THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

What is the evidence for using CNS stimulants to treat ADHD in children?

Exposing children to medication for an extended period of time is concerning for parents and clinicians. **A recent review of British Columbia's Pharmanet data revealed that methylphenidate (Ritalin®, Ritalin SR®, Biphentin®, Concerta®) is the most common long-term (> 2 years) medication to which BC children are exposed.** Methylphenidate is classified as a central nervous system (CNS) stimulant. Other CNS stimulants include: dextroamphetamine (d-amphetamine) [Dexedrine®, Dexedrine SR®] and mixed amphetamine salts (d-amphetamine and l-amphetamine) [Adderall XR®]. These medications are most commonly prescribed for children with a spectrum of attention and behaviour problems, currently designated Attention-deficit hyperactivity disorder (ADHD). It is beyond the scope of this letter to review this complex and controversial disorder and all its treatments.

This Letter summarizes and critiques the key published randomized controlled trial (RCT) evidence for the use of CNS stimulants in children. We present the benefits and harms for short-term RCTs (< 1 year), medium-term RCTs (1-2 years) and long-term RCTs (> 2 years). Rational therapeutic principles and clinical implications of treating children with stimulants are relevant to the use of any drug during human development. Adverse and potentially irreversible drug effects on growth and development are possible, and long-term drug-induced benefits and harms may not be demonstrable until much later in life. It is therefore particularly important in children to have long-term RCT evidence as to whether drug therapy benefits outweigh harms.[1]

Best available short-term (< 1 year) evidence

Benefits

Many RCTs have assessed the short-term efficacy of CNS stimulant drugs on children's behaviour. Although a Cochrane Review on this topic is not available, the Cochrane Library provides references to 13 other systematic reviews on this topic. The two most relevant to this Letter's question are Schachter et al.[2] and King et al.[3] Schachter et al. identified 62 RCTs of methylphenidate versus placebo published between 1981 and 1999, and involving 2897 participants (88% male) with a median age of 9 years. The trials were small (mean sample size 47 subjects), used a cross-over design (84%) and were brief (mean duration of treatment = 3 weeks). The reviewers meta-analyzed teacher and parent ratings of a hyperactivity index (range 0 to 31; lower is better) - a measure of hyperactive or impulsive disruptive behaviour. The methylphenidate effect size was a 6 point reduction from 14 for teachers and a 4 point reduction from 14 for parents. However, Schachter et al. judged that these effect size estimates were likely an overestimate due to publication bias (non-publication of RCTs with negative results) and stronger treatment effects in trials with inadequate blinding. King et al. reviewed 65 RCTs up to July 2004, both placebo-controlled and head-to-head comparisons of methylphenidate and d-amphetamine. The reviewers summarized the trials but did not meta-analyze outcomes. Similarly to Schachter et al, they noted inadequate reporting of study methodology, possible bias, limited reliability of results and inadequate reporting of adverse events. They concluded that CNS stimulants reduce teacher and parent ratings of hyperactivity and found no significant difference between methylphenidate and d-amphetamine for efficacy or adverse effects, mainly owing to lack of evidence.

Harms

The Schachter et al. review meta-analyzed data from the 10 RCTs that reported adverse events.[2] This analysis demonstrated statistically significant increases with methylphenidate compared to placebo for the following adverse events: decreased appetite (NNH* 4), insomnia (NNH 7), headache (NNH 22), stomach ache (NNH 9) and dizziness (NNH 11).

**NNH = Number needed to treat to cause one harmful event.*

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Best available medium-term (1 to 2 years) evidence

Benefits

The best medium term evidence for CNS stimulant treatment is provided by the U.S. National Institute of Mental Health 14 month Multimodal Treatment (MTA) active comparator RCT of children with ADHD.[4] The MTA study randomized 579 children aged 7 to 9 to one of 4 open-label arms: CNS stimulants alone (mostly methylphenidate), behavioural therapy alone, CNS stimulant plus behavioural therapy (combined) or usual care in the community (majority treated with CNS stimulants). The non-blinded teacher rated hyperactive/impulsive scale (range 0 to 3) was statistically significantly lower at 14 months in the two CNS stimulant groups (0.8) as compared to the behavioural therapy group (1.1) and usual care (1.3). This approximate difference was maintained over the 14 months of the trial. **However, blinded classroom observer ratings were not significantly different between the 4 groups.** In addition children's self-ratings on the Multidimensional Anxiety Scale for Children did not differ between the 4 groups. Measures of academic achievement, the Wechsler Individual Achievement Test (reading, math and spelling, mean for age = 100, range 40-160) were mostly not significantly different; the only exception being a higher reading subscale score for combined therapy, 99, than behavioural therapy, 96, or usual care, 95.

Harms

Non-blinded adverse effects in the two CNS stimulant treated groups were monitored monthly. At end point 49.8% reported mild adverse effects, 11.4% reported moderate adverse effects and 2.9% reported severe adverse effects.

Best available long-term (> 2 years) evidence

Benefits

There are no RCTs assessing benefits and harms of long-term stimulant therapy in children. The only randomized long-term follow-up comes from an extension of the MTA trial, described above. Of 579 children randomized, 485 (84%) were followed up and restudied at 3 years.[5]

At 3 years post-randomization the percentage of children taking medication >50% of the time was: behavioural 45%; stimulant 72%; combined 70%; and usual care 62%. Five outcomes that were previously statistically different or particularly clinical relevant were measured at 3 years. **There were no significant differences between therapy groups for any of these 5 outcomes.** Furthermore, the proportion of children meeting the diagnostic criteria for ADHD had dropped to about 50% and was not different between the 4 therapy groups.

Harms

At 3 year follow-up the incidence of delinquency and substance abuse did not differ between the 4 therapy arms (delinquency, 27% for the entire group, per group data not reported; substance abuse, 22% for stimulant, 19% for usual care, 16% for combined and 13% for behavioural).[6] The effect of stimulant medication on growth rates was also assessed. Children who were consistently medicated (n=70) for the 3 years during and after the MTA study grew on average 2 cm less in height and weighed on average 2.7 kg less than children who were never medicated (n=65) during the same 3 years.[7]

Conclusions

In children designated to have ADHD, CNS stimulants:

- Improve teacher and parent ratings of hyperactive/impulsive disruptive behaviour.
- Do not improve children's ratings of anxiety nor measures of academic achievement.
- Do not change the incidence of delinquency or substance abuse at 3 years.
- Decrease height and weight at 3 years.
- Have not been studied for their long-term effects on standardized exams, quality of life, school completion, employment, longevity and future health.

Recommendations

Large multi-year RCTs assessing CNS stimulants are needed that follow treated and untreated cohorts into adulthood and measure: delinquency, substance abuse, educational achievement (standardized exams, years completed, etc.) employment or economic performance and long-term morbidity and mortality.[1]

Better benefit and harm evidence is necessary before long-term CNS stimulant treatment can be recommended.

The draft of this Therapeutics Letter was submitted for review to 54 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

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