Clinical Perspectives on Attention-Deficit/Hyperactivity Disorder (ADHD):

Long-term, Naturalistic Follow-ups in Childhood and in Adulthood

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To my beloved family

Abstract

Nylander, E. (2022). *Clinical Perspectives on Attention-Deficit/Hyperactivity Disorder (ADHD): Long-term, Naturalistic Follow-ups in Childhood and in Adulthood*. Department of Psychology, University of Gothenburg, PO Box 500, SE-405 30, Gothenburg, Sweden.

The overall aim of this thesis was to evaluate the long-term outcome of Attention-Deficit/Hyperactivity Disorder (ADHD) in childhood and in adulthood, as it is presented in typical patients in real-world settings.

Study I assessed treatment outcome and predictive factors after 1 year in 253 children with ADHD. We compared drug treatment with regular counselling with regard to their effectiveness in reducing core ADHD symptoms and improving real-life functioning. The evaluations were made through telephone interviews (Brief Child and Family Phone Interview; BCFPI) with a parent. BCFPI contains a number of subscales, we used: ADHD, Oppositional Defiant Disorder (ODD), Separation Anxiety, General Anxiety Disorder (GAD), Depression, Overall functioning, Family situation, and Parental depression. Regardless of treatment mode, our results clearly indicated reduced symptom severity on most relevant subscales. According to the effect sizes, the treatment effects were largest with regard to ADHD-, ODD-, and Child functioning subscales. When analysing the two treatment modes separately, the medicated patients improved between referral and 1-year follow-up on subscales ADHD, ODD, GAD, Depression, Child functioning, and Family situation; the counselled patients improved over time on subscales of ODD and Depression only. Comparing the two treatment groups directly revealed differences only with regard to subscales ADHD (large effect size) and Child functioning (medium effect size). Potential confounders obscured unanimous interpretation: firstly, the medicated group was on average diagnosed more rapidly and hence received treatment for a longer period of time. Secondly, medicated children had more appointments and their parents attended the proffered ADHD-programs to a greater extent. This means that one cannot safely attribute the improvement to the medication alone. Important predictors for improvement of parent-rated ADHD symptoms and overall functioning level included male sex, on-going medication, previous symptom severity, and overall functioning level. Exploratory analyses revealed that successful treatment of ADHD, regardless of treatment mode, also significantly ameliorated comorbid symptoms.

The aim of Study II was to evaluate treatment outcome and predictive factors after 5 years in 137 of the children from Study I. They were still younger than 18 at the time of follow-up. As in Study I, we wished to compare drug treatment to regular counselling with regard to their effectiveness in reducing core ADHD symptoms and improving real-life functioning. We also wished to map temporal patterns and compare the three measurement points (referral, 1-year outcome, and 5-year outcome). The evaluations were made through BCFPI telephone interviews with a parent. Overall, children with ADHD improved after 5 years, both according to symptom severity and improved real-life functioning. No differences between treatment groups were found on any BCFPI subscale, including the ADHD- and the Child functioning subscales. Thus, the superiority of medication, apparent at the 1-year follow-up, had dissipated at the 5-year follow-up. Important predictors for the treatment outcome of parent-rated ADHD symptoms and functioning level after 5 years included baseline ADHD- and ODD-symptom severity as well as baseline functioning level and how the child's symptoms affected family life.

Study III monitored 52 persons diagnosed with ADHD in adulthood over 5 years. We recorded self-report symptom ratings (Brown ADD scale [BADDS]; Adult Self-Report Scale [ASRS]) and clinicians' ratings (Global Assessment of functioning [GAF]; Clinical Global Impressions scale -Severity [CGI-S]) of symptom severity at baseline and again at the 5-year follow-up. We attempted to identify outcome (core ADHD symptom severity and real-life functioning) predictors using rating scores at baseline, along with measures of medication intensity, psychiatric comorbidity, cognitive ability, age, and sex. After 5 years, patients were improved with fewer and/or less severe ADHD symptoms compared with baseline. Note, however, that the average patient still had clinically significant levels of symptoms with functional deficits. Baseline self-reports of ADHD symptoms predicted their own 5-year outcome and low baseline functioning level predicted improved global functioning at follow-up. Factors that typically predicted treatment outcome in ADHD in many previous studies, such as medication, comorbidity, IQ, age, or sex did not anticipate long-term outcomes according to this study.

The aim of Study IV was to investigate Quantified behavioural Test (QbTest+) performance in a group of 67 adult patients diagnosed with ADHD. Forty-one of them completed a second QbTest+ 4 years later. This computer-based attentional test is often employed in the assessment of ADHD. Overall, there was large individual variability in QbTest+ scores at baseline, but the majority (65%) scored in the clinical range despite being on stimulant treatment during the test. Out of the 13 patients who suspended medication prior to the test, 11 (85%) scored above the clinical cut-off. There were modest concurrent associations between QbTest+ cardinals and symptom self-ratings. Performance on the QbTest+ was improved at the follow-up test and fewer patients scored in the clinical range (34%). The scores on the QbInattention cardinal at baseline correlated positively with BADDS and ASRS self-ratings at the 4-year follow-up.

Keywords: Attention-deficit Hyperactivity disorder, ADHD, adult ADHD, childhood ADHD, lifespan ADHD, naturalistic studies, long-term outcome, clinical evaluation, QbTest, ADHD medication, stimulants

Swedish summary (svensk sammanfattning)

Psykiatriska diagnoser kan erbjuda ett gemensamt språk för svårigheter att fungera i sin vardag och i sitt liv. De kan fungera vägledande för att få veta vilka behandlingar som har hjälpt patienter med samma diagnos tidigare. Men hur kan vi veta om psykiatrisk behandling hjälper? För att kunna svara på detta finns stora kontrollerade, randomiserade studier som mäter specifika behandlingseffekter. Men det krävs också studier av patienter som inte på något sätt påverkats av att de ingår i en forskningsstudie. Denna typ av verklighetsnära, naturalistiska forskning syftar till att beskriva hur bra behandlingar fungerar i den kliniska vardagen. Nackdelen är att metoden ger sämre kontroll när det gäller datainsamlandet. Den stora fördelen är att den ger en bild av den orörda verkligheten.

Attention-Deficit/Hyperactivity Disorder (ADHD) är en av de vanligaste diagnoserna i svensk psykiatri, både bland barn och vuxna. Den är ofta livslång och kopplad till flera psykosociala risker. Det förekommer ofta komplicerande samsjuklighet. ADHD-diagnosen har skapat debatt och ifrågasatts, samtidigt som den hjälpt många människor till behandling och ett bättre liv. ADHD är ett stort aktuellt forskningsområde, inte minst avseende kontrollerade behandlingsstudier rörande effekten av olika farmakologiska behandlingsalternativ. Utvärderingar av hur olika behandlingsmetoder fungerar i verkligheten är långt färre.

I föreliggande avhandling försöker jag att kartlägga hur behandling vid ADHD fungerar i den kliniska verkligheten. Hjälper de insatser som psykiatrin idag erbjuder? Hur går det för patienterna efter att de fått en ADHD-diagnos, verkar diagnosen göra skillnad för patienten på längre sikt?

* * *

Avhandlingen består av fyra empiriska studier som är baserade på forskningsmaterial om barn med ADHD från barn- och ungdomspsykiatrin i Region Halland, samt på forskningsmaterial rörande vuxna med ADHD från St. Göran-projektet i Stockholm. Studierna är långtidsuppföljningar av konsekutiva psykiatripatienter som bedömts uppfylla diagnoskriterier för ADHD. De två första studierna avser att besvara frågan om hur barn med ADHD mår och fungerar vid tidpunkten för diagnosen samt vid uppföljningar 1 respektive 5 år senare. Råmaterialet utgjordes av semistrukturerade telefonintervjuer med en av föräldrarna. De två påföljande studierna avser belysa hur vuxna med ADHD mår och fungerar vid tidpunkten för diagnosticering samt 4–5 år senare. Här användes diagnostiska intervjuer, skattningsskalor och ett objektivt aktivitets- och uppmärksamhetstest.

I studie I (n = 253) var det första syftet att jämföra de patienter som tar ADHD-medicin mot patienter som får sedvanlig barnpsykiatrisk uppföljning utan medicinering, för att se om ADHD-symptomen minskar och/eller om funktionsnivån ökar. Ett andra syfte var att identifiera predicerande faktorer för behandlingsutfallet efter ett år. Data insamlades via semistrukturerade telefonintervjuer (Brief Child and Family Phone Interview; BCFPI) med patienternas föräldrar inför klinisk bedömning (ADHD-diagnos) och ett år senare. I 98% av intervjuerna var det samma förälder vid båda intervjutillfällena, 220 av de intervjuade föräldrarna var mödrar. Under året har patienterna fått diagnosticerad ADHD och sedvanlig behandling. 185 (73%) medicinerade vid 1-årsuppföljningen och 68 (27%) fick sedvanlig barnpsykiatrisk uppföljning utan medicinering. Patienterna erbjöds även föräldrastöd (individuellt eller i grupp) och information till skolpersonal om behov av stöd och anpassning. Patienterna hade medicinerat olika länge vid tidpunkten för 1-årsuppföljning, beroende på tidpunkt för förskrivning av medicinen. Resultaten i studie I visade

att gruppen som helhet förbättras under det första året enligt de flesta subskalorna. Den största behandlingseffekten avsåg ADHD- och trotssymptom samt barnets övergripande funktionsnivå. De medicinerade patienterna förbättrades och fick lindrigare ADHD-symptom och blev mindre trotsiga, mindre ångestfyllda och mindre nedstämda. De ökade sin funktionsnivå i vardagen och familjesituationen blev mer positiv. De patienter som inte medicinerade förbättrades enbart genom att bli mindre trotsiga och mindre nedstämda. Det förelåg faktorer som kan ha påverkat tillförlitlighet: de medicinerade patienterna diagnosticerades tidigare i förloppet och hade således hunnit få längre behandling än de övriga. Vidare deltog de medicinerande barnens föräldrar i större utsträckning i de psykosociala stödåtgärderna. Det går alltså inte att tolka förbättringen som resultat av medicineringen enbart. Prediktiva faktorer för positivt 1-årsutfall innefattande att vara pojke, ha pågående medicinering, ha låg symptombörda och god övergripande funktionsnivå vid behandlingsstart.

I studie II (n = 137) var syftet att undersöka 5-årsutfall av de av patienter ur studie I som 5 år senare ännu inte fyllt 18 år. Det första syftet var att undersöka skillnaderna mellan medicinerade patienter och patienter som enbart fått sedvanlig barnpsykiatrisk uppföljning utan medicinering, i avseenden att reducera ADHD-symptom och öka funktionsnivån. Ett andra syfte var att kartlägga mönster och jämföra de tre mätpunkterna: vid vårdsökande (innan diagnosen), ett år senare och fem år senare. Ett tredje syfte var att identifiera faktorer som predicerar femårigt behandlingsutfall. Resultaten visade att barnen förbättrades både avseende symptom och funktion. Den skillnad mellan behandlingsgrupperna som noterades i studie I fanns inte längre kvar vid femårsuppföljningen: inga statistisk säkerställda skillnader mellan de barn som medicinerats och de som inte medicinerats kunde observeras vid 5-årsuppföljningen. Prediktiva faktorer för förändring i ADHD-symptom och funktionsnivå efter fem år var ADHD- och trotssymptomens svårighetsgrad vid vårdsökande men också hur barnets symptom påverkade familjelivet enligt förälderns skattning.

I studie III (n = 52) var syftet att utvärdera 5-årigt utfall i en grupp vuxna patienter med ADHD som diagnosticerats i vuxen ålder och som har pågående psykiatrisk kontakt. Vi använde Global Assessment of Functioning (GAF) och Clinical Global Impressions scale -Severity (CGI-S), samt självskattningarna Brown ADD Scale (BADDS) och WHOs Adult ADHD Self-Report Scale (ASRS). Resultaten visade att patientgruppen som helhet förbättrades under undersökningsperioden, men de låg fortfarande på klinisk nivå avseende ADHD-symptom och funktionspåverkan. Första mätningens självskattningar (BADDS och ASRS) predicerade sina egna utfall vid 5-årsuppföljningen, i betydelsen att hög skattningsgrad av ADHD-symptom vid första mätningen tenderade ge högre skattningsgrad även vid 5-årsmätningen. De patienter som hade stor funktionspåverkan vid första mätningen var de som visade störst förbättring vid 5-årsuppföljningen. Vanliga typiska påverkansfaktorer i behandlingsutfallsstudier så som medicinering, samsjuklighet, IQ, ålder eller kön hade ingen påvisbar inverkan på 5-årsutfallet i vår studie.

I studie IV (n = 67) undersöktes patienter med ADHD (som förskrivits centralstimulantia) med QbTest+. Detta är ett test som ofta används inom psykiatrin för att mäta typiska symptom vid ADHD via sina tre kardinalparametrar QbActivity (aktivitetsgrad), QbImpulsivity (impulsivitet) och QbInattention (ouppmärksamhet). Av de 67 patienterna var det 13 som missat att ta sin medicin på testdagen; dessa jämfördes med dem som tagit sin medicin enligt ordination inför testet. Resultaten visade att 65% presterade på klinisk nivå; motsvarande siffra för de för dagen omedicinerade patienterna var 85%. Det förelåg visst samband mellan QbTest+-prestation och självskattningarna (BADDS och ASRS). 41 patienter genomförde ett QbTest+ 4 år senare. På gruppnivå var resultaten förbättrade efter 4 år och färre patienter presterade över klinisk tröskel (34%).

Kardinalparametern QbInattention vid första mätningen var positivt korrelerad med patientens självskattning på BADDS och ASRS fyra år senare.

* * *

Huvudfyndet i föreliggande avhandling är framförallt att individer som fått en ADHD-diagnos och får behandling inom psykiatrin blir bättre med tiden. De blir inte friska, i avseendet befriade från ADHD-symptom och med normaliserad funktionsnivå, men de förbättras både avseende symptomgrad och funktionsnivå. Förbättringen efter lång tid återfanns både bland barn och vuxna. Ett andra fynd i barnens fall var att den största förbättringen sågs under det första behandlingsåret; därefter planade effekten ut. Vad det beror på förblir spekulation. En tanke är att bästa möjliga förbättring är nådd med den tillgängliga behandling som finns: de har fortsatt ADHD och behandlingen kan förbättra men inte normalisera symptom och fungerande. Ett tredje fynd är att ADHD-medicinernas långtidseffekter är svåra att identifiera i denna patientgrupp. Ett problem med att undersöka sådana mediciners effekt under lång tid under naturalistiska omständigheter är att tillståndet som sådant komplicerar följsamhet till behandling men också att patienterna själva måste få vara fria att välja sitt deltagande i sin behandling. En tanke är att det hade behövts mer omfattande psykosocialt stöd för att få till en fungerande långtidsbehandling. En annan tanke är att patienterna fortsätter i behandling om de själva upplever sig ha nytta av den - de blir (mer) motiverade att fortsätta. En sista trolig förklaring är att effekten också kan bero på det statistiska fenomenet regression mot medelvärdet. Sammanfattningsvis ger föreliggande avhandling en inblick i långtidseffekterna av psykiatrisk diagnostik och behandling i verkligheten.

List of papers

This thesis is based on the following studies, referred to in the text by their roman numerals:

I. Nylander, E., Andersson, B., Tjus, T., & Hansen, S. Treatment outcome in child ADHD at a Swedish outpatient clinic: The first year. Manuscript.

II. Nylander, E., Andersson, B., Hansen, S., & Tjus, T. Treatment outcome in child ADHD at a Swedish outpatient clinic: Five years later. Manuscript.

III. Nylander, E., Floros, O., Sparding, T., Rydén, E., Hansen, S., & Landén, M. (2021). Five-year outcomes of ADHD diagnosed in adulthood. *Scandinavian Journal of Psychology, 62*, 13-24. https://doi.org/10.1111/sjop.12692

IV. Nylander, E., Sparding, T., Floros, O., Rydén, E., Landén, M., & Hansen, S. (2022). The Quantified behavioural Test plus (QbTest+) in adult ADHD. *Nordic Psychology*, Advance online publication. https://doi.org/10.1080/19012276.2022.2036628

Abbreviations

ADHD	Attention-Deficit /Hyperactivity Disorder
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
ASRS	The WHO Adult ADHD Self-Report Scale
BADDS	Brown Attention-Deficit Disorder Scale
BCFPI	Brief Child and Family Phone Interview
CBT	Cognitive Behavioural Therapy
C-GAS	Children's Global Assessment Scale
CGI-S	Clinical Global Impressions scale –Severity
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders 1994/2013
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examination
GAD	General Anxiety Disorder
GAF	Global Assessment of Functioning Scale
MTA	Multimodal Treatment study of children with ADHD
ODD	Oppositional Defiant Disorder
OPLS	Orthogonal Partial Least Squares
p	General psychopathology factor
PCA	Principal Component Analysis
QbTest+	Quantified Behavioural Test plus
PLS	Partial Least Squares
RCT	Randomized Controlled Trials
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
TAU	Treatment As Usual
VIP	Variable Influence on Projection
WHO	World Health Organization

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Elin Nylander
Gothenburg, May 2022

Contents

INTRODUCTION

When researching what works for whom in psychiatry, Randomized Controlled Trials (RCT) have generally been considered the gold standard (Gilbody et al., 2002; WHO Scientific Group on the Treatment of Psychiatric Disorders & World Health Organization, 1991). RCTs build on strictly controlled and artificial experimental conditions for examining the effects of a drug- or a psychotherapy intervention. However, clinicians also need to know how a particular treatment works in everyday settings for real patients with all possible confounders present at all times. Is the treatment under study as effective in the real world as it seems to be under more experimental conditions? This question calls for research on effectiveness (as opposed to efficacy) that can tell us more about the true effects of treatment (Gilbody et al., 2002).

The present work concerns studies on treatment effectiveness in the case of Attention-Deficit/Hyperactivity Disorder (ADHD), an heritable, neurodevelopmental, spectrum disorder (Hodgkins et al., 2012), affecting both children and adults. ADHD is in many cases a life-long, impairing condition associated with multiple negative consequences (e.g., Banaschewski et al., 2010; Chang et al., 2014; 2016; Dalsgaard et al., 2015; Fredriksen et al., 2014; Kooij et al., 2019; Molina et al., 2007; Sun et al., 2019).

Treatment guidelines for ADHD are mostly derived from efficacy studies using highly compliant patients, with clear-cut primary diagnoses, and no (or mild) comorbid symptoms (Bridge et al., 2009; Hoagwood et al., 1995; Sourander et al., 2007; Weisz, Donenberg, Han, & Kauneckis, 1995; Weisz, Donenberg, Han, &Weiss, 1995). However, studies like these do not tell us much about real outcomes because such patients are uncommon in practice. Hence I argue for the necessity of shedding light on the long-term trajectory of the ADHD disorder as it is presented in typical patients and in real-world settings (Asherson et al., 2016) across the lifespan.

ADHD: Basic facts

Childhood ADHD has a prevalence of 3–7% (Faraone et al., 2015; Polanczyk et al., 2007; Polanczyk et al., 2015; Thomas et al., 2015). The median age of onset in US children is 6 years, severe ADHD having an earlier onset (4 years) than mild ADHD (7 years; Visser et al., 2014). The prevalence of US children ever diagnosed with ADHD increased by 42% from 2003 to 2011 (Visser et al., 2014). A Danish registry study showed an increase in ADHD diagnoses in Denmark over 15 years (Mohr-Jensen et al., 2015). In Sweden, clinically diagnosed ADHD among children increased more than five-fold over 10 years (2004–2014; Rydell et al., 2018). The prevalence of adult ADHD across twenty countries has been estimated at 2.8%, ranging between 1.4 and 3.6% (Fayyad et al., 2017).

The clinical female-male sex ratio in childhood ADHD has been estimated to 1:4–1:9 (Polanczyk et al., 2007; Rucklidge, 2010). However, in a more recent study the clinical female-male sex ratio in adults was found to be 1:2.5 (Mowlem et al., 2019), suggesting a possible under-recognition of female ADHD in the clinics (Kooij et al., 2019; Mowlem et al., 2019).

ADHD is strongly heritable. Estimates from more than 30 twin studies have reported the genetic inheritance of ADHD to 77–88% (Faraone & Larsson, 2019). A recent exploratory genome-wide study (Demontis et al., 2019) involving > 55,000 participants strongly tied 12 sites on the genome to an increased ADHD risk. For each of these 12 loci a particular DNA sequence type increased the likelihood of ADHD, but each by just a very tiny fraction (0.8–2.0%). The ADHD-related gene variants are not necessarily rare or disruptive, but for the most part common polymorphisms of the DNA sequence in uncommon and unfortunate combinations. Rare and disruptive gene variants are also found in ADHD and are considered to contribute to the persistence of the disorder (Demontis et al., 2019). However, there are still many additional ADHD risk loci to discover, each contributing to the risk by a minute amount. Thus, ADHD is characterized by marked polygenicity. The gene variants implicated in the disorder partly overlap with those underlying several other psychiatric conditions (Faraone et al., 2015).

At the group level, the brain looks somewhat different in people with ADHD. For example, in a study investigating the volumes of various basal forebrain structures involving more than 3,000 participants, Hoogman et al. (2017) documented differences in the size of the hippocampus, the basal ganglia (nucleus accumbens, caudate nucleus), and especially in the amygdala. The differences relative to healthy controls were small, unlikely to be due to stimulant medication, and tending to dissipate with age (Hoogman et al., 2017). The authors described the differences in terms of a delay of maturation. Given this brain maturation delay hypothesis, it is noteworthy that a 6-year old child born in November/December is about twice as likely to be diagnosed with ADHD than a peer born in January/February (Halldner et al., 2014; see also Caye et al., 2020).

Diagnosing ADHD

Since the 1950s the American Psychiatric Association has compiled a handbook for psychiatric disorders, the Diagnostic and Statistical Manual of mental disorders (DSM). It was not until the second edition in 1968 that the ADHD-like condition of Hyperkinetic Reaction of Childhood was included (Epstein & Loren, 2013). The diagnostic criteria of ADHD according to the latest edition, DSM-5 (American Psychiatric Association, 2013), are shown in Table 1. They include symptoms of inattention and impulsivity/hyperactivity, which should be graded as mild, moderate, or severe, or even as ‘in partial remission’ if full diagnostic criteria are no longer being met (Epstein & Loren, 2013). According to recent authoritative conceptions, ADHD is a fluid state within individuals, rather than a fixed, trait-like characteristic (Epstein & Loren, 2013; Hinshaw, 2018; Kooij, 2010).

An important diagnostic criterion for ADHD is that symptoms should be present in childhood (≤ 12 years of age; Table 1). Symptoms of ADHD in adulthood are mostly assumed to have started long ago in childhood as adult ADHD is considered a continuation of a childhood-onset disorder. However, recent debate has questioned whether this really is the case: can ADHD begin in adulthood? There are findings suggesting this alternative trajectory (Agnew-Blais et al., 2016; Caye et al., 2017; Moffitt et al., 2015). According to these, late-onset ADHD patients are mostly females, have higher IQ, and fewer behavioural problems than those diagnosed in childhood (Agnew-Blais et al., 2016). Other late-diagnosed ADHD patients report some clinical ADHD symptoms at some point during childhood and may have been misclassified in childhood (Cooper et al., 2018).

By contrast, other studies of the childhoods of adults diagnosed in adulthood showed a three-fold increase in childhood ADHD symptoms compared with healthy controls. They also had more comorbid symptoms, such as autistic traits, learning difficulties, tics, and oppositional behaviour.

For example, 42% of the adult ADHD cases had a childhood psychiatric diagnosis (other than ADHD) compared with 1% of the controls (Taylor et al., 2019). Hence, the psychiatric history is highly relevant in the assessment of adult ADHD. The jury is still out pondering the question of whether ADHD truly can emerge in adulthood (Sibley et al., 2018; Taylor et al., 2019).

Another clinically interesting group is the adults with impairing sub-threshold ADHD. Even though they do not meet the full ADHD criteria, they are of clinical concern, because they often seek healthcare for various problems and functional deficits. They do not meet the criteria for the (stimulant) treatment they might need (Faraone et al., 2006; Faraone & Biederman, 2016). Kooij et al. (2019) also alert clinicians to sub-threshold ADHD symptoms in children, who will likely develop full-scale ADHD at some point. These considerations highlight the importance of careful assessment (Kooij et al., 2019; Sibley et al., 2018).

Table 1

ADHD symptoms according to DSM-5

A. ≥ 5 symptoms per category in adults, ≥ 6 symptoms per category in children	
B. Onset ≤ 12 years of age	
C. The condition is noticeable (not necessary impairing) in ≥ 2 different settings	
D. The condition has impact on occupational, academic, or social functioning	
E. The condition is not better accounted for by any other psychiatric disorder(s)	
Inattention	Hyperactivity/Impulsivity
a) Lack of attention to details, careless mistakes	a) Fidgetiness (hands/feet) or squirms in seat
b) Difficulty sustaining attention when not interested	b) Leaves his/her seat frequently
c) Does not seem to listen	c) Running around (children) or experience a, more or less, constant feeling of (inner) restlessness (adolescents/adults)
d) Does not follow-through on instructions, easily side-tracked	d) Excessively loud or noisy
e) Difficulty organising tasks and activities	e) Seems to always be 'on the go'
f) Avoid tasks demanding sustained mental effort	f) Talks excessively
g) Loses and misplaces objects often	g) Blurts out answers, bursts into conversations
h) Easily distracted	h) Difficulty waiting for his/her turn
i) Forgetful in daily life and activities	i) Repeatedly acts without thinking

Diagnostic procedure

A 6- or 7-year old child has just started first grade, but the school-start did not go as expected. The child has trouble adjusting to the new situation, to the new expectations and cannot mobilize the concentration and focus needed in class. These problems affect not only learning, but also the social relations with peers, and the family situation at home.

Before the first appointment at the child- and adolescent psychiatric outpatient clinic, the nature of the problems might be screened using a standardized instrument. For example, in the Swedish Region of Halland, the Brief Child and Family Phone Interview (BCFPI; Cunningham et al., 2009) is used to screen every parent seeking child- and adolescent psychiatric healthcare for their child. BCFPI covers broad psychiatric symptoms, overall functioning, and family factors. It has been standardized for two age groups (6–12 years and 13–17 years), separated by sex. Each question has three or four response options depending on subscale, e.g., never, sometimes, often, or always (Cuthbert et al., 2011; Gordon et al., 2006).

The first appointment at the child- and adolescent psychiatric outpatient clinic is typically held with parents and the child together. It is common that the child is described as energetic, with poor sleep, and sometimes also with an edgy temper (but also as an inspiring, lovable, and loving child). The first screening is rigorous and quite time-consuming as many areas need to be addressed, not only psychiatric conditions but also psychosocial factors and family situation. Thereafter, if an ADHD assessment is in question, the child and the parents complete several inventories measuring symptoms and everyday functioning. A common inventory is the Brown ADD Scale (BADDS), which is a 40-item self-report scale covering executive functioning. Individual items are rated on a scale from 0 to 3 (never to almost daily) and the items are clustered into five subscales. BADDS is primarily designed to measure the inattentiveness of the ADHD symptomatology.

For adults in ADHD assessment, a common self-report scale is the WHO Adult ADHD Self-report Scale (ASRS), with 18 items (or a six-item screener version) that correspond to the 18 DSM criteria of ADHD. It includes questions about both the inattentive and the hyperactive/impulsive symptoms (Kessler, Adler, Barkley et al., 2005). A difficulty when assessing adult ADHD is the lack of interviewees to report on everyday symptoms, but also for the patients to recall their childhood symptoms (for example by the Wender Utah Rating Scale; Ward, 1993).

In most clinics, the ADHD assessment includes an intelligence test to rule out intellectual disability but also to map the cognitive profile. At times, a continuous performance test is used to complement the assessment. One of the most commonly used is the Quantified behavioural Test (QbTest; Knagenhjelm & Ulberstad, 2010). Its child version takes 15 minutes, the adult version 20 minutes. The QbTest generates a standardized score for each of three ADHD core symptoms: QbActivity, QbImpulsivity, and QbInattention.

The clinician usually ranks the patient's overall functioning level. The Global Assessment of Functioning (GAF in adults, and Children's Global Assessment Scale [C-GAS] in children) ranges from 100 (extremely well-functioning) to 1 (extremely severe impairment). GAF is used to rate overall psychological functioning plus social and occupational functioning, e.g., how well the patient is handling everyday problems. In adult psychiatry another common clinician used inventory is the Clinical Global Impressions scale (CGI). It is a 3-item scale measuring symptom severity, global improvement, and/or therapeutic response.

Should the assessment end with a diagnosis of ADHD, information about the condition is given, as well as a plan for further healthcare interventions, such as patient/parental information about ADHD, medical treatment options, and/or liaison with teachers for individual arrangements in the school environment.

Clinical features of ADHD outside the diagnostic ADHD frame

The clinical presentation of ADHD is heterogeneous and often includes symptoms not mentioned in diagnostic manuals. For instance, Hirvikoski et al. (2009) report higher levels of stress in everyday life and higher post-stress cortisol levels. Asherson et al. (2016) and Kooij et al. (2019) list several typical problem areas commonly accompanying ADHD, but as of today categorized outside the diagnostic frame: sleep problems, executive dysfunction, mood-swings/emotional dysregulation, and excessive mind wandering.

Sleep problems

Disturbed sleep is reported by up to 70% of both adults (Asherson et al., 2016) and of children (Cortese et al., 2009) with ADHD. In comparison, around 25% of children in the general population has sleeping problems (van Litsenburg et al., 2010). In adults, the sleep problems are frequently accompanied by other symptoms, such as restless legs or cataplexy (Bjorvatn et al., 2017). ADHD patients are commonly described as 'night owls' or 'not a morning person'. Interestingly, Bijlenga et al. (2019) even suggest a redefinition of ADHD where circadian rhythm disturbances are seen as driving the ADHD symptoms.

Executive (dys)function

Executive dysfunction is shown in multiple psychiatric conditions and includes working memory, inhibition, sustaining and shifting attention, organizing and prioritizing, regulating alertness, sustaining effort and processing speed, regulating temper, managing frustration, and self-regulation of behaviour (Asherson et al., 2016). Whether or not executive dysfunction causes ADHD is debated, since cognitive tests mostly fail to predict ADHD symptoms and impairment (Barkley & Murphy, 2010; Kooij et al., 2010). However, in clinical practice, descriptions of executive difficulties has been shown to be related to ADHD, and being responsive to stimulant treatment (Adler et al., 2013). Some experts even consider ADHD as a primarily executive dysfunctional deficit (Kooij et al., 2010). Even if these deficits are not always captured in cognitive tests, they are often shown in how ADHD patients struggle with tasks in their daily life (Kooij et al., 2010).

Mood-swings and emotional dysregulation

Many children and adults with ADHD suffer from quick irritability and frequent mood swings, causing troubles in their daily life. If excessive in children, it is often diagnosed as oppositional defiant disorder (ODD), since it is a common comorbid mood disorder in ADHD (vide infra). Problems with emotional regulation are present in many conditions other than ADHD, such as anxiety, mood disorders, substance abuse, and personality disorders (Asherson et al., 2016; Kooij, 2010). Still, it is important to know if the mood swings are caused by the ADHD or not, and to find proper treatment interventions. According to Kooij (2010), if the mood swings are chronic, quickly changing a couple of times during the day, often reactive to something, and appearing as a low frustration tolerance, one could assume it is caused by the ADHD.

Excessive mind wandering

The human mind incessantly wanders from different topics throughout time and life, affected by inner and outer stimuli. This is a normal experience in all human beings (Smallwood & Schooler, 2015). The focus drifts away from an on-going task to intrinsically self-generated thoughts that capture the mind (Frick et al., 2019). However, mind wandering can also be detrimental to performance in demanding tasks. Unsurprisingly, ADHD is associated with excessive mind wandering (Bozhilova et al. 2018) in both adults (Franklin et al., 2017) and in children (Frick et al., 2019).

ADHD as personality

Interestingly, ADHD can be conceptualized as a characteristic, sometimes maladaptive, personality profile (Jacobsson et al., 2021). In short, the 'ADHD personality' can be described in terms of high neuroticism/emotional lability, low conscientiousness (e.g., disinhibition, rashness, irresponsibility), and low agreeableness (e.g., critical, trying to push limits, sceptical; Jacobsson et al., 2021). From this perspective, it comes as no surprise that ADHD is associated with outright dis-

orders of personality. For example, in a population-based study of 2 million Swedes, ADHD adults were 19 times likelier of being diagnosed with Borderline Personality Disorder compared with those without ADHD (Kuja-Halkola et al., 2021). Personality assessment may potentially constitute an additional tool for evaluating risk of ADHD (Jacobsson et al., 2021).

Comorbidity, overlapping psychopathology, and transdiagnostic frameworks

As alluded to several times, comorbidity is common in ADHD (Kooij, 2010; Wilens et al., 2002). One in five psychiatric patients have ADHD (Kooij, 2010). Unrecognized ADHD can contribute to the chronicity of comorbid disorders (Kooij, 2010) and psychiatric comorbidity is of clinical importance as it sometimes affects the ADHD treatment response (Instanes et al., 2016). As an example, Lundervold et al. (2016) found that a larger number of severe ADHD symptoms, was associated with a higher total score on a questionnaire measuring depression. ADHD in children is often simultaneously present with other neurodevelopmental disorders (i.e., autism spectrum disorder [ASD] or dyslexia) because of genetic overlap between the conditions (Kooij et al., 2010; van Dijk et al., 2012). Other common comorbidities in childhood ADHD are ODD (Banaschewski et al., 2010), anxiety disorders (Jarrett, 2013; Jensen et al., 2001; March et al., 2000), and depression (Jerrell et al., 2015). The combination of ADHD and ODD in childhood has been linked to worse psychosocial functioning in adulthood as well as an elevated risk of developing bipolar disorder later in life (Harpold et al., 2007).

The most common comorbid psychiatric disorders in adult ADHD are the mood disorders, such as depression, dysthymia, bipolar disorder, and/or borderline personality disorder. These are commonly misdiagnosed: they are often ADHD in disguise, according to Vannucchi et al. (2019) and Kooij et al. (2019). ADHD is also associated with substance use (Capusan et al., 2019; Chen et al., 2018) including nicotine and alcohol (Elkins et al., 2007). The association between ADHD and substance use is explained by shared genetics and surrounding environmental influences rather than as a direct cause of ADHD (Elkins et al., 2007). According to a large Swedish registry study, adults with ADHD also run a larger risk of being diagnosed with metabolic conditions, such as type 2 diabetes mellitus and hypertension (Chen et al., 2018). ADHD is associated with a 70% increased risk of obesity in adults, and a 40% increased risk for obesity in children (Cortese et al., 2016).

Asherson et al. (2016) describe three subgroups with regard to ADHD and comorbidity. First, ADHD can mimic other disorders because of symptom similarities. These patients are likely to respond well to ADHD drug treatment. In a second group ADHD co-exists with parallel neurodevelopmental disorders, such as ASD, dyslexia, or intellectual disability. These patients are less likely to respond to ordinary ADHD treatment; in fact, they often worsen. A third group develops comorbidity as a consequence of ADHD rather than as a parallel condition. For these patients it is important to identify the ADHD, since treating only the comorbid symptoms will most likely be ineffective.

Within-syndrome heterogeneity vs. across-syndrome similarity

ADHD with comorbidity is more common than straightforward, clear-cut cases, both in children (Fernell et al., 2013; Gillberg, 2010, 2014) and in adults (Andersson et al., 2020). This overlap in symptomatology challenges current diagnostic systems and paves the way for novel conceptual approaches, attempting to identify pathological processes that cut across traditional diagnostic boundaries (Posner et al., 2020). The assumption of such transdiagnostic perspectives is that

shared vulnerability processes can be targeted in order to treat a range of different clinical conditions with similar, overlapping deficits (Posner et al., 2020).

One way in which to conceptualize this new thinking is the 'discovery' of an overarching general psychopathology factor (*p*; Caspi et al., 2014; Martel et al., 2017). The proposal is that symptoms typically aggregate into specific psychiatric diagnoses; these diagnoses cluster into either internalizing or externalizing domains, which in turn aggregate into the normally distributed dimension of *p*. The higher *p*-score, the worse the person fares with respect to psychopathology severity, duration of disorder, presence of comorbidity, adult life impairment, childhood developmental history, heredity of psychiatric illnesses, and brain functioning (Caspi et al., 2014).

Another transdiagnostic approach is Gillberg's concept of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examination). It refers to multiple neurodevelopmental symptoms emerging before the age of 5, and includes symptoms later found in diagnoses such as ADHD, ODD, or ASD, causing problems for young children (Gillberg, 2010, 2014). Similar to the *p*-factor (Caspi et al., 2014), the ESSENCE concept attempts to deal with the significant overlap between syndromes that in today's psychiatric parlance often are referred to, and treated as, separate categories (Gillberg, 2010). The immoderate categorizing of neurodevelopmental problems into diagnoses can at times prevent progress in the development of effective therapeutic interventions (Sonuga-Barke, 2009).

Treatment of ADHD

There is no cure for ADHD. However, there are several treatment options available for coping with or reducing the symptoms. The treatment options range from psychosocial interventions to drugs. A multidisciplinary approach is the most effective treatment in ADHD, combining drug treatment and psychosocial treatment options (Kooij et al., 2019).

Pharmacological treatment

The American physician Charles Bradley discovered the amphetamines' positive effect on unfocused children's behaviour already in 1937. This is considered to be the first attempt to treat behaviour we today would call ADHD. However, it took decades before Bradley's work got into the spotlight again (Lange et al., 2010).

Today, the mainstay of pharmacological treatment of ADHD is stimulant drugs, such as methylphenidate (Seixas et al., 2012). Thus, many expert panels (Cortese et al., 2018; NICE Guideline, 2018; Subcommittee on Attention-Deficit/Hyperactivity Disorder, 2011) recommend stimulant treatment for children and adolescents, with an add-on of parental interventions and adjustments in the school environment, and also behavioural therapy for the adolescent. For adults as well, stimulant drugs are regarded as first-line treatments, and as part of a multimodal approach including psychoeducation (Cortese et al., 2018; Kooij et al., 2019).

Stimulants increase extracellular catecholamine levels in the brain. They do this by blocking transporters located on catecholaminergic nerve endings, which re-uptake dopamine and/or noradrenaline from the synaptic cleft (reviewed by Rubia et al., 2014). Several changes in brain activity have been recorded following stimulant exposure in ADHD patients. The most common one, however, is an increased activation of the inferior frontal cortex on the right hemisphere (Rubia et al., 2014). This is interesting because this brain area, the right inferior frontal cortex, forms part of a system subserving cognitive inhibitory control (reviewed by Aron et al., 2014). It is also part

of the ventral attention system and is therefore crucially involved in various orienting mechanisms, including selective and sustained attention (reviewed by Corbetta et al., 2008).

The dispensing of stimulants in Sweden has increased during the past few years. In 2013, as many as 43 of 1,000 boys aged 10–17 were dispensed drugs because of ADHD (the National Board of Health and Welfare, 2014; Zetterqvist et al., 2013), which represents roughly a quadrupling of the number receiving medication in 2007 (cf. Zoëga et al., 2010). Clearly, the traditional European 'low-medication culture' (Taylor, 1999), with home- and school-based psychological approaches for ADHD as first-line remedies, has declined in our country. In total, among 5–64 year-olds, 146,000 were dispensed ADHD drugs during 2020 in Sweden (the National Board of Health and Welfare, 2021).

A problem with ADHD medication is compliance: especially adolescents and adults tend towards discontinuation or frequent stop/start patterns of ADHD medication. For example, Bejerot et al. (2010) found that only 50% of adult ADHD patients remained on medication 2 years after commencement. Also, in a study of several thousands of adult ADHD patients, Chang et al. (2014) found that only half of the investigated cohort was on medical treatment.

Non-pharmacological treatment options

Although stimulants help ameliorate ADHD symptoms, some patients might still experience symptoms or significant functional deficits in their everyday life and therefore be in need of further support (Kooij et al., 2019; NICE guideline, 2018). The evidence is complex and conflicting as to whether to support or refute non-medical interventions in ADHD (Caye et al., 2019). Perhaps the heterogeneity of the disorder and the difficulty with compliance explain the ambiguities regarding outcomes following psychosocial interventions. However, non-medical treatment options are sometimes preferred because they are less controversial than drug treatment (Berger et al., 2008; Kovshoff et al., 2013; Schatz et al., 2015). ADHD treatment guidelines do recommend behavioural interventions in the treatment of ADHD, preferably as an add-on to drug treatment (NICE Guideline, 2018; Wolraich et al., 2019).

There are several non-medical interventions available, but not all of them are suitable for all patients. There are also multiple promising future non-pharmacological treatment options such as mindfulness, biofeedback, and coaching programs to help the patient handle the demands of an everyday life (Caye et al, 2019). Here I will consider the more traditional treatment options.

Interventions using behavioural techniques, such as psychoeducation, parent training, social skills training, and liaison with school staff, remain the best established, most recommended, and most commonly used forms of psychosocial treatment in child ADHD (Caye et al., 2019; NICE guideline, 2018). For the youngest children, it is offered through parental training interventions (Faraone et al., 2015), commonly in a group setting and following a schedule (Lantz et al., 2021; Stattin et al., 2015). Parent training is also a common add-on treatment to medical treatment in severe cases of child ADHD (NICE Guideline, 2018), where combined non-medical and medical interventions have proven to be the most effective (Daley et al., 2017; Sonuga-Barke et al., 2013). Other important behavioural interventions are adjustments in the classroom, for example adapting a classroom structure to optimize the learning situation for the child. Additionally, behavioural interventions involve educating teachers to understand each individual child with ADHD, not just about ADHD as a diagnosis. Even if behavioural parent training cannot be recommended as a stand-alone first line treatment in child ADHD according to a Cochrane meta-analysis (Zwi et al., 2011), it nevertheless improves parenting skills, heighten medication compliance, and can even reduce comorbid symptoms (Daley et al., 2017).

In adults, cognitive behavioural therapy (CBT; including psychoeducation and skills training) can reduce ADHD symptoms, alleviate associated emotional symptoms, and improve functional impairment across several everyday life areas (Hirvikoski et al., 2011; Philipsen et al., 2015; Young et al., 2017). Psychoeducational programs, in group settings for patients with ADHD and their next of kin, have been shown to be a practicable and an effective treatment option to increase life satisfaction in adult psychiatric outpatients (Hirvikoski et al., 2017). However, overall, the evidence regarding non-medical treatment options is deemed ambiguous and in need of large randomized studies (Caye et al., 2019).

Brief digression: Three views of ADHD

Restless, fidgety children with problems adapting to academic expectations have probably been around forever and it is just recently we diagnose the extremes as having ADHD (Hinshaw, 2018). I note, along with Hinshaw & Scheffler (2014) and many others, that this diagnosis is controversial in some quarters and has been subject to intense media attention during the past.

I identify (at least) three overarching views of ADHD. The evolutionary perspective is exemplified by Stewart-Williams' book, The Ape that Understood the Universe – how the Mind and Culture Evolve (2019). Here, ADHD is described as an example of an evolutionary mismatch between today's modern society and human nature. Children (of any primate species) are designed to run around and play, and ADHD is what happens when society forces them to sit behind a desk for hours and expect them to concentrate and learn (Stewart-Williams, 2019). Stewart-Williams (2019) argues that ADHD children would probably fit in perfectly in an ancestral-type environment.

The antipsychiatric view of ADHD is critical to the diagnosis as such (and to most of psychiatry). Proponents point to the escalating number of ADHD diagnoses around the world and that the hyperdiagnosing of hyperactivity is due to the lack of resources for children whom 'just doesn't fit the mall' (see Hinshaw, 2018). The critics also target the fact that amphetamine-like drugs constitute first-line treatment in ADHD, abetted by arguments about Big Pharma spreading misleading information (Moncrieff & Timmi, 2010; Schwarz, 2016; Hinshaw, 2018). In his book, Anatomy of an Epidemic, a noted American science writer questions the results of the largest treatment study of childhood ADHD ever conducted, The MTA Study (vide infra). He declares that it showed that medicated patients got worse and got into more troubles with delinquency, as a direct cause of stimulants (Whitaker, 2010). This is clearly not true.

The neurodevelopmental view (and in my view, the soundest, even if the other points of view do have some merits) focuses on genes, brain functioning, and gene x environment correlations. Today, the heredity in ADHD is well known, the genes implicated in ADHD partly overlapping with those of several other psychiatric conditions (Faraone et al., 2015). Whatever the exact genetic architecture of ADHD, it clearly affects brain development (Hoogman et al., 2017). As Hoogman et al. (2017) put it: '...patients with ADHD do have altered brains and therefore /.../ ADHD is a disorder of the brain' (Hoogman et al., 2017, p. 317). Their message to clinicians and parents is meant to reduce stigmatization and improve understanding of the condition.

The convincing evidence for genes as one of the primary risk factors for ADHD do not exclude the importance of environmental factors. Indeed, there are numerous environmental, potentially harmful, exposures associated with ADHD. For example, a review of the association between low socioeconomic status and ADHD reported that children of low socioeconomic conditions are

twice as likely to be diagnosed with ADHD than their more privileged peers (Russell et al., 2016). Importantly, however, environmental exposures that are associated with ADHD need not necessarily be causing it (Posner et al., 2020). For example, the home environment is created by parents and is therefore influenced by their genes. Their children share these genes. If some of these genes provide genetic risk for ADHD, then a spurious (causal) relationship between the home environment and the ADHD can emerge (Posner et al., 2020). In some ways, the home environment can be regarded as a marker for genetic risk rather than a causal environmental risk factor.

Long-term treatment effects on real-life outcomes

In the following, I review the results of extant naturalistic studies of the long-term outcome in children and in adults. Taken together, they show that ADHD treatment does help in important ways. For example, in Swedish men with ADHD, medication was associated with a 32% reduction in criminality rate (Lichtenstein et al., 2012) and a 58% risk reduction of having a serious transport accident (Chang et al., 2014). According to Arnold et al. (2015), ADHD patients in any treatment had better long-term outcomes than their non-treated counterparts. However, patients seldom attain normalization or the levels observed in healthy controls (Shaw et al., 2012).

The beneficial short-term effect of current ADHD treatment is rather well characterized by a number of studies (Döpfner et al., 2011; Wehmeier et al., 2015; MTA Cooperative Group, 1999; Storebø et al., 2015; Banaschewski et al., 2010; Kooij et al., 2019). By contrast, long-term naturalistic studies (i.e., $\geq$ 2 years) are much fewer, both in children and in adults (Shaw et al., 2012), and, in particular, studies of sufficient quality (Hodgkins et al., 2012). This situation has arisen because of compliance problems, comorbidities, and poor systems for follow-ups in healthcare clinics (Shaw et al., 2012).

According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (Statens beredning för medicinsk och social utvärdering [SBU], 2013), we lack research on ADHD treatment outcome in our country, particularly naturalistic long-term studies of real-life patients with complex symptomatology, multiple diagnoses, and psychosocial difficulties such as alcohol abuse in family, low socioeconomic status, or parental illness. Naturalistic research is needed to map the long-term pros and cons of stimulants, together with evaluations of non-medical interventions such as academic support, parental treatment programs, supportive treatment, or psychosocial interventions for parents (SBU, 2013).

Outcomes in childhood

I have identified 17 long-term studies of childhood ADHD (see Table 2). The first three derive from the oft-cited, large-scale Multimodal Treatment Study of Children with ADHD (MTA) study conducted in the US, where outcomes of three state-of-the-art treatments plus ordinary community care for ADHD were examined. It started as a 14-month RCT study. It then became naturalistic and continual follow-ups were conducted at 24- and 36-months plus at 6–8-years (Hechtman et al., 2016; Hinshaw et al., 2015; Jensen et al., 2001; Jensen et al., 2007; March et al., 2000; Molina et al., 2009; Roy et al., 2017; The MTA Cooperative Group, 1999; 2004). The 579 participants had ADHD combined type and were randomly assigned into four treatment groups: medication, behaviour therapy, their combination, or treatment-as-usual (TAU).

At 14-months, the medicated treatment groups (i.e., medication and combination group) were clearly superior to the non-medicated group and the TAUs with regard to both ADHD and ODD

(The MTA Cooperative group, 1999). In addition, the combined treatment group was superior to the non-medicated group and the TAU-group concerning internalizing symptoms, teacher-rated social skills, and parent-child relations, and reading achievement; by contrast, the group receiving medication only did not differ from the non-medicated group and the TAU-group with regard to these variables (The MTA Cooperative Group, 1999).

The difference between the two medicated groups and the non-medicated group plus the TAUs persisted at the 24-month follow-up for both ADHD- and ODD symptoms, but the effect sizes halved (The MTA Cooperative Group, 2004). Interestingly, the differences between treatment groups were completely lost at the 36-months follow-up (Jensen et al., 2007).

The authors report that medication patterns changed significantly from 14 to 36 months, as the study became naturalistic. Many patients stopped their medication while many non-medicated patients commenced. Patients with the greatest difficulties seemed to continue medication and the ones improving or with milder symptoms tended to quit or never even start (Jensen et al., 2007).

In continual follow-ups of the MTA sample into adolescence, no differences were found between the original treatment groups with regard to academic grades, arrests, or psychiatric hospitalizations. It is noteworthy, though, that the children seemed to fare worse on most of the variables studied when compared with healthy controls (Molina et al., 2009). The authors report that the initial 36 months of the ADHD trajectory explained 55% of the 6–8-year outcome. Importantly, treatment mode during the first 14 months was not a key predictor for functioning in adolescence. Rather, the best forecast was made on the basis of symptom severity, conduct problems, intellectual and social abilities, and, interestingly, ADHD symptom treatment response, regardless of treatment mode (Molina et al., 2009).

Conners et al. (2001) conducted an alternative statistical analysis of the MTA study data. This analysis showed that the differences between treatment groups at 14 months were smaller than those originally reported.

In a Dutch observational study, van Lieshout et al. (2016; 347 children, ADHD combined subtype) examined treatment outcome after 6 years, the patients being in late adolescence at the end of the study. The authors reported two interesting results. Firstly, parental ADHD, more severe ADHD symptoms and lower functioning level at referral predicted persistence of ADHD symptom at the 6-year follow-up. Secondly, functional deficits in late adolescence were predicted by young age at referral, greater ADHD symptom severity, and lower functioning level at referral. The intensity of stimulant treatment was unrelated to either ADHD symptoms or functioning level 6 years later.

In their 10- and 16-year follow-ups of boys with ADHD, Biederman et al. (2010, 2012) shed light on the continuity between paediatric and adult ADHD. They report that 65% no longer met full criteria for ADHD after 10 years. Persistent ADHD was associated with more psychiatric comorbidity, educational problems, and interpersonal problems. The boys with persistent ADHD after 10 years also reported higher levels of familial mood disorders (Biederman et al., 2010). After 16 years the boys with ADHD (now adults) were significantly more impaired than healthy controls considering neuropsychological, psychosocial, and educational functioning (Biederman et al., 2012). A clinically important finding in the 16-year follow-up was the persistence of neuropsychological deficits despite the decline in core ADHD symptoms (Biederman et al., 2012).

Associations between worse ADHD symptoms and functional deficits were also described by Haynes et al. (2015; 704 European children with ADHD). In this study, symptom worsening was associated with initial use of psychoeducation, parental occupation, and poorer educational outcomes. Patients who responded to drug treatment at baseline reported improved Quality of Life scores after 2 years (Haynes et al., 2015). Further, also in line with van Lieshout et al. (2016), Powell et al. (2011) conclude in their observational study of 410 Danish children that patients need individual monitoring and that their stimulant dose be modified periodically to obtain optimal outcome.

A UK study over 5 years by Langley et al. (2010; 126 children with ADHD) concluded that despite clinical recognition, confirmation of diagnosis, and freely available treatment, the late adolescents still experienced difficulties. Ten per cent of the sample seemed to have recovered in both symptom severity and functioning level after 5 years (Langley et al., 2010). This level of symptomatic and functioning remission is comparable to that reported by van Lieshout et al. (2016), where 13.5% of the sample were remitted or assessed as subthreshold ADHD.

The MTA-study, on the other hand, reported that 70% of the children had remitted at the 8-year follow-up (Molina et al., 2009). Likewise, Lecendreux et al. (2019) found that approximately 70% where deemed to no longer meet diagnostic criteria for ADHD as 18-year olds, 9 years after being diagnosed. In their sample of 492 French adolescents with ADHD, only 28% met full diagnostic criteria, but actually 11% of them met subthreshold ADHD criteria only (Lecendreux et al., 2019). Hence, Lecendreux et al. (2019) pinpoints the potential clinical utility of a subthreshold diagnostic category, as they support the suggestion of a dimensional conceptualization of the disorder (Lecendreux et al., 2019), where ADHD would be considered more of a spectrum, rather than a single heterogeneous endpoint diagnosis (Heidbreder, 2015).

To my knowledge, the only Swedish study on this topic was conducted by Lundh et al. (2013). They followed 1,169 children with ADHD receiving TAU during 2006–2010. Only patients who commenced and completed treatment within this time period were included, which, given the chronicity of ADHD, means either low treatment needs or discontinuation due to non-effect or problems with side-effects. Hence, the ADHD patients included might be less representative for the ADHD population as a whole. Be that as it may, Lundh et al. (2013) found that the improvement rate as a whole was quite modest, with number of appointments and case management by a physician predicting better outcome. Medication with stimulants was not associated with improvement rate. Lundh et al. (2013) hypothesized that the absence of stimulant effect on improvement was due to the fact that those patients benefitting from medication were more likely to stay in treatment and hence to be excluded from the study group (since their study group only included patients quitting treatment).

Study I and II are 1- and 5-year follow-ups, respectively, of children with ADHD in a child psychiatric outpatient clinic

Table 2

Naturalistic studies investigating long-term childhood ADHD outcomes, ordered in descending order of relevance for the empirical work presented in this thesis

Publication and origin	*n*	Study length (years)	Significantly improved or remitted (%)	Main predictors of improvement	Role of ADHD medication for improvement (0/1)	Outcome summary/comments
MTA group (2004) USA	579	2 Participation rate 93%	37% Med 48% Comb ('Excellent responders' SNAP-IV)	Continuing medication use.	1	Medical treatment showed persistent superiority over non-medical options, but not as great as 14-month follow-up.
Jensen et al. (2007) USA	579	3 Participation rate 84%	Improvement regardless of treatment group	Female sex, not being on public assistance, and no parental inattention problems.	0	The advantage of drug treatment over non-medical options seen at 14- and 24- months had dissipated.
Molina et al. (2009) USA	579	6–8 Participation rate 75–78%	Maintenance of improvement (from the 3 y follow-up) relative to baseline.	Early clinical presentation in childhood: severity of ADHD symptoms, conduct problems, intellect, sociodemographic advantages, and responding to (any) ADHD treatment.	0	Type or intensity of initial ADHD treatment in childhood (7–9.9 y) did not predict 6–8 y functional outcome. Early ADHD symptom trajectory is prognostic.
van Lieshout et al. (2016) The Netherlands	347	6	13.5%	Baseline older age, no parental ADHD, milder ADHD symptoms, and less impairment (parent-reported).	0	Stimulants had no impact on 6y outcome (symptoms and functioning). Results confirm symptom severity and family history of ADHD, as important risk factors.
Biederman et al. (1996) USA	128	4	15%	No familial ADHD, no psychosocial adversity, and no present comorbid conduct-, mood-, or anxiety disorder.	0	85% had persistent ADHD. The study prospectively confirms that a majority of children with ADHD will continue to express the disorder 4 y later.
Biederman et al. (2010) USA	110	10	22%	Low levels of psychiatric comorbidity, and absence of functional (educational and interpersonal) problems.	0	78% had persistent ADHD in some way. 65% no longer met full criteria for ADHD. 97% of persistent ADHD cases had at some point been prescribed ADHD drugs, at 10 y follow-up only 30% medicated.
Biederman et al. (2012) USA	79	16	39%	NA[1]	0	The ADHD cases were significantly more impaired than controls in neuropsychological, psychosocial, and educational functioning. Differences could not be explained by other on-going psychiatric conditions.

Table 2, continued

Haynes et al. (2015) Europe		2	NA[1]	Parental occupation, Better educational outcomes, less or no initial use of psychoeducation and initial treatment response.	NA[1]	Only pharmacotherapy treatment responders for 3- to 8- months in naturalistic settings, included.
Langley et al. (2010) UK	126	5	6%	Not having a mother with childhood CD symptoms.	0	Near 70% continued to meet full diagnostic ADHD criteria and exhibited antisocial behaviour, criminality, and drug problems, after 5 y. Higher social class and IQ were associated with fewer comorbid CD symptoms.
Lecendreux et al. (2015) France	875	4	34%	No family history of ADHD, no comorbid ODD at baseline, and milder symptoms of inattentiveness.	NA[1]	14% of children with subthreshold symptoms will convert into full diagnosis within 4 y. This might call for monitoring of children with subthreshold ADHD.
Lecendreux et al. (2019) France	492	9	72%	Milder baseline ADHD symptoms and no comorbid ODD.	NA[1]	Findings of subthreshold ADHD supporting the dimensional conceptualization of the disorder.
Lundh et al. (2013) Sweden	12,613 ADHD: 1,169	4	NA[1]	Number of appointments, case management by physician, group volume of parent counselling. Lower functioning, older age, fewer comorbid diagnoses, less psychosocial problems, at baseline	0	Only case closed included. Drug treatment was not associated with improved C-GAS. Non-medicated patients received more psychosocial interventions than medicated patients.
Schweren et al. (2019) The Netherlands	148	6	11%	NA[1]	0	Stimulant treatment is not associated with long-term course of ADHD symptoms.
Vallejo-Valdivielso et al. (2019) Spain	518	2.75	57–75% obtained positive treatment outcome	Baseline lower ADHD-RS scores, no comorbidity, fewer altered neuropsychological test scores, and higher IQ score, were associated with positive response to stimulant treatment.	1	Positive treatment outcome was defined as a 30% improvement in self-ratings (ADHD-RS), and a CGI-S rating of 1 or 2.
Charach et al. 2004 USA	79	5	NA[1]	Adherence to stimulant treatment was associated with greater improvement according to teacher-ratings.	1	Adverse side effects persisted at 5 y follow-up according to parents.

Table 2, continued

Powell et al. (2011) Denmark	410	6	NA[1]	NA[1]	NA[1]	Stimulant doses needed are dynamic over time and dependent of many individual factors. Individual factors influence outcome. Patients need individual monitoring and their stimulant dose modified continuously.
Hong et al. (2014) South Korea	300	3	NA[1]	NA[1]	NA[1]	Within the first 6 months more than 40% dropped out of treatment. 20% continued stimulant treatment ≥3 y.

[1]Not applicable

Outcomes in adulthood

In adulthood, many patients continue to be symptomatic (see Kooij et al., 2019), but sadly only a minority receives proper treatment, at least in Europe (Retz et al., 2011). I have tracked down five long-term naturalistic studies concerned with adult ADHD diagnosed in adulthood (Table 3).

Common to most of them is the problem of dropouts (Bejerot et al., 2010; Bijlenga et al., 2017; Edvinsson & Ekselius, 2018). For example Bejerot et al. (2010) found, in a Swedish sample of 133 ADHD patients, that 50% dropped out of drug treatment during a period of 2 years. The reasons for dropping out were lack of efficacy (15%), problems with adverse effects of medication (8%), suffering from anxiety or depression (17%). Around 40% did not specify any clear reason. Another Swedish example is the 6-year follow-up of 124 ADHD patients in which 50% had quit drug treatment at follow-up (Edvinsson & Ekselius, 2018).

In the Netherlands, Bijlenga et al. (2017) obtained similar results as Bejerot et al. (2010). In their sample of 96 ADHD patients, only about half of the medicating patients remained in medical treatment after 3 years. Non-adherence to drug treatment was associated with worse overall functioning, lower mood, and poorer sleep (Bijlenga et al., 2017).

Patients staying in treatment tend to fare better than the dropouts (Bejerot et al., 2010; Bijlenga et al., 2017; Edvinsson & Ekselius, 2018; Lensing et al., 2013; Torgersen et al., 2012). For example, Torgersen et al. (2012) found that stimulant treatment predicted longer treatment duration in a sample of 117 highly impaired and highly comorbid, Norwegian adults with ADHD, as they had a median duration of as long as 33 months at follow-up after 3 years. In a similar way, Lensing et al. (2013) found, in a sample of 368 Norwegian ADHD patients followed-up after 4 years, that medical treatment lasting longer than 2 years was associated with better functioning than medical treatment for 2 years or less. In contrast to this, Bijlenga et al. (2017) found associations between worse overall functioning and poorer adherence to treatment in their 3 years follow-up.

Study III is a 5-year follow-up of adult patients diagnosed with ADHD in adulthood at a Swedish specialized ADHD clinic

Table 3

Naturalistic studies investigating long-term adulthood ADHD outcomes (diagnosed in adulthood), in descending order of relevance for the empirical work presented in this thesis

Publication	*n*	Study length (years)	Improved (%)	Treatment Dropouts (%)	Main predictors of improvement	Role of ADHD medication for improvement (0/1)	Outcome summary /comments
Bejerot et al. (2010) Sweden	133	2	50%	50%	Experienced treatment effect on core ADHD symptoms, and adherence to treatment.	1	50% remained in treatment after 2y. 15% dropped out due to lack of efficacy. Clinical response at 6/9 months predicted 2y treatment adherence.
Bijlenga et al. (2017) The Netherlands	96	3	NA[1]	33%	Baseline self-reported functioning, mood, and better sleep quality at 6 months was associated with adherence at follow-up.	1	78% medicated, about half of them medicated after 3y. Adherence was good for patients staying in drug treatment. Comb. ADHD type was associated with non-adherence.
Edvinsson & Ekselius (2018) Sweden	124	6	33%	50%	No significant predictors found.	0	Medication did not lead to remission. On-going medication was associated with higher self-reported functional improvement.
Lensing et al. (2013) Norway	371	4.5	21.5%	37%	Medical treatment for longer than 2y. No comorbidity.	1	Most patients remained in treatment after 4y. Current treatment was associated with better overall functioning.
Torgersen et al. (2012) Norway	117	3	NA[1]	NA[1]	Longer stimulant treatment duration.	1	It is possible to treat severely impaired and highly comorbid adults with ADHD with stimulants over several years.

[1]Not applicable

Research on ADHD outcomes

Having reviewed the basic knowns and unknowns about ADHD, I now consider issues pertaining more closely to the empirical work presented in this thesis. More specifically, I address subjective and objective tests, the role of informants, and of appropriate statistics when researching ADHD outcomes.

Ecological validity of neuropsychological tests

Historically, neuropsychological tests were developed for detecting and localizing brain damage, mostly shot-wounded soldiers. Today the very same tests are used to assess cognitive ability (Chaytor & Schmitter-Edgecombe, 2003). Their ecological validity in psychiatric clinical prac-

tice can be questioned: what is being measured and how do test scores correspond to reality (Spooner & Pachana, 2006)? With regard to ADHD, neuropsychological testing is mostly made to determine overall mental ability or identify individual coping strategies that can be beneficial in the treatment process (Kooij, 2010). No single neuropsychological test can determine whether an individual meets DSM criteria for ADHD (Kooij, 2010).

There is, however, a commercially available continuous performance test, the QbTest (described in detail in Study IV in present thesis), that has been especially developed to aid in the detection and assessment of ADHD (Knagenhjelm & Ulberstad, 2010). Its sensitivity and specificity ranges between 86% and 90% in both children and adults (Edebol et al., 2012, 2013b; Ulberstad 2012a, 2012b). The QbTest is often used in Swedish psychiatric healthcare and can identify a fair share of adults with ADHD (Hirsch & Christiansen, 2017; Hollis et al., 2018; Hult et al., 2018; Söderström et al., 2014). However, problems with sensitivity and specificity also have been reported (Brunkhorst-Kanaan et al., 2020; Johansson et al., 2018). For example, the sensitivity for confirming ADHD diagnosis has ranged between 47–67% (Hult et al., 2018) and 90% (Groom et al., 2016), with a specificity of 72–84% in children (Hult et al., 2018), and 70% in older adults (Bijlenga et al., 2019). The accuracy of the ADHD diagnosis increased when combining QbTest with self-reports (Bijlenga et al., 2019; Emser et al., 2018), signalling a clinical importance of combining objective and subjective measures in the assessment of ADHD.

Study IV investigates QbTest+ performance in adults with ADHD

The informant

The informant plays a decisive role in the assessment of ADHD, but different informants tend to disagree as to the nature or intensity of the problems (De los Reyes et al., 2015). The overall correlation between different informants (parents, teachers etc.) of children's externalizing problems is a mere $r = 0.30$ (De los Reyes et al., 2015). For example, the choice of parent informant (i.e., mother or father) had a profound impact on the parent-teacher concordance, as fathers rated their child to have fewer problems than did mothers or teachers (Sollie et al., 2013). Swanson et al. (2017) reported that parents tended to rate their adolescent children's ADHD symptoms higher than the children themselves; healthy children's parents were more accurate. One explanation is that many mental health concerns are context-dependent to a significant degree (De los Reyes et al., 2015). With respect to ADHD, the classroom context may be more revealing than the home environment. Ullebø et al. (2012) found that teachers reported high scores of hyperactivity/impulsivity more frequently in boys than in girls, according to the parents, the sex difference was less marked. By contrast, Bied et al. (2017) reported that parent- and teacher ratings were indistinguishable from each other: they both yielded moderate to good diagnostic accuracy. There is currently no empirically based consensus on how to integrate parent- and teacher ratings in the diagnosing of ADHD (Martel et al., 2015).

Concerning parental reports of child ADHD, studies fail to find biases according to presence/absence of parental ADHD (Faraone et al., 2003). However, parenting stress has been associated with disagreements between parent and teacher (van der Oord et al., 2006). Low socioeconomic status was associated with higher levels of ADHD in ratings by both parents and teachers (Lawson et al., 2017).

Inventories

For clinical screening and triaging, the BCFPI is a useful structured interview for parents requesting child- and adolescent psychiatric outpatient healthcare for their children (Cunningham et al., 2009). As described earlier, it covers many psychiatric symptoms, overall functioning, and family factors, and it has been standardized for two age groups (6–12/13–17 years of age) separated by sex. Each subscale concerning psychiatric symptoms are linked to the corresponding DSM category (Boyle et al., 2009). Eight subscales were included in present work: ADHD, ODD, Separation Anxiety, GAD, Depression, Child Functioning, Family situation, and Informant mood. The family factor subscales can facilitate service planning as it gives a picture of the situation surrounding the child. However, each subscale contains six to eight questions, and each question has three to four response options. The responses for each subscale are expressed as T-scores, which were used in Study I and Study II. A T-score ≥ 70 is above the 98th percentile (worse than 98% of the normal population; two standard deviations above mean) and indicate significant difficulties. A T-score ≥ 65 is above approximately the 93rd percentile, and is considered clinically significant and in need of further examination. In Study I and Study II, the threshold of 65 was chosen, in line with other studies (e.g., Gordon et al., 2006).

Boyle et al. (2009) found that the ability of BCFPI to classify childhood psychiatric disorders approximated that provided by the Diagnostic Interview Schedule for Children version IV. The item structure of the subscales was supported by confirmatory factor analysis (Cunningham et al., 2009) and the test-retest reliability for the BCFPI classifications varied between .45 and .62 (Boyle et al., 2009). Boyle et al. (2009) found a general trend suggesting better performance for externalizing symptoms (e.g., ODD; ADHD) than for the internalizing symptoms (e.g., GAD).

A commonly used self-report for adolescents and adults is the BADDS, a 40-item self-report scale covering everyday situations involving executive functioning and attentive ability. It is primarily designed to measure the inattentiveness aspect of ADHD. Individual items are rated on a scale from 0 (never) to 3 (almost daily). Thereafter the items are clustered into five subscales and a total score. The total score can range from 0 to 120, and a clinical threshold of 50 indicates 'probable ADHD' (Brown et al., 2011). In Study III and IV the adult version of BADDS was used.

Another common self-report scale for adults is the ASRS. It is an 18-item self-report scale corresponding to the 18 DSM ADHD criteria (covering both the inattentive and the hyperactive/impulsive symptomatology). Responses are given on a five point Likert scale from 1 to 5 (never to always). Clinical thresholds of 'highly likely ADHD' is 24; of 'likely ADHD' is 17–23, and scoring 0–16 indicates 'unlikely ADHD', as proposed by Yeh et al. (2008). However, there is a short-version of the ASRS; a six-item screener of ASRS that has shown to outperform the full 18-item checklist in sensitivity, specificity and total classification accuracy (Kessler, Adler, Ames et al., 2005). Overall ASRS has shown good reliability and validity for evaluation of ADHD in adults (Adler et al., 2006).

Statistics

In the empirical work presented here, patients are monitored by the use of scales (and their subscales), interviews, and background variables (medication, comorbidity, age, sex, and so on). This generates massive data sets where the number of variables may approach the number of participants. Moreover, some variables, such as the subscales of an inventory, may correlate with one another. Classical statistical methods are ill suited to handle datasets of this kind (see Cumming, 2014; Eriksson et al., 2013). We have made use of multivariate statistics as implemented

by the SIMCA software (Eriksson et al., 2013) in an attempt to address this challenge. It copes with square, short-and-wide, or long-and-lean datasets, handle multicollinearity well, and make regularities in the dataset apparent in one single statistical decision, hence avoiding the problem of multiple comparisons. For instance, when we model follow-up outcomes on the basis of variables collected at baseline, then the multivariate SIMCA regression procedure identifies the part of the systematic variation in the baseline variables that specifically relates to the follow-up results. It transforms data into information by identifying hidden latent variables that drive multiple, loosely related, individual observations into certain patterns.

SUMMARY OF STUDIES

The overall aim of the four naturalistic studies of this thesis was to investigate the long-term outcome in ADHD patients in both childhood and in adulthood. In the first two studies, the patients came from the child- and adolescent psychiatric outpatient clinics of the Swedish Region of Halland. The first study investigated the 1-year outcome of children diagnosed with ADHD. One of the main aims was to compare drug treatment to ordinary counselling appointments with respect to their effectiveness in reducing ADHD symptoms and improving everyday functioning. A second aim was to identify predictive factors at intake for these 1-year outcomes. The second study investigated the 5-year treatment outcome of children from the original study (Study I). Like the first, we compared drug treatment with counselling with regard to symptom reduction and functioning level improvement. Besides identifying baseline predictors of change, we also looked at temporal patterns by comparing the three measurement points (i.e., referral, the 1-year follow-up, and the 5-year follow-up).

The ensuing studies concerned ADHD diagnosed in adulthood. The patients were recruited from the St. Göran Project carried out within the Northern Stockholm Mental Health Service (see Sparding et al., 2015). The third study evaluated the 5-year outcome in a group of adult patients diagnosed in adulthood and receiving routine psychiatric health care. The evaluation was made through self-reports (BADDS and ASRS) and clinicians' ratings (GAF and CGI-S). The fourth and final study evaluated QbTest+ performance in adult ADHD patients with on-going drug treatment. We also compared QbTest+ performance at baseline with a second test approximately 4 years later.

Study I

Aims

In Study I we investigated the 1-year treatment outcome of 253 consecutive children with ADHD. The aim was to compare drug treatment to sporadic counselling with respect to their effectiveness in reducing ADHD symptoms and improving the child's overall functioning level. We also wished to identify factors predicting these 1-year outcomes.

Methods

Study I used data from a child- and adolescent psychiatric outpatient clinic in the Region of Halland derived through BCFPI telephone interviews with parents of children diagnosed with ADHD within their first treatment year. Patients were selected on the basis of an ADHD diagnosis in the medical records, not because of their result on the ADHD subscale in the telephone interview.

The child- and adolescent psychiatric outpatient clinic in Halland has implemented a procedure in which information is systematically collected at referral and at a 1-year follow-up, making evaluations like the one in Study I possible. A regional central intake unit triages patients to the appropriate healthcare level by conducting a BCFPI with a parent. Using this database, the present

study assesses parental reports of their children's symptoms and behaviour at baseline and one year later. The diagnostic procedure was not always structured, and comorbid conditions were not consistently assigned a diagnostic code in the medical record.

The medicated patients were treated according to medical guidelines; some were also medicated for disorders other than ADHD. In present study, medication was registered as present or absent at the BCFPI follow-up; by this procedure 185 (73%) were medicated at follow-up, 68 (27%) received counselling only. The medicated patients also received counselling interventions. Patients assigned to counselling were offered parental support individually or in group settings, plus information to teachers. Since all information (apart from BCFPI interview data) is collected from medical records, the children were coded as medicated if on drug treatment at the time of the 1-year follow-up.

Measurements

The Brief Child and Family Phone Interview (BCFPI) is a structured, clinical intake and outcomes telephone interview with parents of children requesting child- and adolescent psychiatric healthcare (Cunningham et al., 2009). It covers broad psychiatric symptoms, overall functioning, and family factors. It has been standardized for two age groups, 6–12 years and 13–17 years, separately for each sex. The results of the structured questions of BCFPI are expressed as T-scores. Each question has 3 or 4 response options depending on subscale, e.g., never, sometimes, often, (and always). BCFPI have been used for evaluation in earlier studies of ADHD (Cuthbert et al., 2011; Gordon et al., 2006). In the present study the following subscales were used: ADHD: 12 questions; ODD: 6 questions; Separation Anxiety: 6 questions; GAD: 6 questions; Depression: 6 questions; Child Functioning: 8 questions about the child's functioning level; Family Situation: 7 questions on the impact of the child's behaviour on family functioning in daily life, and Informant Mood: 6 questions about parental depressive symptoms.

Statistics

Results are expressed as means and 95% confidence intervals, unless noted otherwise. Two-way ANOVAs (SPSS Statistics for Mac, Version 22.0) investigated group differences at intake, with statistical significance being adjusted family-wise according to the sequential Bonferroni-Holm method (see Cramer et al., 2016). Treatment effects were evaluated by *t*-tests; statistical significance was adjusted according to the sequential Bonferroni-Holm method to avoid Type I errors. Effect sizes are expressed as η^2 and are regarded as small if η^2 is 0.01–0.06, medium at 0.06–0.14, and large when > 0.14, according to Cohen's (1988) rules of thumb.

Multivariate partial least squares analyses of BCFPI intake data were performed by using the SIMCA-P 13.0 software (Umetrics; Eriksson et al., 2013). Special use was made of the Orthogonal Partial Least Squares (OPLS) regression method. It splits the systematic variation in the independent variables (i.e., intake BCFPI in the present case) into two parts, one being predictive of the dependent variable (e.g., BCFPI follow-up ADHD scores) and one being uncorrelated (orthogonal) to it. This filters away irrelevant information in the predictor data set and maximizes the explained covariance between predictors and follow-up scores. Statistical significance of a component was assessed by cross-validation. The relationship between the dependent and the relevant predictive independent variables, now in the shape of a novel latent variable, is represented by the scaled and centered regression coefficients, together with the variable influence on projection (VIP) parameter. The VIPs summarizes the importance of the various independent variables in forming the novel latent variable (Eriksson et al., 2013). VIPs ≥ 1 are considered

very significant for the model (Eriksson et al., 2013) and this criterion is consequently used in Study I for interpreting the OPLS results.

Main findings

In Study I, overall outcomes, regardless of treatment mode, clearly indicated reduced symptom severity on most relevant subscales at the 1-year follow-up (Figure 1). According to the effect sizes, the treatment effects were largest with regard to the ADHD-, ODD-, and Child functioning subscales.

When analysing the two treatment modes separately, differences as well as similarities were apparent. The medicated patients improved between referral and 1-year follow-up on subscales of ADHD, ODD, GAD, Depression, Child functioning, and Family situation; the counselled patients, by contrast, improved on subscales ODD and Depression only. When we compared the two treatment groups directly we found differences only with regard to subscales ADHD (large effect size) and Child functioning (medium effect size).

Potential confounders obscured interpretation: first, the medicated group was on average diagnosed more rapidly and hence received longer treatment. Second, medicated children had more appointments and their parents attended the proffered ADHD programs to a greater extent. This means that one cannot safely attribute the improvement to the ADHD medicine alone. Important predictors for improvement of parent-rated ADHD symptoms and overall functioning included male sex, on-going medication, previous symptom severity, and overall functioning level.

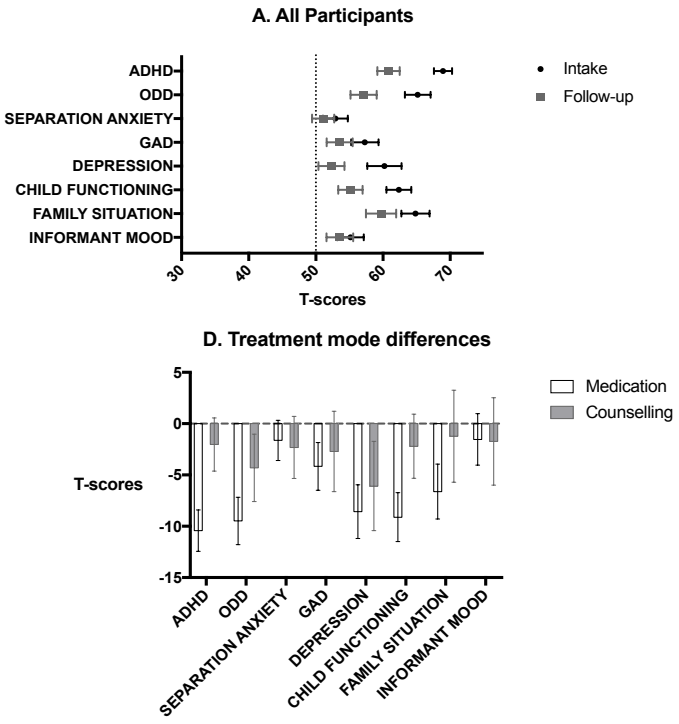

Figure 1. 1-year improvement in BCFPI subscales scores for patients receiving ADHD medication or counselling. The results are represented as means and 95% confidence intervals.

In post hoc exploratory analyses, we compared comorbid symptoms following 'successful' (defined as a decrease by ≥ 10 T-scores on the ADHD subscale between intake and follow-up) or 'unsuccessful' (i.e., decrease by < 10 T-scores on the ADHD subscale) treatment for ADHD. We restricted the analyses to those whose ODD-, Depression-, or GAD scores were severe (≥ 65). Figure 2 shows that, compared with those children responding less well, 'successful' ADHD treatment appeared associated with non-trivial reductions in ODD-, Depression-, and GAD symptoms.

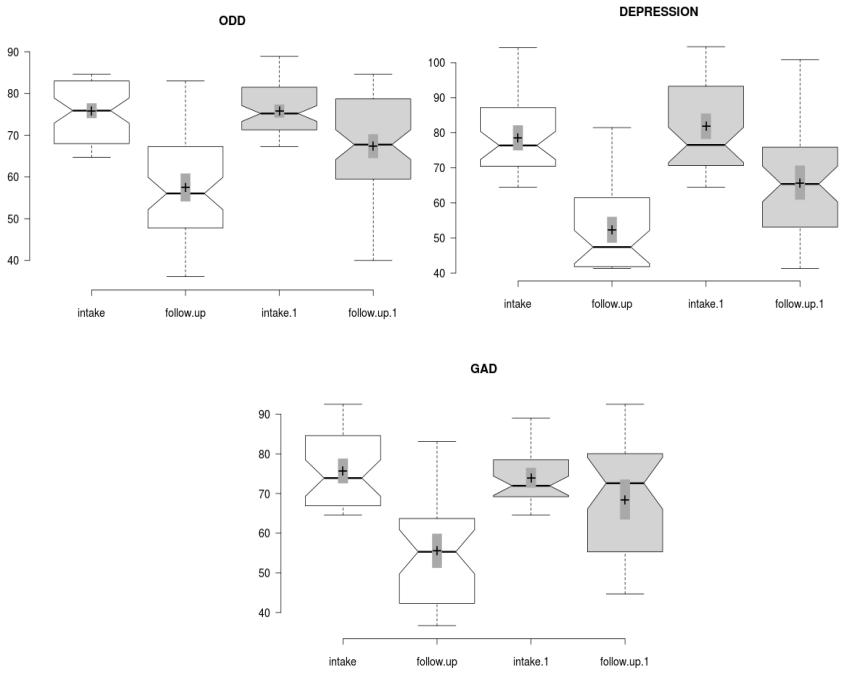

Figure 2. BCFPI T-scores of ODD-, Depression-, and GAD symptoms in ADHD patients responding well (a decrease of ≥ 10 between follow-up scores and intake scores; white boxplots) or poorly (< 10 points; light grey boxplots) to ADHD treatment, and who scored ≥ 65 on the relevant scale. Centrelines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles. Non-overlapping notches give roughly 95% confidence that the two medians differ. Pluses and darkly shaded rectangles show means and 95% confidence intervals, respectively.

Study II

Aims

In Study II we present the 5-year treatment outcome of 137 of the 253 children with ADHD from Study I (and referred to child- and adolescent psychiatric outpatient clinic treatment before 13 years of age). We again compared medication with counselling with regard to their ability to reduce ADHD symptoms and improve overall functioning. A second aim was to map out temporal

patterns by comparing the three measurement points (i.e., referral, 1-year outcome, and 5-year outcome). A third aim was to identify factors predicting 5-year outcomes.

Methods

Study II assessed parents' BCFPI reports of their children's symptoms and behaviour at three time points: at referral, at 1 year after referral, and at 5 years after referral. During the first year the children had received a diagnosis of ADHD and were given treatment, i.e., medication or counselling (see Study I). At the 5-year follow-up, parents were interviewed again, regardless of whether their children currently received treatment or not.

Eligible for the present study were those patients included in Study I who had not yet turned 18 at the time of the 5-year BCFPI interview. Out of these 168, 137 participated in the present study. One hundred of these patients were medicated at the 1-year follow-up and of these, 80 patients were still medicated at the 5-year follow-up.

Measurements

A third BCFPI (described in connection with Study I) was administered 5 years after referral.

Statistics

Treatment effects were assessed by 2-way mixed ANOVAs, followed by simple effects for group differences, using Wilk's λ algorithm (SPSS Statistics for Mac, Version 22.0). Effect sizes are expressed as η^2 and are regarded as small if η^2 is 0.01–0.06, medium at 0.06–0.14, and large when > 0.14, according to Cohen's (1988) rules of thumb.

The OPLS regression procedure described in connection with Study I was used to identify significant predictors (Eriksson et al., 2013).

Main findings

In Study II, overall, the children with ADHD were symptomatically and functionally improved after 5 years. The percentage of patients scoring ≥ 65 was reduced by about 25 percentage points with regard to the ADHD-, ODD-, and the Family situation subscales (Table 4). Around 40% of the sample showed marked improvements (i.e., by ≥ 10 T-scores) on the subscales for ADHD, ODD, Depression, Child Functioning, and Family situation.

No significant differences were found between treatment groups on any BCFPI subscale, including the ADHD- and the Child functioning subscales. Thus, the superiority of medication apparent at the 1-year follow-up had dissipated at 5-year follow-up.

Regardless of treatment mode, there were significant improvements between referral and the 5-year follow-up with respect to the subscales of ADHD, ODD, Depression, Child Functioning, and Family situation, most of them with large effect sizes. There was no reliable significant main effect for treatment mode, implying that the patients receiving medication or counselling improved at an equal rate. The drop-line plots in Figure 3 show values on the BCFPI subscales for ADHD and Child Functioning, respectively, before treatment and at the 5-year follow-up for each participant, grouped according to treatment mode.

Important predictors for the 5-year treatment outcome of parent-rated ADHD symptoms and overall functioning level were baseline ADHD- and ODD symptom severity, baseline overall functioning level, and the extent to which the child's symptoms affected the family's situation.

Table 4

Percentage of patients reporting symptoms at clinical levels (T-scores ≥ 65) at referral and at 5-year follow-up (FU), plus changes in T-scores by ≥ 10 scores from referral to 5-year follow-up

	% ≥ 65 T-SCORE			% ≥ 10 T-SCORE IMPROVEMENT
	Referral	5-year FU	Referral-5 year FU	Referral-5 year FU
ADHD	70.1	43.0	27.1	42.3
ODD	59.1	35.0	24.1	43.1
Separation Anxiety	16.1	16.1	0.0	17.5
GAD	19.7	20.6	0.9	25.0
Depression	32.1	18.2	13.9	37.2
Child Functioning	38.0	19.0	19.0	43.8
Family situation	51.1	24.8	26.3	44.3
Informant Mood	15.8	14.8	1.0	18.3

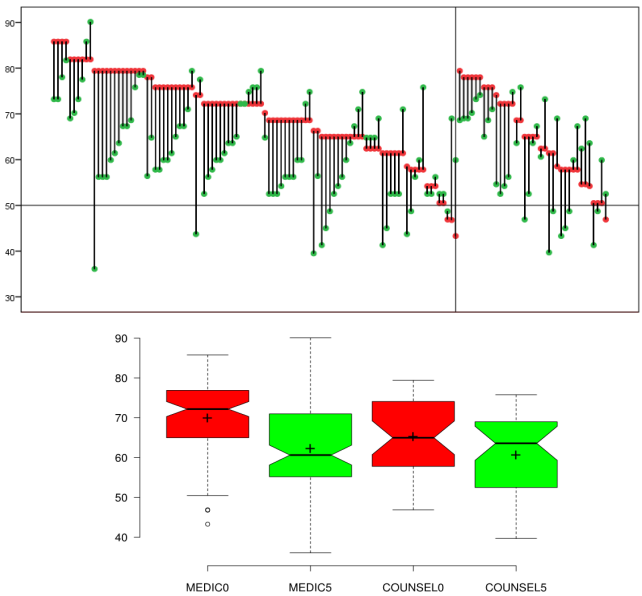

Figure 3. Upper panel: drop-line plot showing individual values on the BCFPI subscale for ADHD before treatment (red dots) and at the 5-year follow-up (green dots). Patients receiving medication are to the left of the vertical line; those receiving counselling are to the right. Lower panel: box plots summarizing the data shown in the left panel. Red boxes: before treatment; green boxes: 5-year follow-up. Centrelines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; outliers are represented by dots; crosses represent sample means.

Study III

Aims

In Study III, we followed 52 adults diagnosed with ADHD in adulthood over 5 years, and contrasted with 73 healthy controls. All patients received routine psychiatric health care. We compared self-report symptom ratings and clinicians' ratings of symptom severity at baseline and at the 5-year follow-up. Employing multivariate regression methods, we attempted to identify outcome (defined as symptom severity and real-life functioning) predictors using rating scores at baseline along with measures of medication intensity, psychiatric comorbidity, cognitive ability, age, and sex.

Methods

Adults diagnosed with any type of ADHD and healthy controls were assessed at baseline and at the 5-year follow-up, using GAF, CGI-S, BADDS, and ASRS.

Measurements

Global Assessment of Functioning (GAF) ranges from 100 (extremely well functioning) to 1 (extremely severe impairment). GAF is used to rate overall psychological functioning plus social and occupational functioning, e.g., how well the patient is handling everyday problems, during the preceding month. The GAF was included as axis V in DSM-IV and has been widely used in routine clinical settings around the world (Monrad-Aas, 2010; Piersma & Boes, 1997; Söderberg et al., 2005).

Clinical Global Impressions scale- Severity (CGI-S) is a 3-item scale measuring symptom severity, global improvement, and therapeutic response. In the present study, the symptom severity item was included, which summarizes the clinician's global impression of symptom severity. The CGI-S is rated on a 7-point scale, from 1 to 7 ('not ill at' all 'to extremely ill') at the time of examination. Psychometric evaluations have reported good internal consistency and concurrent validity (Leon et al., 1993), although some problems with validity or test-retest reliability also have been noted (Beneke & Rasmus, 1992).

Brown ADD Scale (BADDS; Rucklidge & Tannock, 2002) is a 40-item self-report scale assessing executive functioning. Individual items are rated on a scale from 0 to 3 (never to almost daily). The items are clustered into five subscales. BADDS is primarily designed to measure the inattentiveness of the ADHD symptomatology. Total score can range from 0 to 120, and the clinical cut-off score of 50 indicates 'probable ADHD'.

The WHO Adult ADHD Self-Report Scale (ASRS) measures ADHD in adults and has 18 items, which correspond to the 18 DSM criteria of ADHD, and includes questions about both the inattentive and the hyperactive/impulsive symptoms. The responses are given in a five-point Likert scale from 1 (never) to 5 (always). The ASRS has shown good reliability and validity for evaluation of ADHD in adults (Adler et al., 2006). According to Yeh et al. (2008), a score of ≥ 24 (for either inattention or hyperactivity/impulsivity) indicates 'highly likely ADHD'; 17–23 points indicate 'likely ADHD', and 0–16 indicate 'unlikely ADHD' for the full version (ASRS-18).

Statistics

Descriptive statistics are presented as means/medians and 95% confidence intervals/interquartile ranges, unless noted otherwise. Treatment effects were evaluated using paired *t*-tests (SPSS Statistics for Mac, Version 22.0); statistical significance for BADDS total and its five subscales was adjusted according the sequential Bonferroni-Holm method to avoid Type I errors (see Holm, 1979).

The OPLS regression procedure described in connection with Study I was used to identify significant predictors (Eriksson et al., 2013).

Main findings

As Study III was a routine clinical practice observational study, we had no control over medication type, discontinuation, doses, or visits over the course of 5 years. However, according to the medical records, 44 (84.6%) of the patients had medicated with central stimulants during at least one prescription period. Thirty-four (65.4%) patients were on medication at both baseline and at follow-up. Although we recognize that this does not necessarily imply continuous medication, we nevertheless assumed that this group were on ADHD medication more regularly than the rest of the patients. They therefore formed the 'medicated' group in the statistical analyses. However, for 22 patients in this group of 34, the exact number of months being on medication was available: the median was 48 months but with considerable variability (interquartile range: 26 months). There were no apparent relationships between the length of medical treatment and outcomes according to the GAF and BADDS within the group of 22 patients for which the exact number of being on medication was known: *r*'s -0.19 and 0.15, respectively.

After 5 years, the ADHD patients had reduced symptoms compared with baseline, even though they still had clinically relevant levels of symptoms and remained functionally deficient (Figure 4). Thus, the symptom burden decreased over the course of 5 years according to both self-reports and clinicians' judgements.

ADHD symptom rating scales (ASRS and BADDS) predicted their own 5-year outcome, such that high baseline scores predicted worse outcome 5 years later. Lower (worse) clinician-rated functioning score (GAF) was associated with a larger improvement at follow-up. Retrospective WURS childhood ADHD ratings, comorbidity, pharmacological treatment, IQ, and sex had no bearing on the outcomes 5 years later.

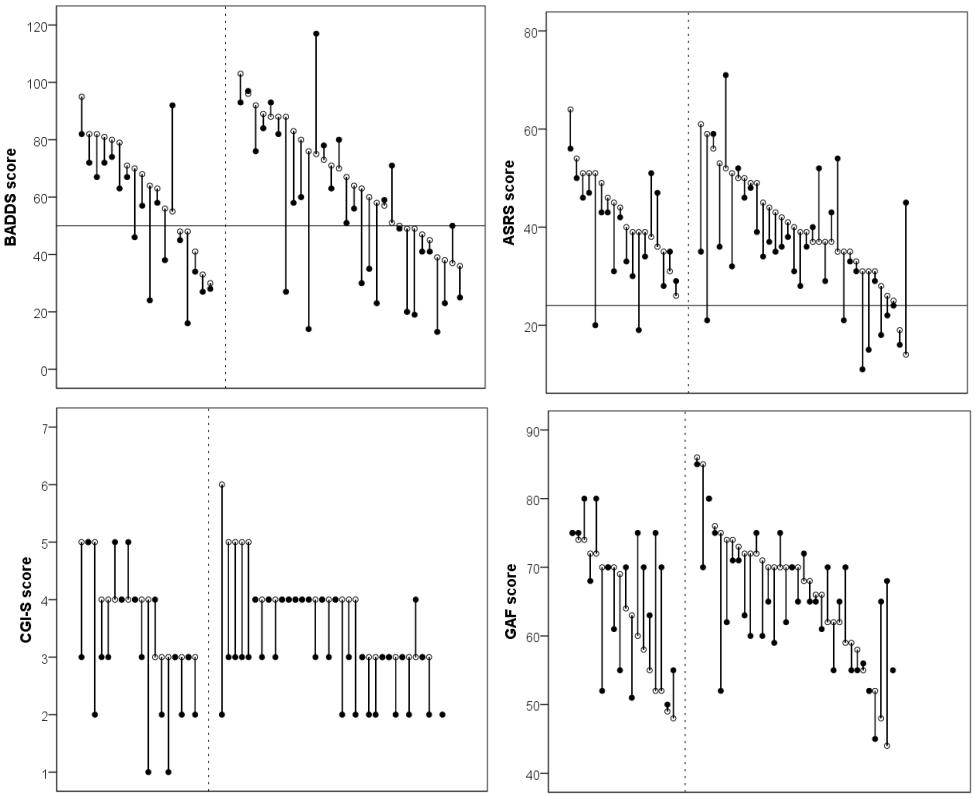

Figure 4. Drop-line plots showing individual scores on BADDS, ASRS, CGI-S, and GAF at baseline (open circles) and at the 5-year follow-up (filled circles) in adult patients with ADHD. The horizontal lines denote clinical cut-offs. Participants to the right of the vertical dotted line are patients receiving ADHD medication at both baseline and follow-up; those to the left represent the rest.

Study IV

Aims

Study IV mapped QbTest+ performance in a group of adult patients diagnosed with ADHD (the diagnostic process itself did not involve the QbTest+). We also explored whether QbTest+ performance at baseline correlated with concurrent subjective symptom ratings and/or clinicians' reports and at a follow-up 4 years later.

Methods

The sample consisted of 67 patients with on-going ADHD drug treatment. Thirteen (19%) missed taking their ADHD medication on the day of testing. The remaining 54 patients took their medication as prescribed. Forty-one patients completed a second QbTest+ approximately 4 years later. At this time point, 12 patients missed their medicine prior to the test, whereas the rest (n = 29) medicated as usual. Between baseline and the 4-year follow-up, 26 dropouts were registered. No statistical differences (BADDS, ASRS, GAF, CGI-S) were found when comparing the dropouts to the 41 patients followed-up after 4 years.

Measurements

The QbTest+ is a 20-minute computerized continuous performance test measuring activity level, impulsivity, and inattention. Instructions on how to take the test is given verbally and thereafter by the means of a standardized film (QbTech AB) presenting the procedure of the test. The patient then performs a one-minute pre-test to make sure the instructions are understood. The test takes place in a room with minimal visual and auditory stimuli. The test instructor is present in the room but in such discrete way that it does not affect the test-taker during the test. During testing, the patient sits in front of a computer screen and is presented with 600 stimuli (25% of which are randomly distributed targets), one-by-one at a pace of two seconds per presentation. There are four different kinds of stimuli, differentiated by colour and form. The test-taker is instructed to press a hand-held clicker when two consecutive stimuli are identical by colour and form. Other stimulus sequences are non-targets (no clicker-press).

The QbTest+ generates a composite score for each of three ADHD core symptoms. The first, QbActivity, is recorded by a motion-tracking system and provides a weighted index of movements during the test, in terms of total distance, vividness and change of position. The second, QbImpulsivity, is a weighted index of various commission errors (responses to non-targets). QbInattention, finally, is a weighted composite of reaction time averages and variability, plus omission errors (non-responses to targets). The scores are expressed as *z*-scores (called Q-scores by the test developers). A Q-score ≥ 1.25 on at least one of the parameters indicates that the participant may have ADHD (Knagenhjelm & Ulberstad, 2010).

Descriptions of ASRS, BADDS, GAF, and CGI-S are found in connection with Study III.

Statistics

Results are presented as medians and interquartile ranges. Non-parametric statistical tests (SPSS Statistics for Mac, Version 22.0) were chosen because of their robustness to violations of normality and because of their usefulness in psychiatric studies (see Urbano Blackford, 2017). Within-groups differences were assessed using the Wilcoxon matched-pairs signed-ranks test. The Median test was used to test between-groups differences. Associations between variables were computed as Spearman correlations.

Main findings

In Study IV, among the patients who medicated as usual on the day of testing, 65% scored above the clinical cut-off on at least one of the QbTest+ cardinals. Out of the 13 patients who forgot to take their ADHD medication prior to the test, 85% scored above the clinical cut-off on at least one of the QbTest-variables. Figure 5 illustrates the considerable individual variation in QbTest+ performance. Table 5 shows the concurrent correlations between the QbTest+ cardinals and symptom self-ratings. Significant associations were observed between QbActivity and ASRS scores, and between QbInattention and BADDS scores, both being in the $r = .3$ range.

At the 4-year follow-up, QbTest+ performance was improved and fewer patients scored in the clinical range (34%). The scores on the QbInattention cardinal at baseline correlated positively and significantly with BADDS- ($r = .49$) and ASRS self-ratings ($r = .52$) at the 4-year follow-up, as did QbActivity and ASRS scores ($r = .40$; Table 5). These associations should be affirmed by independent studies before being fully accepted. If confirmed, QbTest+ scores might be used along with other measures to predict the likely long-term prognosis of the disorder.

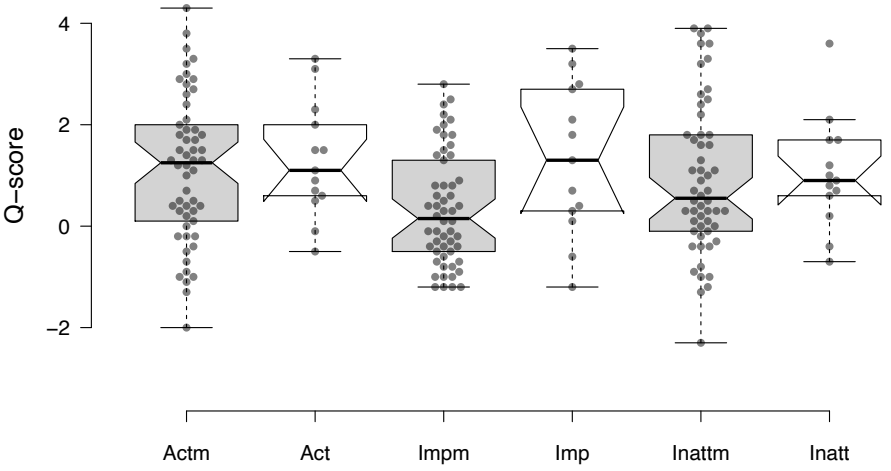

Figure 5. Box plots representing QbTest+ performance in 67 patients diagnosed with ADHD. Some (n = 13) suspended taking their ADHD medicine on the day of testing (white boxes) and the others (n = 54) had medicated as usual (light grey boxes). Centrelines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles. The notches represent the 95% confidence interval for each median. Non-overlapping notches give roughly 95% confidence that two medians differ.

Table 5

Spearman correlation coefficients in non-medicated patients with ADHD (n = 13) between QbTest+ cardinals and self-reports (BADDS, ASRS) and clinical measures (GAF, CGI-S) at baseline (n = 13 [12 for CGI-S]; upper panel) or at the 4-year follow-up (n = 7–8; lower panel)

	BADDS	ASRS	GAF	CGI-S
Concurrent Q-score associations with rating scale scores at baseline				
QbActivity	.19	.30*	.04	-.10
QbImpulsivity	-.02	.05	-.04	.07
QbInattention	.32*	.13	-.08	-.17
Baseline Q-score associations with rating scale scores 4 years later				
QbActivity	.26	.40*	-.06	.11
QbImpulsivity	.29	.22	-.33	.21
QbInattention	.49**	.52**	-.18	.22

*Correlation is significant at the 0.05-level (2-tailed); **Correlation is significant at the 0.01-level (2-tailed)

GENERAL DISCUSSION

The overall aim of the four naturalistic studies presented here was to investigate the long-term outcome in children and adults with ADHD as it is presented in typical patients and in real-world settings.

The first study investigated the 1-year outcome of 253 children diagnosed with ADHD. The second study investigated the 5-year treatment outcome of 137 of these. The ensuing two studies concerned ADHD diagnosed in adulthood and its long-term outcomes. The third study monitored outcomes in 52 ADHD patients receiving routine psychiatric health care. The final study evaluated QbTest+ performance in 67 adult ADHD patients with on-going drug treatment; 44 of these were re-evaluated approximately 4 years later.

The studies were all naturalistic in nature. Hence the patients were free to choose treatment type together with their physician and we did not control patients' start-/stop patterns concerning treatment interventions. We recorded treatment at the time of the baseline interview and the follow-up interviews. For the adults, we registered an estimate of months in medical treatment, but not their exact treatment pattern over time.

Findings from these four studies will be discussed below, starting with the main findings.

Long-term improvement

The main finding in this work is that patients with ADHD in psychiatric outpatient care improve over the years (see Study I, II, III, and IV). This confirms many previous studies summarized previously in this thesis. Importantly, however, in both children and adults, both symptoms and functioning remained at clinical levels despite improvement over 5 years, confirming the well-known persistence of ADHD (Sibley et al., 2016; Roy et al., 2016). I can think of at least three reasons as to why ADHD patients do not normalize in symptoms and in functioning from specialized treatment.

First, and most importantly, ADHD is a persistent neurodevelopmental disorder (Hoogman et al., 2017) for which there is currently no cure. Treatment is about symptom reduction and support for improved everyday functioning. Second, the lack of perseverance characterizing the personality of ADHD patients will make it difficult for them to engage in treatment over long periods of time, as proper executive functions are necessary for building a stable life situation. Problem with self-regulation is a core feature in ADHD and form part of the particular personality profile observed in ADHD (Jacobsson et al., 2021). Finally, one cannot wholly exclude the possibility that the milder ADHD symptoms observed at most follow-ups are partially the result of the statistical regression-towards-the-mean phenomenon, along with brain maturational processes occurring independently of various psychiatric ministrations. Perhaps the small-sized basal forebrain structures reported on by Hoogman et al. (2017) in children with ADHD catch up on their own with

advancing age. Voltaire's *bon mot* may have some truth to it: 'L'art de la medicine consiste à amuser le malade pendant que la nature le guérit'[1].

Exploratory work in Study I suggested that improvement was not restricted to ADHD symptoms only. Cases in which treatment was especially successful in lowering ADHD symptoms also enjoyed profound reductions in ODD, Depression, and GAD as well. Our exploratory analyses should be considered preliminary and in need of confirmation. They do, however, echo a study showing that stimulant treatment of children with ADHD reduces anxiety (Snircova et al., 2016).

Effectiveness of ADHD medication

The second main finding in present work is that patients' improvement in the long run was not associated with whether they have medicated or not. This was true both for children (Study II) and adults (Study III). These findings support previous research, summarized by Hinshaw et al. (2015, p. 39): 'The key paradox is that while ADHD clearly responds to medication and behavioural treatment in the short term, evidence for long-term effectiveness remains elusive.'

Results in Study I clearly demonstrated the familiar short-term (1-year) benefits of medication in children (see for instance Banaschewski et al., 2010; Storebø et al., 2015; The MTA Cooperative Group, 1999). In our case, though, there was a troubling confound as medicated patients also received more attention (e.g., more appointments). By contrast, the 5-year follow-up (Study II) showed that the differences in improvement between medicated and drug-free patients had dissipated and that no significant differences between treatment groups remained. This result too is in line with the large-scale MTA study of childhood ADHD (Jensen et al., 2007; Molina et al., 2009) and several others (Biederman et al., 2010, 2012; Lundh et al., 2013; van Lieshout et al., 2016). The lack of an identifiable medication effect was also apparent among the adults (Study III) where medication (together with age, sex, IQ, and comorbidity) had little impact on treatment outcome after 5 years according to our analyses.

Compliance problems might in part account for the lack of long-term medication effects. Hence, multiple studies have reported erratic compliance to medical treatment, especially in adolescents (Banaschewski et al., 2010; Zetterqvist et al., 2013) and adults (Bejerot et al., 2010; Bijlenga et al., 2017; Edvinsson & Ekselius, 2018). Adolescents and young adults with ADHD often drop out of drug treatment, because of side effects, disliking drugs, or developing skills to handle their life without medication (Wong et al., 2009). Perhaps low compliance is to be expected, given one of the core problems of ADHD: a low level conscientiousness with forgetfulness and rashness (Jacobsson et al., 2021). People with this trait will have trouble managing proper pill dispensing over time: 'drugs don't work in patients who don't take them' (see Osterberg & Blaschke, 2005, p. 487). Herein might lie an explanation for the frequent observation that more severe ADHD symptoms are associated with less improvement. Treatment compliance problems are perhaps underestimated in ADHD research.

How does one go about to increase drug treatment compliance? In both childhood and adult ADHD, non-medical interventions seem effective, at least when compared with unmedicated patients (Arnold et al., 2015; Daley et al., 2017; The MTA Cooperative Group, 1999). For example, we found (Study I) that non-medical treatment interventions were underused in non-medicated children (38% vs. 10% attended parental ADHD education class during the first year).

[1] 'The art of medicine consists in amusing the patient while nature cures the disease'

This is unfortunate, considering the importance of psychosocial interventions for overall outcome (Chronis et al., 2006; Concannon & Tang, 2005; Jensen et al., 2007; Stattin et al., 2015), plus the fact that not all patients (and/or parents) want drug treatment for various reasons (Berger et al., 2008).

Another question is whether the lack of effect of medication in the long run is due to methodological failures. There are ethical problems associated with running long-term RCT studies. Therefore, such studies tend to be naturalistic, with less stringent designs. Shorter-term studies are easier to conduct in a more structured efficacy design. According to this line of reasoning, the difference between short-term and long-term study results could be a question of differences in stringency (Kooij et al., 2010; 2019).

Finally, one could envisage the perhaps somewhat overly pessimistic thought that no current form of ADHD treatment is effective in the long run (Banaschewski et al., 2010), or that the neurochemical effect of the catecholamine reuptake inhibitors used in ADHD treatment somehow changes with long-term use. Indeed, a celebrated theory of addiction builds on the very fact that certain parts of the brain undergo tolerance to such stimulant drugs upon repeated administration, whereas other parts in the same brain undergo sensitization (Robinson & Berridge, 2003). Does chronic administration of ADHD medicines induce tolerance to the beneficial effects (i.e., reduced ADHD symptoms) and/or sensitization to unwanted side effects?

Predictors

All four studies in the present thesis evaluated predictive factors in some way. In our studies on adults, significant baseline predictors of symptom improvement at follow-up included low levels of self-reported problems. Perhaps the most striking finding was that baseline QbAttention score on the continuous performance test rather strongly predicted adult patients' scores on BADDS and ASRS 4 years later (Study IV). To my knowledge this has not been previously observed. An objective measure predicting subjective symptom ratings 4 years later is notable but should of course be subject to replication.

As to the children, significant baseline predictors of improvement one year later included being a boy, receiving medication, and having low scores on ADHD-, ODD-, and Family situation subscales. In the ensuing Study II, significant predictors for improvement after 5 years were being a boy and having low scores on the subscales of ADHD, ODD, Child functioning, and Family situation. In line with both Study I and Study II, previous research (e.g., Molina et al., 2009; van Lieshout et al., 2016) has shown that children with severe ADHD symptomatology at baseline tend to continue to score high (though less so) also after treatment. Predictors other than those identified by us include parental ADHD (van Lieshout et al., 2016), parental distress (Rockhill et al., 2013), and family adversity or poverty (Ingram et al., 1999; Rieppi et al., 2002). The individual prognosis has also been associated with IQ scores (Hinshaw, 2007), school problems, problems with self-esteem (Ingram et al., 1999), and early recognition of the disorder (Fredriksen et al., 2013).

In this context it might also be relevant to mention the main predictors of ADHD persistence from childhood to adulthood: ADHD severity early on, comorbid major depressive disorder, conduct disorder, and receiving treatment for ADHD (Caye et al., 2016).

The role of the informant

We based the data collection on parental interviews (mostly mothers) in both Study I and Study II. According to the BCFPI subscale Informant mood there were few signs of depressive problems on average. This was reassuring, given the depression distortion hypothesis, which proposes that sadness strongly influences the responses of informants (Richters et al., 1992). Incidentally, that hypothesis does not seem to have much empirical support (De los Reyes et al., 2015). Likewise, parental ADHD (which we did not measure) does not impact substantially on maternal reports of the child's ADHD symptoms (Faraone et al., 2003).

Among adult ADHD patients, there are often fewer informants available compared with children, making the assessment a question of the patient's self-reporting skills and awareness of their own symptoms and difficulties. We know that ADHD patients tend to underrate their own symptoms (Manor et al., 2012), as it is difficult for someone with lifelong ADHD symptoms to compare one's own situation to that of someone without ADHD (Kooij, 210). In the present work we complemented the self-reports with clinicians' ratings of overall functioning (GAF) and symptoms (CGI-S; Study III), together with the QbTest+ (Study IV). The patients studied here were special as a group; in that their IQ was one standard deviation above average and that few had (reported) substance use problems. This might explain the fact that they were diagnosed as adults, as higher IQ often confers better coping abilities (see Milioni et al., 2017).

Generally speaking, the self-rated ADHD symptoms (BADDS and ASRS) and clinician-rated functioning levels (GAF) agreed modestly, both at baseline and at follow-up. Moderate concordances between self-ratings and investigator ratings have been reported earlier (Kooij et al., 2008; Silverstein et al., 2018). There were also modest associations between the three QbTest+ cardinals and symptom self-ratings.

QbTest+ in the assessment of ADHD

Study IV assessed QbTest+ performance in adults with ADHD while on medication. Their median Q-scores were below the suggested clinical threshold. As a group, then, the average participant managed quite well during the 20-minute test when the three Qb-cardinals were considered one at a time. Their normal performance might have resulted from the fact that they were on ADHD medication, which improves QbTest+ performance (Bijlenga et al., 2015; Edebol et al., 2013a; Ginsberg et al., 2012). Their performance might also have been due to milder symptoms and/or better coping skills due to their higher IQ, as alluded to earlier (see Milioni et al., 2017; Agnew-Blais et al., 2016). My personal experience is that some patients can get their act together during a 20-minute test, but still have significant symptoms and functional deficits in everyday life.

Even though the group medians for the three Qb cardinals were unremarkable in our patients, the majority of them (65%) were pinpointed by the test algorithm to have the disorder: they scored at a clinical level on at least one of the three cardinals. A small group of patients had forgot to take their ADHD medication on the morning of the test. Out of these, 85% scored in the clinical range on the QbTest+.

In my view, the greatest asset of the QbTest is its ability to promote contact with the patient. It helps in the communication with patients and parents, by for instance illustrating a child's inability to sit still and learn for long periods of time. Showing that a child misses out on 40% of the QbTest targets can bring to life how much he/she misses in class, and why individual adjustments

are necessary. On the other hand, awkward situations can arise, as when a patient clearly describes difficulties in everyday life but scores perfectly normally on the QbTest.

Another risk with tests like the QbTest is excessive belief in the test scores. This is why the QbTest+ should be used together with other assessment tools (clinical interviews, rating scales) in the diagnostic process; it is not meant to be a stand-alone test. Many mental disorders are associated with cognitive problems involving attention, impulsivity, and/or activity (Millan et al., 2012).

Methodological discussion

Statistical considerations

For all the studies presented here, one would have wished for larger sample sizes. In the present naturalistic research, we did not have any influence over the number of patients; rather, we set up a time window during which we gathered all patients seeking healthcare and being diagnosed with ADHD within that time. Small sample sizes not only reduce the chance of detecting true effects but also diminish the likelihood that an uncovered statistically significant effect is true (Button et al., 2013). For example, a simulation study showed that correlation coefficients stabilize around the true population value of $r = 0.3$ when sample sizes approach 250 (Schönbrodt & Perugini, 2013). Moreover, veridical estimation of interaction effects in analyses of variance often requires more observations than does estimation of main effects (Cumming, 2014). We have attempted to minimize the number of erroneous conclusions due to power failure by correcting for multiple significance tests (Study I and II), by using multivariate tests designed to handle short-and-wide data sets with inter-related variables (Studies I-III) and by using non-parametric statistics where appropriate (Study IV).

As to the multivariate methods used here to find predictors of clinical change, we chose to adopt partial least squares (PLS) regression modelling, as implemented by the user-friendly SIMCA software. Attractive features of this suite of procedures include that they handle data tables with many variables and few observations (i.e., participants in our case), cope with collinearity and missing data, while being quite robust to noise and to skewed data distributions (Eriksson et al., 2013). The procedures are periodically extended and modified to improve versatility (e.g., Eriksson et al., 2012). PLS-based methods are seldom seen in psychological/psychiatric research papers (but see Henningsson et al., 2001; Sparding et al., 2015), but figure prominently in other areas in the social sciences, as well as in the natural sciences. However, as advocated by Willaby et al. (2015) among others, PLS-based techniques have useful applications also in psychological research, not least in clinical settings where sample sizes often are constrained. They go on to show that PLS-related methods, with their modest sample size requirements, can reproduce the results of structural equation modelling, which require much larger samples (Willaby et al., 2015).

However, we acknowledge that there are dissenting voices as to the utility of the PLS-based methods. For example, Rönkkö et al. (2015), Rönkkö and Evermann (2013), and Evermann and Rönkkö (2021) regard the modest sample size requirement of the PLS technique as an 'urban myth' and maintain that PLS-based methods produce inconsistent and biased models of reality. Criticisms such as these, on the other hand, have been rebutted by, for example, Henseler et al. (2014), who conclude that '…PLS is not a panacea, but certainly an important technique deserving a prominent place in any empirical researcher's statistical toolbox'. The papers cited above –

both the criticisms and the rebuttal – are written in a highly technical and specialized jargon, whose details, we willingly concede, go beyond our grasp.

Clearly, then, as in other sciences, there are diverse and contrasting informed opinions also in statistics. As a further example, a long list of authors has suggested that the *p*-value typically used for determining statistical significance ($p < .05$) should be changed to $p < .005$ in order to increase reproducibility in psychology and the life sciences (Benjamin et al., 2018); other researchers object, especially when it comes to clinical research (e.g., Di Leo & Sardanelli, 2020). At times, end-users of statistical tools, such as those of us primarily interested in ADHD but not versed in advanced statistical theory, find it hard to navigate the byzantine statistical maze.

Miscellaneous limitations

One would have wished for more detailed information when retrospectively examining the medical records. For example, in Study I and Study II, the paucity of details meant that we had no information as to patients' ADHD subtypes and there were few notes on comorbidity. The latter might indicate improper assessment, where only the main condition was diagnosed. In Study II we do not know for sure how many of the patients switched treatment arms, due to deficient reporting. We assumed that the patients followed the treatment arm to which they were assigned at referral. Additional limitations were that the BCFPI-interviews were conducted with one parent only and that we did not interview the children themselves. The main reason for this was that we used clinical data, and the default interviewing method in the child- and adolescent psychiatric outpatient clinics in Halland is with a parent. There was no child version of the BCFPI interview (in the Region of Halland database). However, there was a version for adolescents, which was used intermittently. In the rear-view mirror, it would be interesting to add the adolescents' responses to the present results, as parents tend to rate their teenagers' symptoms higher than the child itself (Swanson et al., 2017). Or expressed differently: as young ADHD patients underrate their own symptoms (Manor et al., 2012). In this context, one can also contemplate the ethical and doable aspects of engaging adolescents with ADHD in an hour-long telephone interview. Would the answers be reliable?

Information as to the exact nature of the non-medical interventions was also found wanting. In Study III and Study IV, the most important limitation was the lack of detailed information as to the medications: type of stimulant, dosages, individual stop/start-patterns, and parallel on-going medication. The low rate of comorbid diagnoses among the patients might indicate that the sample was not representative of the adult ADHD population in all respects. Another limitation is the fact that the same clinician rated both GAF and CGI-S, and that they probably had access to medical records comprising baseline scores when rating follow-up scores.

According to Kooij et al. (2019), semi-structured interviews are preferable in ADHD assessments. By contrast, we used the BCFPI interview with fully structured questions and fixed response options, and we conducted it over the phone. This medium obviously has shortcomings, and may have affected the informant's focus. An advantage with telephone interviews, however, is the availability and high response rates: 95% of all families referred to the child- and adolescent psychiatric outpatient clinics in Halland during the relevant timespan, and with a child diagnosed with ADHD during that time, responded.

Despite these shortcomings one hopes that the present studies contribute to the field by providing information about real-life outcomes for real-life patients in real-life settings in our country.

Prospects

One of the main results of the present studies is that the long-term, as opposed to the short-term, benefits of ADHD medication are uncertain, thus confirming a number of previous investigations (e.g., Jensen et al., 2007; Lundh et al., 2013; van Lieshout et al., 2016). If this finding should prove correct, then the development of novel ADHD drugs with therapeutic actions also in the long run should be a top priority. However, according to Caye et al. (2019), such drug candidates are not coming anytime soon; most current pharmacological developments in this area concern modifying extant drugs such that they will cover wider intervals of the day.

In this light, non-pharmacological interventions take on even greater importance: how can we optimize the behavioural, cognitive, and psychosocial treatments in such a way that they can replace the dwindling drug effects? Incidentally, this is not unheard of in psychiatry. DeRubeis et al. (2008), in a large-scale study of major depression spanning 2 years, compared the long-term effects of cognitive therapy and antidepressant medication. They found that the antidepressant effect of psychotherapy was more enduring and robust than that observed following medication.

As mentioned earlier, ADHD treatment guidelines do recommend behavioural interventions, particularly to preschool children or as an add-on to drug treatment (NICE Guideline, 2018; Wolraich et al., 2019). Unfortunately, the evidence is conflicting as to how to regard these non-medical interventions (Caye et al., 2019). In fact, a recent practitioner review concluded that behavioural interventions '…cannot be supported as a front-line treatment for core ADHD symptoms' (Daley et al., 2017). The same review suggests, however, that behavioural interventions work better with regard to parenting practices and conduct problems (Daley et al., 2017). The heterogeneity of the disorder and the difficulty with compliance explain part of the ambiguities regarding outcomes following non-pharmacological interventions.

A methodological problem in this field is that informants are nearly always unblinded (Daley et al., 2017). For example, in evaluations of the effectiveness of parent training, the informant is usually the parent receiving the training. It is thus hard to rule out the possibility that reported improvements are merely changes in parent perception and attitude, rather than in actual behaviour. Indeed, the effect sizes of behavioural interventions on ADHD symptoms are quite large according to unblinded informants (parents) and close to nil according to independent blinded observers (Daley et al., 2017). By contrast, blinded measures of conduct problems and on parenting do suggest positive effects (Daley et al., 2017).

The quest for better future psychosocial ADHD treatments should entail not just whether they are effective, but also isolate the active ingredient(s) that drive clinical change (Sebastian et al., 2021). Fifty eminent research teams were recently commissioned to pinpoint the active ingredients with regard to the treatment of youth internalizing symptoms (Sebastian et al., 2021); many of these proposed sub-components might well prove relevant also for ADHD interventions, not least because of the comorbidity between the two conditions. Thus, under the heading 'human connections' we find family support and school connectedness, i.e., areas addressed in some ADHD interventions such as classroom adjustments. Under the heading 'beliefs and knowledge' is found mental health literacy, i.e., learning about ADHD in our case. The 'cognitive and attentional skills' category contains proposed active ingredients such as helpful attentional and interpretational thinking patterns, decentering (perspective-shifting), emotional controllability and learning to be more hopeful. These items are targeted in ADHD treatment by cognitive behavioural therapy, cognitive training programs, and perhaps by neurofeedback procedures. By identifying and honing such putative active ingredients in non-pharmacological interventions, I hope

that more effective psychosocial treatments will be able to help patients with ADHD in the long-term.

Ethical considerations

Study I and Study II was approved by the Regional Ethics Committee in Lund, Sweden (reference number: 2014/840). All parents consented orally to participation. Study III and study IV was approved by the Regional Ethics Committee in Stockholm (2005/554-31/3 and 2011/1700-32), conducted in accordance with the latest Helsinki Protocol. For participation in Study I and II all parents consented orally prior to the telephone interview and they were informed about the possibility to quit without further notice. Before the data collection started they were informed in a letter about the study and with a specific time and day for the interview for the possibility of preparations. Similarly, all adult patients and controls consented both orally and in writing to participation in Study III and IV. Since all patients only participate with interview material and information from their medical records, the risk for the participants is considered very low.

There are some ethical concerns about this type of longitudinal study designs. First, the patients might feel obliged to continue their participation once they started. Second, they might feel obligated to respond to all questions since they said yes to participation. To get around this potential discomfort for the informants, they were carefully informed about their possibility to whenever they felt to, they could quit participation without explaining why. The interviewers in Study I and Study II were psychiatric healthcare staff, educated to handle questions of a delicate character. They also had first-rate knowledge to handle parental questions afterwards regarding the ensuing psychiatric help. Further, in Study III and IV, the patients were carefully interviewed by specialized psychiatrists and tested (QbTest+) by a psychiatric specialist nurse. A third ethical concern is that of adolescents participating with their data in Study II, even though they were not interviewed themselves. Retrospectively, we ought to have conducted interviews with the adolescents as well, and collected their consent to participation with their data. Throughout the work, ethical considerations have been present in how data was collected, handled, and presented.

Clinical implications

The clinical implications of present studies are in my view the following:

First, clinicians should inform the patient of the long-term positive prospects, provided that he/she stays in treatment. This suggestion is based on the finding that, on average, ADHD patients in treatment improve over time, regardless of treatment intervention (see Study I, II, and III) and it echoes the advice given by others (Bejerot et al., 2010; Bijlenga et al., 2017; Edvinsson & Ekselius, 2018; Lensing et al., 2013; Molina et al., 2009; Torgersen et al., 2012). However, medicated patients (children) seemed to improve more rapidly, as they were given more attention (medical and non-medical) during their first year in treatment (Study I). Another related aspect is how much improvement one realistically might expect. According to our findings, the average patient improves in the long run but does not normalize. As there is no cure for ADHD, many patients in treatment will still have problems because of the underlying disorder.

Second, clinicians should consider the risk of poor compliance to drug treatment. As noted before, ADHD patients easily drop out of treatment or have difficulties with compliance in the long run (Banaschewski et al., 2010; Bejerot et al., 2010; Bijlenga et al., 2017; Edvinsson & Ekselius,

2018; Zetterqvist et al., 2013). A good approach might be to address the compliance problems in advance and to offer frequent follow-ups at the clinic to ensure compliance.

Third, clinicians should strive to offer cohesive and time-effective assessments, as we found that the children diagnosed rapidly were the ones who improved the most at the follow-up 1 year later. Needless to say, this must be made without jeopardizing the quality in any way. The clinician should keep in mind the profound impact of a diagnosis for the individual. This is riskier than one might think at first, considering the long waiting lists for ADHD assessment in our country. The view that the job is done when the patient is diagnosed is a profound risk, as the diagnosing is rather the beginning.

Fourth and finally, clinicians should not forget the importance of add-on non-medical interventions in stimulant treatment. We found in the present work that the non-pharmacological treatment was unacceptably underused. Evidence clearly supports the combination of treatment options to maximize treatment.

Conclusion

In conclusion, the four studies in this thesis demonstrate that patients with ADHD in routine psychiatric health care do improve over the course of several years, independent of treatment type. The findings also support previous research that long-term outcome of drug treatment in ADHD remains unclear, even though the short-term benefits are well established. Taken together, this thesis gives a unique picture of real-life conditions for ADHD patients over several years.

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