How do doctors choose and prescribe ADHD medication?

Professor Peter Hill
The point of ADHD medication

- To strengthen nerve transmission in the brain, especially in the frontal lobes
Frontal lobe in blue
Cortex is the dark purple outside layer, full of nerve cells.
Cortex development by age

Shaw 2007
Replication Almeida 2010
Regions where the ADHD group had delayed cortical maturation, as indicated by an older age of attaining peak cortical thickness.

Shaw P. et.al. PNAS 2007;104:19649-19654
Less frontal lobe brain activity in ADHD

Neurophysiology - blood flow

SPECT

Kuperman et al. 1990
ADHD brain activity on fMRI
Nerve pathways using dopamine as a neurotransmitter
Noradrenaline tracts
Normal SPECT

Underside view
SPECT: view from below

ADHD at rest

ADHD concentrating
Effect of stimulant medication

ADHD resting

ADHD after stimulant

www.amenclinics.com
Normal SPECT

Underside view
ADHD medication

- Makes nerve pathways in frontal lobe cortex more effective
- by helping nerve cells pass messages between themselves using neurotransmitters
- usually by increasing the amount of neurotransmitter available
The vocabulary of prescribing: the names of drugs
Drug name: chemical

2-piperidineacetic acid, α-phenyl-, methyl ester
Drug name: scientific generic

methylphenidate

(mee thyle fenni date)
Drug name: brand

[Image of a small bottle of Ritalin, an anti-depressant.]
Brand names of methylphenidate in the UK

- Medikinet
- Ritalin
- Tranquilyn
- Equasym XL
- Medikinet XL
- Concerta XL
- Delmosart
- Matoride XL
- Xaggitin XL
- Xenidate XL
Brand names differ between countries

Lisdexamfetamine

- **UK:** *Elvanse*
- **USA & Canada:** *Vyvanse*
- **Republic of Ireland:** *Tyvense*
- **Brazil:** *Venvanse*
- **Chile:** *Samexid*
Thus

• Chemical name

• Scientific generic name

• Brand name
In practical terms, all ADHD medicines in the UK have at least two names.

<table>
<thead>
<tr>
<th>Generic (scientific, official)</th>
<th>Manufacturer’s brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylphenidate</td>
<td><em>Ritalin, Medikinet, Tranquilyn,</em></td>
</tr>
<tr>
<td></td>
<td><em>Equasym XL, Medikinet XL</em></td>
</tr>
<tr>
<td></td>
<td><em>Concerta XL Delmosart,</em></td>
</tr>
<tr>
<td>dexamfetamine</td>
<td><em>Amfexa, for dexamfetamine</em></td>
</tr>
<tr>
<td>lisdexamfetamine</td>
<td><em>Elvanse for lisdexamfetamine</em></td>
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<tr>
<td>atomoxetine</td>
<td><em>Strattera</em></td>
</tr>
<tr>
<td>guanfacine</td>
<td><em>Intuniv</em></td>
</tr>
</tbody>
</table>
NHS doctors are encouraged to prescribe ‘generically’ using the generic name on the prescription to enable a pharmacist to dispense any medicine with that generic name, irrespective of brand.
Cost of 30 x 10mg tablets

• ‘methylphenidate’ £3.97 (AAH) - £5.49 (Kent)
• Tranquilyn £3.97
• Medikinet £5.49
• Ritalin £6.68
Cost of 30 x 36mg tablets

- Concerta XL £42.45
- Matoride XL £21.22
- Delmosart £21.23
- Xaggitin XL £21.22
- Xenidate XL £21.21
Either

• ‘methylphenidate’ 10mg x 3 daily for 30 days
  £11.91
• Xenidate XL 36mg daily for 30 days
  £21.21
• Concerta XL 36mg daily for 30 days
  £42.45
But......
Problem 1.

• Medium duration XLs are not the same

• So, for them, doctors are instructed in the BNF, (the ‘prescribers’ bible’) to use brand names
MPH blood levels
<table>
<thead>
<tr>
<th>Product</th>
<th>Stated content</th>
<th>0-4hrs</th>
<th>4-8hrs</th>
<th>8-12hrs</th>
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</tr>
</tbody>
</table>
Problem 2

‘Bioequivalence’

• term used by licensing authorities (MHRA, EMA, FDA etc)

• a ‘bioequivalent’ new ‘generic’ drug need only produce 80% of the blood levels produced by original brand

• bioequivalence is not exact equivalence
  – not many doctors and pharmacists know that!
Generics


  – Matoride XL, Delmosart, Xaggitin XL pK data in the SPC are identical word for word to Concerta XL (!)
  – Xenidate XL AUC appreciably less than Concerta XL 110.5 cf. 125.4 ng/ml/h (11% less)

Statement by e.g. EMA that drug is bioequivalent to the original lead product doesn’t mean it’s exactly the same
Problem 3

• All longer lasting methylphenidate XLs not the same

• *Concerta XL, Delmosart, Matoride XL, Xaggitin XL* all ‘OROS’ system drugs that use osmotic pressure to pump out medication from complex tablet

• *Xenidate XL* isn’t an OROS: uses a wax matrix: releases 11% less than *Concerta XL*
Classification of ADHD drugs

**Stimulants**
- methylphenidate
- dexamfetamine
- lisdexamfetamine (*Elvanse*)

**Nonstimulants**
- atomoxetine (*Strattera*)
- guanfacine (*Intuniv*)

- powerful, act immediately, alerting, can only use during day
- less powerful, take time to get going, slightly sedating, effect lasts for 24 hours
Choice of medicine at any point

• Quality of supportive evidence
Quality of supportive evidence

• Meaning scientific trials
• Nearly always from pharma industry trials of their drug
• Hardly any trials comparing drugs head to head
• Hardly any trials of combinations of drugs
• NICE very choosy about quality of trials, older ones often excluded
Choice of medicine at any point

• Quality of supportive evidence
• Marketing authorisation (licence)
Licence

• Is a marketing authorisation given to a manufacturer
• Specifies dose, what it’s for, which age groups
• Usually granted on basis of scientific trials in adults
• Most children’s medicines are therefore off-licence
• Nothing to do with doctors but management keen on licensed medicines because ‘safer’
Choice of medicine at any point

• Quality of supportive evidence
• Marketing authorisation (licence)
• Power
## Comparative efficacy: Mean (95% credible interval) ADHD-RS-IV total score change

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (95% CI)</th>
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<tbody>
<tr>
<td>LDX</td>
<td>-14.98</td>
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<tr>
<td>MPH-extended release</td>
<td>-9.33</td>
</tr>
<tr>
<td>GXR</td>
<td>-8.68</td>
</tr>
<tr>
<td>ATX</td>
<td>-6.88</td>
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</table>

No suitable MPH-IR trials for analysis

Joseph A  *Eur Child Adolesc Psychiatry* 2017 26:875-897
Discontinuation due to Adverse Events: Relative Risk

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>MPH-IR</td>
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<tr>
<td>MPH-ER</td>
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<td>ATX</td>
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<td>LDX</td>
<td>3.11</td>
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<tr>
<td>GXR</td>
<td>4.49</td>
</tr>
</tbody>
</table>

Placebo 0.2

Joseph A  *Eur Child Adolesc Psychiatry* 2017 26:875-897
Choice of medicine at any point

- Quality of supportive evidence
- Marketing authorisation (licence)
- Power
- Familiarity and reputation
Reputation

• Fuelled by mistaken concerns
  – Atomoxetine (Strattera) causes suicidal behaviour
  – Lisdexamfetamine is addictive
  – Stimulants usually stunt growth

Etc…….

American ADHD forums….OMG!
Choice of medicine at any point

- Quality of supportive evidence
- Marketing authorisation (licence)
- Power
- Familiarity and reputation
- Anticipated adverse effects
Anticipated adverse effects

• E.g.
  – appetite suppression in a girl with anorexia nervosa
  – difficulty with sleep onset

etc
Choice of medicine at any point

- Quality of supportive evidence
- Marketing authorisation (licence)
- Power
- Familiarity and reputation
- Anticipated adverse effects
- Pharmacology
Pharmacology

- If (lis)dexamfetamine (*Elvanse*) not much good, atomoxetine (*Strattera*) unlikely to work because it has the same action, in fact rather less so.

Both are noradrenaline re-uptake inhibitors but lisdexamfetamine also releases noradrenaline from neuron into synapse.
Choice of medicine at any point

- Quality of supportive evidence
- Marketing authorisation (licence)
- Power
- Familiarity and reputation
- Anticipated adverse effects
- Pharmacology
- Availability
Local formulary

• List within NHS locally of which drugs doctors can prescribe

• Very much driven by cost
For example: SWLSTG: only Xenidate XL

<table>
<thead>
<tr>
<th>Dose and Route of Administration</th>
<th>All preparations are for oral administration. Dosage and timing will depend upon the patient and the form of the medicine: Methylphenidate</th>
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<tbody>
<tr>
<td></td>
<td>Standard / Immediate release preparations</td>
</tr>
<tr>
<td></td>
<td>Ritalin® 10mg tablets &amp; Medikinet® 5mg, 10mg, 20mg</td>
</tr>
<tr>
<td></td>
<td>o Initiate at 5mg OD or BD; increase dosage if necessary weekly, by increments of 5-10mg per day</td>
</tr>
<tr>
<td></td>
<td>o Usual maximum dosage 60mg per day in divided doses (usually at intervals of 3-4 hours)</td>
</tr>
<tr>
<td></td>
<td>Modified release preparations</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line - Xenidate-XL® 18mg, 36mg MR tablets</td>
</tr>
<tr>
<td></td>
<td>o Initiate at 18mg daily; increase dose gradually according to needs and response of the patient.</td>
</tr>
<tr>
<td></td>
<td>o Usually up to 54mg daily (max 108mg daily unlicensed).</td>
</tr>
<tr>
<td></td>
<td>o Concerta-XL® is available for the 27mg strength</td>
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<tr>
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<td>Equasym XL® 10mg, 20mg, 30mg MR capsules – consists of an immediate-release component (30% of the dose) and a modified-release component (70% of the dose)</td>
</tr>
<tr>
<td></td>
<td>o Initiate at 10 mg once daily in the morning before breakfast, increased gradually if necessary</td>
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<tr>
<td></td>
<td>o Usually up to 60 mg daily.</td>
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<td>Medikinet XL® 10mg, 20mg, 30mg, 40mg MR capsule – consists of an immediate-release component (50% of the dose) and a modified-release component (50% of the dose)</td>
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<tr>
<td></td>
<td>o Initiate at 10 mg once daily in the morning before breakfast, increased gradually if necessary</td>
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<td>o Usually up to 60 mg daily.</td>
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</table>
National guidance (NICE etc)

Decide stimulant or nonstimulant on basis of

- Abuse risk?
- Tics?
- Duration?
- Sleep?
- Patient choice

*stimulant*  
- Methylphenidate
- (Lisdexamfetamine)

*non-stimulant*  
- Atomoxetine
- Guanfacine
Guidance algorithms/flow charts

• Usually monotherapy (just one drug at a time)
  – choices between medications in sequence

• Change medicine
  – if it’s ineffective
  – when the dose maximum reached
  – if there is toxicity
  – if there are unmanageable side effects
Knowing when to change medication

• **Effect**
  - need to measure (rating scales)

• **Side effect**
  - can usually be managed, though

• **Dose**
  - ‘maximum’ dose reached
  - usually the one in the licence
Maximum dose?

- Stevens et al. *J Child Adolesc Psychopharmacol* 2010 20:49-54
- in 17 teenagers needing high dose of Concerta XL (126-270mg/day), normal plasma levels of drug, no toxicity, no adverse heart effects, no relationship between dose by mouth and blood level
Clinical Gains from Including Both Dextroamphetamine and Methylphenidate in Stimulant Trials

Bjørn E. Ramtvedt,1 Elisabeth Røinås,1 Henning S. Aabeck, MD,1 and Kjetil S. Sundet, PhD2

72% respond to either MPH or DEX alone (equal proportions)
If trial both MPH and DEX sequentially,
92% have favourable response

National guidance (NICE etc)

Decide stimulant or nonstimulant on basis of:
- Abuse risk?
- Tics?
- Duration?
- Sleep?
- Patient choice

stimulant

- Methylphenidate
- (lis)dexamfetamine

non-stimulant

- Atomoxetine
- Guanfacine

"National guidance (NICE etc)"

Decide stimulant or nonstimulant on basis of:
- Abuse risk?
- Tics?
- Duration?
- Sleep?
- Patient choice

stimulant

- Methylphenidate
- (lis)dexamfetamine

non-stimulant

- Atomoxetine
- Guanfacine
How to choose between atomoxetine (*Strattera*) and guanfacine (*Intuniv*)?

- **Guanfacine**
  - may reduce tics
  - no appetite suppression
  - sleepiness

- **Atomoxetine**
  - may help ADD when slow cognitive processing the problem
  - gut problems
Virtually no UK guidance on combinations

- Stimulant plus guanfacine (*Intuniv*)
- Adding different medicines for sleep problems
- Adding low-dose aripiprazole or risperidone
- Adding SSRIs for anxiety

etc etc
Guidelines: a two-edged sword

• Can support good decisions and practice
• Can be used by managers restrictively (tramlines rather than guidelines)
• Narrow in their emphasis on single drugs only
• Discourages experimentation - meaning we become more dependent on pharma company drug trials and American literature
• Individual clinicians need more freedom to use their own judgement
Thank you
The synapse between two neurons
The synapse (between two neurons)
Dopamine synapse

[Diagram of a dopamine synapse with labels such as vesicle, synaptic space, receptors, presynaptic neuron, axon, postsynaptic neuron, neurotransmitter, transporter, and dendrite.]
Noradrenaline synapse
Methylphenidate action 1

METHYL-PHENIDATE BLOCKS DAT
(STANDARD STORY)
Hypothesised mode of action: methylphenidate

Methylphenidate targets dopamine and noradrenaline transporters

- Methylphenidate targets DAT and NET, inhibiting DA and NA reuptake, and therefore increasing DA and NA levels in the synaptic cleft.\textsuperscript{1-9}

Studies in animals\textsuperscript{10,11} and in vitro studies\textsuperscript{12} have been inconclusive regarding the effect of methylphenidate on the release of dopamine and noradrenaline into the synapse.

Methylphenidate action 2

METHYLPHENIDATE HIJACKS DAT AND REVERSES ACTION
Dexamfetamine action

Dexamfetamine gets in through the dopamine transporter and then displaces dopamine from storage vesicles as well as disabling the transporter.
Hypothesised mode of action: amfetamines

Amfetamine is thought to have a dual mode of action on dopamine and noradrenaline

- Amfetamine targets DAT and NET, inhibiting DA and NA reuptake and therefore increasing DA and NA levels in the synaptic cleft\(^1\)\(^-\)\(^5\)

- Amfetamine also enters the presynaptic neuron, preventing DA/NA from storing in the vesicles. In addition, AMF promotes the release of catecholamines from vesicles into the cytosol and ultimately from the cytosol into the synaptic cleft\(^6\)\(^-\)\(^10\)

Hypothesised mode of action: atomoxetine

Atomoxetine targets the noradrenaline transporter

- Atomoxetine targets the NET, inhibiting the reuptake of NA, therefore increasing NA levels in the synaptic cleft\(^1,2\)

---

Two key actions on post-synaptic neuron

• Improving stimulus to noise ratio
• Increasing size and frequency of dendritic spines
Hypothesised mode of action: guanfacine

Guanfacine is thought to target post-synaptic α2A-adrenergic receptors

- Guanfacine targets postsynaptic α2A-adrenergic receptors, mimicking NA
- Preclinical evidence suggests that guanfacine can modulate synaptic transmission in the prefrontal cortex (PFC) according to the following post-synaptic effects:
  - Stimulation of α2A-adrenergic receptors reduces cAMP production, closing HCN channels and improving the efficiency of synaptic transmission
  - Suppression of excitatory post-synaptic potentials (EPSPs)
  - Such mechanisms are hypothesised to fine tune neurotransmission in the PFC according to the context
- In-vitro studies suggest that guanfacine may also promote the maturation and increase the number and density of dendritic spines