ADHD in adults: advances in pharmacological interventions

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Aetiology

Genetic factors (D4 and D5 receptor genes, SNAP-25 genes)

Environmental factors (prematurity, low birth weight?, maternal smoking?)
The Anatomy of ADHD

What parts of the brain are involved?

3 key areas of the brain are implicated in ADHD:

– CORTICAL REGIONS
  • Prefrontal cortex
  • Anterior Cingulate Cortex

– SUBCORTICAL REGIONS
  • Limbic system (including Amygdala)
  • Basal ganglia

– The CEREBELLUM
Neurobiology of ADHD

• The neurobiology of ADHD is complex, and not fully understood
• It has been established that both Dopamine and Noradrenaline are dysfunctional
• It seems to be not so much about “deficit” but about dysregulation or imbalance
• Other neurotransmitters thought to be involved include Glutamate and Serotonin, potentially shedding some light on the memory and mood aspects of ADHD
How we know dopamine and noradrenaline are involved?

- The most commonly used drugs in the treatment of ADHD (stimulants) act on dopaminergic and noradrenergic synapses
- Methylphenidate induces dopamine changes in the caudate
- There is significant association of ADHD with dopamine genes
- Imaging studies showing changes in brain regions activated by dopamine
## Neurotransmitter profile of the major drugs used in ADHD

<table>
<thead>
<tr>
<th>Noradrenaline</th>
<th>Noradrenaline+Dopamine</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td>dl-threo-Methylphenidate</td>
<td>Bupropion</td>
</tr>
<tr>
<td>d-amphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamphntamine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacodynamics of Amfetamine

- ‘monoamine releasing agent’, via “reverse transport” stimulating the release of dopamine & noradrenaline into the synapse from the pre-synaptic nerve terminal (monoamine reuptake transporter inverse agonist).
- by blocking the intraneuronal vesicular monoamine transporter (VMAT2)
- Inhibits monoamine oxidase (MAO)
- Block reuptake of DA and NE noradrenaline by DAT and NAT
- Acts on both the prefrontal cortex and the subcortical striatum (DA levels in the striatum increase several thousand fold)
- Rapid increases in synaptic NE and DA, with no response ceiling, underpin its early onset and large effect size and it also accounts for its potential for recreational abuse (if used outside guidelines)
- At high doses amfetamines have a serotoninergic effect
Amfetamines (Phenyl-ethyl-amines)

- Formulations available in the UK:
  - Immediate release dexamfetamine (Dexedrine)
  - Lisdexamfetamine (Elvanse/Vyvanse) – an extended release pro-drug

- Formulations available abroad include:
  - Dexamfetamine extended release
  - Mixed amphetamine salts (Adderall)
Pharmacodynamics of Methylphenidate

- Acts predominantly as a ‘monoamine releasing agent’, stimulating the release of DA & NE into the synapse from the pre-synaptic nerve terminal

- Acts on both the prefrontal cortex and the subcortical striatum (The effect on striatal dopamine is particularly marked, with levels increasing by a factor of 1000 – there is no ceiling to this effect)

- Also (to a much lesser degree) MPH blocks reuptake of DA and DA by the dopamine and the noradrenaline transporters (DAT and NAT)

- Acts on both the prefrontal cortex and the subcortical striatum

- Rapid increases in synaptic NE and DA, with no response ceiling
Methylphenidate (Piperidine)

- Formulations available in the UK:
  - Methylphenidate immediate release (IR)
  - Methylphenidate slow release:
    - Extended release (ER)
    - Osmotic release

- Formulations available abroad:
  - Methylphenidate transdermal patches
Non-stimulants

- Atomoxetine
- Bupropion
- Modafinil
- Clonidine
- Guanfacine
- Tricyclic anti-depressants
- Duloxetine (SNRI)
- Reboxetine (NRI)
Pharmacodynamics of Atomoxetine

Selective noradrenaline reuptake inhibitor (NARI)

Moderate increases of DA and NE in the prefrontal cortex but no effect in subcortical brain structures

- Initiation of effect may take weeks (similar to an antidepressant)
Stimulants

- Enhance the efflux and function of both DA and NA
- In both cortical and subcortical regions
- Rapid onset of action with no ceiling on drug effect
Medication efficacy and safety

• The **efficacy of stimulants** (methylphenidate & amfetamine) and non-stimulants (atomoxetine) has been **demonstrated in many RCTs** and confirmed by meta-analyses

• Stimulants have **medium effect sizes** ~0.5 and non-stimulants ~0.4; there are no head-to-head studies in adults

• Efficacy and safety of ADHD medication has been shown in **longer term studies** up to 2 years
Methylphenidate efficacy for adults with ADHD: a meta-regression analysis Castells et al., CNS Drugs 2011; 25: 157-169

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Std. Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman 2006</td>
<td>0.72</td>
<td>0.19</td>
<td>7.7%</td>
<td>0.72 [0.35, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Bouffard 2003</td>
<td>0.63</td>
<td>0.29</td>
<td>5.0%</td>
<td>0.63 [0.06, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Carpentier 2005</td>
<td>0.3</td>
<td>0.33</td>
<td>4.2%</td>
<td>0.30 [-0.35, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Gualtieri 1985</td>
<td>0.31</td>
<td>0.51</td>
<td>2.2%</td>
<td>0.31 [-0.69, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Jain 2007</td>
<td>0.54</td>
<td>0.24</td>
<td>6.2%</td>
<td>0.54 [0.07, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Kuperman 2001</td>
<td>-0.31</td>
<td>0.47</td>
<td>2.5%</td>
<td>-0.31 [-1.23, 0.61]</td>
<td></td>
</tr>
<tr>
<td>Levin FR 2006</td>
<td>-0.26</td>
<td>0.28</td>
<td>5.2%</td>
<td>-0.26 [-0.81, 0.29]</td>
<td></td>
</tr>
<tr>
<td>Levin FR 2007</td>
<td>0.06</td>
<td>0.2</td>
<td>7.3%</td>
<td>0.06 [-0.33, 0.45]</td>
<td></td>
</tr>
<tr>
<td>Medori 2008</td>
<td>0.42</td>
<td>0.12</td>
<td>10.2%</td>
<td>0.42 [0.18, 0.66]</td>
<td></td>
</tr>
<tr>
<td>Reimherr 2007</td>
<td>0.83</td>
<td>0.26</td>
<td>5.7%</td>
<td>0.83 [0.32, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Rosler 2009</td>
<td>0.45</td>
<td>0.13</td>
<td>9.8%</td>
<td>0.45 [0.20, 0.70]</td>
<td></td>
</tr>
<tr>
<td>Schubiner 2002</td>
<td>0.7</td>
<td>0.3</td>
<td>4.8%</td>
<td>0.70 [0.11, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Spencer 1995</td>
<td>1.01</td>
<td>0.31</td>
<td>4.6%</td>
<td>1.01 [0.40, 1.62]</td>
<td></td>
</tr>
<tr>
<td>Spencer 2005</td>
<td>1.3</td>
<td>0.28</td>
<td>5.2%</td>
<td>1.30 [0.75, 1.85]</td>
<td></td>
</tr>
<tr>
<td>Spencer 2007</td>
<td>0.51</td>
<td>0.16</td>
<td>8.7%</td>
<td>0.51 [0.20, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Tenenbaum 2002</td>
<td>0.07</td>
<td>0.29</td>
<td>5.0%</td>
<td>0.07 [-0.50, 0.64]</td>
<td></td>
</tr>
<tr>
<td>Wender 1985</td>
<td>0.57</td>
<td>0.25</td>
<td>5.9%</td>
<td>0.57 [0.08, 1.06]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.48 [0.32, 0.65]

Heterogeneity: Tau² = 0.05, Chi² = 32.87, df = 16 (P = 0.008), I² = 51%
Test for overall effect: Z = 5.88 (P < 0.00001)
Methylphenidate efficacy for adults with ADHD: a meta-regression analysis Castells et al., CNS Drugs 2011; 25: 157-169

Meta-regression of SMD against dose of methylphenidate.

Dose is expressed as 10 mg increments of methylphenidate (or 5mg of dexmethylphenidate)
NICE recommendations for adults

- Drug treatment is the first-line treatment in adults
- Methylphenidate is the first-line drug
- If methylphenidate is *ineffective* or *unacceptable* then atomoxetine or dexamphetamine can be tried 2\textsuperscript{nd} line
- If the following apply:
  1. Residual impairment
  2. No response
  3. Medication is not an option
  4. The person chooses to avoid medication

........then CBT should be considered
First option and other recommendations in 10 ADHD treatment guidelines

- Methylphenidate IR
- Methylphenidate MR
- Dexamphetamine
- Atomoxetine
- Mixed amphetamine salts
- Tricyclic antidepressants
- Bupropion
- Clonidine
- Modafinil
- Guanfacine

First option and other recommendations in 10 ADHD treatment guidelines

Seixas, Weiss, Müller,
under review
Stimulant use concerns

- Potential recreational abuse and diversion
- Side effects
- Social and medical attitudes to ADHD

- Led to limited use in UK and Europe
- Classified as controlled drugs under the UK Misuse of Drugs Act 1971 with all members of being placed in Class B.
Clinical Challenges

Therapeutic coverage

Innovations in formulation technology and drug delivery systems: once daily formulations improve adherence

Abuse liability

(a) Atomoxetine
(b) Once daily formulations – partially
(c) Amphetamine prodrug (Lisdexamfetamine) : less risk of abuse
Lisdexamfetamine dimesylate (Elvanse/Vyvanse)

- **extended release pro-drug of d-amfetamine**
- pharmacologically inactive
- unlikely to cross the blood – brain barrier
- after absorption into the bloodstream is metabolised by red blood cells to yield d-amfetamine and the amino acid L-lysine
- can be administrated once daily

- side effect profile similar to d-amfetamine

- Gradual and sustained increase in brain drug concentration and striatal dopamine efflux reducing further the pleasurable effects of d-amfetamine
- **Pose a reduced risk for recreational abuse**

- IV or oral administration did not enhance the pharmacological potency of LDX in the CNS

David J Heal at al. Journal of Psychopharmacology 2013; 27(6) 479-496
Double-blind, placebo-controlled study of the efficacy and safety of **lisdexamfetamine** dimesylate in adults with ADHD

Adler et al., J Clin Psychiatry 2008; 69: 1364-73
UK licences

• Methylphenidate (IR, ER), atomoxetine and dexamfetamine (IR) are licenced for the treatment of ADHD in childhood/adolescence
• Atomoxetine has become the first (and only) medicine in the UK to be approved specifically for treatment initiation in adults with ADHD (May 2013)
• Concerta XL also has had a continuation licence, since 2011 (for individuals treated for ADHD as a child)
• Lis-dexamfetamine (Elvanse) became the first stimulant pro-drug licenced in Europe for the treatment of ADHD.
“Off-label” prescribing in adult ADHD

Therefore prescription of ADHD medication in adults is often “OFF LABEL”

but crucially,

supported by NICE and BAP guidance & the BNF
Guanfacine

- extended-release guanfacine (Intuniv)
- a selective agonist for the $\alpha_{2A}$-adrenergic receptor, although the actual mechanism of action is not known.
- approved for the treatment of ADHD in children 6 to 17 years of age in USA
## Investigational drugs in adult ADHD
(published studies only)

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Promising</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic</strong></td>
<td></td>
<td>MK-0929, Selegeline</td>
</tr>
<tr>
<td><strong>Noradrenergic</strong></td>
<td>Desipramine, Duloxetine, Guanfacine, Reboxetine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td><strong>Cholinergic</strong></td>
<td>ABT-418, ABT-894</td>
<td>AZD-1446, Galantamine, Pozanicline</td>
</tr>
<tr>
<td><strong>Glutamatergic</strong></td>
<td>ORG-26576</td>
<td></td>
</tr>
<tr>
<td><strong>Histaminergic</strong></td>
<td></td>
<td>Bavisant, MK-0249</td>
</tr>
<tr>
<td><strong>Serotoninergic</strong></td>
<td></td>
<td>Buspirone, Paroxetine</td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>Metadoxine</td>
<td>Lithium, Modafinil, NS-2359</td>
</tr>
</tbody>
</table>
### RCTs of licensed non ADHD medications (other than bupropion)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reference</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buspirone</td>
<td>Sutherland et al. 2012</td>
<td>☐</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Wilens et al. 1996</td>
<td>➡</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Bilodeau et al. 2012</td>
<td>➡</td>
</tr>
<tr>
<td></td>
<td>Taylor &amp; Russo 2000</td>
<td>➡</td>
</tr>
<tr>
<td></td>
<td>Arnold et al. 2012</td>
<td>☐</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Weiss et al. 2006</td>
<td>(◖)</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Riahi et al. 2010</td>
<td>➡</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Amiri et al. 2012</td>
<td>(◖)</td>
</tr>
</tbody>
</table>

☑ = equals placebo, ➡ = better than placebo, () = small sample size (phase 2 study)
## Alternative treatments in ADHD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type of study</th>
<th>Conclusions</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homeopathy</td>
<td>Cochrane review of RCTs (168)</td>
<td>No effect</td>
<td>No valid treatment</td>
</tr>
<tr>
<td>“Feingold hypothesis” diet / Elimination of</td>
<td>Controlled trial, Meta-analysis (Nigg 2012), Systematic review &amp; Meta-analysis</td>
<td>Some children with ADHD may respond to dietary intervention / elimination (effect sizes small,</td>
<td>To be used in selected groups with demonstrated food allergies</td>
</tr>
<tr>
<td>food additives or colourings</td>
<td>(Sonuga-Barke 2013)</td>
<td>more research needed)</td>
<td></td>
</tr>
<tr>
<td>Sugar restriction diets</td>
<td>Placebo controlled challenge</td>
<td>No effect</td>
<td>No valid treatment</td>
</tr>
<tr>
<td>Amino acid supplementation</td>
<td>Placebo controlled trial</td>
<td>Some improvement with some aa. Up to 3 weeks, but not sustained.</td>
<td>Low quality evidence. Treatment not recommended, risks identified</td>
</tr>
<tr>
<td>Treatment</td>
<td>Type of study</td>
<td>Conclusion</td>
<td>Recommendation</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------------------</td>
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</tr>
<tr>
<td>Fatty acid supplementation (Omega 3)</td>
<td>SR and Meta-analyses (Bloch 2012, Sonuga-Barke 2013), Cochrane review (Gilles 2012)</td>
<td>FA supplementation may reduce ADHD Sx (in some children and adolescents) – mod effect sizes, more research needed</td>
<td>Consider use to augment traditional treatments or when medication not wanted / tolerated</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>No placebo controlled studies in ADHD</td>
<td>Modest effect in hyperactivity Sx of fragile X syndrome</td>
<td>No valid treatment</td>
</tr>
<tr>
<td>Dimethylaminoethanol</td>
<td>Open trials</td>
<td>Some effect, not superior to MPH, RCT’s flawed (old methodol)</td>
<td>Modest effect, modern trials needed.</td>
</tr>
<tr>
<td>Vitamin supplements</td>
<td>Placebo cntr trials</td>
<td>No effect</td>
<td>No valid treatment</td>
</tr>
<tr>
<td>Iron, Zinc , Mg supplementation</td>
<td>Open trials</td>
<td>No effect</td>
<td>No valid treatment</td>
</tr>
</tbody>
</table>
Conclusions

- Clear consensus on efficacy of treatment with stimulants and non-stimulants
- Stimulants have higher effect sizes (0.5-1.0) than non-stimulants (0.4)
- Effect size related to maximum dose
- Innovations in formulation technology and drug delivery systems (once daily preparations) and extended release amphetamine prodrug have addressed problems with therapeutic coverage and risk of abuse
- More studies required to understand the full range of actions of ADHD medications and the individual variations that may limit efficacy or cause side effects