ADHD in Adulthood
Pharmacological Treatment of ADHD: Easy steps

Leeds and York Partnership NHS
NHS Foundation Trust
IF WE'RE JUST LOOKING TO LEVEL THE PLAYING FIELD, WHY DON'T YOU JUST DRUG THE FEW KIDS WHO DON'T HAVE ADHD?

WHAT? AND FOREGO ALL THE COOL PERKS FROM THE DRUG COMPANIES?
Charles Bradley

1937 – he administered Benzedrine Sulphate to young patients diagnosed with behavioural disorders
15 out of 30 responded with improvements in

• school performance

• motivational drive

• “appeared subdued because they began spending their leisure time playing quietly or reading, whereas formerly they had wandered aimlessly about antagonising and annoying others”

• Others showed “a sense of well being. A widening of interest in all things around them and a diminished tendency to be preoccupied with themselves”
Medication offers relief...not a cure
THE ADHD GLASSES
Looking for the benefits

• Improvement in symptom scores AND in impairment and functioning
  – Improved self esteem and awareness
  – Stronger relationships
  – Greater consistency in parenting
  – Better physical and mental health
  – More financial stability
  – Reduction in offending or aggressive behaviours
  – Occupational stability
NICE Guidance

• “Drug treatment is first line” for moderate or severe levels of impairment
• Methylphenidate is first line
• If ineffective or unacceptable, then atomoxetine or dexamfetamine can be tried
• Drug treatment commenced only under the guidance of a psychiatrist or nurse prescriber specialising in ADHD, or other clinical prescriber with training in the diagnosis and management of ADHD
Off License Prescribing

- No stimulants are licensed in UK for newly diagnosed adults
- “it remains an anomaly that many drugs that considered to be safe and effective in children and adolescents are not licensed for use in adults” (NICE)
- Concerta XL is licensed for adults continuing treatment from adolescence
- Prescribing off license requires “adequate evidence and experience to attend to clinical needs not met by licensed medicines”
- BAP considered to be adequate evidence and experience
- Off license use in other areas e.g. Antipsychotics, antiepileptics
However as of June 2013...

MHRA licensed Atomoxetine “to begin treatment of ADHD in adult patients but only when pre-existing symptoms during childhood can be confirmed by a third party”

10 clinical trials involving 4800 patients
And in July 2015..

- Lisdexamphetamine (Elvanse) Adult launched as the only stimulant to be licensed for initiation in adults

- Although still not recognised in NICE
Pre-treatment Evaluation

Record

• History of exercise syncope, undue breathlessness, other cardiovascular symptoms
• Heart rate and Blood pressure
• Weight

Do an ECG if

• Past medical or family history of serious cardiac disease, hypertension, history of sudden death in young family members or abnormal findings on observations
• And also a 24 hour BP if repeated high readings in clinic
• (can treat if controlled hypertension)

Carry out risk assessment for substance misuse and drug diversion
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever been told by a doctor that you have heart disease?</td>
<td></td>
</tr>
<tr>
<td>Do you ever get chest pain on exertion?</td>
<td></td>
</tr>
<tr>
<td>Have you ever passed out or fainted whilst exercising?</td>
<td></td>
</tr>
<tr>
<td>Has anyone in your family developed heart disease before the age of 60?</td>
<td></td>
</tr>
<tr>
<td>Has anyone in your family died of heart disease before the age of 60?</td>
<td></td>
</tr>
<tr>
<td>Do you know if you have high blood pressure or an increased cholesterol</td>
<td></td>
</tr>
<tr>
<td>BP/Pulse is it regular?</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Physical Examination (Done by GP)</td>
<td></td>
</tr>
<tr>
<td>ECG, ECHO and 24 hr BP if indicated</td>
<td></td>
</tr>
</tbody>
</table>
Classification of ADHD Drugs

ADHD drugs

Neurotransmitter

- Noradrenaline selective
  - Atomoxetine
  - Guanfacine
- Noradrenaline + Dopamine
  - dl-threo-Methylphenidate
  - d-threo-Methylphenidate
  - dl-Amphetamine
  - d-Amphetamine
- Dopamine selective
  - Bupropion
- Dopamine selective

Mechanism of action

- Monoamine reuptake inhibitors
  - Atomoxetine
  - Bupropion
- Monoamine releasing agents
  - dl-Amphetamine
  - d-Amphetamine
- Psychostimulant reuptake inhibitors
  - dl-threo-Methylphenidate
  - d-threo-Methylphenidate
- α₂-Adrenoceptor agonists
  - Guanfacine

*Not approved for the treatment of ADHD
Stimulants

• Schedule 2 Controlled Drugs therefore need prescription written with total tablets in words and figures

• Formulations:
  – Methylphenidate Instant Release
  – Methylphenidate slow release:
    • Extended release
    • Osmotic release
  – Dexamphetamine Instant Release
  – Lisdexamphetamine
Methylphenidate (MPH)

• Synthesised by Leandro Panizzon in 1944.
• Inhibitor of DA reuptake

• Also has high affinity for noradrenaline transporter
• Acts on both prefrontal cortex and the subcortical striatum
• Main action through blockage of DA transporter
MPH Formulations

• Immediate Release tablets (Ritalin)
  – Duration of effect 2-4 hours
  – 5, 10, 20mg tablets
  – 2-4 x daily

• Modified release
  – Beaded formulation capsules
    • Equasym XL
    • Medikinet XL
  – Osmotic Release OROS system
    • Concerta XL (beware generics eg. Marotide)
Longer acting Methylphenidate

**CONCERTA XL**
- 22% Immediate Release
- 78% Extended Release
- 1st peak 1-2 hours
- 2nd peak 6-8 hours
- Duration of Action 8-12 hours

**EQUASYM XL**
- 30% Immediate Release
- 70% Extended Release
- 1st peak 1-2 hours
- 2nd (but lower) peak 4-5 hours later
- Duration of Action 6-8 hours

**MEDIKINET XL**
- 50% Immediate Release
- 50% Extended Release
- 1st peak 2-3 hours
- 2nd peak 3-4 hours later
- Duration of Action 6-8 hours
Short or Long acting?

**Short Acting**
- Rapid onset
- Individual Titration
- On-off effects (unstable effect)
- Fine control over symptoms level
- Multiple dosing, dependent on clinical need
- Potential for diversion/abuse
- May precipitate anxiety

High Functioning patients, or those who wish to retain control over level of symptoms; stable effect undesirable, not needed or not wanted

**Long Acting**
- Slow onset
- Standard dosing
- Sustained effect (stable effect)
- General reduction in symptoms
- Once daily dosing
- Limited potential for diversion/abuse
- Less likely to precipitate anxiety

High risk patients; alcohol or drug abuse compliance (where due to forgetfulness); stable effect desirable
## MPH Titration Regimens

<table>
<thead>
<tr>
<th></th>
<th>MPH IR</th>
<th>Concerta XL</th>
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</thead>
<tbody>
<tr>
<td><strong>MPH IR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 5mg</td>
<td>5mg</td>
<td>18mg / 27mg</td>
</tr>
<tr>
<td>Average 10mg</td>
<td>10mg</td>
<td>+ / - MPH IR</td>
</tr>
<tr>
<td>Average 15mg</td>
<td>15mg</td>
<td>+ / - MPH IR</td>
</tr>
<tr>
<td>Average 20mg</td>
<td>20mg</td>
<td>+ / - MPH IR</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25mg</td>
<td>25mg</td>
<td>54mg</td>
</tr>
<tr>
<td>30mg</td>
<td>30mg</td>
<td>72mg</td>
</tr>
<tr>
<td><strong>Concerta XL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 18mg / 27mg</td>
<td></td>
<td>90mg</td>
</tr>
<tr>
<td>Average 36mg</td>
<td></td>
<td>+ / - MPH IR</td>
</tr>
<tr>
<td>Average 54mg</td>
<td></td>
<td>+ / - MPH IR</td>
</tr>
<tr>
<td>Average 72mg</td>
<td></td>
<td>+ / - MPH IR</td>
</tr>
<tr>
<td>Average 90mg</td>
<td></td>
<td>+ / - MPH IR</td>
</tr>
</tbody>
</table>
## Dosage equivalents (mg)

<table>
<thead>
<tr>
<th>MPH I/R</th>
<th>Concerta XL</th>
<th>Equasym XL</th>
<th>Medikinet XL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily dosage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10mg</td>
<td>-</td>
<td>10</td>
<td>10</td>
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<tr>
<td>15mg</td>
<td>18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20mg</td>
<td>-</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>30mg</td>
<td>36</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>40mg</td>
<td>-</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>45mg</td>
<td>54</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>60mg</td>
<td>72</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>Max dose 100mg</td>
<td>Max dose 108mg</td>
<td>Max dose 100mg</td>
<td>Max dose 100mg</td>
</tr>
</tbody>
</table>
Trial and Error

• May respond to different formulation of MPH even if struggle with one

• Can combine an immediate release and long release
  – e.g. I/R MPH together with Concerta in morning to give boost

• Could give twice daily Medikinet / Equasym but be careful about sleep!
Dexamphetamine

- 5mg tablets

- DA (and NA) reuptake inhibitor by competitive inhibition of the transporters (DAT/NAT)

- Also interacts with vesicular monoamine transporter 2 (VMAT2) to displace DA and monoamines
## Dexamphetamine titration

<table>
<thead>
<tr>
<th>Level</th>
<th>5mg</th>
<th>5mg</th>
<th>5mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>5mg</td>
<td>5mg</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
</tr>
<tr>
<td>Average</td>
<td>10mg</td>
<td>10mg</td>
<td>10mg</td>
</tr>
<tr>
<td>Average</td>
<td>15mg</td>
<td>15mg</td>
<td>15mg</td>
</tr>
<tr>
<td>High</td>
<td>20mg</td>
<td>20mg</td>
<td>20mg</td>
</tr>
</tbody>
</table>

Maximum 60mg per day

2-4 doses per day
Lisdexamphetamine “Elvanse”

- Only stimulant licensed to initiate in adults!!
- A “prodrug”
- Drug is “inactive”
- Needs to be broken down by enzymes in red blood cells so increasing its duration, regardless of route of ingestion
- Can be broken and taken with water, yoghurt
- IV use produced similar “likeability” parameters to placebo
- Once daily, duration for 12-13 hours
- Start 30mg, increase by 20mg increments to maximum 70mg
Interactions and Contraindications

Interactions

- Dexamphetamine metabolised by 2D6 inhibitors (avoid significant enzyme inhibitors e.g. fluoxetine, paroxetine, TCAs)
- Carbamzepine reduces levels of MPH
- MPH increases levels of warfarin and tricyclics

Contraindications

- Phaeochromocytoma
- During treatment or within a minimum of 14 days of discontinuing MAOIs
- Hyperthyroidism
- Drug or alcohol dependence
- Severe depression
- Acute psychosis
- Anorexia Nervosa
- Suicidal tendencies
- Uncontrolled Bipolar Type 1
- Pre-existing cardiovascular disorders
- Pre-existing cerebrovascular disorders, vasculitis or stroke
Titration phase

- Dose should be titrated against symptoms and side effects over 4-6 weeks
- If side effects troublesome, consider a dose reduction
- Consider using alternate formulations and/or medications
- Manage the patients expectations and disappointments
- Remember...Non-response or intolerable side effects doesn’t preclude a good response to the other medication
Follow up

• Via telephone and / or visit (doctor, nurse, other prescriber)
• Initially weekly / fortnightly to titrate to adequate dose, but be flexible
• Then increase to monthly, three monthly, six monthly
• Consider using standard review template recording:
  – Medication, doses, timing
  – Response of key symptoms and side effects/unwanted effects (sleep, appetite, emotional lability)
  – Record BP, HR and weight
  – Comparison with days when meds omitted or times warn off
  – Consider repeating screening / functional questionnaires
• Gather informant feedback as much as possible
Side effects

- Reduced appetite
- Nausea
- Sleep disturbance
- Headache
- Dizziness
- Agitation
- Feeling worse or different when medication wears off

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>FREQUENCY</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Not at all</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Dryness of the skin</td>
<td></td>
</tr>
<tr>
<td>Dryness of the eyes</td>
<td></td>
</tr>
<tr>
<td>Dryness of the mouth</td>
<td></td>
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<tr>
<td>Throat</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Stomach aches</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
</tr>
<tr>
<td>Appetite reduction</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Frequent urination</td>
<td></td>
</tr>
<tr>
<td>Tics</td>
<td></td>
</tr>
<tr>
<td>Sleep difficulties</td>
<td></td>
</tr>
<tr>
<td>Mood instability</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td>Agitation/excitability</td>
<td></td>
</tr>
<tr>
<td>Sadness</td>
<td></td>
</tr>
<tr>
<td>Heart palpitations</td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td>Feeling worse or different when medication wears off (rebound)</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
</tbody>
</table>
Managing side effects

• Appetite suppression
  – Take medication with or after meals
  – Eat when medication not active (and larger meals)
  – Eat smaller snacks regularly
  – Drink high energy fluids
  – Consuming high calorie foods of good nutritional value
  – Consult dietician

• Sleep difficulties
  – Consider avoiding late night doses although in some has positive effect (e.g MPH 5mg at approx. 6pm)
  – Sleep hygiene
  – Consider hypnotic, low dose TCA, melatonin
Managing side effects

• Zombie state
  – Usually overmedicated, can appear withdrawn, over focused
  – Reduce dose / change
• Anxiety
  – Jittery, irritable or nervous
  – Determine whether after meds or when wearing off
  – Lower dose
  – If comorbid anxiety, more likely to occur and consider very low initial doses (e.g. MPH 2.5mg and 2.5mg increments)
Managing Rebound

- Subjective experience can be worse than un-medicated state
- Can experience hyperactivity, impulsivity AND irritability, anxiety and rage attacks
- Use frequent dose intervals or combine long acting and short acting formulations
- Add an antidepressant
- switch
Non-stimulant treatment
Atomoxetine

• NICE recommends as 2\textsuperscript{nd} line treatment

• Consider when:
  – A stimulant is not tolerated or produces side effects (tics, anxiety)
  – There are concerns about stimulant misuse or diversion
  – In “graduates”
Atomoxetine (Strattera)

• Selective noradrenaline reuptake inhibitor
• Studies show both Noradrenaline and Dopamine are co-released by noradrenergic neurones in the prefrontal cortex
• Can take 6-12 weeks for effect
• Only contradiction is Phaeochromocytoma
• Caution in liver impairment, CYP2D6 inhibitors (increase Atomoxetine levels)
• Capsules 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg
Atomoxetine titration

• NICE:
  – For adults weighing < 70kgs, initial dose should be approx 0.5/kg/day
    • Dose should be increased after 7 days to approx 1.2mg/kg/day
  – For adults > 70kgs the initial total daily dose should be 40mg/day
    • Increase dose after 7 days up to a maintenance dose of 80 - 100mg/day (max dose is 120mg/day)
  – Consider lower starting dose and slower titration if concerns about side effects
• Clinical practice – consider titration weekly 18mg/25mg, then 40mg and further 20mg increments to avoid side effects
• Can divide doses, e.g. morning and late afternoon/early pm
Side effects of Atomoxetine

Tends to cause unpleasant but not life threatening SEs (but which do lead to stopping)

• Anorexia
• Nausea and Vomiting
• Dry mouth
• Dizziness and palpitations
• Hot flushes and sweating
• Can cause both postural hypotension and hypertension
• Also associated with agitation, irritability and suicidal thinking

• Liver damage is a rare side effect (risk is 1/50000). Should warm patients about it. Routine LFTs are not recommended
### Monthly costs of ADHD medication (BNF March 2013)

<table>
<thead>
<tr>
<th>Medication</th>
<th>30mg/day</th>
<th>60mg/day</th>
<th>90mg/day</th>
<th>100mg/day</th>
<th>100mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate I/R</td>
<td>£19</td>
<td>£33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerta XL</td>
<td>£42</td>
<td></td>
<td>£116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equasym XL</td>
<td>£35</td>
<td></td>
<td></td>
<td>£130</td>
<td></td>
</tr>
<tr>
<td>Medikinet XL</td>
<td>£34</td>
<td></td>
<td></td>
<td>£142</td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>£37</td>
<td></td>
<td>£96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera)</td>
<td>£62</td>
<td></td>
<td></td>
<td>£124</td>
<td></td>
</tr>
<tr>
<td>Lisdexamphetamine (Elvanse)</td>
<td>£58</td>
<td></td>
<td></td>
<td>£83</td>
<td></td>
</tr>
</tbody>
</table>
Longer term monitoring for Stimulants and Atomoxetine

- Weight should be measured 3 months and then 6 monthly after drug treatment has started.
- BP and HR monitored each dose change and routinely 3-6 monthly.
- Agree shared care agreement with primary care (initiate prescribing by specialist, continuation and monitoring in primary care).
- NICE “drug treatment should be continued for as long as it remains clinically effective.”
- Assessment of clinical need, benefits and side effects be reviewed at least “annually” with views of patient, significant others considered.
- Assessment undertaken by whom?
Other options

• Guanfacine (preferential α2A-adrenoceptor agonist – licensed in N America and now for children and adolescents in UK)
• Bupropion
• Venlafaxine / duloxetine
• Modafinil
• Clonidine
• Omega-3-fish oils
Cardiovascular complications of Stimulants and Atomoxetine

- Both lead to clinically important increases in BP and/or HR
- Assess if associated with physical symptoms and if clinically hypertensive / tachycardic
- Redo measurements at GPs and consider 24hr BP and / or ECG
- Liaise with GP and / or Cardiologist re continuing ?with addition of antihypertensive
- Note sudden deaths are no more common than in background population rates
Abuse of medications

- Stimulants has been shown to reduce substance misuse due to better personal achievements/social integration.
- They are popular amongst university students (motives) and students should be warned when prescribing.
- Need to consider both kinetics (how fast drug gets in and out of brain) and dynamics (what it does in the brain).
- Faster and bigger effects increase risk of drug liking:
  - iv > oral
  - Cocaine > amphetamines > methylphenidate
- Slow onset from oral dosing minimises abuse.
- Many patients dislike the drugs (adolescents and adults).
- Have option of longer release stimulants and also atomoxetine.
Improving adherence

• More than half patients do not adhere fully to medical advice (in any condition)
• Regular communication (remember who we’re dealing with!)
• Counselling about condition, medication, expectations etc.
• Communicate with spouse, parent, close friend
• Clear instructions regarding regimen and need for supervision if necessary
• Simple drug regimens if possible
• Respond to concerns
• Some flexibility about monitoring
• Review whether still symptomatic
Responses to treatment..

- Can be very rapid
- “I feel in control”
- “I feel normal”
- “The buzzing has stopped”
- “I can sit and have stopped annoying my partner”
- “I can read a book for 15 minutes”
- “My moods are now stable”
Ideas for Outcomes

• Symptom scales (e.g. Connors)

• **Weiss Functional Impairment Rating Scale**
  – Domains of:
    • Family
    • Education
    • Work
    • Life Skills
    • Self Concept
    • Social
    • Risk
MANAGING COMORBIDITY
Mood Symptoms

• Chronic mood instability often responds to stimulants
• Chronic low self esteem – can respond to control of symptoms and increase functioning (e.g. job) and consider psychological interventions
• Treat episode of depression with antidepressants (before ADHD treatment if possible)
Bipolar Disorder

• Episodes of depression and hypomania – treat with mood stabilisers prior to even considering adding ADHD treatment

• If episode of hypomania during treatment, lower dose/stop ADHD meds and add mood stabiliser
Anxiety

• Consider if is untreated ADHD
• If somatic anxiety, treat with SSRIs either before or during treatment if becomes more prominent
• Use low dose stimulants increasing slowly
• Consider CBT (may only be effective once ADHD treatment in place)
Personality Disorder

• ?Which is primary
• Treat ADHD with medication if significant symptoms of ADHD associated with significant impairment
• May not be able to tolerate psychotherapy until ADHD symptoms reduce
Schizophrenia / other psychosis

• If acutely psychotic, avoid ADHD treatment

• Consider combining antipsychotic with stimulants or atomoxetine if clear history of symptoms and impairment before and after onset of psychosis (caution)
Substance dependence

• Work together with addiction services

• Substance use needs to be “stable”

• Consider atomoxetine but do not totally dismiss use of stimulants, even if illicitly abusing
Potential benefits for reduction in ADHD symptoms in SUD patients

• Increased level of function, enabling person to focus on work and other useful activities
• Increased level of interest in daily activities and reduced need for risk-taking activities, including drug taking
• Reduced need to self-medicate to control ADHD symptoms
• Increased ability to attend and focus on, and therefore benefit from individual or group therapy sessions
• Increased resilience and the ability to cope with failures without resorting to alcohol or drug use
• Improved self-esteem and awareness
Autistic Spectrum Disorder

• Stimulants effective
• Psychostimulant side effects more common, typically dysphoria and perseveration or cognitive rigidity
• Start low, go slowly, monitor more frequently
• Effect of atypical antipsychotics on hyperactivity is good
QUESTIONS???