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Clinical Development

Methylphenidate Article 31 Referral

EMEA/H/A-31/886

Feasibility Assessment of a Study of Long-term Effects of Methylphenidate on Cognition and Psychiatric Outcomes

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Document type:	Health Authority Response
Document status:	Final
Release date:	30 October 2009
Number of pages:	18

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1 Introduction

On 22 June 2007, a referral to the CHMP was made by the European Commission under Article 31 of Directive 2001/83/EC, as amended. The subject of the referral concerned the impact of potential safety concerns on the risk/benefit balance of methylphenidate-containing products. The safety concerns considered by the CHMP included: cardiovascular adverse events including sudden death, cerebrovascular disorders and psychiatric disorders as well as the effects of methylphenidate on growth and the effects of long term treatment with methylphenidate.

The referral procedure started on 19 July 2007, and an Opinion was reached on 22 January 2009. Among the follow-up measures agreed with CHMP was the requirement that the Marketing Authorisation Holders would assess the feasibility of a long term safety study, as agreed in the Letter of Undertaking, dated 19 January 2009 and adopted by the European Commission on 27th May 2009.

This information is provided on behalf of the following Marketing Authorisation Holders for methylphenidate-containing medicinal products in the EU: Novartis, Johnson & Johnson, Shire, Medice and Laboratorios Rubió (also referred to as the "Consortium").

1.1 CHMP request

As presented in the Letter of Undertaking, the CHMP requested that the Marketing Authorisation Holders for methylphenidate-containing medicinal products provide *a detailed feasibility assessment for a scientifically valid, well-designed and suitably powered long-term safety study to examine specific endpoints for the following outcomes:*

i) adverse cognitive outcomes

ii) adverse psychiatric outcomes (e.g. mood disorders, hostility and psychotic disorders).

The MAHs will consider including predominantly EU-based data, and the feasibility assessment will also comment on what non-EU sources of data could be used as an alternative.

If the feasibility assessment shows that a scientifically valid, well-designed and suitably powered study is viable, then the MAHs commit to provide a detailed protocol.

Cumulative exposure of at least 18 months and long-term follow-up duration of at least 5 years for individual subjects, as proposed by CHMP, is considered in this feasibility assessment.

2 MAHs Response

2.1 ADHD and comorbidity

2.1.1 AHDH and psychiatric comorbidity

It is well established that ADHD co-occurs with other psychiatric disorders, including disruptive behavioral disorders such as oppositional defiant disorder, conduct disorder; and

mood disorders such as depression, bipolar disorder; and anxiety disorders (Spencer, et al 2007). In both children and adults diagnosed with ADHD, the very high level of associated psychiatric comorbidity puts those with "pure" ADHD (i.e., ADHD only) in a distinct minority. For example, the Multi-Modal Treatment Study of Children with ADHD (MTA) conducted in the US and involving 579 children aged 7-10 years assessed psychiatric comorbidities including mood, anxiety and disruptive behaviour disorders and concluded that fewer than one-third (31.8%) of patients were diagnosed with only ADHD (Jensen, et al 2001).

Studies have shown that oppositional defiant disorder and ADHD co-occur in between 40% and 60% of all cases (Elia, et al 2008; Wilens, et al 2002), and that a substantial number of those will later develop conduct disorder in adolescence (Faraone, et al. 1997; Biederman, et al 1991). Of those ADHD patients with a comorbidity, 14.0% had a mood/anxiety disorder, 29.5% had oppositional defiant disorder or conduct disorder (ODD/CD), and 24.7% had a mood/anxiety disorder plus ODD/CD. This high level of comorbidity has been confirmed in culturally and regionally diverse epidemiologic samples as well as in clinical samples and is preceding pharmacological treatment (Biederman, et al 1991; Rhode, et al 2005; Ralston, et al 2004; Steinhausen, et al 2006).

Minor depression was found in 21.6% of 342 children and adolescents with ADHD (Elia, et al 2008). In a study of 140 children with ADHD, the prevalence of comorbid major depression was 29% and antisocial disorders, such as conduct disorder, occurred in 11% of these children, both significantly more prevalent than in normal children (Spencer, et al 2007; Biederman, et al 1992). Bipolar Disorder was reported in 26% of 165 preschool children with ADHD, and in 18% of 381 school age children with ADHD by Wilens, et al (2002) in a study of children with ADHD referred for psychiatric evaluation at a US site.

Anxiety disorder has been found to co-exist in up to about 25% of cases in epidemiological and clinical samples (Biederman, et al 1991). Generalized anxiety disorder was found in 15.2% of 342 children with ADHD (Elia, et al 2008). Comorbid oppositional defiant disorder together with ADHD has been reported to range from 40.6% to over 62% (Elia, et al 2008; Wilens, et al 2002) and comorbid conduct disorder from 30% to 50% (Biederman, et al 1991). In a large study conducted in 10 European countries it was shown that ADHD is associated with multiple co-existing psychiatric problems, behavioral problems, poorer psychosocial functioning and had important clinical consequences in terms of greater severity of ADHD (Ralston, et al 2004; Steinhausen, et al 2006).

2.1.2 ADHD and cognition

With respect to cognitive function, overlap between ADHD and learning disabilities has been consistently reported in the literature and has also to be considered to be part of the natural history of ADHD. The reported degree of overlap ranges from 10% to 92%. This variability is most likely due to differences in selection criteria, sampling, and measurement instruments, as well as inconsistencies in the criteria used to define both ADHD and learning disabilities in different studies. The prevalence of learning disabilities varies by definition, and a more restrictive definition showed an overlap of 20% to 25% (Spencer, et al 2007; Biederman, et al 1991).

A review of several studies published by Loe and Feldman (2007) described a significant link between ADHD itself and negative academic and educational outcomes. Children with ADHD have been shown to suffer from poor academic functioning with poor reading and arithmetic test scores (Biederman, et al 1996; Barry et al, 2002), increased rate of grade retention (Barkley, et al 1990) and low rates of high school graduation and post-secondary education (Mannuza, et al 1993).

Very recent results from a follow-up study conducted in France (GAZEL youth cohort study) confirmed the link between ADHD and negative academic outcomes (Galera et al, 2009). The children with attention deficit/hyperactivity symptoms at baseline had a much higher risk of negative academic outcomes, i.e. a higher risk for grade retention (Odds ratio (OR) 3.58; 95% confidence interval (CI) 2.38-5.39), a much higher failure to graduate from secondary school (OR 2.41; 95% CI 1.43-4.05), and higher risk of obtaining a lower level diploma (OR 3.00; 95% CI 1.84-4.89). The information in this study was obtained via mailed questionnaires at baseline (response 62%) and during the 8 year follow-up (response 49%). These results were adjusted for a wide range of potential confounding variables and even remained significant after accounting for school difficulties at baseline.

The evidence available suggests that the comorbid psychiatric and cognitive disorders discussed above are quite common in children with ADHD and are associated with the disease itself. These disorders occur prior to methylphenidate treatment. In addition, it is important to note that the high rate of co-morbidity in preschool aged children, who largely have not been exposed to methylphenidate on a long-term basis, is contrary to the hypothesis that co-morbid psychiatric conditions are an effect of long-term methylphenidate exposure.

Rather these co-morbidities reflect common predisposition or risk factors and are associated with ADHD itself. As the clinical severity of these co-morbid disorders is likely also associated with a higher need of pharmacological treatment, it has to be considered a confounding factor that might introduce bias in non-randomized long-term studies. In such a situation, it becomes difficult, if not impossible, to determine which excess risk of an outcome in a cohort of treated individuals could be causally related to drug exposure, as opposed to being related to the underlying ADHD.

2.2 Previous studies investigating the potential long-term effects of MPH exposure on psychiatric outcomes and cognition

Most of the evidence to substantiate the treatment effects of MPH on adverse psychiatric outcomes and cognition is coming from relatively short clinical trials. In a publication by Vittielo (2001) on the long-term effects of stimulant medications on the brain, the author states that "results of randomized controlled studies in children are available only for up to 1-2 years of treatment. Longer controlled studies would be extremely difficult, if not impossible, to implement, given the practical and ethical challenges of maintaining children on randomly assigned treatments for many years."

These challenges have also resulted in few observational studies in peer-review journals that investigated the effects of MPH on psychiatric outcomes or cognition under conditions of routine clinical care. As a note of caution, all of the published long-term studies have limitations and do not fulfill the rigorous requirements from CHMP with respect to chronic exposure and long-term follow- up, as none of them fulfills all the requirements of the CHMP

request in terms of duration of exposure, duration of follow-up, and both endpoints discussed in this feasibility assessment. Nevertheless, they can be used to further help to evaluate the potential signal of interest.

We summarized the available evidence investigating MPH treatment in children and potential effects on behavioural symptoms of ADHD, as well as on cognition and academic performance and social functioning. The designs and main findings of published observational studies that investigated the potential association of MPH exposure and long-term psychiatric and cognitive endpoints are displayed in Table 6-1 (Appendix 1).

We identified 10 observational studies; eight were conducted in the US, one in Canada, one in Israel. Limitations of the published studies include: lack a comparator group not exposed to MPH (Hechtmann, et al 2004; Wilens, et al 2003; Cherland and Fitzpatrick, 1999; Gadow, et al 1999), based on relatively small numbers only (Berger, et al 2008; Hechtmann, et al 2004; Carlson, et al 2000; Gadow, et al 1999; Charles, et al 1979), or limited follow-up time; only Molina, et al (2009) and Carlson, et al (2000) had a follow-up time of more than five years. It has to be considered that the study of Molina, et al (2009) started with a fixed randomized schedule over 14 months and therefore cannot be considered to be a purely observational study. Carlson, et al (2000) only focused on cognitive functioning.

Treatment with psychostimulants was shown to improve the behavioral symptoms of ADHD as well as the cognitive function, academic performance, and social functioning. These benefits have been demonstrated in well-controlled clinical trials and in prospective cohort studies. The results from studies with specific MPH exposure (see summary characteristics for MPH exposure in Appendix 1) are further supported by studies investigating stimulants in general. Treated children achieved better academic outcomes than untreated children, (Barbaresi, et al 2007; Powers et al, 2008) and showed an increase in IQ scores when taking medication over a follow-up period of at least one year (Gimpel, et al 2005).

In a prospective observational follow-up study Biederman et al (2008) presented findings that revealed no evidence that stimulant treatment is associated with the risk for subsequent substance use in children and adolescents when they reach young adulthood.

In summary, despite their limitations, these studies consistently show no evidence of any worsening of psychiatric symptoms or cognition during treatment with MPH. In contrast, they even point in the direction of an improvement of behavioral symptoms and cognitive function over time. This lends further support to a positive benefit-risk assessment of long-term treatment of children and adolescents with ADHD with MPH under conditions of routine clinical care.

Notably, two recent studies by Molina, et al (2009) and Scheffler, et al (2009) have been published since the discussion of the potential signal and the conclusion of the Article 31 referral. Both studies contribute materially to the body of literature on the long-term effect of stimulants including assessments over a period of five years or longer. Both studies are consistent in their findings with an absence of negative psychiatric and/or cognitive effects associated with long-term treatment of children and adolescents with ADHD with methylphenidate. They can be considered supporting evidence to dismiss the hypothesis that long-term use of methylphenidate in children and adolescents with ADHD is associated with a greater risk of adverse psychiatric outcomes and/or adverse effects on cognitive function.

Molina, et al (2009) extend the results of the prospective Multimodal Treatment Study of ADHD (MTA) from the previously reported three year data to include assessments at six and eight years from the first exposure to MPH. Children were randomly assigned in an open-label, randomized, controlled study to receive one of four treatment approaches for 14 months, and thereafter were basically treated according to routine clinical practice without fixed assignment. The results of the 8 year follow-up evaluation actually suggest that there is evidence of a beneficial effect of ADHD treatment approaches on cognition and that there may be a beneficial effect on the course of comorbid psychiatric disorders over time. Given the limitations of the study with a strict exposure protocol for the first 14 months only, it might be difficult to conclude that the beneficial effects seen years later seen in the study are entirely due to MPH treatment. However, the data available are strongly supportive for the absence of harm due to MPH treatment over an extended period. In addition, treatment response was not influenced by presence of psychiatric co-morbid conditions at baseline.

Scheffler, et al (2009) examined long-term cognitive performance and concluded that medication treatment (90% of subjects in the study were on stimulant medications) of attention deficit/hyperactivity disorder is positively associated with academic achievement during elementary school. Using five consecutive waves between kindergarten and the fifth grade from the US nationally representative Early Childhood Longitudinal Study—Kindergarten Class of 1998–1999, the investigators found that medicated children had a mean mathematics score that was 2.9 points higher (comparable with gains attained during 0.19 school years over the 6 years period) than the mean score of un-medicated peers with attention-deficit/hyperactivity disorder. Children who were medicated for a longer duration (at 2 waves) had a mean reading score that was 5.4 points higher (comparable with gains attained during 0.29 school years) than the mean score of unmedicated peers with attention-deficit/hyperactivity disorder.

In summary, the long-term observational data are in line with the patterns known from clinical trials and substantiate the absence of an adverse psychiatric effect of MPH treatment and a positive effect on cognition and support a positive benefit risk assessment of treatment in children with ADHD. These data do not indicate any signal of worsening of psychiatric conditions or cognition during treatment with MPH. While the study designs of previous long-term studies are different from those that would need to be incorporated into the study requested by CHMP, existing long-term study data should be considered as relevant supportive information.

2.3 Requirements of a comparative study to investigate long-term effects

The CHMP requested the assessment of the feasibility of a comparative study under the rigorous criteria of at least 18 months of methylphenidate exposure and at least 5 years follow-up to investigate the potential long-term effects of chronic use of methylphenidate (MPH) on cognitive function and psychiatric outcomes, including incidence of psychiatric co-morbidities that are frequently associated with ADHD (mood disorders, hostility and psychotic disorders).

As commented by the Rapporteur during the Article 31 Referral, there is an apparent lack of adequately designed and powered pharmaco-epidemiological data on the chronic use of

methylphenidate (MPH) and its potential long-term effects on psychiatric and cognitive outcomes. A prominent reason for this lack of data is the inherent difficulty in studying the potential association of MPH exposure with endpoints that are also part of the natural course of ADHD. In addition, it is reasonable to assume that these psychiatric co-morbidities are related to the severity of the ADHD symptomatology and overall psychiatric condition of patients and therefore associated with the need for treatment (Connor, et al 2003; Hurtig, et al 2007).

The required components of a scientifically valid, well-designed and suitably powered long-term safety study to validate or refute the hypothesis that long-term use of methylphenidate in children and adolescents with ADHD is associated with a greater risk of adverse psychiatric outcomes and/or adverse effect on cognitive function under conditions of routine clinical care (observational study) are discussed below:

2.3.1 A suitable comparator group

The most important component of such a study would be the availability of a suitable comparator group that has a similar baseline risk as the MPH exposed children. Comorbid psychiatric and cognitive conditions associated with ADHD make the selection of an untreated or normative comparator group unsuitable for the following reasons:

Untreated ADHD (i.e. no pharmacological treatment) comparator group

- As outlined in section 2.1 the comorbid conditions of interest are very prevalent among patients with ADHD. It is reasonable to assume that they are associated with the severity of the ADHD symptomatology and overall psychiatric condition of these patients and therefore with the likelihood of pharmacological treatment. Patients who have been diagnosed with ADHD, but are not being treated, would be expected to differ substantially from the treated population in terms of baseline risk for comorbid psychiatric and cognitive disorders (because of the lower severity of their ADHD). This will lead to a failure to distinguish any potential negative treatment effects from the effects of the comorbidity on the outcome of ADHD (confounding by indication or severity of disease). Patient factors that are related to treatment choice are not easily measurable, which makes it difficult to disentangle the baseline risk of comorbid conditions from the possible effects of MPH exposure. Confounding by indication or severity of disease leads to a severe bias with flawed results. This would diminish the utility of the study to validate or refute the scientific hypothesis.
- In an Intent-to-Treat situation, a significant number of patients in the comparator group would be expected to receive pharmacological treatment (MPH) for ADHD during the very long observation period, thereby reducing the likelihood that the comparator group would not have been exposed to MPH treatment throughout the prospective follow-up period.

General Population (i.e. non-ADHD) comparator group

- The baseline risk for comorbid psychiatric or cognitive conditions in children with ADHD is greatly magnified when compared to children without ADHD.

The bias would preclude drawing any valid conclusions. This is evident when looking at the results from the MTA study for the risk of adverse psychiatric outcomes over an 8-year follow-up period (Molina, et al 2009). In addition to the four randomized groups with a fixed treatment schedule for the first 14 months, a general comparator group was included. The results from the control group were always considerably different from the children with ADHD, irrespective of ADHD treatment.

2.3.2 Sample size calculation for a study including children with ADHD, chronic exposure to MPH, and the assessment of long-term outcomes

From a purely statistical point of view, the number of children included in the study would need to be very large in order to have enough children who remain on methylphenidate treatment for 18 months and then are successfully followed up for the 5-year outcomes. Table 2-1 shows the n per group included in the final analysis necessary to detect a 25% or 50% risk increase for relevant outcomes based on a power of 80% and a two-sided alpha of 0.05.

In addition, the attrition rate in this type of long-term study must be taken into account when determining the necessary sample size. Novartis MPH trials of 7 weeks, 12 weeks and 6 months showed dropout rates of 22%, 29% and 39%, respectively. Therefore, the dropout rate for the 18-month treatment phase of this study is projected to be approximately 60%.

Table 2-1 Hypothetical sample size for comparing two proportions based on a power of 80% and a two sided alpha of 0.05, and a projected 60% drop-out rate

		Prevalence of comorbid condition in unexposed group				
		40%	30%	20%	10%	2%
Odds ratio 1.5 (excess risk 50%)	N per group	408	447	562	957	4244
Need to enroll (assumed drop-out rate 60%)	Total	2040	2235	2810	4785	21220
Odds ratio 1.25 (excess risk 25%)	N per group	1327	1483	1902	3304	14891
Need to enroll (assumed drop-out rate 60%)	Total	6635	7415	9510	16520	74455

(calculation according to Fleiss, et al 1980)

To illustrate the necessary sample requirement for a common and rather unspecific comorbid condition with a baseline prevalence of 30%, it would be necessary to have included n=447 subjects in each comparison group and for them to complete the study to exclude an excess risk of 50% (which would result in a prevalence of 45% in the exposed relative to 30% in the unexposed and equals a minimally detectable Odds ratio of 1.5). Once a drop-out rate of 60% is accounted for, the final number of subjects that need to be recruited becomes 2235.

The number becomes much higher if a very specific psychiatric outcome is investigated. For example if psychosis, mania or hypomania with a baseline risk of 2% is investigated; it would be necessary to have included n=4244 subjects in each arm and have them complete the study

to exclude an excess risk of 50%. Once a drop-out rate of 60% is accounted for, the final number of subjects that need to be recruited becomes 21220. With an inevitably high rate of continued attrition during the 5-year open-label study, it is unlikely that the required number of patients can be documented and that such a study could be completed within an acceptable time-frame.

2.3.3 Ability to minimize and adjust for confounding factors during observation period

An additional and major challenge is the requirement from CHMP to assess 5-year patient outcomes in relation to a cumulative treatment period of at least 18 months. Because of the long study period between initiation of treatment and assessment of outcomes, it is very likely that changes in environmental factors will affect the study and may confound any real relationship between treatment and outcome and potentially result in bias. Further, as patients are monitored through adolescence and may reach adulthood during the study observation period, the nature and course of the underlying disorder, as well as psychiatric comorbidities, may change. Finally, because we are considering effects that are not specific to treatment, it would be nearly impossible to attribute accurately any observed effects to treatment that may have been stopped well over three years previously.

3 Contact with other expert groups

The MAHs have been in contact with the European Network on Hyperkinetic Disorders (EUNETHYDIS). EUNETHYDIS is currently planning to start a research project which may be of potential relevance to the questions addressed in this feasibility study. EUNETHYDIS has been exploring the option of a prospective study on long-term safety of ADHD drug treatment. In the latest contacts we had with EUNETHYDIS, it appears they are still investigating the feasibility of a prospective study but they have concluded that a randomisation design would not be feasible. As described earlier in this document, finding a relevant control group allowing credible conclusions without a randomization design will be problematic, particularly for studying psychiatric or cognitive outcomes.

Nevertheless, the MAHs will remain in regular contact with EUNETHYDIS in order to further explore the possibility of any long-term safety study initiative fulfilling the criteria set in the Art. 31 action letter.

4 Summary and overall conclusions

The MAHs have evaluated the feasibility of an observational, comparative long-term study to validate a signal of adverse psychiatric or cognitive outcomes from the long-term use of MPH in children and adolescents with ADHD. A scientifically valid, well-designed and suitably powered long-term safety study to examine specific endpoints for adverse cognitive and adverse psychiatric outcomes, according to the rigorous criteria of the CHMP (cumulative exposure of 18 months and long-term follow-up of five years) is not considered to be feasible.

The difficulty stems in part from the fact that the endpoints of interest are part of the natural course of the disease, may also be related to the severity of the ADHD symptomatology and the overall psychiatric condition of the patients and the resulting treatment needs, leading to

confounding by indication. In addition, due to the limited ability to measure and adjust for factors associated with treatment assignment, the selection of a suitable comparator group is not considered feasible under conditions of routine clinical care. Furthermore, the sample-size necessary to detect an increased risk of an adverse psychiatric or cognitive outcome and the projected high dropout rate makes it unlikely that enough patients could be recruited for the study within an acceptable time-frame in an observational setting.

The available observational studies, which were systematically reviewed and included in this feasibility assessment - some of which were published recently and were not available when the requirement for a long-term safety study to investigate the potential signals was discussed within CHMP - do not indicate any signal of worsening of psychiatric symptoms or cognition during treatment with MPH and even suggest a beneficial long-term effect of MPH on the course of psychiatric disorders and cognitive function over time.

In lieu of conducting the requested long-term safety study, and considering the fact that currently available data from observational studies (including prospective cohort studies) indicate no signal of an adverse psychiatric effect or negative effect on cognition, it is proposed to closely monitor ongoing external research efforts (including contact to EUNETHYDIS) to collect additional relevant safety information, and monitor all available data as part of pharmacovigilance activities. These data will be presented as part of the PSUR reports.

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6 Appendices

6.1 Appendix 1: Studies investigating possible long-term effects of long-term methyphenidate (MPH) use on psychiatric outcomes, psychotic outcomes and cognition in children

Please note that the method used for the literature search strategy is presented in the footnote of the Table 6-1*.

Table 6-1 Studies investigating possible long-term effects of long-term MPH use on psychiatric outcomes (psychotic disorder, mood disorder, hostility) and cognition in children

Author (Year), country	Study population, study design, number of participants, age, gender	Duration of exposure (Ex) and follow-up time (FU)	Outcome definition	Result	Comments
Molina et al (2009), US	Multi-site, randomized, open-label, prospective study including children with attention-deficit /hyperactivity disorder assigned to medication management (MedMgt), behavior therapy (Beh), combination (Comb) and usual community care (CC)), n=579, mean age 8.5 yrs. (range 7.0 to 9.9 yrs.) at baseline, 19.7% females. Include also a local normative control group (n=289).	Ex: 14 months, FU: 8 years (response 75%).	Wide range of psychiatric outcomes, functioning and behavior variables (among them SNAP, CD, SCAPI, depression scales, SSRS, psychiatric diagnosis based on DISC-IV).	- Clear improvements in all functioning and behavior variables, irrespective of treatment according to baseline (including inattention, hyperactivity, oppositional defiant disorder, aggression). - Psychosis, mania and hypomania occurred very infrequent; no indication that associated with medication (1.7% Comb, 2.0% MedMgt, 0.9% Beh, 2.9% CC). - Type of intensity of 14 months treatment does not predict functioning 6 to 8 years later, but early ADHD symptom trajectory is prognostic.	First findings in the ADHD treatment literature to document for a wide range of symptoms and functioning outcomes, the sustained absence of long-term detrimental effects of an initial period of randomly assigned treatment.
Scheffler et al (2009), US	US sample of 594 children with attention-deficit/hyperactivity	Up to five year exposure and	Standardized mathematics and reading test scores to	Medicated children had a mean mathematics score that	The 2.9-point mathematics and

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	disorder, followed in 5 survey waves between kindergarten and fifth grade from the nationally representative Early Childhood Longitudinal Study—Kindergarten Class of 1998–1999 employing a first-differenced regression model, which controlled for time-invariant confounding variables.	follow-up.	evaluate academic achievement.	was 2.9 points higher than the mean score of unmedicated peers with attention-deficit/hyperactivity disorder. Children who were medicated for a longer duration (at >2 waves) had a mean reading score that was 5.4 points higher than the mean score of unmedicated peers with attention-deficit/hyperactivity disorder.	5.4-point reading score differences are comparable with score gains of 0.19 and 0.29 school years, respectively, but these gains are insufficient to eliminate the test-score gap between children with attention-deficit/hyperactivity disorder and those without the disorder.
Berger et al (2008), Israel	Observational survey of ADHD patients, n=50 children, mean age 12 years and 6 months, 40 boys, 10 girls.	Ex: At least 6 months (average 23.5 months). 32.5% of families refused to participate in the study.	Focused on attitudes towards treatment. Questionnaire for parents and children with 4 sections: epidemiology, source of information, common knowledge, compliance.	After treatment start most participant believed MPH is safe. After an average of 23.5% months of treatment 56% of parents and 16% of children were still concerned about long-term effects of MPH.	Study focused on perspectives and believes of parents and children. Concern regarding adverse long-term effects (not specified) was mainly caused by negative information before treatment start and not by actual experience.
Mannuzza et al (2008), US	Prospective cohort study, n=176 caucasian subjects with ADHD treated with MPH and n=178 caucasian control subjects with no ADHD diagnosis, at initiation 6-12 yrs., 100% males.	Ex: 23.2 months, FU: late adolescence (mean age: 18.4±1.3 years), and adulthood (mean age:	Psychiatric outcome (substance abuse): - Adolescents: Diagnostic interview schedule (including mood, anxiety and psychotic disorders) (subjects and parents)	- 45% of the treated participants developed substance use disorder at some time in their life. - Only late-treated probands differed significantly from non-ADHD comparison	Mood, anxiety and psychotic disorders were not evaluated compared to the control group. Early age at MPH initiation does not increase

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		25.3±1.3 years) (retention rate at adulthood 85%).	- Adults: Schedule for assessment of conduct, hyperactivity, anxiety, mood, and psychoactive substances.	subjects (44% versus 29%) but not the early-treated probands.	risk for negative outcomes and may have beneficial long-term effects.
Hechtman et al (2004), US	Randomized, open-label, parallel group study (2 centers). Random assignment to MPH alone, MPH plus multimodal psychosocial treatment and MPH plus attention control treatment. n= 103 children, aged 7.0 to 9.9 yrs. of age, boys and girls, not specified.	Ex: 2 years, FU: 2 years.	Academic performance: Stanford Achievement Test (children), Homework Problem Checklist (parents), Emotional status: Children's Depression Inventory (CDI), Piers-Harris Children's Self-Concept Scale.	Significant improvement occurred across all treatment groups (academic achievement, homework performance, self-esteem, self-ratings of depression) and maintained over 2 years.	No non-interventional comparator group available. However, significant short term improvements related to MPH treatment were maintained over 2 years.
Wilens et al (2003), US	Multicentre, open-label, nonrandomized, cohort study, n=407 children (289 completed 12 months treatment), 6 to 13 yrs. old, 83% males.	Ex: 12 months, FU: 12 months (response 71%).	Effectiveness - Parents and teachers: Inattention/over-activity with aggression (IOWA Conners) rating scale. Global assessment scale) - Teachers: Peer interactions: Adverse events - Tics, quality of sleep etc..	Effectiveness was maintained for up to 12 months. 84.5% reported at least one adverse event and (60.4% investigators deemed related to MPH – majority were judged to be mild and expected. Psychiatric AEs: Anxiety 2.2%, emotional lability 2%, hostility 2%, depression 1.5%. Tics improved in the majority during study (62.5%, whereas in 6.4% tics developed.	No comparison group available. Overall MPH leads to improvement of tics. With exception of tics no systematic collection on comorbid psychopathology.
Carlson et al (2000), US	Retrospective cohort study looking at patients treated with MPH for hyperkinetic reaction of childhood between 1967 and 1972 comparing children with more severe	Ex: 34.7 months in children with more severe comorbidity, 40.8 months in others,	DSM-II and DSM-IV diagnoses	- Boys with symptoms of childhood mania did not respond differently to MPH than boys without. - No suggestion that	No long-term effect of long-term treatment with MPH suspected. Small sample size.

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	comorbidity such as irritability, oppositional defiant or conduct disorder, and anxiety andd/or depression (23% of children) all having a subtype of ADHD, and children with fewer comorbid symptoms, mean age at referral 9.3 years, n=75 children, 100% boys.	FU: 12-14 yrs..		stimulants caused to develop a manic or hypomanic course or that one could have anticipated these adult disorders from a differential response to stimulant treatment in childhood.	
Cherland and Fitzpatrick (1999), Canada	Retrospective cohort study of children with ADHD (chart review), baseline between 1989 and 1995, average age not reported, n=192 with ADHD diagnoses, n=98 had treatment (mostly MPH), 146 males, 46 females.	Ex: not specified, FU: 1 year 9 months.	DSM-III-R, DSM-V, psychiatric interview, psychometric testing, Conners' teacher rating scale –revised as performed in routine clinical care.	- Of the n=98 with stimulant medication 9 developed psychotic symptoms (3 had amphetamine intoxication, 1 had psychotic symptoms, 3 mood-congruent psychotic symptoms, 1 had insufficient information.	No comparator group (ADHD patients on treatment were not compared with the ADHD patients without treatment). Small sample size.
Gadow et al (1999), US	Double-blind, placebo-controlled MPH evaluation followed by a prospective, nonblind, follow-up study of children with ADHD and chronic multiple tic disorder, n=34 children, mean age 8.8 yrs. (range 6.8 to 11.9 yrs.), 31 boys, 3 girls.	Ex: 8 weeks, FU: 2 years, follow up visit/number receiving stimulants (28/27), (33/30), (29/26), (29/26).	MOMS, peer conflict scale, GTRS, Stimulant side effects checklist, revised Conners' parent rating scale, CSI-3R, clinical tic measures.	- No evidence that motor and vocal tics changed in frequency or severity compared to placebo phase or during maintenance therapy.	2 year follow-up was not blind and did not have comparator group.
Charles et al (1979), US	98 ADHD children in 16-week MPH placebo-controlled study. 36 positive responders included in 3 years follow-up study. Mean age 8 years 1 month (range 6 years 1 month to 11 years 5 months), 31 boys, 5 girls.	Ex: approx. 3 years if not discontinued (13 children spontaneously discontinued MPH but were included in analysis), FU: approx. 3 yrs.	IQ scores (WISC), Global Functioning, Conner's Scale	- Verbal IQ scores did not differ significantly between final visit and pre-drug visit. - Performance IQ did not differ between the 2 groups but significantly improved from pre-drug visit to on-drug visits.	Sustained improvement seems to be related to other factors then long-term treatment. On the other hand it can be concluded that treatment does not have a negative effect.

* The following search terms were included in the literature search: "Methylphenidate (MeSH Term) AND Time (MeSH Term) AND epidemiology (Text Word)", "Methylphenidate (MeSH Term) AND long term effect (Text Word)", "Methylphenidate (MeSH Term) AND (psychotic disorder (MeSH Term) OR affective disorders psychotic (MeSH Term)", "Methylphenidate (MeSH Term) AND mood disorder (MeSH Term) AND epidemiology (Text Word)", "Methylphenidate (MeSH Term) AND ADHD (MeSH Term) AND mood disorder (MeSH Term)", "Methylphenidate (MeSH Term) AND hostility (MeSH term)", "Methylphenidate (MeSh Term) AND cognition (MeSH Term)". In addition cross-referencing was used to identify additional studies.