

Long-term outcomes associated with stimulant medication in the treatment of ADHD in children

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Acknowledgments



MICADHD

Current Knowledge

Well described short term-benefits of methylphenidate and dexamphetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD) symptoms

Majority of these studies span between 2 weeks and approximately 6 months.

General consensus amongst medical researchers that methylphenidate and dexamphetamine are effective in managing the short-term symptoms of ADHD

the treatment of ADHD is about to be further stoked with the release of a long-term health study in Western Australia tomorrow.

Kids on ADHD drugs 'poor at school'

It should end the ADHD debate. We should stop the use of stimulants for ADHD in children.

..there is often a lot of hysteria around ADHD medications that is not always founded.

Now we know there are some short-term impacts which may help the child, but long-term they're not likely to result in significant improvement.

Their decision will now be made with better information as to the benefits and the risks, and so will help in making the right decision for that child.

..even if they stopped taking them, had higher blood pressure. A rise in blood pressure is often associated with problems later in life, either stroke or heart attack. **MP wants ADHD drug ban**

World's first long term research shows ADHD drugs harm Children's Hearts and Minds

"The ADHD industry's claim that without medication ADHD children risk academic failure has been shown to be complete bull,"

It's limited and that's why I suggest that people should take note of these findings and do more

Current Knowledge

Debate as to whether these short-term effects translate to long-term benefits to a child's academic performance and/or social and emotional wellbeing

Few studies examining the relationship between stimulant medication-use and long-term social and emotional outcomes (such as peer relationship quality, depression and anxiety) - no significant effects were observed

Current Knowledge

The long-term academic outcomes associated with stimulant medication have been better studied..

- * long-term academic gains associated with the use stimulant medication (Barbarese, Katusic, Colligan, Weaver, & Jacobsen, 2007; Powers et al., 2008), particularly with regard to mathematics skill (Scheffler et al., 2008).
- * No effect of stimulant medication on the academic outcomes of children with ADHD (Carlson & Bunner, 1993; Charles & Schrain, 1981; Loe & Feldman, 2007); including a meta-analysis (Jadad, Boyle, Cunningham, Kim, & Schachar, 1999).
- * Significant academic improvement in the short-term, but that benefits are no longer present after three years (M. T. A. Cooperative Group, 2004a; J. M. Swanson et al., 2007).

Background

Approximately 5.3% of children under the age of 18 years are diagnosed with ADHD

The proportion of Australian children meeting the diagnosis requirements for ADHD has been estimated at approximately 8% (AIHW, 2003).

The WA Stimulant Regulatory Scheme indicated that approximately 1.26% of all children in the state had received either dexamphetamine or methylphenidate in the treatment of ADHD during that year (Department of Health, 2008).

Side effects

Methylphenidate and dexamphetamine have both been associated with a 'less than expected' growth trajectory for both height and weight during childhood and adolescence

methylphenidate and dexamphetamine result in statistically significant increases in blood pressure and heart rate by approximately three to four mmHg and heart rate by approximately five beats per minute.

long-term implications of the cardiovascular effects of stimulant medication-use over a number of years have not yet been adequately explored.

Study Aim

Longitudinal data from the Raine Study

- * long-term associations between stimulant medication-use during childhood and adolescence by outcome.
- * Outcome measures at 14 years of age
 - * Social, Emotional, Educational, Physical, and Cardiovascular.

Raine Study

Western Australian Pregnancy Birth Cohort (Raine) Study is an ongoing longitudinal study following 2,868 children

- * Pregnancy cohort of women enrolled at or before the 18th week of gestation
- * Since 1989, data has been collected from the participants (both the mother and her child) at regular intervals including when the child turned 1, 2, 3, 5, 8, 10, 14 and 17 years old.

Raine ADHD Study

Two samples

- * all children in the Raine study sample for whom 14-year follow-up data were available (n = 1785).
- * Raine study children who had been diagnosed with ADHD for whom data was available at the 14 year follow-up (n = 131).
- * Exclusions - Children diagnosed with an intellectual disability

Stimulant Use Measures

In the past six months has your child taken/used any prescription medication(s)?

- * Stimulant Exposure Categories:

- * Received no medication; Received medication at one follow-up point; Received medication at 2 follow-up points; Received medication at 3 follow-up points

- * Any Use Categories:

- * Never received medication; Ever received medication

- * Recent Use Categories:

- * Received no medication; Received medication in the past; Currently receiving medication (not used at all time points in the past); Consistent use of medication at all time points

Measures

Family Structure	Mother's Age	Family Income	Mother's Education	Performance IQ	Pubertal Development
Biological father living with mother	14 - 20yrs;	<\$12,000;	Lower School	Wisc III. Block design	Tanner staging
Biological father living away from mother	21 - 27yrs;	\$12,000 - \$35,000;	Upper School		
	28 - 34yrs;	>\$35,000	Trade Certificate/ Diploma		
	35 - 46yrs		University/ College Degree		

Outcome Measures

Externalising behaviours	Social emotional measures. Self Perception	Social Functioning	Teacher-rated Academic Performance	Absenteeism	Enjoyment of School
Conduct Disorder Behaviour Checklist (CBCL) (Fergusson, 1991).	Harter Adolescent Self-Perception Scale (ASPP) (Harter, 1986)	Harter Adolescent - Social Acceptance (ASPP-S) (Harter, 1986)	child is performing at or above average	10% or more of the available days - "high absenteeism"	
Externalising Behaviour Subscale (CBCL-Externalising)	Scholastic Competence Social Acceptance			less were classified as "low/average absenteeism"	
Attentional Problems (CBCL-Attention)	Athletic Competence, Physical Appearance, Behavioural Conduct, and				

Physical Measures

Height and Weight

- * Raw height and weight measurements corrected for gender and age by calculating z-scores.

Cardiovascular Function

- * Measurements of systolic blood pressure, diastolic blood pressure, and resting heart rate using Dinamap.

Analysis

Multivariable Modelling

- * to identify the relationships between stimulant medication and child outcomes at 14 years whilst controlling for a number of covariates.
- * For continuous out come measures: general linear models (GLM), controlling for propensity for medication, symptom severity and other child and family measures
- * For dichotomous measures binary logistic regression models (controlling for the same measures) were conducted and adjusted odds ratios were calculated.

Analysis

Change in normative-referenced measures

- * compare normative referenced measures that were taken at two time points prior to medication-commencement (at five years); and at 14 years of age.
- * The relative changes from time-point one to time-point two for CBCL-E and CBCL-A were calculated (referred to as 'Change Scores').
 - * A positive change score reflects an increase/elevation in the symptom, whereas a negative change score indicates and improvement.
- * Generalised Linear Models, controlling for propensity score and sociodemographic measures, were conducted to identify the association between medication use and change in symptom severity over time.

Controlling for potential systematic differences between medication groups

1) controlling for symptom severity,

* Attention Problems (CBCL-A), and Externalising Behaviour (CBCL-E) at age 5 years.

* But.....Limitations of “Symptom Severity Control”

* The CBCL is parent-rated and subjective

* The version of the CBCL used in the Raine study was prior to the 2001 revision. As such, the measure is not well-designed to detect attentional problems (Heubeck, 2000)

* Behaviour and attention at five years of age may not necessarily be good predictors of behaviour and attention at later ages

Controlling for potential systematic differences between medication groups

2) controlling for sociodemographic measures,

- * Income of Family, Family Structure, Mother's Age, and Gender of the Child
Adjusted for in all multivariable models:

3) calculating a 'propensity score'.

- * Propensity scores were converted to a binary measure ('high' and 'low' likelihood of receiving medication) and this was included as a covariate in the multivariable models.

Results

Of the 1785 adolescents in the sample, 131 (7.3%) had received a diagnosis of ADHD by the 14-year follow-up.

- * 75.6% male versus 48.9% male in non-ADHD-diagnosed
- * 22% 'lower income' families (<\$12,000) versus 12.0% of the non-ADHD diagnosed
- * 14.6% born to mothers < 20 years versus 8.8% non ADHD
- * 18% did not have their biological father living in the same house at the time of birth versus 9.4% of children who never received a diagnosis of ADHD.

Medication

Ever received medication

- * 131 children in the ADHD-diagnosed subsample,
 - * 21 (16.0%) reported the use of stimulant medication at all three follow-up points (8, 10, 14 years),
 - * 42 (32.1%) at two follow-up points, and
 - * 39 (29.8%) at one of the follow-up points.
 - * 29 (22.1%) reported no use of stimulant medication at any of the follow up points.

Use of Stimulant Medication

Current use of medication

- * 21 (16.0%) were using medication at age 14 and had used it consistently since being diagnosed with ADHD
- * 40 (30.5%) were using medication at 14, but had not consistently used it in the past
- * 41 (31.3%) had used medication in the past but were not using it at age 14
- * 29 (22.1%) had not reported using stimulant medication.

Results

Results: Social and Emotional Outcomes

No significant differences based on medication-use were noted for the following measures taken at 14 years of age: depression, self-perception, and social functioning.

Results: Social and Emotional Outcomes

Depression (BDI)

* Higher scores indicate a higher level of depressive affect.

* No significant effect of Stimulant Exposure on BDI score

Stimulant Exposure	n	Estimated marginal mean	Std. Error	95% CI
None	20	42.76	2	38.85 - 46
1 time point	25	44.84	2.14	40.64 - 49
2 time points	37	43.42	1.92	39.67 - 47
3 time points	18	44.57	2.56	39.55 - 49

Self Perception Harter Adolescent Self-Perception Profile

- * Poorer self-perception in children diagnosed with ADHD
- * Higher scores indicate a more positive self-perception.
- * No significant effect of Stimulant Exposure on ASPP score: $F(3, 84) = .831, p = 0.48$.

Stimulant Exposure	n	Estimated marginal mean	Std. Error	95% CI
None	20	128.9	4.97	119.0 - 138.8
1 time point	24	123.9	5.16	113.7 - 134.1
2 time points	37	126.7	4.68	117.0 - 136.4
3 time points	17	132.6	6.22	120.3 - 145.0

Results: Social and Emotional Outcomes

Social functioning - Harter Adolescent Self-Perception Profile - Social Functioning subscale (ASPP-S)

- * Higher scores indicate better social functioning.
- * Lower level of social function within children diagnosed with ADHD
- * No significant effect of Stimulant Exposure on ASPP score: $F(3, 87) = .55, p = 0.65$.

Stimulant Exposure	n	Estimated marginal mean	Std. Error	95% CI
None	20	30.32	2.25	25.85 - 37.00
1 time point	25	29.41	2.36	24.73 - 34.10
2 time points	38	28.6	2.09	24.46 - 32.74
3 time points	18	31.46	2.85	25.80 - 37.12

Academic results

Academic Performance

- * Of the ADHD-diagnosed subsample (n = 77), 49.4% were classified by their teacher as performing below age level.
- * Of the sample without a diagnosis of ADHD (n = 964), 16.5% were classified as performing below a level. This difference was statistically significant.
- * The adjusted odds ratio for the use of stimulant medication in predicting “below average” classroom performance was 10.47 (95% CI: 1.12 - 97.49)

Absenteeism

- * Not significant

Enjoyment of school

- * The mean Enjoyment of School score for non-ADHD-diagnosed children (n = 1383) was 33.84 (SD 6.75). The difference of 1.49 was statistically significant ($t(1495) = 2.24, p < .05$), indicating less school enjoyment in children diagnosed with ADHD. No significant effect of stimulant exposure.

Media comments

£ Kids on ADHD drugs 'poor at school'

£ Harms minds and bodies!

Results: Academic

Enjoyment of School

- * Higher scores indicating greater enjoyment of school
- * The mean Enjoyment of School score for non-ADHD-diagnosed children ($n = 1383$) was 33.84 ($SD = 6.75$). The difference of 1.49 was statistically significant ($t(1495) = 2.24, p < .05$), indicating less school enjoyment in children diagnosed with ADHD.
- * no significant effect of Stimulant Exposure on Enjoyment of School score: $F(3, 82) = 1.9, p = 0.90$

Stimulant Exposure	n	Estimated marginal mean	Std. Error	95% C
None	20	33.03	2.6	27.87 - 38
1 time point	23	34.58	2.72	29.18 - 39
2 time points	35	34.02	2.45	29.14 - 38
3 time points	18	35.73	3.25	29.27 - 42

Results: Physical

Height and Weight

- * Height: There was no significant difference in average height or weight (at 14 years of age) when comparing children who were consistently on medication to those who were never on medication.
- * Non-significant trends indicated very little difference in growth measures between the 'consistently medicated' and 'never medicated' groups.

Physical Results - Media response

- Blood pressure effects: Stroke or heart attack risk.
- A child's heart function may be affected by long-term stimulant use and may remain affected even after stopping medication

Results: Cardiovascular Function

Diastolic Blood Pressure: children who had consistently received stimulant medication at all time points - significantly greater diastolic blood pressure than children who had never received medication (10.79 mmHg higher).

Children who had consistently received stimulant medication at all time points (including when cardiovascular health was measured) also had a significantly greater diastolic blood pressure than children who were currently receiving medication but had not in the past (7.05 mmHg higher).

These findings suggest that an elevation in diastolic blood pressure may not be due solely to the immediate short-term effects of stimulant medication on cardiovascular function.

Results. Diastolic BP

Estimated marginal means for diastolic blood pressure by current stimulant medication use (adjusting for gender, propensity, CBCL-E, CBCL-A, mother's age, family structure, family income)

Systolic Blood Pressure and Resting Heart Rate showed no significant difference based on stimulant medication use.

Diastolic Blood Pressure: children who had consistently received stimulant medication at all time points - significantly greater diastolic blood pressure than children who had never received medication (10.79 mmHg higher)

Stimulant Exposure	n	Estimated marginal mean	Std. Error	95% CI
None	20	55.79	2	51.81 - 59.77
In the past	29	60.46	2.1	56.29 - 64.63
Currently, inconsistent in past	34	59.53	1.84	55.87 - 63.19
Consistently	18	66.58	2.57	61.48 - 71.68

Blood Pressure implications

Interpreting these results is difficult. Current information about the levels of increased CVS risk associated with raised DBP pertain to adult studies of DBP above 70-75 mmHg and are not interpretable at levels below that.

Key ADHD symptom measures

On average, externalising behaviour and attentional problems did not appear to improve or worsen significantly between the ages of 5 and 14 in children with ADHD, regardless of medication use.

These were parent rated measures.

Limitations

Small sample size,

Difficulties controlling for systematic differences between comparison groups,

Difficulty in controlling for symptom severity,

Medication being grouped

Inability to measure dosage and adherence to medications,

Lack of validation of ADHD diagnosis,

Inability to identify subtypes

Missing values in weight/height and academic rating.

Lack of account of comorbidities or additional medications which may have

Conclusions

Unique long-term view of a wide range of outcomes and their associations with the use of stimulant medication in the treatment of ADHD

Whilst limitations to the current study prevent causal relationships from being identified, the associations that were noted strongly suggest that more methodologically rigorous into the long-term outcomes associated with ADHD should be conducted