th>Description</th>
<th>Value</th>
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<tr>
<td>Small</td>
<td>0.2</td>
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<tr>
<td>Medium</td>
<td>0.5</td>
</tr>
<tr>
<td>Large</td>
<td>0.8</td>
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</table>
Before the 2015 Cochrane review…

Last 15 years: **15** meta-analyses on MPH

*Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008*
Effect size MPH

ES = 0.79

Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis

Stephen V. Faraone · Jan Buitelaar
MPH vs. other meds

Leucht et al., Br J Psychiatry 2012
NICE 2006:

“The evidence from short-term randomised placebo-controlled trials suggests that methylphenidate is an effective treatment to reduce core symptoms of ADHD in children who continue to take the medication”
2015 Cochrane review

Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD) (Review)


38 parallel-group trials (5111 participants)

147 cross-over trials (7134)

ES: 0.77 (0.64-0.90)
Conclusions

“All 185 trials were assessed to be at high risk of bias”

“The quality of the evidence was very low for all outcomes”

Storebø et al., Cochrane Database Syst Rev, 2015
Conclusions (cont’d)

“The low quality of the underpinning evidence means that we cannot be certain of the magnitude of the effects”

“If methylphenidate treatment is considered, clinicians might need to use it for short periods, with careful monitoring of both benefits and harms, and cease its use if no evidence of clear improvement of symptoms is noted, or if harmful effects appear”

Storebø et al., Cochrane Database Syst Rev, 2015
Is the evidence base of methylphenidate and adolescents with attention-deficit disorder flawed?

Pieter J. Hopmans

Response to the Letter of the Editor by Storebø et al.

Methylphenidate for ADHD in children and adolescents: throwing the baby out with the bathwater

Tobias Banaschewski,¹ Jan Buitelaar,²,³ Celine S L Chui,⁴ David Coghill,⁵ Samuele Cortese,⁶,⁷ Emily Simonoff,⁶,⁸ Ian C K Wong,⁴,⁹ on behalf of the European ADHD Guidelines Group
The devil is in the details...
Study inclusion

• Active control conditions (including MTA)

• Preschoolers

0.77 -> 0.89
Appraisal of study quality

How to GRADE the evidence

Evidence varies from

- HIGH ★★★★★
- MODERATE ★★★★
- LOW ★★★
- VERY LOW ★★

➢ Randomised controlled trials start as high quality
➢ Observational studies start as low quality
Determinants of quality

5 factors that can **lower** quality

1. Limitations of detailed design and execution *(risk of bias criteria)*
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision *(number of events and confidence intervals)*
5. Publication bias
Risk of bias

- **Selection bias** *(random sequence generation; allocation concealment)*
- **Performance bias** *(blinding participants/personnel)*
- **Detection bias** *(blinding assessor)*
- **Attrition bias** *(incomplete outcome data)*
- **Reporting bias** *(selective reporting)*
- **Other bias**
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Storebø et al., 2015

Quality of the evidence (GRADE)

a) Downgraded **two** levels due to high risk of bias

b) Downgraded **one** level due to inconsistency: moderate statistical heterogeneity
Vested interests?

“‘Risk of bias’ table should be used to assess specific aspects of methodology and not vested interests per se “

Sterne JA. Why the Cochrane risk of bias tool should not include funding source as a standard item. Cochrane Database Syst Rev 2013

“We wanted to explore the influence of industry-funded versus publicly-funded sources. No between-group differences were found”

Punja et al., Cochrane Database Syst Rev, 2015
At least 1 unclear/high = HIGH RISK

179 trials: HIGH RISK
The “survivors”

• 6 survived: all green!!

But.......

Risk of deblinding

NOCEBO
Does the risk of bias impact on the ES ??

“No evidence suggested that the intervention effect varied according to risk of bias (low risk of bias versus high risk of bias)”

Storebø et al., Cochrane Database Syst Rev, 2015
a) Downgraded two levels due to high risk of bias

b) Downgraded one level due to inconsistency: moderate statistical heterogeneity
Heterogeneity

- Primary outcome: $I^2 = 37\%$

*Cochrane handbook*: “Heterogeneity up to 40% ‘might not be important’”

- Without MTA: $I^2 = 25\%$

- Punja et al.: $I^2 = 50\%$
Adverse events

• **No evidence** that methylphenidate was associated with an increase in **serious adverse events** (RR= 0.98, 95% CI 0.44-2.22)

• 60% greater risk for trouble **sleeping/sleep problems** (RR 1.60, 95% CI 1.15-2.23) and 266% greater risk for **decreased appetite** (RR 3.66, 95% CI 2.56-5.23)
Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents

Samuele Cortese,1,2,3,* Martin Holtmann,4,* Tobias Banaschewski,5 Jan Buitelaar,6 David Coghill,7 Marina Danckaerts,8 Ralf W. Dittmann,5 John Graham,9 Eric Taylor,10 Joseph Sergeant,11 on behalf of the European ADHD Guidelines Group†
Duration of treatment

• 1 to 425 day

• Average: 75 days
Some reflections on the MTA...

• 14-month RCT; observational follow-up

• Medication lost effectiveness?

• Self selection patients?

• Importance of carefully titrated pharmacological treatment?
Observational studies

• 25,656 patients with ADHD: significant reduction in **criminality** rates during ADHD pharmacological treatment (*Lichtenstein et al., NEJM, 2012*)

• 806,182 person-years of follow-up: no increased risk of **serious cardiovascular events** (*Habel et al., JAMA 2011*)

• 21,186 patients with ADHD: no association MPH-risk of **cancer** (*Steinhausen et al., JCAP, 2013*)
Brain effects

Rubia et al., Biol Psychiatry, 2014
Nakao et al., Am J Psychiatry, 2011
Moving forward....
Network meta-analysis...ongoing
INDIRECT COMPARISON

DIRECT COMPARISON

RCT 1

Placebo ⇔ Treatment A

DIRECT COMPARISON

RCT 2

Treatment A ⇔ Treatment B

“in common”
INDIRECT COMPARISON

DIRECT COMPARISON

RCT 1

Placebo ↔ Treatment A

Treatment A ↔ Treatment B

“in common”

DIRECT COMPARISON

RCT 2

INDIRECT COMPARISON
Network of experimental comparisons

Network

- sertraline
- milnacipran
- paroxetine
- duloxetine
- escitalopram
- bupropion
- fluoxetine
- reboxetine
- mirtazapine
- fluvoxamine
- citalopram
- venlafaxine
Network of experimental comparisons
Research priorities

• Long-term effects on cognition, academic functioning, global functioning, quality of life

• Sequencing non pharmacological/pharmacological interventions
ADDITIONAL SLIDES
# Inconsistency in bias rating

## Examples

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Funding</th>
<th>Conflicts of interest</th>
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<td>Coghill, 2007</td>
<td>local trust through Tenovus Scotland initiative</td>
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<tr>
<td>Jensen, 1999 (MTA)</td>
<td>National Institute of Mental Health, Bethesda, Maryland</td>
<td>Several study authors have affiliations with medical companies</td>
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ARCHIVAL REPORT

Effects of Methylphenidate on Cognitive Functions in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: Evidence from a Systematic Review and a Meta-Analysis

David R. Coghill, Sarah Seth, Sara Pedroso, Tatiana Usala, John Currie, and Antonella Gagliano

BIOL PSYCHIATRY 2014;76:603–615
Working memory

Figure 1. Forest plot with standardized (Std.) mean difference, effect size, and homogeneity statistics for meta-analysis comparing the effects of methylphenidate and placebo on executive aspects of memory. CI, confidence interval.
Reaction time variability

Figure 4. Forest plot with standardized (Std.) mean difference, effect size, and homogeneity statistics for meta-analysis comparing the effects of methylphenidate and placebo on reaction time variability. CI, confidence interval.
**Inhibition**

<table>
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<th>Study or Subgroup</th>
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<th>Std. Mean Difference (IV, Random, 95% CI)</th>
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<td>Coghill et al, 2007 (27)</td>
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<td>DeVito et al, 2009 (41)</td>
<td>-1.39 [-2.07, -0.71]</td>
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<td>Douglas et al, 1988 (65)</td>
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<td>Douglas et al, 1988 (65)</td>
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<td>Epstein et al, 2007 (84)</td>
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<td>Hawk et al, 2003 (91)</td>
<td>-0.36 [-1.04, 0.32]</td>
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<td>Hawk et al, 2003 (91)</td>
<td>0.21 [-0.46, 0.89]</td>
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<td>Hood et al, 2005 (54)</td>
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<td>Konrad et al, 2004 (73)</td>
<td>-0.28 [-0.64, 0.07]</td>
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<td>Konrad et al, 2005 (92)</td>
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<td>Langleben et al, 2006 (97)</td>
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<td>O'Driscoll et al, 2005 (98)</td>
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<td>Overtoom et al, 2003 (42)</td>
<td>-0.02 [-0.72, 0.67]</td>
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<tr>
<td>Rhodes et al, 2006 (35)</td>
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<td>Rhodes et al, 2006 (35)</td>
<td>0.32 [-0.25, 0.89]</td>
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<td>Scheres et al, 2003 (39)</td>
<td>-0.63 [-1.23, -0.02]</td>
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<td>Scheres et al, 2003 (39)</td>
<td>-0.59 [-1.24, 0.06]</td>
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<td>Solanto et al, 2009 (38)</td>
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<tr>
<td>Tannock et al, 1995a (63)</td>
<td>-0.21 [-0.73, 0.32]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**: -0.41 [-0.55, -0.27]

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 35.63$, df = 24 (P = 0.06); $I^2 = 33\%$

Test for overall effect: $Z = 5.75$ (P < 0.000001)

**Figure 5.** Forest plot with standardized (Std.) mean difference, effect size, and homogeneity statistics for meta-analysis comparing the effects of methylphenidate and placebo on response inhibition. CI, confidence interval.
Use of ADHD drugs 'increases by 50% in six years'  

Prescriptions for Ritalin and other ADHD drugs double in a decade

The Telegraph

ADHD is vastly overdiagnosed and many children are just immature, say scientists

13 Aug 2013

15 Aug 2015

10 Mar 2016
UK estimated prevalence

ADHD (DSM-IV)

• Boys: 3.62%
• Girls: 0.85%
• Total: 2.23%

HKD (ICD-10)

• Total: 1.5%

Ford et al., JAACAP 2003; Taylor et al., ECAP, 2004
Administrative treatment prevalence
2003-2008

McCarthy et al., BMC Pediatrics 2012
Plateau

• < 16 years

• General Practice Research Database

• At least one prescription of any ADHD drug

• 0.46 %

Beau et al., Pharmacoepidemiology and Drug Safety, 2012
Non NHS primary care prescriptions

<table>
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<tr>
<th>N items methylphenidate</th>
<th>N items methylphenidate</th>
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<td>Primary care</td>
<td>Privately prescribed</td>
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<tr>
<td>793,749</td>
<td>5,170</td>
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</table>

*Care Quality Commission, Annual Report 2014*

<table>
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<th>Costs methylphenidate</th>
<th>Costs methylphenidate</th>
<th>Costs methylphenidate</th>
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<td>FP10HP</td>
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<td>27,234</td>
<td>5,423</td>
<td>741</td>
</tr>
</tbody>
</table>

*Health and Social Care Information Centre, 2014*
Geographic variation

Smoothed methylphenidate spending (net ingredient cost per child) 2011

Rowlingson et al., *BMJ Open*, 2013
Geographic variation

- **Scotland**: 0.7%

*Services Over Scotland (ADHD-SOS) Follow-up Review, 2012*

<table>
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<th>Nation</th>
<th>Adjusted incidence rate ratio (95% CI)</th>
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<td>Scotland</td>
<td>0.97 [0.91, 1.04]</td>
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<td>Wales</td>
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<tr>
<td>Northern Ireland</td>
<td>1.26 [1.14, 1.39]</td>
</tr>
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</table>

*Hire et al, J Att Dis, 2015*
Worldwide estimated prevalence

ADHD: 5.29%

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<th>Year</th>
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<td>Netherlands</td>
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<td>Australia (NSW)</td>
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<td>Hong Kong</td>
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<td>Germany</td>
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<tr>
<td>Italy</td>
<td>2011</td>
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</table>
Administrative treatment prevalence
1996-2001

• 5-14 years

• UK general practice research datalink (GPRD)

• Diagnostic code for “ADHD” and use of MPH

• 0.5% boys

Jick et al., British Journal of General Practice, 2004
Administrative treatment prevalence 2003-2008

McCarthy et al., BMC Pediatrics 2012
Distribution by region

Wong et al., Health Technology Assessment, 2009
1998-2010

- CPRD
Gaps between treatment courses

Raman et al., Psychiatric Services 2015
Databases UK

• General Practice Research Datalink (GPRD)

• IMS Disease Analyzer-Mediplus (Mediplus)

• General Practice Administration System for Scotland (GPASS)

• Medicines Monitoring Unit (MEMO)

• QRESEARCH
1999

- 15 years
- UK general practice research datalink (GPRD)
- Both a drug prescription and diagnosis of ADHD
- 1.32/1000

Wong et al., *Health Technology Assessment*, 2009
2006

• 15 years

• UK general practice research datalink (GPRD)

• Both a drug prescription and diagnosis of ADHD

• 8.31/1000

Wong et al., Health Technology Assessment, 2009
1999

• 21 years

• UK general practice research datalink (GPRD)

• Both a drug prescription and diagnosis of ADHD

• 0/1000

Wong et al., *Health Technology Assessment*, 2009
2006

• 21 years

• UK general practice research datalink (GPRD)

• Both a drug prescription and diagnosis of ADHD

• 0.43/1000

Wong et al., *Health Technology Assessment*, 2009
<table>
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<td>2006</td>
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<td>2013</td>
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Persistence

Kaplan-Meier plot of duration of initial treatment course

Raman et al., Psychiatric Services 2015
SES and prescription rates

Hire et al., J Att Dis, 2015
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<tr>
<th>Name</th>
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<tr>
<td>anselmi</td>
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<td>wong</td>
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Courtesy of Dr Polanczyk, March 2016
# Inconsistency in bias rating

## Examples

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<th>Conflicts of interest</th>
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<td>Rapport, 1987</td>
<td>Funding: NIH</td>
<td>Conflicts of interest: no information</td>
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<td>Coghill, 2007</td>
<td>This work was supported by a local trust through a Tenovus Scotland initiative. Conflicts of interest: Some study authors have affiliations with different pharmaceutical companies</td>
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<td>Jensen, 1999 (MTA)</td>
<td>This study was supported by several grants from the National Institute of Mental Health, Bethesda, Maryland</td>
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