EDITORIAL

The challenges to demonstrating long-term effects of psychostimulant treatment for attention-deficit/hyperactivity disorder

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Purpose of review

Questions about the long-term effects of psychostimulant medication are frequently raised in the public domain. There is a need to articulate the methodological challenges to addressing this question, both to assist in the interpretation of existing research and to inform future research.

Recent findings

Two peer-reviewed studies and one published report have attempted to address the issue of long-term effects of psychostimulant medication. One is favourable, one found no benefit, and the third showed harm. All three studies struggled to deal with methodological challenges such as the variable time course of the disorder, variability in persistence and adherence with treatment, and self-selection for treatment continuation.

Summary

Future research examining the long-term effects of psychostimulant treatment will of necessity be naturalistic, but must be able to control for treatment quality, treatment adherence, and natural variation in the course of attention-deficit/hyperactivity disorder. It would be helpful to distinguish between long-term effects of treatment and effects of long-term treatment.

Keywords

attention deficit disorder with hyperactivity, dextroamphetamine, longitudinal studies, methylphenidate

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Introduction

Is it necessary to demonstrate the long-term effects of pharmacological treatment for childhood mental disorders such as attention-deficit/hyperactivity disorder (ADHD)?

As regards the benefit side of the equation, some experts have argued that relief of symptoms in childhood is a worthy enough goal in itself. Pliszka [1], commenting on the 8-year follow-up data from the Multimodal Treatment Study for ADHD (MTA), states 'Psychiatry is not alone in having treatments that are highly effective in the short-term but do not seem to alter the underlying disease process. Indeed, a recent review of treatments in childhood asthma shows that inhaled corticosteroids and long-acting beta agonists clearly improve acute symptoms of asthma but do not ''alter the natural progression of the childhood asthma nor halt progressive airway damage''. No one would suggest, however, that treating an acute asthma attack is unwarranted, and therefore, neither should the effectiveness of short-term stimulant treatment of ADHD be disparaged' (p. 1122).

Yet, at some point along the course of history of treatments for ADHD, there has been speculation that treatment (particularly pharmacological treatment) in childhood will promote better functioning in adulthood. The genie has, therefore, been 'let out of the bottle', and the question of long-term benefit must be addressed. From the perspective of harm, there is no doubt that sections of the community are concerned with the possibility that adverse effects in the long term may outweigh benefit [2,3]. These concerns surface regularly in the media [4]. Public concern about the safety of pharmacological treatment is sometimes exploited in promotional material for complementary medicines for ADHD [5].

Methodological challenges

There are substantial methodological challenges to demonstrating the long-term effects of pharmacological treatment for ADHD.

(1) There is variability in the natural course of the disorder [6], making it uncertain whether improvement is

treatment-related or the result of an age-dependent but individually variable decline in symptoms.

(2) There is variability in exposure to treatment due to variation in persistence and adherence. Among 16 945 Canadian patients aged 19 years or less who were treated with methylphenidate, the mean duration of therapy was 19.5 months [7], whereas among 379 patients aged less than 18 years in Rochester, Minnesota, mean duration was 33.8 months [8]. In a prospective study of 134 Italian children with ADHD, 46% were persisting with treatment after 36 months [9]. In the large Canadian cohort, only 18% of the sample showed a chronic persistent pattern of adherence to treatment [7].

An 8-year follow-up to the MTA study found 32.5% of participants were medicated more than half the time [10]. Analysis of salivary samples taken from participants in the drug treatment arm of the MTA during the first 14 months of the study showed that, on more than 20% of occasions, the child had not taken the methylphenidate on the morning of assessment, although, according to parental report, adherence was over 96% [11]. These examples all serve to demonstrate that, over an 8–10-year follow-up, only a small minority of patients are likely to have been adherent to treatment consistently, and, by follow-up, most are likely to be untreated. Such variability in exposure means that benefits and harms may be falsely attributed to treatment.

(3) There is variability in concurrent treatment. Combined pharmacotherapy occurs in about 20% of both child and adult patients [12,13]. Agents used in addition to psychostimulants include α-2 adrenergic agonists [14], selective noradrenergic reuptake inhibitors [15], antidepressant drugs [16], antipsychotic drugs [17], and anticonvulsants [18]. Up to two-thirds of patients prescribed psychostimulants may also use complementary or alternative medicines for their ADHD [19]. As a consequence, it may be uncertain which treatment is exerting the effect.

(4) In naturalistic studies, there is self-selection for treatment initiation and continuation such that participants' characteristics may exert more influence on outcome than treatment. Two longitudinal population studies, for example, found that around 20% of children who were thought to have ADHD were never medicated [8,20••]. In the MTA study, in which participants were randomized to one of four treatment arms for 14 months, self-selection became apparent once the randomized phase of the study had been completed. At 3-year follow-up, the proportion of participants initially randomized to either of the study medication arms and who continued to take medication more than 50% of the time had fallen from 91 to 71%, whereas 45% of those initially randomized to receive behavioural therapy but no medication were now taking medication [21]. In contrast, the rate of medication use among the community control group remained steady at around 60% [21].

(5) Variations in the quality of treatment influence outcomes through appropriate selection of medication type, dosing schedule, and attention to factors that promote adherence. Under the controlled conditions of the first 14 months of the MTA study, those children who received methylphenidate in the experimental arm of the study were more adherent, used lower average doses, and had better outcomes than those receiving medication in the community [21].

(6) The presence of some comorbid disorders may lead to a differential response to treatment. Comorbid psychiatric conditions are identified in over 60% of clinic patients who have ADHD [22]. With the exception of autism [23], the presence of comorbidity does not seem to diminish the short-term response of ADHD symptoms to psychostimulant medication, but long-term influences remain uncertain [24]. A noteworthy finding of the randomized phase of the MTA study was that participants with comorbid anxiety responded as well to behavioural treatment as they did to medication alone or a combination of medication and behavioural treatment [25].

(7) Physical parameters associated with ADHD may be mistaken for treatment effects. An example is the concern that prolonged use of psychostimulant medication will cause growth retardation. Differences in growth are apparent when children with ADHD are compared with normal controls, but differences are statistically nonsignificant when the comparisons are made with unmedicated children with ADHD [26]. This observation suggests that there are disorder-specific growth delays [26].

(8) Family environment might be expected to influence response to treatment, and there are indeed examples

Key points

- Three studies addressing long-term effects of psychostimulant treatment for attention-deficit/hyperactivity disorder have produced mixed results.
- Significant challenges to demonstrating the long-term effects of psychostimulant treatment include variability in the natural course of the disorder, variability in persistence and adherence with treatment, variability in treatment quality, self-selection for treatment continuation, and the confounding effects of concurrent treatment, comorbid disorders, associated physical parameters, family environment and school environment.
- It would be helpful to distinguish long-term effects of treatment from effects of long-term treatment, as they are not synonymous.

to demonstrate this from the randomized phase of the MTA. Participants from lower-educated families responded equally well to medication or combined therapy, whereas children from higher-educated families responded preferentially to combined therapy [27]. Parental depression was associated with a diminished response to treatment [28]. The influence family environment may exert on longer-term response to psychostimulant medication remains uncertain.

(9) The school environment might logically be expected to influence the response to treatment for ADHD, especially as the core features of the disorder affect school functioning. While school-based intervention was a feature of studies such as the MTA [29], the role of the school environment as a mediator of treatment response has yet to be systematically evaluated.

Review of studies

The author identified three studies that have examined the effects of treatment for ADHD for 5 years or longer [8,10,20••]. The characteristics of these studies are summarized in Table 1.

The Rochester study involved examining school and medical records of a birth cohort [8]. The study was possible because of a prenegotiated agreement to allow access to cumulative school and medical records for the cohort. The case records of 5718 individuals were retrospectively reviewed when they reached a mean age of 17.2 years, identifying 379 with a history of ADHD. Two hundred and ninety-five of the participants with ADHD had received treatment with a psychostimulant medication at some stage.

Response to medication was based on a chart review of notes made by the clinician during clinic visits and was coded by a researcher as 'favourable', 'no response', or 'response unknown'. Medication response was coded as 'favourable' when a clinician had reported a global improvement in the child's ADHD symptoms. Medication response was recorded only for the clinic visits that occurred while the patient was receiving treatment. A favourable response was recorded approximately 75% of the time. The occurrence of side-effects for each visit was recorded as 'yes' or 'no'. There was no attempt to group the side-effects into categories or body systems.

Children who were in the age band of 10–11 years experienced the most favourable response to treatment, after which response rates tapered to be lowest in the age band 16+ years. Rates of side-effects were highest in patients aged 5 years and less (greater than 15%) and lowest in the age band 12–13 years (approximately 6%). Average duration of treatment, at 33.8 months, was longer than in comparable studies. Analyses of school records, which compared those children who were ever treated with a psychostimulant with those who were never treated, found no differences in reading achievement or school dropout rates, but those receiving treatment had fewer days absent from school and were less likely to have repeated a grade [30]. Longer duration of treatment was associated with lower absenteeism rates. There was a modest positive correlation between dose of stimulant and the most recent reading achievement score [30].

Strengths of the study include the generalizability of the findings, the solid attempt to identify and include nonreferred cases, the high level of documentation of clinical and academic variables, and the fact that clinical outcomes were linked directly to medication taking. Limitations of the study are the use of global clinical outcomes only, that the clinical outcomes were uncontrolled, and the likelihood there was self-selection for treatment continuation. The study did not speak of long-term effects on growth, cardiovascular function, or central nervous system effects.

The MTA study has been reported out to 8-year follow-up [10]. The sample consists of 436 individuals with ADHD randomized to one of three fixed treatment regimes (see Table 1) for 14 months and a further 119 individuals randomized to treatment as usual within the community. Participants were aged between 7 and 9.9 years at entry to the study. As discussed above, following the controlled phase of the trial, the groups converged in their rates of medication treatment. Differences between the treatment groups apparent after 14 months on a range of clinical, educational, and functional outcomes (see Table 1) were no longer statistically significant after 3 years, and were, again, nonsignificant after 8 years [10]. Outcomes were also examined with respect to whether the patient had received psychostimulant treatment for at least 50% of the time for the 12 months prior to the 8-year follow-up evaluation. Only maths achievement was significantly better in those individuals who were medicated in the 12 months prior to 8-year follow-up compared with those who were not [10]. Strengths of the MTA study are the systematic diagnostic evaluation, the systematic and comprehensive outcome evaluation, and the careful regulation of treatment for the first 14 months. Limitations of the study are that the study was not designed to detect treatment effects at 8 years, the likelihood there was self-selection of treatment continuation, the lack of an untreated comparison group, and variable treatment adherence.

The Raine study consists of secondary analyses of a longitudinal pregnancy cohort study of health and well being, reported at 14 years [20••]. Analyses are based

Table 1 Characteristics of studies examining longer-term (>5 years) effects of psychostimulant treatment for attention-deficit/hyperactivity disorder

Study	Sample ascertainment	*n* treated	*n* comparison	Duration	Mean age follow-up	Measures	Outcome
Rochester (MN, USA) [8]	Birth cohort born between 1 January 1976 and 31 December 1982	295 with ADHD	74 untreated with ADHD	Retrospective	17.6–18.6	Global response; school functioning; side-effects	Benefit
MTA (multisite USA) [10]	Clinic referred children randomized to one of four treatment conditions for 14 months	Randomized to methylphenidate ($n=110$); methylphenidate and behavioural treatments ($n=119$) or community management (60% medicated) ($n=104$)	112 randomized to receive behavioural treatment only	8 years	15–17.9	ADHD symptoms; ODD symptoms; antisocial behaviour; impairment; depression; anxiety; academic; social functioning; psychiatric hospitalization; accident/citation/ticket	No effect
Raine (West Australia) [20••]	Pregnancy cohort obtained from obstetric hospital in Perth, WA 1989	106 with ADHD treated at some time, 21 reported use at all three follow-ups, 42 at two follow-ups and 39 at one follow-up	25 with ADHD never treated	9 years	13–14	CBCL; depression; self-perception; social functioning; school functioning; growth; heart rate; BP	Uncertain benefit; possible harm

ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; CBCL, child behaviour checklist; ODD, oppositional defiant disorder.

on 1785 individuals, representing a 62% retention rate. One hundred and thirty-one individuals were identified as having been diagnosed with ADHD by a clinician at any of three data collection points. Sixteen percent of individuals with ADHD were receiving psychostimulant medication at 8, 10, and 14 years, and 62% at some time during follow-up. Twenty-two percent were never medicated. Exposure versus no exposure to stimulant medication had a statistically significant effect favouring no exposure on teacher-rated academic underachievement, and DBP, which was on average 10 mm higher for those currently medicated.

In contrast, there was a statistically nonsignificant trend favouring exposure to medication on ratings of externalizing behaviour and attentional problems. There were no differences between the groups on ratings of depression, self-perception, social functioning, school absenteeism, school enjoyment, height, weight, SBP, and resting heart rate. Strengths of the Raine study are its ecological validity and the attempt to control for nonrandom assignment to treatment by calculating and including as a covariate in the analyses a propensity score. Limitations of the study are the absence of a check for the validity of the ADHD diagnosis, no measure of severity, limited information about treatment (adherence, dose, and dosing schedules), inconsistent reporting of analyses (some of which are based on ever medicated, sometimes on consistently medicated, sometimes on currently medicated), misrepresentation (for example, DBP finding is not a long-term effect), and no statistical correction for multiple analyses.

Conclusion

The issue of the long-term benefit and safety of psychostimulant medication is likely to recur in the news cycle, and will be, at least, in the back of the mind of any reporter who covers a story about ADHD. The three studies reviewed in this paper have made admirable attempts to address the issue, but, as yet, the conclusion is equivocal. Evidence will come, of necessity, from naturalistic studies, which will need to meet three tests:

(1) was treatment of adequate quality?
(2) was adherence attended to?
(3) did the study control for variability in the natural course of the disorder?

We must also better distinguish long-term effects of treatment (which are relevant to up to 80% of people with ADHD) from effects of long-term treatment (which, owing to low adherence and persistence, are relevant to as few as 16–18% of people ever treated for ADHD).

The Rochester study and the 14-month follow-up of the MTA sample demonstrate that current active

psychostimulant treatment (of any duration) is associated with symptomatic and functional improvement. We might hope that appropriate and timely exposure to psychostimulant treatment during childhood would set a patient on a more favourable developmental trajectory, even in the absence of treatment continuation. None of the studies reviewed in this article convincingly demonstrate such an effect, but the methodological challenges were great.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 360–361).

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This published report describes the most recent of three studies that have attempted to address the long-term effects of psychostimulant treatment for ADHD. The study found no benefit and some possible harms of treatment. The report is critiqued in more detail in the body of this article.

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