Journal of Psychiatric Research 142 (2021) 204–209

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Long-term medication for ADHD and development of cognitive functions in children and adolescents

Mats Johnson *, Jakob Åsberg Johnels, Sven Östlund, Katarina Cedergren, Zerina Omanovic, Kerstin Hjalmarsson, Klara Jakobsson, Jenny Högstedt, Eva Billstedt

Gillberg Neuropsychiatry Centre, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ARTICLE INFO

Keywords:
ADHD
Autism
Long-term medication
Cognitive function

ABSTRACT

Objective: Long-term effects of ADHD medication on cognitive functions are not well known. This study investigates development of cognitive functions and ADHD symptoms on well-controlled medication for 1 year in children and adolescents.

Study design: This study is part of an ongoing open uncontrolled trial of long-term medication for ADHD in children and adolescents aged 6–18 years with any form of ADHD, and frequently comorbid autism spectrum disorder (ASD, 29%) or autistic traits (24%). Other comorbidities were oppositional defiant disorder, dyslexia/language disorder, borderline intellectual functioning, developmental coordination disorder. This analysis includes 87 participants (61 boys, 26 girls) who completed Wechsler tests at baseline and after 12 months. ADHD symptoms were investigator-rated on the ADHD Rating Scale-IV at the same time points.

Results: The whole group of children and adolescents showed significant improvements in Wechsler Full Scale IQ (FSIQ, mean at baseline 92.6, at 12 months 97.95), and on the Index Scales Verbal Comprehension, Working Memory and Processing Speed, after one year of well-controlled ADHD medication. Comorbid dyslexia/language impairment predicted a larger rise in FSIQ, but not gender, ADHD presentation or comorbid ASD. Robust improvements in ADHD symptoms were observed (mean ADHD-Rating Scale score at baseline 34.6, and at 12 months 18.3).

Conclusions: Cognitive test scores and ADHD symptoms were improved on well-controlled medication for 1 year in children and adolescents with ADHD, autism and other comorbidities. The main study limitation is the open uncontrolled trial design.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a pervasive and impairing neurodevelopmental disorder (American Psychiatric Association, 2013) with an estimated worldwide prevalence of about 3-5% (Polanzcyk et al., 2015). It carries long-term risks for adverse life outcomes regarding academic/occupational and everyday functioning (Sayal et al., 2018). Numerous studies have documented efficacy of ADHD medication on core symptoms in the short term (Cortese et al., 2018), but effects on cognitive development and long-term outcome are less well known. The assessment of the role of ADHD medication for long-term outcome is difficult since adherence to the medication is often brief and inconsistent. The large Multimodal Treatment of ADHD (MTA) trial showed robust treatment effects after 14 months of well-controlled medication (MTA Cooperative Group 1999) - especially in the group who received multimodal treatment - but in the following observational part of the trial only around 71% of the children were still on “high-use medication” (i.e taking the medication more than 50% of the time) after 2–3 years, and at the 8-year follow-up only 32,5% (Jensen et al., 2007; Molina et al., 2009), which limited the possibilities to interpret long-term treatment effects.

Recent reviews and meta-analyses of large population database studies including children and adults indicate that ADHD medication significantly reduces risks for several negative outcomes including academic impairments, mood disorders, criminality, Substance Use Disorders (SUDs), accidents, and that outcomes were better in periods when individuals were on medication than in periods off medication (Chang et al., 2019; Boland et al., 2020). A Swedish register study reported that children with ADHD taking medication for three months improved their academic achievement (Jangmo et al., 2019). Reduced rates of

* Corresponding author. Gillberg Neuropsychiatry Centre, Sahlgrenska Academy, Gothenburg University, Kungsgatan 12A, 411 19 Gothenburg, Sweden.
E-mail address: mats.johnson@gnc.gu.se (M. Johnson).

https://doi.org/10.1016/j.jpsychires.2021.07.055
Received 25 March 2021; Received in revised form 6 July 2021; Accepted 31 July 2021
Available online 2 August 2021

comorbidities in patients on ADHD medication have also been reported (Biederman et al., 2009). Other reviews (Coghill et al., 2017; Cortese, 2020) have shown that long-term clinical trials are few, but there are some promising results. A study with double-blind randomization to continued or discontinued ADHD medication (methylphenidate) after at least 2 years of treatment showed remaining symptom benefits with continued medication (Matthijssen et al., 2019). A long-term randomized withdrawal trial after 6 months treatment with Lisdexamfetamine (LDX), demonstrated benefits in quality of life and functioning compared to placebo (Banaschewski et al., 2014). All these findings emphasize the importance of providing high-quality treatment to children and adolescents with ADHD.

Follow-up of medication in ADHD has traditionally relied on symptom scales rated by parents, patients, teachers or investigators. Although ecological validity of rating scales such as the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS-IV) was found to be relatively high in controlled studies (Szomlaiski et al., 2009), such ratings are subjective and dependent on the informants and the interpretation of symptoms in different contexts. There may be a risk of over- or underestimating symptoms and of missing symptom changes which are less evident but may still affect overall functioning.

To give a comprehensive picture of medication long-term effects we collect several outcome measures in our ongoing prospective two-year open-label trial of Long-term Medication for ADHD (LMA trial). These measures include the development of ADHD core symptoms, comorbidities, cognitive functions (IQ), global functioning, functioning in various contexts, and quality of life. The present study, focusing on ADHD medication long-term effects on cognitive functions, is part of the LMA trial. The results from the other LMA trial outcomes will be published separately.

In previous research on ADHD medication and IQ development, meta-analyses have indicated that short-term treatment of ADHD was associated with small improvements in IQ scores, but long-term studies are few (Tsai et al., 2013). A Swedish double-blind placebo-controlled RCT of amphetamine treatment for 15 months in 35 children reported a mean increase of 4.5 Full Scale IQ (FSIQ) points on the WISC-R (Wechsler 1974), compared to a 0.7-point increase in a small (n = 8) placebo group (Gillberg et al., 1997). Another study of 24 children taking stimulants (methyphenidate or amphetamine) over at least 1 year, compared to a small control group without medication (n = 7), showed a mean increase of 6.92 FSIQ points on WISC-III (Wechsler 1991) in the medication group and 2.71 in the control group (Gimpel et al., 2005). A larger uncontrolled study of 103 children with ADHD who stayed on methylphenidate treatment for one year, reported a mean increase of their WISC-III FSIQ scores of 2.9 points (Tsai et al., 2013). Thus, there is some evidence suggesting that long-term ADHD medication may contribute to improved cognitive performance, but the evidence base is limited by difficulties in performing long-term studies in large samples, especially regarding controlled trials, and little is known about moderators of cognitive gain following ADHD medication.

2. Objectives

The objectives of this study were to investigate the development of cognitive functions measured by the Wechsler scales (Wechsler, 2003, 2014), and to look for baseline predictors (gender, ADHD presentation, comorbid subgroups, baseline Wechsler scores) of long-term cognitive improvements, during one year of well-controlled ADHD medication. A secondary objective was to measure ADHD symptom scores over the same period. We expected participants at group level to score higher on the Wechsler scale at the 12-month follow up, yet we also hypothesized that there would be individual differences in the degree of change.

3. Material and methods

3.1. LMA trial design

The present study is part of our ongoing LMA trial. All patients had been referred to the Child Neuropsychiatry Centre (CNC) at Sahlgrenska University Hospital in Gothenburg, Sweden for detailed neuropsychiatric assessment by experienced teams of child psychiatrists, pediatricians, psychologists, special education teachers and speech-language pathologists. Diagnoses were established according to DSM-5 criteria.

Children and adolescents aged 6–18 years, with ADHD of any presentation according to DSM-5, intellectual level in the normal range according to psychological testing and team diagnostic assessments, and with symptoms and impairment sufficiently severe to justify ADHD medication, were invited to participate in the trial. To obtain a sample similar to that seen in clinical practice and thereby enhancing the ecological validity of the trial, all comorbidities were allowed except intellectual disability, bipolar disorder, conduct disorder, substance use disorder, psychosis, severe autism or other severe comorbid or medical conditions which would make participation unsuitable. Although the frequency of comorbidities is high in patients with ADHD seen in clinical practice (Gillberg, 2014), for instance Autism Spectrum Disorder (ASD), few studies have examined long-term effects of medication for these combined disorders. Between March 31, 2014 and June 30, 2020, 150 children and adolescents were screened for participation in the LMA trial, and 128 were included. The present study is based on Wechsler data from all participants who had completed the first year in the trial at the time of writing (n = 87).

The LMA trial protocol includes clinical visits for screening, baseline, and Visits 1–7 for follow-up at 1, 2, 3, 6, 12, 18 and 24 months. Questionnaires and interviews were used to assess ADHD symptom severity, functional impairments, comorbidities, quality of life, and adverse events. ADHD symptoms were tested with a computer-based continuous performance test with an additional motion tracking system designed to measure activity (Qbtest) (Ulberstad, 2012; Hall et al., 2014). These results will be published in detail separately.

Baseline Assessment was performed by a physician and a clinical psychologist. Data regarding ADHD symptom severity, investigator-rated on the ADHD Rating Scale-IV (ADHD-RS; Du Paul et al., 1998), functional impairments, adverse events, comorbidities and vital signs were collected by the clinician. The cognitive ability of the participant was assessed by the psychologist by Wechsler testing. Medication for ADHD (methylphenidate, LDX, atomoxetine or guanfacine) was initiated, tailored to the needs of each subject.

Visits 1–7 On-medication follow-up visits. Data on symptom severity (ADHD-RS), functional impairments, adverse events and vital signs were collected. The Qbtest was repeated at Visits 1 and 5.

Visit 5 Follow-up visit 12 months after baseline. In addition to the measures mentioned above, Wechsler tests were repeated, and the presence of comorbidities were assessed by parent/patient interview.

3.2. Participants in the present study

The first 87 participants (26 girls, 61 boys) consecutively included in the LMA trial who had ADHD-RS and Wechsler data from baseline and Visit 5 (12 months) were selected for analysis in the present study. Mean age at baseline was 11.54 years (SD = 3.64, range 6–18.9). All participants had a confirmed diagnosis of ADHD, 66 (76%) with combined presentation and 21 (24%) with inattentive presentation (Table 1). ASD was a common comorbidity (n = 25; 29%), and an additional 21 (24%) participants had subclinical ASD (autistic traits). Oppositional Defiant Disorder (ODD) was diagnosed in cases with more severe irritability/oppositional behavior (n = 13 (15%), but an additional 36 participants (41%) had subclinical ODD, i. e with several symptoms but not meeting full diagnostic criteria). Other comorbid neurodevelopmental diagnoses were dyslexia or language disorder, borderline intellectual functioning

Table 1
Baseline characteristics.

Mean age (SD, range)	11.54 years (SD = 3.64, 6–18.9)		
	n (%)		
Male	61 (70)		
Female	26 (30)		
ADHD Inattentive presentation	21 (24)		
ADHD combined presentation	66 (76)		
Comorbidities n (%)	Whole group	ADD	ADHD
Autism Spectrum Disorder	25 (29)	8 (38)	17 (26)
Oppositional Defiant Disorder	13 (15)	1 (5)	12 (18)
Dyslexia/Language Disorder	14 (16)	8 (38)	6 (9)
Borderline Intellectual Functioning	12 (14)	5 (24)	7 (11)
Developmental Coordination Disorder	10 (11)	2 (10)	8 (12)
Tics	8 (9)	1 (5)	7 (11)
Full Scale IQ Mean (SD, Range)	92.6 (12.86, 58–128)		
ADHD-RS Total Score Mean (SD)	34.60 (7.99)		

(BIF), developmental coordination disorder (DCD), and tics (Table 1). The most frequent comorbidities in participants with inattentive ADHD were ASD (n = 8; 38%), dyslexia/language disorder (n = 8; 38%) and BIF (n = 5; 24%). In participants with combined ADHD the most common comorbidities were ASD (n = 17; 26%), ODD (n = 12; 18%) and DCD (n = 8; 12%). After the neuropsychiatric assessment all families received psychoeducation to the child and parents, and information was given to teachers about the child's individual needs. No patients received psychological interventions during the trial. Medications were stimulants (n = 74), atomoxetine (n = 3) or guanfacine (n = 6). Four participants discontinued the stimulant medication 6 months after baseline due to adverse effects (low mood and appetite), but remained in the trial, had continued ADHD symptom improvements, and completed the 12-month follow-up off medication. All the other participants continued their medication at all post-baseline visits. Compliance (number of days with missed doses/number of days in period) was measured by parent and patient report, and was generally high (93%, range 74–100%).

3.3. Instruments

The Wechsler intelligence scales (Wechsler, 2003, 2014) are worldwide the most used tests to measure intellectual functioning in children and adults. The scales give an overall measure of cognitive ability, Full Scale IQ (FSIQ), and measures on several Index Scales (Verbal, Visuospatial, Fluid, Working Memory, Processing Speed). During this study, a new WISC (Wechsler intelligence scales for children) edition was released, WISC-V. Therefore, some children were assessed with the older edition WISC-IV at baseline (n = 20), but WISC-V was used for all children at 12 months. Studies have shown high correlations between the FSIQ on the different versions suggesting that they measure similar constructs (Wechsler, 2014).

The ADHD-Rating scale-IV (ADHD-RS; Du Paul et al., 1998) is an 18 items scale of the DSM-IV symptoms of inattention, hyperactivity and impulsivity. It is scored on a 4-point scale and composed of two subscales - inattention and hyperactivity/impulsivity. A higher score reflects greater symptom load. The ADHD-RS was developed as a parent-rated scale and has been used as an investigator-rated scale in many medication trials in children and adolescents with ADHD (Coghill et al., 2017). The psychometric properties have been found adequate by the original authors and this has been supported by independent research (Makransky and Bilenberg, 2014).

3.4. Ethical considerations

The study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Gothenburg ethical committee (no. 897–13). Written informed consent/assent was obtained from the children and both parents after the nature of the procedures had been fully explained. The trial is registered in ClinicalTrials.gov, identifier NCT03250013.

3.5. Statistical analysis

The statistical software SPSS, version 25, was used for all data analysis. Change in Wechsler scores from baseline to follow-up was examined using paired *t*-test. Stability in individual differences was examined using Pearson correlation coefficient. When examining associations between dichotomous baseline predictors and change in Wechsler scores (i.e. subgroup analyses) we utilized non-parametric Mann Whitney U tests due to small and unequal sample sizes.

4. Results

ADHD symptoms were robustly improved from baseline to 12 months. Mean ADHD-RS scores at baseline were 34.60 (SD 7.99), and at 12 months 18.34 (SD 6.96). Normalization of ADHD symptoms was reached in 41/87 (47%) of the participants, defined as an ADHD-RS score of 18 or less, i.e. only mild symptoms remaining. Normalization was more frequent in the inattentive ADHD subgroup (16/21, 76%) than in the combined ADHD subgroup (25/66, 38%). The whole group (n = 87) showed significantly higher Wechsler scores at 12 months compared to Baseline, on FSIQ (mean at baseline 92.6 and at 12 months 97.95, $p < .001$), Verbal Comprehension, Working Memory and Processing Speed (Table 2). Furthermore, correlations were strong between individual scores at baseline and at 12 months, i.e. participants who had high scores at baseline also had high scores at 12 months (Table 2 and Fig. 1) on the FSIQ and Index Scales (Verbal, Perceptual Reasoning/Visuospatial Index, Working Memory) except for Processing Speed, which showed a surprisingly low correlation. This low correlation might be influenced by differences in the subscale tests between different Wechsler versions. A subgroup comparison between the 4 participants who remained in the trial but discontinued their medication after 6 months, and the 83 participants who continued medication to the 12-month follow-up, showed no significant difference in FSIQ change ($p = .73$).

4.1. Baseline predictors

A discrepancy (Δ) score between baseline and 12-month FSIQ scores was calculated in order to identify possible baseline predictor variables for improved scores on the Wechsler. Specifically, we compared subgroups based on the following categorizations, respectively, on the discrepancy score: gender (male/female), ADHD presentation (inattentive versus combined), comorbid ASD (yes/no) or comorbid dyslexia and/or language impairment (yes/no). The only significant result from these subgroup analyses was that those with comorbid dyslexia/language impairment made a relatively larger raise in FSIQ from baseline to 12 months ($\Delta M = 11.21$, $SD = 8.75$) relative to those without this comorbidity ($\Delta M = 4.23$, $SD = 9.72$), Mann Whitney $U = 289.00$, $p = .01$. The comorbid group also had lower baseline FSIQ scores (81.64, $SD = 9.76$) than those without dyslexia/language impairment (94.70, $SD = 12.35$), $U = 825$, $p < .001$. Note that a dependent samples *t*-test conducted only on participants without comorbid dyslexia/language impairment was significant from baseline to 12 months, so while those with dyslexia/language impairment improved the most in FSIQ, the subgroup without this comorbidity also improved ($p < .001$).

Table 2
Wechsler FSIQ and subscale scores at baseline and 12 months, and correlations between the baseline and 12-month values.
FSIQ = Full Scale IQ, Verbal = Verbal Comprehension Index, Perceptual/VSI = Perceptual Reasoning Index in WISC-IV/Visuospatial Index in WISC-V, Working Memory = Working Memory Index, Speed = Processing Speed Index.

	Mean	N	SD	Paired comparison T, p-value	Correlation
FSIQ baseline	92,5977	87	12.86		
FSIQ 12 months	97,9540	87	14.03	5.06, p < .001	.734, p < .001
Verbal	96,4483	87	14.89		
Verbal 12 months	100,4253	87	16.03	3.60, p = .001	.779, p < .001
Perceptual/VSI baseline	100,5862	87	14.70		
Perceptual/VSI 12 months	102,8391	87	15.86	1.90, p = .06	.740, p < .001
Working memory baseline	87,8953	86	13.37		
Working memory 12 months	90,9535	86	13.26	2.44, p = .017	.619, p < .001
Speed baseline	87,6628	86	11.91		
Speed 12 months	92,1512	86	12.60	2.70, p < .01	.212, p = .050

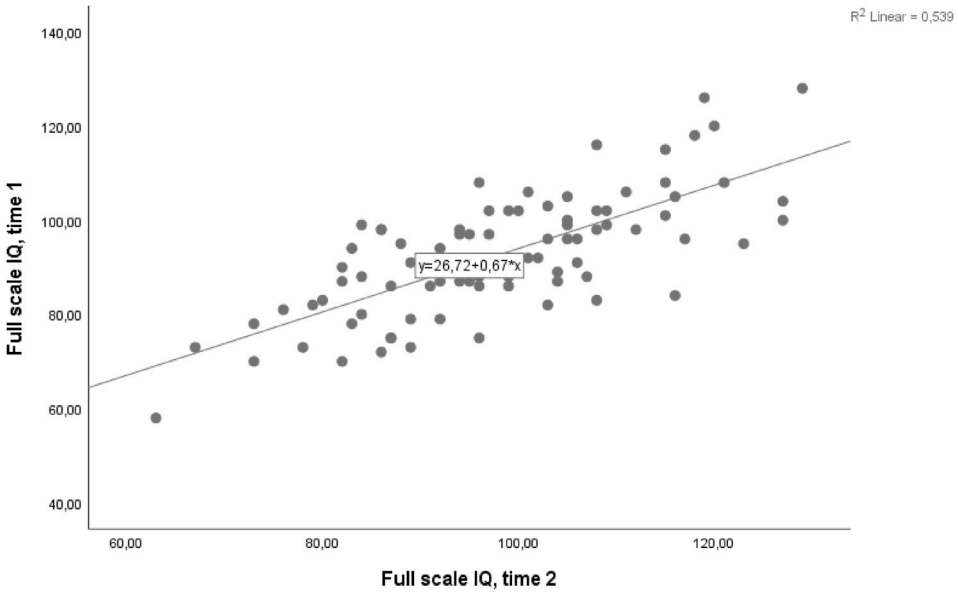

Fig. 1. Correlation between FSIQ at baseline and at 12 months.

5. Discussion

This study showed significant improvements in Full Scale IQ as measured by the Wechsler Scales, and on the Index Scales Verbal Comprehension, Working Memory and Processing Speed, after one year of well-controlled medication for ADHD in children and adolescents. Our results support the findings in earlier long-term studies with smaller samples compared to control groups (Gillberg et al., 1997; Gimpel et al., 2005), and shows somewhat larger FSIQ changes than those reported in the study by Tsai et al. (2013). These earlier studies, however, used older WISC-versions (WISC-R and WISC-III) in which the subtests were different, so the results cannot be directly compared to our study. Analysis of possible baseline predictors in our study indicated that co-morbid dyslexia/language impairment predicted a larger rise in FSIQ from baseline to 12 months. The participants with this comorbidity also had lower baseline FSIQ scores. It is possible that attention deficit is particularly detrimental for cognitive test performance in children with dyslexia/language impairment, who otherwise are known to perform variably on IQ tests (e.g., Siegel, 2006). Gender, ADHD presentation or comorbid ASD did not predict differences in FSIQ scores at 12 months. The clinical significance of small improvements in IQ tests is unclear, but a possible interpretation of the cause is that medication has reduced the disturbance from ADHD symptoms, thus enabling the child to use more of their cognitive potential. In clinical experience it is often seen that the child's school performance, academic results and behavior improves, in some cases considerably, after some time on ADHD medication.

Our findings are also in line with the large population database studies showing that improvements in academic achievement and reduced risk for several negative outcomes can be seen in periods on medication compared to periods off medication (Chang et al., 2019; Jangmo et al., 2019, Boland et al., 2020). A recent clinical trial highlighted the importance of careful optimization of stimulant treatment and concurrent behavioral therapy. The 8-week open optimization phase in that study showed high response rates and remission of aggression in 63% of 151 children with ADHD, and additional mood-stabilizing medication could be avoided (Blader et al., 2021).

Thus, current research suggests that several improvements may be gained on well-controlled ADHD medication, but are probably reduced or lost if medication is discontinued. This agrees well with the observational follow-up over several years after the MTA trial 14-month well-controlled medication period, when many participants discontinued their medication and initial treatment gains dissipated (Jensen et al., 2007; Molina et al., 2009). The compliance to medication in our study was generally high (93%), and only 4 participants discontinued their medication before 12 months. ADHD symptoms measured on the ADHD Rating Scale-IV were substantially improved, reaching normalized levels in 47% of the participants (normalization defined as an ADHD Rating Scale total score of 18 or less, i.e. scores of 1 or less on each item, meaning that symptoms were present "sometimes, rarely or never"). A similar categorical definition was used in the MTA trial to describe treatment success (Swanson et al., 2001).

The results from our study thus support the findings in earlier research and extend them to a sample highly comorbid in ASD. The improvements in cognitive functions during long-term well-controlled ADHD medication seen in this and other studies suggests that functional benefits may be reached through such treatment strategies. Future research designed to monitor comprehensive functional and quality of life outcomes in long-term trials could help us learn more about effects of significance in everyday life and give evidence to better inform practitioners and patient families about treatment options. The present study is part of our ongoing LMA trial, which has been extended to 2 years follow-up to yield more data on long-term functional and quality of life outcomes, and these data will be published separately.

5.1. Limitations

Limitations in the present study are the open uncontrolled design, which means that other factors than the medication may influence the results, and the relatively small sample size. Strengths are the long-term follow-up, the prospective naturalistic study design, and the inclusion of patients with comorbidities, most notably ASD, which makes the setting more similar to the one seen in everyday clinical practice.

Funding

Investigator-Initiated study funded by Shire International GmbH (Switzerland, part of Takeda IIR-SWE-000546), Wilhelm and Martina Lundgrens vetenskapsfond, Stiftelsen Petter Silfverskiölds Minnesfond, Fredrik and Ingrid Thurings stiftelse. The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. Qbtech supported our use of the QbTest and provided test data from their database for our analysis.

Author contributions

All authors contributed to study design, data analysis, data interpretation, and drafting and revision of the manuscript, and gave final approval of the version to be submitted for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosures

MJ has received research grants from Shire/Takeda and been engaged as a speaker or consultant by PCM Scientific, Evolan, Shire, SFI Health and New Nordic. All other authors report no conflicts of interest.

Acknowledgements

The authors are grateful to all the children and their families for participating in the study.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. APA, Washington, DC.

Banaschewski, T., Johnson, M., Lecendreux, M., Zuddas, A., Adeyi, B., Hodgkins, P., Squires, L.A., Coghill, D.R., 2014. Health-related quality of life and functional outcomes from a randomized withdrawal study of long-term lisdexamfetamine dimesylate treatment in children and adolescents with attention-deficit/hyperactivity disorder. CNS Drugs 28, 1191–1203.

Biederman, J., Monuteaux, M.C., Spencer, T., Wilens, T.E., Faraone, S.V., 2009. Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. Pediatrics 124 (1), 71–78.

Blader, J.C., Pliszka, S.R., Kafantaris, V., Foley, C.A., Carlson, G.A., Crowell, J.A., Bailey, B.Y., Sauder, C., Burleson Daviss, W., Sinha, C., Matthews, T.L., Margulies, D. M., 2021. Stepped treatment for attention-deficit/hyperactivity disorder and aggressive behavior: a randomized, controlled trial of adjunctive risperidone, divalproex sodium, or placebo after stimulant medication optimization. J. Am. Acad. Child Adolesc. Psychiatry 60 (2), 236–251. https://doi.org/10.1016/j.jaac.2019.12.009. Epub 2020 Jan 30.

Boland, H., DiSalvoa, M., Frieda, R., Woodworth, K.Y., Wilens, T., Faraone, S.V., Biederman, J., 2020. A literature review and meta-analysis on the effects of ADHD medications on functional outcomes. J. Psychiatr. Res. 123, 21–30.

Chang, Z., Ghirardi, L., Quinn, P.D., et al., 2019. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. Biol. Psychiatr. 86 (5), 335–343.

Coghill, D.R., Banaschewski, T., Soutullo, C., Cottingham, M.G., Zuddas, A., 2017. Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. Eur. Child Adolesc. Psychiatr. 26, 1283–1307.

Cortese, S., 2020. Pharmacologic treatment of attention deficit–hyperactivity disorder. N. Engl. J. Med. 383 (11), 1050–1056.

Cortese, S., Adamo, N., Del Giovane, C., et al., 2018. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 5, 727–738.

Du Paul, G.J., Anastopoulos, A.D., Power, T.J., Read, R., Ikeda, M.J., McGoey, K.E., 1998. Parent ratings of attention-deficit/hyperactivity disorder symptoms: factor structure and normative data. J. Psychopathol. Behav. Assess. 20, 83–102.

Gillberg, C., Melander, H., von Knorring, A.L., Janols, L.O., Thernlund, G., Hagglof, B., Eidevall-Wallin, L., Gustafsson, P., Kopp, S., 1997. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms. A randomized, double-blind, placebo-controlled trial. Arch. Gen. Psychiatr. 54, 857–864.

Gillberg, C., 2014. ADHD and its Many Associated Problems. Oxford University Press.

Gimpel, G.A., Collett, B.R., Veeder, M.A., Gifford, J.A., Sneddon, P., Bushman, B., Hughes, K., Odell, J.D., 2005. Effects of stimulant medication on cognitive performance of children with ADHD. Clin. Pediatr. 44, 405–411.

Hall, C.L., Walker, G.M., Valentine, A.Z., Guo, B., Kaylor-Hughes, C., James, M., Daley, D., Sayal, K., Hollis, C., 2014. Protocol investigating the clinical utility of an objective measure of activity and attention (QbTest) on diagnostic and treatment decision-making in children and young people with ADHD-'Assessing QbTest Utility in ADHD' (AQUA): a randomised controlled trial. BMJ Open 4 (12), e006838. https://doi.org/10.1136/bmjopen-2014-006838.

Jangmo, A., Stålhandske, A., Chang, Z., Chen, Q., Almqvist, C., Feldman, I., Bulik, C.M., Lichtenstein, P., D'Onofrio, B., Kuja-Halkola, R., Larsson, H., 2019. Attention-deficit/hyperactivity disorder, school performance, and effect of medication. J. Am. Acad. Child Adolesc. Psychiatry 58 (4), 423–432. https://doi.org/10.1016/j.jaac.2018.11.014.

Jensen, P.S., Arnold, L.E., Swanson, J.M., et al., 2007. 3-Year follow-up of the NIMH MTA study. J. Am. Acad. Child Adolesc. Psychiatry 46, 989–1002.

Makransky, G., Bilenberg, N., 2014. Psychometric properties of the parent and teacher ADHD rating scale (ADHD-RS): measurement invariance across gender, age and informant. Assessment 21, 695–705.

Matthijssen, A.-F.M., Dietrich, A., Bierens, M., Kleine Deters, R., van de Loo-Neus, G.H. H., van den Hoofdakker, B.J., Buitelaar, J.K., Hoekstra, P.J., 2019. Continued benefits of methylphenidate in ADHD after 2 years in clinical practice: a randomized placebo-controlled discontinuation study. Am. J. Psychiatr. 176, 754–762.

Molina, B.S.G., Hinshaw, S.P., Swanson, J.M., Arnold, L.E., Vitiello, B., Jensen, P.S., et al., MTA Cooperative Group., 2009. 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 48 (5), 484–500.

MTA cooperative group, 1999. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal treatment study of children with ADHD. Arch. Gen. Psychiatr. 56, 1073–1086.

Polanczyk, G.V., Salum, G.A., Sugaya, L.S., Caye, A., Rohde, L.A., 2015. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. Child Psychol Psychiatry 56 (3), 345–365.

Sayal, K., Prasad, V., Daley, D., Ford, T., Coghill, D., 2018. ADHD in children and young people: prevalence, care pathways, and service provisions. Lancet Psychiatry 5, 175–186. https://doi.org/10.1016/S2215-0366(17)30167-0.

Siegel, L.S., 2006. Perspectives on dyslexia. Paediatr. Child Health 11 (9), 581–587.

Swanson, J.M., Kraemer, H.C., Hinshaw, S.P., et al., 2001. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J. Am. Acad. Child Adolesc. Psychiatry 40, 168–179.

Szomlaiski, N., Dyrborg, J., Rasmussen, H., Schumann, T., Koch, S.V., Bilenberg, N., 2009. Validity and clinical feasibility of the ADHD rating scale (ADHD-RS). A Danish Nationwide Multicenter Study. Acta Paediatr. 98 (2), 397–402. https://doi.org/10.1111/j.1651-2227.2008.01025.x.

Tsai, C., Huang, Y., Wu, C., Hwang, F., Young, K., Tsai, M., et al., 2013. Long-term effects of stimulants on neurocognitive performance of Taiwanese children with attention-deficit/hyperactivity disorder. BMC Psychiatr. 13, 330.

Ulberstad, F., 2012. QbTest Technical Manual. QbTech AB, Stockholm.

Wechsler, D., 1974. Wechsler Intelligence Scale for Children—Revised. Psychological Corporation, New York.

Wechsler, D., 1991. The Wechsler Intelligence Scale for Children—Third Edition. The Psychological Corporation, San Antonio, TX.

Wechsler, D., 2003. The Wechsler Intelligence Scale for, children—fourth ed. Pearson, London.

Wechsler, D., 2014. Wechsler Intelligence Scale for, children—fifth ed. Pearson, Bloomington, MN.