High dose stimulant medication in the management of attention deficit hyperactivity disorder (ADHD): a retrospective cohort study

Sally Poulton¹,² Lindsey Ross² Veena Sapre²
Christina Stanislaus²

¹ Sydney Medical School Nepean, University of Sydney
² Nepean Hospital of Department of Paediatrics
Disclosure

- Speakers fees and non-financial support from Shire/Takeda
- The research presented here was unfunded
Stimulants for ADHD

- First line drug treatment of ADHD in adults and children
- Accepted clinical practice: dose titration to optimize the dose, balancing
  - Beneficial effects
  - Adverse effects
- There is a maximum recommended dose
  - Is there ever a conflict between dose titration and the maximum dose of stimulant?
  - How should such a conflict be managed?
What do the guidelines say?

- NHMRC – no maximum dose is specified [1]
- AAPAP – “to achieve maximum benefit with minimum adverse effects.” [2]
- European guidelines 2004 – titrate methylphenidate to 0.7mg/kg/day or 54mg/day [3]
- NICE – maximum dose referred to but not specified [4]: implied formulary maximum

No acknowledgement that the maximum dose might be a problem
No guidance on how to manage this situation

4. National Institute for Health Care Excellence. Attention deficit hyperactivity disorder (update) [D] Evidence review for safety of pharmacological treatment. NICE guideline NG87 Intervention evidence review March 2018
Meta-analysis of studies establishing the dose of methylphenidate by titration: rationale for chosen dose range

7 RCTs

- Maximum dose 20-72 mg/day
- Maximum dose 1.4-1.5 mg/kg/day

20 cohort studies

- Maximum dose 30-90 mg/day
- Maximum dose 0.8-1.4 mg/kg/day

---

Meta-analysis of studies establishing the dose of methylphenidate by titration: rationale for chosen dose range

7 RCTs
- 2 cited dose range used in previous studies*
- 5 gave no justification

20 cohort studies
- 2 cited FDA/formulary maximum
- 1 cited dose range used in previous studies*
- 17 gave no justification

*Cited studies gave no justification

Findings

- No definitive scientific justification for any maximum dose for titration
- No life-threatening adverse effects
- Methylphenidate gives a higher rate of adverse effects (anorexia, insomnia) than placebo
Do these dose restrictions, which appear to have no clear scientific basis, affect clinical practice?

Online survey distributed to doctors known to be interested in treating ADHD (currently 78 respondents)

- Members of AADPA
- Members of NBPSA
- People on Shire/Takeda mailing list of clinicians who treat ADHD

(Questions designed with assistance from Roger Patterson)
What is your professional group?

- Paediatrician
- Adult Psychiatrist
- Child and adolescent psychiatrist
- GP

Percentage of respondents
How long have you been treating ADHD?

- Less than 5 years
- 5-10 years
- 10-20 years
- More than 20 years

Percentage of respondents

0 5 10 15 20 25 30 35
What proportion of your patients have ADHD?

- Less than 10%
- 10-50%
- More than 50%

Percentage of respondents
In which state do you practice?

- ACT
- NSW
- NT
- Queensland
- SA
- Tasmania
- Victoria
- WA
- New Zealand

Percentage of respondents
What is the age range of your patients with ADHD?

- Children and adolescents: 50%
- Adolescents and adults: 20%
- Adults: 30%
- All ages: 10%
Do you ever see patients who appear to need a higher dose than the Product Information?

- Never
- Rarely (less than 5 times ever)
- Sometimes (more than 5 times ever, but less than 5 times per year)
- Often (more than 5 times per year)

Percentage of respondents
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percentage of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>15</td>
</tr>
<tr>
<td>Rarely (less than 5 times ever)</td>
<td>30</td>
</tr>
<tr>
<td>Sometimes (more than 5 times, but less than 5 times per year)</td>
<td>25</td>
</tr>
<tr>
<td>Often (more than 5 times per year)</td>
<td>10</td>
</tr>
</tbody>
</table>
If a patient did not appear to be optimally treated after reaching the specified maximum, would you exceed this?

- Never
- Yes, with a supporting second opinion
- Yes, and I would apply for approval for high dose prescribing
- Yes, without any further formalities

Percentage of respondents
If you would not exceed the specified maximum, would you

- Accept continuing on a suboptimal dose and take no further action?
- Get a second opinion?
- Try polypharmacy?

Percentage of respondents

0 10 20 30 40 50 60 70
Survey conclusions

Experienced prescribers find the current maximum doses restrictive:

- 37% see >5 patients per year who need more than formulary maximum
- 23% see >5 patients per year who need more than state/territory maximum

- 77% would exceed the maximum
- 15% would use polypharmacy
- 6% would consult a colleague
- 2% would accept suboptimal treatment
So what happens if dose restrictions not followed?
Retrospective review of clinic patients optimised to high dose stimulant using dose titration

Research question:
- Are the children who are optimised to high dose any different?
- Do children on high dose have more side effects?

Methodology
- Retrospective cohort study from practice records (2003-2016) using electronic prescription database
- Compared to controls matched by date of prescription
- All high dose patients had Authority from the NSW Ministry of Health
- Ethics approval for retrospective review from NBMLHD Human Research Ethics Committee
## Maximum doses of stimulant in NSW

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulary maximum</th>
<th>NSW Ministry of Health Prescribing Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin/Ritalin LA</td>
<td>60mg</td>
<td>108mg; 2mg/kg</td>
</tr>
<tr>
<td>Concerta</td>
<td>54mg if &lt;12 yr; 72mg if &gt;12 yr</td>
<td>108mg; 2mg/kg</td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>60mg</td>
<td>50mg; 1mg/kg</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>70mg</td>
<td>70mg</td>
</tr>
</tbody>
</table>

Patients in NSW can be treated at higher doses with authorisation for the NSW Ministry of Health.
Patient management

53 high dose, 117 regular dose

- All were on stimulants for treatment of ADHD
- Dose optimised by titration
- Titration not restricted by any maximum dose
- Dose increased or reduced depending on response
- Monitoring efficacy using rating scales
- Monitoring side effects
- Monitoring growth and blood pressure
Medication and medication dose compared

<table>
<thead>
<tr>
<th>Medicine</th>
<th>High dose N=53</th>
<th>Controls N=117</th>
<th>P (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate mg/day</td>
<td>49.5 (86%)</td>
<td>33.0 (84%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methylphenidate mg/kg/day</td>
<td>1.40</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dexamphetamine mg/day</td>
<td>33.1 (5%)</td>
<td>18.4 (9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dexamphetamine mg/kg/day</td>
<td>0.69</td>
<td>0.49</td>
<td>0.004</td>
</tr>
<tr>
<td>Lisdexamfetamine mg/day</td>
<td>59.0 (9%)</td>
<td>39.8 (7%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Clinical characteristics

- Children on high dose were more likely to be male and have oppositional defiant disorder (ODD)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>High dose</td>
</tr>
<tr>
<td>ODD</td>
<td>Regular dose</td>
</tr>
<tr>
<td>ASD</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Toileting issues</td>
<td></td>
</tr>
<tr>
<td>Intellectual</td>
<td></td>
</tr>
</tbody>
</table>

* p=0.02
** p=0.001
Growth data

- High dose cohort had slower growth in height and weight before reaching high dose threshold (p<0.001)
Reasons for dose increases

- High dose - more likely to be anger-aggression
- Regular dose - more likely to be concentration

![Graph showing reasons for dose increases: Not effective enough, Inadequate duration, Problem: concentration, Problem: anger/aggression, Problem: disruptive behaviour, Problem: defiance, Problem: hyperactivity, Problem: mood, Problem: compliance with multiple dosing. High dose (n=310 dose increases) vs Regular dose (n=303 dose increases).]

- *** * p < 0.001
- * p < 0.05
Summary of findings

- Children on higher dose had higher rates of ODD but were not otherwise more complex.

- Children on higher dose were more likely to have their dose increased for control of their symptoms of ODD.

- Children on higher dose showed more growth attenuation and received more melatonin for insomnia (dose-related side effects).

- No serious adverse effects in either group.
Conclusion

• Dose titration that is responsive to the balance of beneficial to adverse effects appears logical

• It is possible that the margin of safety may be far greater than is implied by current dose restrictions

• Further study is needed