Tidsskriftet
DEN NORSKE LEGEFORENING

Drug treatment of ADHD – tenuous scientific basis

KRONIKK

HENRIK VOGT

E-mail: vogt.henrik@gmail.com
The authors contributed equally to the preparation of this article.
Henrik Vogt (born 1977), specialty registrar in general practice, cand.mag., PhD, and researcher at the Centre for Medical Ethics, University of Oslo.
The author has completed the ICMJE form and declares no conflicts of interest.

CHARLOTTE LUNDE

The authors contributed equally to the preparation of this article.
Charlotte Lunde (born 1971), specialty registrar in child and adolescent psychiatry at the Nic Waals Institute, Lovisenberg Diakonale Hospital, cand.mag., and journalist.
The author has completed the ICMJE form and declares the following conflict of interest: She has an unpaid position as chairman of Lundelab, a company that explores how interactive solutions can help children with mental health issues. The company generates no revenue at present.

Recent systematic reviews reveal a weak evidence base for the use of methylphenidate and amphetamines in the treatment of children and adolescents with an ADHD diagnosis. This should have implications for the follow up and understanding of these patients.

Illustration: Ørjan Jensen/Superpop

Over the past three decades, there has been a large and controversial increase internationally in the diagnosis and pharmacological treatment of ADHD (hyperkinetic disorder, attention deficit hyperactivity disorder) (1). In Norway, this increase gathered pace in the 1990s. The number of children and adolescents under 19 years of age receiving medication for ADHD increased further from 9 263 in 2004 to 18 681 in 2016 (2). Of these, 16 662 were prescribed the amphetamine derivative, methylphenidate (e.g. Ritalin, Concerta).

This increase can only be understood in the context of a strong underlying belief in the efficacy of pharmacological intervention. However, recent publications show that the evidence for treatment efficacy is weak, especially over the long term (3–7).

The long-term MTA study

The so-called MTA study (Multimodal Treatment Study of ADHD) is key to understanding the current state of knowledge (3). The study was initiated in 1994 because substantial use was being made of central nervous system stimulants in ADHD treatment, and yet treatment studies were of poor quality and limited duration.

In the first phase of the study, 579 children (7–10 years) were followed for 14 months after being randomised to four different treatment groups (3). Group 1: an especially systematic pharmacological intervention with monthly specialist follow-up. Group 2: an intensive behavioural therapy programme aimed at home and school. Group 3: a combination of the treatment in group 1 and group 2. Group 4: treatment as usual in the health service, which often entailed less systematic pharmacological therapy.

The six endpoints were adult-reported ADHD symptoms, internalising and externalising symptoms, and the functional measures academic achievement, adult-child interaction, and social skills with respect to peers.

In 1999, the first results from the MTA study revealed a greater reduction in ADHD symptoms in group 1 and group 3 (medication and combined treatment) than in group 2 and group 4 (behavioural therapy and treatment as usual) (3). The addition of behavioural therapy in group 3 produced no statistically significant improvement in symptoms relative to group 1. This result received widespread media attention and was a key justification for the extensive pharmacological treatment of ADHD from the year 2000 onwards (3).

However, after the initial randomised phase, the MTA study continued as an observational study in which 500 children and a control group of 300 children were followed for a further 14 years. The key finding here is that the superior efficacy of systematic medication over the first 14 months disappeared over the course of the next two years (3, 8). Subsequent analyses showed that the combined treatment in group 3 was superior with respect to a composite endpoint consisting of symptoms and functional measures, and that combined treatment in group 3 that led to improvements in parental discipline style could completely normalise behavioural patterns (3).

After six years, the patients who received behavioural therapy alone (group 2) had lower rates of anxiety and depression (4.3 %) than the medication group (19.1 %), the combined treatment group (17.7 %) and the treatment as usual group (16.4 %) (8). In a review, the MTA researchers also concluded that only the combined treatment helped families with the lowest socioeconomic status and reduced the doses of medication required (3).

In spring 2017, the MTA researchers published their latest results (4). The conclusion, 16 years after the start of the study, is that long-term use of central nervous system stimulants is associated with suppression of adult height (1–2 cm on average), but no reduction in symptoms. However, these findings have not had the same impact as the initial results from 1999.

An eye-opening systematic review

Despite the widespread pharmacological treatment of ADHD, the first comprehensive systematic review on the use of methylphenidate in children and adolescents was not published until 2015 (5). A Cochrane group examined 185 randomised controlled trials with more than 12 000 children and adolescents (3–18 years). They concluded that short-term use of methylphenidate may produce a clinically significant reduction in teacher-rated ADHD symptoms, teacher-rated behavioural problems and an improvement in parent-reported quality of life. While there was no increased risk of death or life-threatening adverse effects,

there was a markedly increased risk of other adverse effects. Methylphenidate use, for example, was associated with a 60 % greater relative risk of sleep problems and 266 % greater risk of decreased appetite.

What made the Cochrane study most controversial, however, was its conclusion that the existing studies were of such low quality that it was not possible to say for certain whether methylphenidate is beneficial for children with an ADHD diagnosis. The group justified this statement on the grounds that all 185 studies were at high risk of bias – for example, because the pharmaceutical industry had financed many of them, or because their placebo controls were weak, since the known adverse effects of methylphenidate may have revealed who was receiving the active medication. Moreover, the duration of methylphenidate treatment in the studies was so short (1–425 days, average 75 days) that it was impossible to judge the efficacy of long-term medication use.

Another systemic review that came out after the Cochrane report also concluded that there is a lack of high-quality data, especially with regard to the long-term effects of medication (6). An additional review from Cochrane concludes that the evidence base for the use of amphetamines in ADHD is similarly weak (7). In this context, it is worth noting that the use of these drugs (Attentin, Elvanse) in children and adolescents in Norway has almost doubled over a short space of time – from 1 324 users in 2015 to 2 145 users in 2016 (2).

Heated debate after Cochrane review

The Cochrane publication on methylphenidate triggered strong reactions. The most important was from the European ADHD Guidelines Group, which criticised the Cochrane researchers for having made errors (9, 10). Among other things, they argued that the MTA study should not have been included in the systematic review, as it did not contain a group that received a pure placebo, or no treatment (9). Excluding the MTA study would have made pharmacological treatment appear more effective. The Cochrane researchers thus received criticism for having included the largest study with the longest duration.

The Guidelines Group also believed that it was inappropriate to downgrade the quality of studies on the basis of conflicts of interest related to the pharmaceutical industry. In this context, it is worth pointing out that many of the members of the Guidelines Group report strong ties to the pharmaceutical industry, some of them up to ten different associations (9).

In response, the Cochrane group acknowledged some minor errors, but stood by its conclusions (10). In a final move, the Guidelines Group claimed – without specifying why – that long-term randomised controlled trials are practically and ethically impossible. They point instead to non-randomised epidemiological studies that may suggest positive long-term effects of methylphenidate use on endpoints such as substance abuse, trauma and death (11). However, such studies cannot fully account for confounding causal factors.

The Cochrane group in turn calls for long-term randomised controlled trials, and claims that the continued use of medications without an adequate evidence base may be unethical (12).

Crisis of evidence in the ADHD field

We believe the ADHD field is facing an evidential crisis. Put simply: a large number of children – in Norway tens of thousands – have been medicated over a long period of time on a weak evidential basis. Moreover, the side effects are considerable (3, 5), and the drugs have the potential for misuse (13). Pharmacological treatment must also be viewed in the light of possible adverse effects that have not been sufficiently explored, for example negative psychosocial effects (14).

Research findings and clinical experience both suggest that central nervous system stimulants may have significant short-term efficacy. This can lead to a biased view of the

efficacy of drug treatment, driven by the assumption that this initial efficacy will continue. However, there is no evidence that this is true. This is a serious matter because negative long-term consequences – such as criminality, unemployment and social dysfunction – are often cited as important reasons for treating ADHD. Pharmacological treatment over many years is commonplace (3, 15).

The Norwegian Directorate of Health's guidelines on ADHD/hyperkinetic disorder also note that the benefits of long-term treatment are uncertain (16). According to the guidelines, the effectiveness and adverse effects of treatment should therefore be evaluated regularly, at least once a year (16). However, the guidelines do not state who is responsible for this when the children are no longer being followed up by a specialist. Many therefore risk remaining on these drugs for years without anyone evaluating the effectiveness and adverse effects of the drugs – or whether the individual should still have a diagnosis of ADHD.

Implications for views on ADHD

The systematic reviews generated discussion not only about the pharmacological treatment of ADHD, but also about our understanding of the condition. The increasing diagnosis and pharmacological treatment in the 1990s coincided historically with a reductionist view of ADHD as a neurobiological developmental disorder with strong genetic determinants that requires pharmacological intervention (17). The condition is still frequently described with reference to defective dopamine metabolism (18).

However, after several decades of research, no specific neurobiological mechanisms have been identified that can account for the symptoms (15). Experts now recognise that ADHD must be understood as a multifactorial, context-dependent disorder (15). That month of birth (maturity) is a risk factor for the diagnosis underscores this point (19).

In the conclusion of one article, the MTA group writes: 'The paradox is that, despite their proven short-term benefits, no clinically significant and enduring intervention (or intervention combination) exists for this condition, as of yet. Perhaps this fact should come as no great surprise, given the complex aetiological pathways linked to the emergence and maintenance of this condition.' (3, p. 48).

Put simply, the results from treatment studies reinforce the notion that a simple pharmacological intervention could not realistically be expected to have any great efficacy, given the complex aetiology of ADHD. On this basis, the MTA group argues for a fundamental reconceptualisation of the type of treatment approach required, in order to encompass treatment practices that are more wide-ranging and socially oriented than those used at present (3).

There is no doubt that children with ADHD have genuine and serious problems. However, we cannot ignore the fact that research has yielded only weak evidence to support the extensive use of medication that occurs today. This state of affairs should trigger renewed public and expert discussion on the pharmacological treatment of ADHD in children and adolescents.

REFERENCES:

1. Thomas R, Mitchell GK, Batstra L. Attention-deficit/hyperactivity disorder: are we helping or harming? BMJ 2013; 347: f6172. [PubMed][CrossRef]

2. Reseptregisteret. Antall brukere av metylfenidat 0-19 år. Oslo: Folkehelseinstituttet, 2017.

3. MTA Cooperative Group. Attention-deficit hyperactivity disorder, multimodal treatment, and longitudinal outcome: evidence, paradox, and challenge. Wiley Interdiscip Rev Cogn Sci 2015; 6: 39 - 52. [PubMed][CrossRef]

4. MTA Cooperative Group. Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height

suppression. J Child Psychol Psychiatry 2017; 58: 663 - 78. [PubMed][CrossRef]

5. Storebø OJ, Ramstad E, Krogh HB et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Database Syst Rev 2015; 11: CD009885 [PubMed].. [PubMed]

6. Catalá-López F, Hutton B, Núñez-Beltrán A et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review with network meta-analyses of randomised trials. PLoS One 2017; 12: e0180355. [PubMed][CrossRef]

7. Punja S, Shamseer L, Hartling L et al. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev 2016; 2: CD009996 [PubMed].. [PubMed]

8. MTA Cooperative Group. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009; 48: 484 - 500. [PubMed][CrossRef]

9. Banaschewski T, Buitelaar J, Chui CS et al. Methylphenidate for ADHD in children and adolescents: throwing the baby out with the bathwater. Evid Based Ment Health 2016; 19: 97 - 9. [PubMed][CrossRef]

10. Storebø OJ, Zwi M, Krogh HB et al. Evidence on methylphenidate in children and adolescents with ADHD is in fact of 'very low quality'. Evid Based Ment Health 2016; 19: 100 - 2. [PubMed][CrossRef]

11. Gerlach M, Banaschewski T, Coghill D et al. What are the benefits of methylphenidate as a treatment for children and adolescents with attention-deficit/hyperactivity disorder? Atten Defic Hyperact Disord 2017; 9: 1 - 3. [PubMed][CrossRef]

12. Storebø OJ, Simonsen E, Gluud C. Methylphenidate for Attention-Deficit/Hyperactivity Disorder-Reply. JAMA 2016; 316: 995. [PubMed][CrossRef]

13. Weyandt LL, Oster DR, Marraccini ME et al. Prescription stimulant medication misuse: Where are we and where do we go from here? Exp Clin Psychopharmacol 2016; 24: 400 - 14. [PubMed][CrossRef]

14. Olsvold A. En psykososial undersøkelse av barns, mødres og fedres forståelse og opplevelse av ADHD-diagnose og medisinering. Oslo: Universitetet i Oslo, 2012.

15. Faraone SV, Asherson P, Banaschewski T et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers 2015; 1: 15020. [PubMed][CrossRef]

16. Midtlyng E, Zeiner P, Prietz R et al. ADHD/Hyperkinetisk forstyrrelse – Nasjonal faglig retningslinje for utredning, behandling og oppfølging. Publisert 4.12.2014, sist endret 12.10.2016. Oslo: Helsedirektoratet, 2014.

17. Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 1998; 44: 951 - 8. [PubMed][CrossRef]

18. Hva er ADHD? Oslo: ADHDNorge, 2016. http://adhdnorge.no/voksen/hva-er-adhd/(23.10.2017).

19. Karlstad Ø, Furu K, Stoltenberg C et al. ADHD treatment and diagnosis in relation to children's birth month: Nationwide cohort study from Norway. Scand J Public Health 2017; 45: 343 - 9. [PubMed][CrossRef]

Published: 23 January 2018. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.17.0917
Received 23.10.2017, first revision submitted 7.11.2017, accepted 13.11.2017.