Terje Torgersen

ADHD in adults; comorbidity and long-term central stimulant treatment

A retrospective, naturalistic study

Thesis for the degree of Philosophiae Doctor

Trondheim, May 2013

Norwegian University of Science and Technology
Faculty of Medicine
Department of Neuroscience

NTNU – Trondheim
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the degree of Philosophiae Doctor

Faculty of Medicine
Department of Neuroscience

ISBN 978-82-471-4353-7 (printed ver.)
ISBN 978-82-471-4354-4 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2013:125

Printed by NTNU-trykk

Norsk sammendrag av avhandling:

ADHD hos voksne; samsykelighet og behandling med sentralstimulerende legemidler

ADHD er en tilstand som oppstår i barndommen og preges av hyperaktivitet, impulsivitet og oppmerksomhetssvikt. Symptomene på ADHD vedvarer inn i voksen alder hos mange pasienter, og er forbundet med funksjonssvikt på områder som utdannelse og arbeidsliv. Forekomst av andre psykiske lidelser samtidig (samsykelighet) er stor gjennom hele livsløpet. Sentralstimulerende legemidler (SSL) er godt dokumentert behandling av symptomene ved ADHD. Til tross for god symptomatisk effekt slutter mange pasienter tidlig med behandlingen, og mye er uavklart når det gjelder hvordan SSL behandling fungerer i vanlig klinisk praksis hos voksne.

Vi ønsket å beskrive forekomst av samsykelighet og funksjonssvikt hos voksne pasienter med ADHD. Videre ønsket vi å se på behandlingsforløp og identifisere variabler som predikerte behandlingsvarighet > 3 år. Det tredje målet med studien var å undersøke forekomsten av rusmisbruk i løpet av behandlingsforløpet og identifisere variabler knyttet til eventuelt misbruk. Vi ønsket også å identifisere kliniske og behandlingsmessige variabler relatert til yrkesmessig fungering i voksen alder.

Dette er en retrospektiv, naturalistisk studie på 3 utvalg av voksne pasienter med diagnosen ADHD. Den primære utredningen av pasientene ble gjort i henhold til prosedyrer bestemt av de Sakkyndige team for hyperkinetisk forstyrrelse i perioden 1997-2005. Hovedmengden av data til studien ble retrospektivt hentet fra den psykiatriske journalen. I Paper IV brukte vi i tillegg et spørreskjema.

Vi fant at voksne med ADHD hadde lavere utdanningsnivå og yrkesdeltagelse enn den generelle befolkningen. Mange pasienter hadde samsykelighet som rusmisbruk og personlighetsforstyrrelse. Til tross for de høye nivåene av samsykelighet og funksjonssvikt fikk de fleste pasientene behandling med SSL i lang tid (median varighet var 33 måneder). Behandlingsvarighet mer enn 3 år ble positivt predikert av om pasienten brukte langtidsvirkende SSL, og negativt predikert av om pasienten hadde personlighetsforstyrrelse. Hos pasienter uten tidligere rusmisbruk fant vi at behandling med SSL ikke førte til rusmisbruk. Pasienter som tidligere hadde hatt rusmisbruk hadde ikke høyere tilbakefall enn i grupper av voksne pasienter med rusmisbruk alene. Høy alder ved første SSL behandling og høyere grad av oppmerksomhetssvikt var assosiert med redusert yrkesdeltagelse i voksen alder.

Avhandlingen understreker det høye nivået av samsykelighet og funksjonssvikt ved ADHD hos voksne. Det viser seg allikevel mulig å behandle pasientene med SSL over lang tid, men det må undersøkes nærmere hvordan behandlingen skal gjennomføres hos pasienter med stor samsykelighet. En lengre periode med rusfrihet før SSL behandling kan redusere risiko for tilbakefall, men dette må undersøkes med kontrollerte studier. Studien antyder at tidlig behandling av ADHD er relatert til bedre yrkesmessig fungering i voksen alder, men i likhet med andre naturalistiske studier er det store metodologiske begrensninger. Vitenskapelig mer robuste studier bør gjøres for å undersøke effekten av SSL behandling av barn og unge på funksjonsnivå og samsykelighet i voksen alder.

Navn kandidat:	**Terje Torgersen**
Institutt:	**Institutt for nevromedisin**
Veiledere:	**Professor Kirsten Rasmussen, professor Hans Morten Nordahl, førsteamanuensis Arne Vaaler**
Finansieringskilder:	**Samarbeidsorganet mellom Helse Midt-Norge RHF og NTNU,** **Sykehuset Levanger, Psykiatrisk klinikk,** **og St. Olavs hospital, avdeling Østmarka**

Table of Contents

Acknowledgement 5

Summary 7

List of publications 11

List of abbreviations 12

1. INTRODUCTION 13

1.1 Attention-deficit/hyperactivity disorder 13

1.2 Persistence of ADHD into adulthood 15

1.3 Comorbidity in adult ADHD 16

1.3.1 Comorbid Substance Use Disorders 17

1.3.2 Comorbid Antisocial personality disorder 19

1.4 Functional impairment in adult ADHD 20

1.5 Central Stimulant treatment of ADHD in adults 20

1.5.1 Central Stimulants 21

1.5.2 Effectiveness versus efficacy 23

2. THE PRESENT THESIS 23

2.1 Research questions 25

2.2 Materials and methods 25

2.2.1 Patients 26

2.2.1.1 Recruitment of patients to the present studies 26

2.2.1.2 Diagnostic assessment 27

2.2.2 Measures 28

2.2.2.1 Sociodemographic variables 28

2.2.2.2 Comorbidity 29

2.2.2.3 Prevalence of SUD during CS treatment 29

2.2.2.4 Duration of abstinence from SUD 30

2.2.2.5 CS treatment variables 30

2.2.2.6 Self-Report Questionnaire 31

2.2.3 Procedures 31

2.3 Statistics 32

2.4 Ethics 32

3. RESULTS 33

3.1 Paper I 33

3.2 Paper II 34

3.3 Paper III 36

3.4 Paper IV 37

4. DISCUSSION 38

4.1 Methodological issues 38

4.1.1 Patients 38

4.1.2 Procedures 40

4.2 Discussion on the main findings 42

4.2.1 Comorbidity 42

4.2.2 Functional impairment 45

4.2.3 Variables predicting long-term (> 3 years) CS treatment 47

4.2.4 Prevalence of SUD during long-term CS treatment 51

4.2.5 Variables predicting relapse of SUD during CS treatment 53

4.2.6 Variables predicting occupational outcome in adult ADHD 53

5. CONCLUSIONS 55

6. FUTURE PERSPECTIVES 56

7. REFERENCES 58

8. PAPERS I-IV

9. ATTACHMENTS I-IV

Acknowledgements

The work with the present thesis started in 2004 when I was working as a staff psychiatrist at Sykehuset Levanger, Department of Psychiatry. Dr. Marit Bjartveit was a very enthusiastic and supportive Head of the Department, and created an environment in which research was both encouraged and desired. The combination of this positive attitude towards research, and my meeting with the increasing number of adult patients with ADHD at the clinic, inspired me to start clinical research related to this relatively new group of patients in adult psychiatry. At this time I also met Professor Kirsten Rasmussen at NTNU, Department of Psychology. She was probably the first to do clinical research on adult ADHD in Norway, and accepted to be my main supervisor. Without her warm, encouraging support and patience this project would never have come to an end.

My good friend and colleague Bjørn Gjervan has been an invaluable partner all these years. We have been working together and have been involved in each other's PhD projects. We have shared disappointments and hardship, but also the small victories and the joy of learning to be researchers. The last year our research has resulted in several published papers on adult ADHD and we have started a new ADHD research project.

Bjørn; we said we could do it, and we did it!

The first years of the study the research was done along with my clinical work at Sykehuset Levanger, Department of Psychiatry. The present Head of Department Hilde Ranheim and supervising physician Nils Håvard Dahl has always been supporting and contributed to the creation of clinical psychiatric research at the Department of Psychiatry. I am also very grateful to all my former colleagues at the hospital in Levanger for the creation of a stimulating, fun and professional work environment. My second supervisor professor Hans Morten Nordahl has been an important contributor throughout the project.

In 2006 I received a scholarship from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), and this funding has been essential for the completion of the project.

During the research project I have received support from the research environment at St. Olav's hospital, Department of Østmarka, and AFFU (Avdeling For Forskning og Utvikling) in two periods. Professor Olav Linaker provided me an office in a two year period when I was

commuting between my clinical job at Sykehuset Levanger and my home in Trondheim, and invited me to join the research environment at AFFU.

Two years ago I started a new job at an acute psychiatric ward at Department of Østmarka. Head of Department Pål Sandvik and leader of the acute wards Knut Langsrud has been very supportive and made it possible for me to continue and complete my PhD project. Professor Gunnar Morken at AFFU has also been helpful in the process of publishing my results the last two years. Associate professor and good colleague Arne Vaaler has been a main contributor and my third supervisor the last year. His ability to see what is essential and his enthusiasm for research has been invaluable for me in the final stage of the PhD project.

I am very thankful to all the patients who participated in these studies, and have a deep admiration for their struggle to overcome their health problems.

My wife Inger Lise is the most important person in my life, and without her love and care I could never have finished the project. You are simply the best! I am also grateful to my children Isak, Oskar and Line, and my "bonus" children Mats and Merete, for what they have learned me about life.

Trondheim, November of 2012

Terje Torgersen

Summary

Background: Attention Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition of childhood onset characterised by hyperactivity, impulsivity and attention deficit. The condition persists into adulthood in a significant number of patients, and is clinically heterogeneous in terms of symptoms, comorbidity, functional impairment and clinical course. There is a considerable presence of comorbid psychiatric disorders throughout the lifespan. ADHD in adults is associated with poor functional outcome in important life domains like educational and occupational achievement. Research indicates that especially substance use disorders (SUD) and antisocial personality disorder (ASPD) are linked to adult ADHD. Central stimulant (CS) drugs are considered to be the cornerstone of pharmacological treatment in ADHD. Several clinically important effectiveness variables were understudied when the present studies started; like continuity of CS treatment in ordinary clinical practice, predictors for continuity and reasons for discontinuation of CS treatment, and the impact of comorbid disorders on aspects of CS treatment.

Objectives: The first main objective was to describe psychiatric comorbidity and functional impairment in 3 samples of clinical adult ADHD patients. The second objective was to to investigate CS treatment in a sample of adult ADHD and identify variables predicting long-term (> 3 years) CS treatment. The third objective was to investigate the prevalence of SUD during long-term CS treatment in a sample of adult ADHD and identify variables associated with SUD during treatment, and the fourth was to identify variables predicting occupational outcome in adult ADHD.

Methods: The present study is based on a retrospective, naturalistic design of 3 samples of adults diagnosed with ADHD in North-Trøndelag County in the period 1997 to 2009. The

primary assessment of the patients was done according to procedures published by Expert Committees of Hyperkinetic Disorders/ADHD, as part of ordinary hospital routines. In a second step a report with all information gathered in the first step was sent to the Expert Committee of Hyperkinetic Disorders/ADHD for a definitive recommendation. The majority of data for the present study was retrospectively collected from the medical records by an experienced psychiatrist (the author). Paper IV additionally includes a cross-sectional questionnaire. The main measures were sociodemographic variables, baseline psychiatric comorbidity and the prevalence of SUD during long-term CS treatment, duration of abstinence from SUD before CS treatment started, and several CS treatment variables.

Results: We found that Norwegian adults with ADHD had far lower levels of education and employment compared to the general population, and the patients had high levels of psychiatric comorbidity like SUD and ASPD. Despite the high levels of comorbidity and functional impairment most adults with ADHD received CS treatment for several years (mean duration was 33 months). Treatment duration for more than 3 years was predicted positively by the use of extended release (ER) formulations of methylphenidate (MPH), and negatively by comorbid ASPD. In adult ADHD patients without previous comorbid SUD we found that CS treatment did not precipitate new onset of SUD. In patients with previous SUD the relapse rate during CS treatment was not higher than in adult patients with SUD alone. We also found that later age of first CS treatment and higher inattentiveness ratings were associated with lower level of employment in adulthood.

Conclusions: The present thesis emphasizes the high rates of comorbidity between adult ADHD and other psychiatric disorders like SUD and ASPD. In addition to a further emphasis on the impact of comorbidity on the course of ADHD future research should explore the functional impairment following ADHD in all ages, and identify treatment which is capable of reducing impairment. Further research should also focus on the treatment providing

systems and investigate factors that could enhance CS treatment effectiveness such as compliance. A longer period of abstinence from SUD before CS treatment may reduce the risk for relapse. However, trial derived evidence is lacking and it needs to be examined in a study with a prospective, controlled design. Early treatment of ADHD is shown in the present and some other long-term studies to be related to better adult functioning. However, most long-term studies are open-label extensions or naturalistic studies, with several methodological limitations. Efforts should be made to initiate larger, scientifically more stringent and multisite naturalistic studies to investigate the impact of different treatments on adult functional outcomes.

List of publications:

The thesis is based on the following publications, which are referred to by their roman numerals:

I. Torgersen T, Gjervan B, Rasmussen K. ADHD in adults: a study of clinical characteristics, impairment and comorbidity. Nord J Psychiatry. 2006; 60 (1):38-43.

II. Torgersen T, Gjervan B, Nordahl HM, Rasmussen K. Predictive factors for more than 3 years' duration of central stimulant treatment in adult attention-deficit/hyperactivity disorder: a retrospective, naturalistic study. J Clin Psychopharmacol. 2012 Oct; 32 (5): 645-52.

III. Torgersen T, Gjervan B, Rasmussen K, Vaaler A, Nordahl HM. Prevalence of comorbid substance use disorder during long-term central stimulant treatment in adult ADHD. Atten Defic Hyperact Disord. 2012 Oct 27. [Epub ahead of print]

IV. Gjervan B, Torgersen T, Nordahl HM, Rasmussen K. Functional impairment and occupational outcome in adults with ADHD. J Atten Disord. 2012 Oct; 16 (7): 544-52

List of Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ASPD	antisocial personality disorder
ASRS	adult ADHD self report scale
CAP	child and adolescence psychiatry
CD	conduct disorder
CS	central stimulants
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER	extended release
GAASC	General Adult ADD Symptom Checklist
HD	hyperkinetic disorder
ICD	International Classification of Diseases
IR	immediate release
MAS	mixed amphetamine salts
MPH	methylphenidate
MTA	NIMH multimodal treatment study of ADHD
ODD	oppositional defiant disorder
PD	personality disorder
PPS	pedagogic-psychological services
SUD	substance use disorder

1. Introduction

1.1 Attention-deficit/hyperactivity disorder

Attention Deficit/Hyperactivity Disorder (ADHD) is a heterogeneous neurodevelopmental condition of childhood onset characterised by hyperactivity, impulsivity and attention deficit. The symptoms present in ADHD are found in varying degrees in the general population, and only those who have symptoms to an extreme degree and a functional impairment due to symptoms will fulfil the criteria for the diagnosis. ADHD is recognized as a valid disorder in children and adolescents, and during the last couple of decades also in adults (Clarke et al. 2005;Kooij et al. 2005). Still, the validity of the diagnosis in adults is disputed (Asherson et al. 2010;Matte et al. 2012;Moncrieff and Timimi 2010). A major problem is the lack of diagnostic criteria specific for adults, and the use of criteria developed for children when assessing adult patients (Matte et al. 2012).

ADHD is a designation under the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, (DSM-IV) (American Psychiatric Association 1994). It differs in some aspects from the term Hyperkinetic Disorder (HD) according to the official diagnostic system in Norway; International Classification of Diseases, 10th revision (ICD-10) (World Health Organization 1992). The need for standardization between countries in research and clinical practice has led to an adaptation to the DSM-IV criteria worldwide, including Norway. In conjunction with the upcoming revision of the DSM-IV in 2013 major changes in the diagnostic criteria are discussed, like removing the three ADHD subtypes, changing the age of onset from 7 to 12 years, and fewer symptoms required for a diagnosis of adult ADHD (American Psychiatric Association 2012).

According to DSM-IV ADHD is divided into 3 subtypes; ADHD predominantly inattentive type, ADHD predominantly hyperactive-impulsive type and ADHD combined type. Patients with 6 or more out of 9 hyperactivity/impulsivity symptoms and 6 or more out of 9 inattention symptoms, will be classified as ADHD combined type. This is the most common subtype (Lahey et al. 1994;Wilens et al. 2009;Woo and Rey 2005) and the subtype mostly related to a unfavourable clinical outcome (Sobanski et al. 2008;Sprafkin et al. 2007;Wilens et al. 2009). The ICD-10 diagnosis HD is almost equal to ADHD combined type, but requires 6 out of 9 inattention symptoms, 3 out of 5 hyperactive symptoms and 1 out of 4 impulsive symptoms. Another difference between the diagnostic systems is that ICD-10 more strictly rules out ADHD if other psychiatric disorders are present at the same time.

The ADHD inattentive subtype requires 6 or more out of 9 inattention symptoms. Fulfilling the criteria for this subtype is basically not sufficient for the ICD-10 diagnosis HD. The Norwegian Health Authorities introduced in 1997 an adaptation to the DSM-IV criteria, allowing the ADHD inattentive subtype as sufficient for the diagnosis F90.0 HD. Resent research indicates that the DSM-IV ADHD subtypes do not identify discrete subgroups with sufficient long-term stability to justify the classification of distinct forms of the disorder, and that empirical support is stronger for an alternative model that would replace the subtypes with dimensional modifiers that reflect the number of inattention and hyperactivity-impulsivity symptoms at the time of assessment (Willcutt et al. 2012).

The disorder is clinically heterogeneous in terms of symptoms, comorbidity and clinical course (Thapar et al. 2007). Despite increased research on ADHD in recent years there is still uncertainty when it comes to aetiology and genetics (Thapar et al. 2007). ADHD may not be classified as a categorical diagnosis with distinction between healthy and diseased individuals (Willcutt et al. 2012;Witkiewitz et al. 2012). Many patients with other mental

disorders have symptoms overlapping with ADHD, which can make a reliable differentiation between diagnoses difficult (Goodman and Thase 2009;Montano and Weisler 2011).

The prevalence of ADHD world-wide is estimated to be 5.3% in children and adolescents (Polanczyk et al. 2007). In a World Health Organization survey of Europe, the Americas and the Middle East the estimates of DSM-IV ADHD prevalence in adults averaged 3.4% (range 1.2-7.3 %), with lower prevalence in lower income countries (1.9%) compared with higher-income countries (4.2%) (Fayyad et al. 2007).

1.2 Persistence of ADHD into adulthood

Research indicates that the disorder persists into adulthood in 30-60% of the cases (Mannuzza et al. 1991;Polanczyk and Rohde 2007), but studies have showed that the estimates rely heavily on the definition of persistence (Faraone et al. 2006a). The lack of specific diagnostic criteria for the disorder in adults contributes to the uncertainty in persistence rate (McGough and Barkley 2004). Studies have shown that factors like ADHD symptom severity, functional impairment and psychiatric comorbidity are associated with persistence of ADHD into adulthood (Kessler et al. 2005c;Lara et al. 2009;Mick et al. 2010). Data suggest that among the core symptoms of ADHD the symptoms of inattention persist in a larger degree than hyperactivity and impulsivity (Biederman et al. 2000;Wilens et al. 2009). Clinically important attentional symptoms in adult ADHD may be poor attention and concentration, distractibility, frequent shifting of activities and forgetfulness (Wilens et al. 2009). Associated impairments in adult ADHD are executive function deficits like problems with processing of information, organization and time management (Barkley 1997). Another associated feature of adult ADHD is emotional dysregulation, characterized by mood

instability, emotional over-reactivity, hot temper and irritability (Barkley and Fischer 2010;Reimherr et al. 2005;Sobanski et al. 2010;Wender et al. 1981).

1.3 Comorbidity in adult ADHD

Adding to the complex questions about persistence of ADHD into adulthood is the considerable presence of comorbid disorders throughout the lifespan. A majority of adult ADHD patients have one or more comorbid psychiatric disorders (Barkley et al. 2008b;Nutt et al. 2007). In terms of diagnosis and treatment there is a rationale to divide the most frequently occurring comorbid disorders in adult ADHD into two groups; 1) disorders that are congenital or with childhood onset like pervasive developmental disorders (ICD-10 F84), learning disabilities (ICD-10 F81), Tourettes syndrome and other tic disorders (ICD-10 F95), and disruptive behavior disorders (ICD-10 F91), and 2) common psychiatric disorders like affective disorders (ICD-10 F30-39), anxiety disorders (ICD-10 F40-43) , personality disorders (PD) (ICD-10 F60) and substance use disorders (SUD) (ICD-10 F10-19). There are gender differences in the comorbidity pattern in adult ADHD that reflects gender differences in the general population; more anxiety, depression, eating disorders and borderline personality disorder in women, and more SUD and antisocial personality disorder (ASPD) in men (Biederman et al. 1994;Biederman et al. 2004;Halmoy et al. 2009;Rasmussen and Levander 2009;Rucklidge 2008;Sobanski et al. 2007;Sprafkin et al. 2007).

Despite the high numbers of comorbid disorders in adult ADHD the rates may not be elevated beyond the rates seen in other clinical control groups (Barkley et al. 2008b), and research indicate that only dysthymia, alcohol abuse disorder, SUD, and antisocial behavior disorders like oppositional defiant disorder (ODD), conduct disorder (CD) and ASPD, are specifically linked to ADHD (Barkley et al. 2008b). SUD and antisocial behavior disorders are related to a severe course of ADHD (Mannuzza et al. 1998;Thapar et al. 2006). A number

of studies have showed a robust relationship between the occurrence of ADHD, ASPD and SUD (Barkley et al. 1990;Biederman et al. 1997;Katusic et al. 2005;Mannuzza et al. 1991;McGough et al. 2005).

1.3.1 Comorbid Substance Use Disorders

SUD is characterized by a pattern of continued pathological use of legal and/or illegal substances. This pathological use results in adverse social consequences, such as failure to meet work, family, or school obligations, or legal problems. DSM-IV distinguishes between the substance dependence and abuse by defining substance dependence in terms of physiological and behavioral symptoms of substance use, and substance abuse in terms of the social consequences of substance use.

Studies in samples of adult ADHD patients have showed high prevalence's of SUD, but the estimates are varying. A population study from the US found that 15.2% of adults with ADHD had a SUD, compared with 5.6% of people without ADHD (Kessler et al. 2006). Several studies have shown evidence indicating an overlap between ADHD and SUD that is bidirectional and larger than expected by chance (Wilens et al. 2005a). In clinical samples of adult ADHD with high levels of comorbid disorders the prevalence of comorbid SUD may range between 35 and 55 % (Wilens et al. 2005a). Conversely, in clinically referred and epidemiologically derived groups of substance abusing adolescents and adults the prevalence of ADHD is between 40 and 75 % (Wilens et al. 2005a). The co-occurrence between ADHD and SUD may partially be mediated by comorbid bipolar disorder and antisocial behavior disorders such as ODD, CD and ASPD (Flory et al. 2011;Harty et al. 2011;Kollins 2008;Mannuzza et al. 2008;McGough et al. 2005), but ADHD by itself is probably a significant risk factor for SUD (Biederman et al. 1995;Kousha et al. 2012). Studies have shown that the mean onset of SUD is approximately three years earlier for adolescents with

ADHD compared to control groups (Wilens et al. 1997). Patients with SUD and comorbid ADHD have a more prolonged SUD, and the remission time is considerably longer, compared to SUD patients without ADHD (Kollins 2008).

Clinical assessment of SUD may be challenging because the symptoms of acute and chronic drug intake and abstinence can resemble other medical or psychiatric symptoms like agitation, hallucinations, restlessness, communication difficulties or psychosis (Schuckit 2006). The clinician can fail to ask about alcohol and substance use (Hansen et al. 2000), and it may be underreported by the patients (de Beaurepaire et al. 2007). Studies of on-site urine screening tests for substances in urine have shown a large risk for inaccuracy (Bagoien et al. 2009;Mordal et al. 2010). Among psychiatric patients, when moderate or high prevalence of substance use is suspected, chromatographic methods for testing substances in urine should be considered for screening (Mordal et al. 2010).

A few studies have shown a possible protective effect of early CS treatment against the development of SUD in adulthood (Barkley et al. 2003;Biederman 2003;Katusic et al. 2005;Wilens et al. 2003), but the findings are not robust and there is a need for more research. A small number of controlled studies on CS treatment in adult ADHD with comorbid current SUD have shown no or very limited effect on both the ADHD symptoms and the SUD (Carpentier et al. 2005;Levin et al. 2006;Levin et al. 2007;Schubiner et al. 2002;Wilens et al. 2005b).

1.3.2 Comorbid Antisocial Personality Disorder

ASPD is according to DSM-IV an Axis II personality disorder characterized by a pervasive pattern of disregard for, and violation of, the rights of others that begins in childhood or early adolescence and continues into adulthood. Epidemiological studies have shown that 40-70% of children with ADHD meet the criteria for oppositional defiant disorder (ODD) and/or conduct disorder (CD) (Maughan et al. 2004;Szatmari et al. 1989). In groups of children with ODD and/or CD 40-60% meets the criteria for ADHD (Maughan et al. 2004;Szatmari et al. 1989). According to the ICD-10 system these children are often diagnosed with F90.1 hyperkinetic conduct disorder. It is important to emphasize that ADHD and CD are distinct psychiatric conditions, and that one can distinguish between these conditions in terms of diagnosis and treatment (Newcorn et al. 2009). In young adults disruptive behavior can persist and develop into ASPD. The estimate for ASPD in clinical samples of adults with ADHD varies between 7 and 44% (Barkley et al. 2008b).

The ICD-10 diagnosis dissocial personality disorder is corresponding to the DSM-IV diagnosis ASPD, but research has shown that the diagnostic criteria are remarkably discordant. In a study examining the cross-system concordance between the personality disorders of DSM-IV and Diagnostic Criteria for Research of ICD-10 the authors found the least concordant pair of personality disorders to be antisocial and dissocial (Ottosson et al. 2002). The reasons appear to be different criteria formulations and arbitrary thresholds for diagnoses, and the criteria for dissocial personality disorder may be vague compared with ASPD. Studies have shown a lower diagnostic threshold for ICD-10 to fulfill the criteria for personality disorder diagnoses compared to the DSM-IV (Sara et al. 1996;Starcevic et al. 1997).

1.4 Functional impairment in adult ADHD

ADHD in adults is in several studies associated with poor functional outcome in important life domains like educational and occupational achievement (Fischer et al. 1990;Kessler et al. 2005a;Mannuzza et al. 1993;Mannuzza et al. 1997;Murphy et al. 2002;Rasmussen and Gillberg 2000). Severity of childhood ADHD and comorbidity with CD is reported to correlate with the poor functional outcome in adults (Barkley et al. 1990;Newcorn et al. 2004). Other studies have indicated that occupational outcome might be more related to ADHD itself when the condition is continuing into adulthood (Mannuzza et al. 1993).

ADHD is related to criminality in adults, but research suggests that most of this relationship is mediated by comorbid CD and ASPD. Mannuzza and colleagues found in a prospective follow-up study that the presence of an antisocial/CD in young adulthood almost completely accounted for the increased risk for criminal activities whether or not it was accompanied by a SUD. Continuing ADHD at follow-up, by itself, was not associated with arrest history (Mannuzza et al. 1989). When the present studies started very few studies had addressed the relationship between CS treatment of childhood ADHD and functional outcomes in adulthood.

1.5 Central Stimulant treatment of ADHD in adults

ADHD is recognized as a lifelong condition in many patients, and therapy should for most individuals be long-term (Greydanus et al. 2007;National Institute for Health and Clinical Excellence 2008). A multimodal therapeutic approach is recommended in all ages, including behavioral therapy or cognitive behavioral therapy, psycho-education and

pharmacotherapy (Haavik et al. 2010;National Institute for Health and Clinical Excellence 2008). Pharmacological treatment has been the primary treatment for ADHD in adults, although a growing number of studies have showed that cognitive behavioral therapy also may improve ADHD symptoms in both medicated and not medicated adult ADHD patients (Safren et al. 2005;Safren et al. 2010a;Stevenson et al. 2002).

1.5.1 Central Stimulants

Central Stimulants (CS) like methylphenidate (MPH) and amphetamine (AMP) are considered to be the cornerstone of pharmacological treatment in ADHD. Non-stimulant medications like atomoxetine, bupropion, tricyclic antidepressants and guanfacine have also showed efficacy in reducing ADHD symptoms, but the effect sizes are probably lower compared to CS and there are few studies comparing CS and non-stimulants directly (Faraone et al. 2006b;Gibson et al. 2006;Newcorn 2008;Verbeeck et al. 2009;Wilens et al. 2002).

The calming effect of AMP on hyperactive children was discovered as early as 1937, and MPH was introduced as treatment for the same group in the 1960s (Lange et al. 2010). A large number of randomized, controlled studies and several meta-analyses have shown good short term efficacy of these drugs in all ages (Faraone et al. 2004;Faraone and Glatt 2009;Koesters et al. 2009;Schachter et al. 2001;Smith et al. 2000). There is some evidence for long-term efficacy in children (Jensen 2002;National Institute for Health and Clinical Excellence 2004;Wilens et al. 2002). When the present studies were initiated we could not find randomized, controlled CS treatment studies of adult ADHD lasting longer than 20 weeks, and very few long-term naturalistic or open-label extensions of controlled studies. Studies on effectiveness variables in CS treatment of adult ADHD were also lacking (Weiss et al. 2006).

The response rate of CS in adult ADHD is reported to be somewhat lower than in children and adolescents, and in controlled trials the response rate to CS in adults range between 25 to 78 % (Mattes et al. 1984;Spencer et al. 1996). MPH and AMP have distinct pharmacodynamic properties, and patients often express a preference for one preparation over another. However, in controlled trials of CS treatment in adult ADHD the efficacy of both MPH and AMP are roughly 60 % (Wilens et al. 2011).

All CS act on the catecholaminergic system and are thought to reduce ADHD symptoms by enhancing the availability of dopamine and norepinephrine in parts of the brain (Wilens 2008). The last two decades of innovation in the pharmacotherapy of ADHD has mostly been related to the development of different forms and release properties of MPH and AMP. In contrast to the original immediate release (IR) formulation of MPH, a range of different extended release (ER) formulations have been introduced (Banaschewski et al. 2006). The main argument for introducing these formulations has been the potential for better adherence and continuity to the treatment due to the simplified medication regimen when the patient only need one daily dose. To our knowledge the validity of this hypothesis had not been examined properly when the present study started.

Among the CS drugs MPH has been most used world-wide to treat ADHD in all ages, but the pattern of consumption of different CS varies geographically. A population-based prevalence study from the Nordic countries, including Norway, showed that the MPH/AMP ratio was more than 20:1 (Zoega et al. 2012) in all age groups. A retrospective claims-based analysis of a managed care population in USA showed a MPH/AMP ratio near 50:50 in all ages together, and a ratio of almost 2:3 in adult ADHD patients (Christensen et al. 2010).

1.5.2 Effectiveness versus efficacy

In medicine effectiveness relates to how well a treatment works in clinical practice, as opposed to efficacy, which measures how well it works in well-controlled clinical trials or laboratory studies. In terms of CS treatment of adult ADHD several clinically important effectiveness variables were understudied when the present studies started. Examples of such variables were rates of discontinuation of CS treatment in ordinary clinical practice, predictors for continuity and reasons for discontinuation of CS treatment, and the impact of comorbid disorders on aspects of CS treatment (Peterson et al. 2008;Weiss et al. 2006). In spite of good short-term efficacy in controlled studies there was evidence from more longitudinal studies of early discontinuation and short duration of CS treatment in many adult patients (Aanonsen NO 2004;Biederman et al. 2005;Olfson et al. 2007;Perwien et al. 2004;Weiss et al. 2006). Research indicates that the rate of discontinuation is especially large in the crucial developmental stage of late adolescence (McCarthy et al. 2009). Lack of efficacy and not tolerable adverse effects are common reasons for discontinuation of CS treatment but cannot alone explain the large discontinuation rates in clinical and community based studies. In a chronic and often life-long condition like ADHD one must expect prolonged CS treatment to be necessary to improve symptoms and reduce functional impairment.

2. The present thesis

From 1997 CS treatment of adult patients with ADHD was permitted by the Norwegian Health Authorities. Until then ADHD in adults was an almost unknown condition in Norwegian adult psychiatry. The lack of experience and knowledge about diagnosing and treating the disorder in adults raised numerous questions for the clinicians. The diagnostic

process was complicated and challenging partly due to high rates of comorbid disorders, requiring meticulous differential diagnostic assessments. Further there were challenges in relation to the pharmacological treatment of adult ADHD. CS is classified as narcotics and the use of these drugs was controversial in the public and among health care providers. It was known from research performed in the US that CS treatment of ADHD patients with comorbid SUD was associated with an increased risk for misuse, abuse and diversion of the drugs (Wilens et al. 2006).

Despite many unanswered questions and several controversial issues most clinicians soon realized that this was a severely impaired group of patients with high levels of functional impairment. In light of the suffering of the patients and all the unresolved questions a need to systematize our clinical experiences emerged. At this time the scientific knowledge about adult ADHD was almost entirely based on US studies. Norwegian or Scandinavian studies on the topic were almost lacking. This gave me the idea to initiate a research project; ***ADHD in adults - background, comorbidity and course of treatment***, based on a naturalistic and retrospective methodological approach using medical records as the source of data. As will be described later (Material and methods; Patients; Diagnostic assessment) the Norwegian Health Authorities established in 1997 a system of Expert Committee of Hyperkinetic Disorders/ADHD and mandatory procedures for assessment of adult ADHD. Due to this system large amounts of semi structured data was collected and documented in the medical records. The project had two main aims; 1) describe the clinical characteristics, functional impairment and comorbidity in this newly recognized group of patients in Norwegian adult psychiatry, and 2) investigate the course of long-term CS treatment in adult ADHD by variables like CS treatment duration, predictors of long-term CS treatment and impact of comorbidity on CS treatment.

At the same time another research project was initiated; ***ADHD in adults: The clinical significance of symptoms, functional impairment and quality of life.*** An aim of this study was to explore the relationship between CS treatment in childhood and adult occupational outcome.

2.1 Research questions

To describe psychiatric comorbidity and functional impairment in 3 samples of clinical adult ADHD patients (Paper I-IV)

To investigate CS treatment in a sample of adult ADHD and identify variables predicting long-term (> 3 years) CS treatment (Paper II)

To investigate the prevalence of SUD during long-term CS treatment in a sample of adult ADHD and identify variables associated with SUD during treatment (Paper III)

To identify variables predicting occupational outcome in adult ADHD (Paper IV)

2.2 Materials and methods

The present study is based on a retrospective, naturalistic design of 3 samples of adults diagnosed with ADHD in North-Trøndelag County in the period 1997 to 2009 using data collected from medical records. Paper IV additionally includes a cross-sectional questionnaire.

2.2.1 Patients

2.2.1.1 Recruitment of patients to the present studies

Papers I-III include nearly complete samples of adult ADHD patients consecutively diagnosed and treated with CS from the catchment area of Levanger hospital (90.000 inhabitants) during two partially overlapping time intervals; Paper I includes patients from 1997 to 2003 (N=45). Paper II and III extend inclusions from 1997 to May 2005 (N=117). The 45 patients in Paper I are included in the second sample. The Ministry of Health and Care Services gave permission for one psychiatrist (the author) to read the medical records and collect the data. The patients were informed by postal mail about the study and given the opportunity not to participate. Two patients refused participation.

The sample in Paper IV are based on invitations to participate sent by postal mail to all patients in the catchment areas of Levanger and Namsos hospitals being diagnosed with adult ADHD in the period 1997 to 2009. The hospitals have a total catchment area of 130.000 inhabitants, living in small towns and rural districts in Nord-Trøndelag County in Norway. During the period 586 adult patients had been diagnosed with Hyperkinetic disorder/ADHD according to the Patient Administrative System. A preliminary assessment showed that 79 of the subjects had been incorrectly registered with the diagnosis, 30 patients were found not to have a valid diagnosis, and 6 persons had died. A final number of 471 patients were invited to participate in the study. The response rate was 31.6 % (152 patients). Three patients were excluded due to specific learning difficulties, and the final number of participants in Paper IV was 149.

2.2.1.2 Diagnostic assessment

In the period 1997 to May 2005 the assessment of adult ADHD patients in Norway was done in two steps.

In the first step the primary assessment was done according to procedures published by Expert Committees of Hyperkinetic Disorders/ADHD (Attachment I), as part of ordinary hospital routines. The Expert Committees of Hyperkinetic Disorders/ADHD were established by the Norwegian Health Authorities in 1997 to secure adequate diagnosing and treatment of adult ADHD patients. In the period from October 1997 to May 2005 all patients with ADHD over 18 years who were considered for treatment with CS had to be evaluated and approved by one of three committees. During these years the committees handled more than 5000 applications for treatment, recommending CS treatment in 3397 cases. In May 2005 this system was replaced by National Guidelines for Diagnosing Lifespan ADHD (The Norwegian Directorate of Health 2004). These guidelines continued the assessment procedures introduced by the Expert Committees. Levanger and Namsos hospitals implemented these guidelines, and introduced two additional elements; 1) the General Adult ADD Symptom Checklist (GAASC) (Amen 1997) was replaced by the Adult ADHD Self-Report Scale (ASRS) Version 1.1 (Kessler et al. 2005b), and 2) the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998) was introduced as a mandatory tool for diagnosing comorbidity.

The procedures included a systematic assessment of ADHD according to the ICD-10, research criteria (World Health Organization 1992) (Attachment II), with two modifications: The inattentive subtype of ADHD according to DSM-IV was regarded as sufficient for the diagnosis, and the presence of comorbid psychiatric disorders were not a criterion for exclusion regarding neither the diagnosis of ADHD nor CS treatment. The procedures

included an examination for prior or present symptoms of psychosis, depression, bipolar disorder, anxiety disorders, conduct disorders and SUD. A physical examination, blood tests and electrocardiogram were mandatory. Collateral information about the patients' childhood (<7 years old) were collected from parents, teachers or other relevant persons to confirm whether they met criteria for ADHD in childhood. The patients also had to complete two self-report inventories; the Symptom Checklist 90-items (SCL-90) (DeRogatis et al. 1974) and the GAASC. When comorbid SUD was suspected the patients were required to substantiate at least 3 months of abstinence from SUD before initiating CS treatment, and in many cases also a period after initiation of treatment. Abstinence was in most cases documented by the use of urine tests twice weekly at the office of the general practitioner, and analyzed by using Liquid Chromatography/Mass Spectrometry methodology.

In a second step a report with all information gathered in the first step was sent to the Expert Committee of Hyperkinetic Disorders/ADHD for a definitive recommendation. The clinicians in charge of the treatment would start CS treatment only after a written recommendation was received from the Committee.

2.2.2 Measures

2.2.2.1 Sociodemographic variables

In Papers I-III sociodemographic data like age, gender, level of education and occupational status at the time of data collection were collected from the medical records. In Paper IV this information were obtained from the participants using a self-report questionnaire. Occupational status refers to the individual's source of income. The Norwegian social welfare system comprises social benefits such as unemployment benefit, sickness benefits, vocational rehabilitation, and medical rehabilitation. Due to their temporary nature, these categories are statistically pooled in one group, called temporary social benefit.

Disability pension differs from temporary social benefits as it is most often a lifelong benefit obtained only when treatment and rehabilitation most likely will not enable the individual to attain a job again.

In Paper IV we also wanted to measure the extent of labor force participation, and included in the self-report questionnaire an item about the number of months the patient had been in work for the last year.

2.2.2.2 Comorbidity

Comorbidity with psychiatric disorders was based on information collected from the medical records. A comorbid disorder was diagnosed if the medical record clearly confirmed the criteria of a diagnosis according to DSM-IV (Papers II-IV) or ICD-10 Diagnostic criteria for research (Paper I). In Paper III patients with lifetime comorbid SUD were classified as Comorbid SUD. The group Comorbid SUD was sub-classified into 4 groups according to the main substance of abuse; alcohol, amphetamine, opiates and cannabis. Patients with no lifetime history of SUD were classified as No comorbid SUD.

2.2.2.3 Prevalence of SUD during CS treatment

In Paper III clinical data about SUD during the CS treatment period was collected from the medical records. Relapse or onset of SUD was defined as fulfilling the DSM-IV criteria for one or more of the sub-classes of SUD for at least a week (alcohol, amphetamines, cannabis and opiates). Patients with one or more relapses were classified into the group Relapse of SUD, while patients without relapse were classified into the group No relapse of SUD. Patients without previous comorbid SUD, but with onset of SUD during CS treatment, would be classified as Onset of SUD group.

2.2.2.4 Duration of abstinence from SUD

The duration of abstinence from SUD before CS treatment was estimated based on all available information in the medical records at baseline. The patients were divided into two groups according to the DSM-IV remission specifiers (American Psychiatric Association 1994).

1) Remission < 12 months.

   Early Partial Remission: This classification indicates that one or more, but not all criteria for Dependence or Abuse have been met for at least one month, but less than 12 months.

   Early Full Remission: This classification indicates that no criteria for Dependence or Abuse have been met for at least one month, but for less than 12 months.

2) Remission > 12 months.

   Sustained Partial Remission: This classification indicates that one or more, but not all criteria for Dependence or Abuse have been met for a period of 12 months or longer.

   Sustained Full Remission: This classification indicates that none of the criteria for Dependence or Abuse have been met at any time during a period of 12 months or longer.

2.2.2.5 CS treatment variables

Information about received CS treatment was collected at follow-up December 31, 2008. The total duration of CS treatment was defined as the total number of months the patients had used CS during the period 1997 to follow-up, as described in the medical record. Treatment interruptions that lasted more than 3 months were not included in the total duration. In Paper II treatment duration was dichotomized into two groups; patients with duration of CS treatment less than 36 months or duration of CS treatment 36 months or more. The types of CS used by the patients were MPH IR, MPH ER (Ritalin LA MPH

hydrochloride extended-release capsules or OROS MPH hydrochloride) and dexamphetamine IR. Amphetamine/dexamphetamine ER was not used because it was not available in Norway during the study period. The maintenance dose was registered for MPH only. Reasons for discontinuation of CS treatment was registered, and so was the number of patients switching to a second type of CS and the type of the second CS.

2.2.2.6 Self-Report Questionnaire

The questionnaire included sociodemographic characteristics like gender, age, current level of education, occupational status, and number of months in ordinary work the last year. Occupational status refers to the individual's source of income (Attachment 4). The questionnaire further included the ASRS-version 1.1. The ASRS is the WHOs self-report rating scale for adult ADHD) and is designed to assess current ADHD symptoms. It consists of 18 items based on the DSM-IV diagnostic criteria for ADHD. The items are measured on a 5-point scale with range 0 to 72. Higher scores indicate higher frequencies of symptoms and symptom load. The scale is organized in two sections, each with its own sum score. Items 1 to 9 (Part A) reflects symptoms of inattention and items 10 to 18 (Part B) reflects symptoms of impulsivity or hyperactivity.

2.2.3 Procedures

The majority of data for the present study was retrospectively collected from the medical records by an experienced psychiatrist (the author). The Ministry of Health and Care Services gave permission only for one psychiatrist to read the medical records and collect the data. A data collecting form was made before screening the medical records (Attachment 3). Baseline was set to the time the patient started CS treatment in the period 1997 to 2003 (Paper

I) and May 2005 (Paper II and III). For paper II and III the time for follow up was December 31, 2008; 43 months after the inclusion of the last patient in May 2005. Many patients terminated the CS treatment before December 31, 2008. For these patients follow-up was the time of their last contact with the hospital. For Paper IV the cross-sectional data from the questionnaire (Attachment 2) was completed by the patients in the summer of 2009, and the retrospective data from the medical records collected autumn 2009.

2.3 Statistics

Data were initially analyzed to describe and compare frequencies and prevalence of variables. We used contingency tables (Chi-square tests and Fisher's exact test) for categorical variables, and Students T-test and Mann-Whitney tests for continuous variables. In Paper II and III logistic regression analyses were carried out to explore possible effects of different variables on dichotome outcome measures. Odds ratio for the significant predictive variables was calculated. In Paper IV we conducted bivariate correlation analyses to explore correlations between possible predictor variables. To test the model with the hypothesized predictors we used a hierarchical multiple regression model.

The statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA) version 12 (Paper I), version 17 (Paper II and III), and version 16 (Paper IV).

2.4 Ethics

In the period 1997 to May 2005 the patients had provided a written general consent when they started CS treatment allowing data from their medical records to be used in later research projects initiated by health authorities. For Paper I the Levanger Hospital and the

Regional Research Ethical Committee of Middle Norway gave permission to collect data from the medical records without an additional consent from the patients.

For Paper II and III the Ministry of Health and Care Services gave permission to collect data from the medical records without an additional consent from the patients, but all patients had to be informed by postal mail about the study and given the opportunity not to participate. The Regional Research Ethical Committee of Middle Norway and the Levanger Hospital approved the study.

For Paper IV the study had been approved by the Norwegian University of Technology and science, Faculty of Social science, Department of Psychology and Levanger Hospital, and the Regional Ethical Committee of Middle Norway. Apart from the exceptions described above with respect to the lack of informed consent the studies have been carried out in accordance with the Declaration of Helsinki.

3. Results

3.1 Paper I

Paper I is a naturalistic, retrospective study using data from medical records. The aim of the study were to explore the clinical characteristics, functional impairment and comorbidity of a sample consisting of all patients diagnosed with adult ADHD and starting CS treatment in a specific catchment area during the period 1997 to 2003 (N=45; 11 females and 34 males). The patients were evaluated when they started CS treatment in adulthood. Mean age was 28.3 years (males 29.4, females 25.1). Forty-four patients (97.8%) fulfilled the criteria for DSM-IV ADHD combined type in childhood. All described a chronic course of ADHD symptoms from childhood to adulthood. Twenty- nine (62.2%) had been in contact

with child and adolescence psychiatry (CAP) and/or pedagogic-psychological services (PPS) at school (22 men, 7 women), but only 8 (17.8%) had been diagnosed with ADHD in childhood or adolescence. Nine (20%) had been diagnosed with learning disability, 15 (33%) with CD and four (8.9%) had epilepsy in childhood. Seven patients (15.5 %), all men, had been medicated with CS in childhood for shorter periods (maximum 2 years).

Fourteen patients (31.2 %) were employed or studying. Most patients (78 %) were receiving their income from social welfare benefits. Twenty-one (46.7 %) patients had one or more criminal sentences.

Thirty-nine patients (86.7 %) had at least one life-time comorbid disorder according to ICD-10 Criteria for research. Lifetime major depression (53.0 %), dyssocial personality disorder (44.0 %), alcohol abuse disorder (47.0 %), cannabis abuse disorder (51.0 %) and amphetamine abuse disorder (49.0 %) were the most frequent comorbid diagnoses. There were no significant differences between men and women.

3.2 Paper II

Paper II is a naturalistic, retrospective study using data from medical records. The aim of the study were to examine duration of CS treatment and identifying predictors for long-term treatment (> 3 years) in a sample of almost all patients diagnosed with adult ADHD and starting CS treatment in the period 1997 to May 2005 (N=117; 32 females and 85 males). Almost all patients (96.7 %) fulfilled the criteria for DSM-IV ADHD combined subtype in childhood. All described a chronic course of ADHD symptoms from childhood to adulthood. 22 patients (18.8%) had been diagnosed with ADHD in childhood or adolescence, and 17 patients (14.5 %) had been medicated with CS before age 18. Mean age was 28.6 years (males 28.1, females 30.1).

Lifetime depression (32.5 %), ASPD (29.9 %), alcohol abuse disorder (47.0 %), cannabis abuse disorder (41.9 %), amphetamine abuse disorder (41.0 %) and Any SUD (46.2 %) were the most common comorbid DSM-IV disorders. The variable Any SUD includes amphetamines, cannabis, and/or opiates. There were significant gender differences, with significantly more ASPD ($p= 0.003$) and Any SUD ($p=0.047$) among the men, and borderline personality disorder ($p=0.001$) among the women. Level of educational achievement was very low, and only 21 patients (17.9 %) were employed or studying.

Most patients (94.0 %) started treatment with MPH IR, but 52.1 % changed later to MPH ER (54.1 %) or dexamphetamine IR (45.9 %). The main reasons for changing to a second CS were side effects (29.5 %), lack of effect (23.0 %), compliance problems (21.3 %) and problems related to SUD (6.5 %). The average maintenance dose of MPH IR and/or ER was 58.9 mg/day. The median duration of CS treatment at follow-up was 33.0 months.

In univariate analyses patients with CS treatment duration ≥36 months were significantly more often treated with MPH ER, had significantly more often switched to a second CS, a higher maintenance dose of MPH, and lower prevalence of the adverse effect nervousness. They had significantly less contact with pedagogical and psychological services (PPS) in school, and more comorbidity with SUD and ASPD. A logistic regression analysis of this seven variables with $p<0.05$, and the variable gender, found that use of MPH ER ($p=0.009$) was a positive predictor of CS treatment duration ≥36 months, and comorbid ASPD ($p=0.005$) was a negative predictor of CS treatment duration ≥36 months

3.3 Paper III

Paper III is a naturalistic, retrospective study using data from medical records. The aim of the study were to examine the prevalence and predictors of SUD during CS treatment in a sample of almost all patients diagnosed with adult ADHD and starting CS treatment in the period 1997 to May 2005 (N=117; 85 males and 32 females). The sample is identical to the sample in Paper II.

The Comorbid SUD group (N=65) indicating lifetime history of SUD (alcohol, amphetamine, cannabis and/or opiates) before CS treatment had one or more relapses of SUD in 38 patients (58.5 %) during the CS treatment period. The No comorbid SUD group (N=52) had no incidence of SUD during CS treatment.

Univariate analyses showed that the Relapse of SUD group (N=38) had significantly more comorbid ASPD [27 patients (71.1 %) versus 7 patients (25.9 %), $p<0.001$], younger age when starting CS treatment as adults (26.9 versus 31.6 years, $p<0.001$), and fewer patients with a length of cannabis abstinence more than 12 months before initiation of CS treatment [3 patients (7.9 %) versus 7 patients (25.9 %), $p=0.003$], compared to the No relapse of SUD group. The logistic regression analysis with the 3 significant variables as independent variables showed that length of cannabis abstinence more than 12 months was a significant ($p=0.012$) negative predictor for relapse of SUD.

The Relapse of SUD group had significantly reduced length of CS treatment compared to the No relapse of SUD group (19.3 versus 40.0 months, $p= 0.001$). The duration of CS treatment was almost equal in the No relapse of SUD group and the No comorbid SUD group (40.0 versus 41.1 months). Twenty-seven (71.0 %) patients in the Relapse of SUD group terminated CS treatment because of a relapse of SUD.

3.4 Paper IV

Paper IV is a cross-sectional study using data collected from two different sources; the medical records and a self-report questionnaire. The aims of the study were to describe functional and clinical characteristics, and to identify possible predictors of occupational outcome in a clinical sample of adult ADHD invited to participate (N=149; 78 females, 71 males).

Twenty-three patients (17.4%) had started CS treatment by the age of 18 or earlier, 45 patients (34.1%) had started between the age of 19 and 30, 40 patients (30.3%) had started between the age of 31 and 40, and 24 patients (18.2%) had started by the age of 41 or above.

Lifetime depression (37.8 %), lifetime anxiety disorder (14.6 %), ASPD (9.0 %), alcohol abuse disorder (23.3 %), and SUD (28.1 %) were the most common comorbid DSM-IV disorders. We found significantly more SUD and ASPD among the men.

Forty-eight patients (33.3%) were receiving disability pension and 55 patients (38.2%) were received some type of temporary social benefit. Fifty-two patients (44.4%) had not been in work or studies for the last 12 months, 18 (15.4%) had been working or studying for 1 to 4 months, 9 (7.7%) for 5 to 8 months, and 38 (32.5%) for 9 to 12 months.

Age of first CS treatment was significantly and negatively related to occupational status, $r = -.24$ ($p < .05$). ASRS scores were also negatively related to occupational status, with a significant negative correlation between Part A (inattentiveness) and occupational status, $r = -.20$ ($p < .05$).

Hierarchical regression was applied to test the hypothesis of predictors of occupational outcome. Later age of first CS treatment and higher inattentiveness ratings were associated with lower level of employment.

4. Discussion

4.1 Methodological issues

The present study has a number of strengths: we were able to include almost all adult ADHD patients consecutively starting CS treatment in the catchment area; the assessment of the ADHD diagnosis was rigorous for a naturalistic study with developmental history obtained from collateral informants in most cases; and the duration of follow-up was long (minimum 43 months). These characteristics of the samples in Paper I-III make the present study quite unique in the research literature of adult ADHD. Despite these strengths the study has limitations, and some of the limitations are inherent in the naturalistic and retrospective study design.

4.1.1 Patients

The patients in the present samples consist of predominantly untreated, self-referred adults with ADHD, as opposed to children with ADHD followed to adulthood (Barkley et al. 2008a). The mean age (28.3 and 28.6 years) and the female/male ratio (25/75) in the samples in Paper I-III was almost the same (mean age 28.3, female/male ratio 27/73) as found in another Norwegian study by Rasmussen and Levander (Rasmussen and Levander 2009) describing a sample of 600 consecutive adult ADHD patients from Middle and Northern Norway. The large proportion of males and the low mean age distinguishes the present studies from the majority of randomized, controlled studies of CS treatment. A meta-analysis of 22 controlled studies of pharmacological treatment in adult ADHD found a female/male ratio of 41/59, with a mean age of 38 years (Peterson et al. 2008). The mean age (33.7 years) and the female/male ratio (52/48) in the present sample of invited patients (Paper IV) are more in accordance with the results from this review. The sample described in Paper IV is also similar

to the sample in another Norwegian study of 414 adult ADHD patients invited to participate, showing a mean age of 34.5 years and a female/male ratio of 48/52 (Halmoy et al. 2009). A German study of 70 adult ADHD patients recruited from consecutive referrals to an ADHD specialty outpatient clinic showed a mean age of 36.8 years and a female/male ratio of 46/54 (Sobanski et al. 2007). Kooij and colleagues found an under representation of men and younger people in their validity study from Netherlands (Kooij et al. 2005). These findings may reflect a greater willingness among females and older people to participate in studies. A major strength of the present study is the clinical representativeness and especially the inclusion of young men. Data from this kind of naturalistic sample may give important information that supplements the results from controlled studies of CS treatment in adult ADHD.

While most randomized, controlled studies of CS treatment in adult ADHD exclude patients with comorbid disorders typical for clinical settings, the present study includes almost all patients consecutively diagnosed with ADHD and initiating CS treatment in the catchment area. An objection against the high rates of comorbid disorders in a study like the present is the problem with generalization of the results to samples with less comorbidity. Despite the lack of exclusion criteria in the present study there are many sources of bias associated with the referral procedure (Hartman et al 2002). During the first years of this study the knowledge about adult ADHD was sparse and variable in the Norwegian health care system, among the patients and in the community. General practitioners referral practices for assessment of adult ADHD was probably inconsistent. Patients with serious and ongoing comorbidity may never have reached the point in their health care process where assessment for ADHD was considered. Selection biases are probably present to a lesser degree in the samples in Paper I-III than in the invited sample in Paper IV. Patients responding to an invitation to participate in a research project tend to be more motivated and concerned about their health, and may differ

from the broader target population with respect to gender, age, comorbidity, etc. (Hartman et al 2002).

4.1.2 Procedures

The present data are based on the clinical contact between patient and clinician as described in the medical record thus providing an image of a real world situation. In addition the majority of patients were followed for years and in most cases the clinician knew the patient well.

However, the naturalistic and retrospective approach of the present study provides several limitations. Retrospective collection of data from medical records gives variable amounts and quality of information from one patient to another. The quality of the data depends on a number of factors like frequency of contact between patient and clinician, and quality and amount of documentation in the medical record. Information about sociodemographic data and educational and occupational status is likely to be reliable. The assessment of comorbidity, length of abstinence from SUD and prevalence of relapse of SUD during CS treatment may be less reliable. Information about CS treatment given is likely to be reliable despite we had no other control of the patient's adherence to the prescribed treatment than prescriptions registered and information from the patient. The Ministry of Health and Care Services gave permission for only one psychiatrist to read the medical records and collect the data, and this restriction made it impossible to use more than one investigator and calculate inter-rater reliability.

The patients were diagnosed and treated by several clinicians with heterogeneous experience and competence. This problem was to some extent compensated for by using procedures published by the Expert Committee of Hyperkinetic Disorders/ADHD and a reassessment of all cases by the committee (Paper I-III). The total assessment of the patients in this sample may be considered as comprehensive.

In Paper III the detection of relapse or onset of SUD during CS treatment was an important issue. The clinician treating the patient used in most cases urine tests analyzed by chromatographic methods if SUD was suspected and the patient did not reveal such use. Studies done among patients admitted to Norwegian acute psychiatric wards have shown that SUD is under detected if the clinician uses interview as the only source of information (Flovig et al. 2009;Mordal et al. 2010). However, negative urine tests do not exclude current SUD as the different toxicological techniques have different sensitivity, specificity and analytic range. In urine most drugs can be detected only a few days after intake. Cannabis can be detected for a longer period (Verstraete 2004). The high level of baseline comorbid SUD and the high number of detected relapses of SUD could suggest that the routines for diagnosing and detecting SUD at the clinic were adequate.

According to ICD-10 a diagnosis of ADHD requires the presence of symptoms before 7 years of age. Although retrospective assessment of psychopathology is non-optimal in adults, there are studies indicating that a retrospective diagnosis of childhood-onset ADHD can be made reliably (Spencer et al. 1998;Ward et al. 1993). Furthermore the diagnostic criteria were verified by corroborative information from persons with knowledge about the patients' childhood in a substantial number of our subjects. However, there are uncertainties embedded in the retrospective approach of diagnostic assessment. Acknowledged limitations notwithstanding, the knowledge gained from a retrospective and naturalistic study like the

present is relevant as an addition to empirical studies with more stringent methodology, or where such are lacking, as is the case concerning the present topics.

4.2 Discussion on the main findings

4.2.1 Comorbidity

The prevalence of comorbid disorders was high in the present studies. In Paper I we found that 87 % of the patients had at least one comorbid psychiatric disorder, and this is in line with other studies (Barkley et al. 2008b;McGough et al. 2005).The prevalence's of the most frequent comorbid disorders showed substantial variation between the 3 samples; lifetime major depression ranged between 33 and 53 %, ASPD between 9 and 44 %, alcohol abuse disorder between 23 and 47 %, and any SUD between 28 and 46 %. A dominant trend was that the prevalence's of ASPD, alcohol abuse disorder and SUD were highest in the samples described in Paper I-III, reflecting the inclusion of all patients in the catchment area and the high proportion of young males. Research has consistently showed that the rates of CD, ASPD, alcohol use disorder and SUD are significantly higher for males than females (Biederman et al. 1994;Halmoy et al. 2009;Sobanski et al. 2007;Sprafkin et al. 2007). Conversely, for lifetime major depression the prevalence was higher among patients included in Paper IV than Paper II/III, probably reflecting the high proportion of women in this sample. From the literature on ADHD it appears that female patients have more affective disorders than males (Biederman et al. 1994;Halmoy et al. 2009;Sobanski et al. 2007;Sprafkin et al. 2007). However, this is also reflected in the general population. In a large epidemiological

study from Norway the lifetime prevalence of major depression in men was 9.9% versus 24% among women (Kringlen et al. 2001).

There were no significant differences between the genders in ADHD symptoms in the samples in Paper II-IV, but the females had significantly higher levels of psychiatric symptoms as measured by SCL-90 Global Severity Index, and this is in line with previous research (Biederman et al. 1994;Cumyn et al. 2009;Rasmussen and Levander 2009;Robison et al. 2008).

Compared to previous studies following children with ADHD to adulthood (Mannuzza et al. 1993;Mannuzza et al. 1998;Weiss et al. 1985) the comorbidity rates of the samples in the present Papers I-III are high. The prevalence rates of ASPD, alcohol use disorder and SUD are more like previous studies of self-referred adults with ADHD (Biederman et al. 1993;Murphy and Barkley 1996). More recently published clinical samples of self-referred adult ADHD patients from Norway and Germany present comorbidity rates lower than the present study (Halmoy et al. 2009;Rasmussen and Levander 2009;Sobanski et al. 2007). There may be several reasons for the high comorbidity rates in the present study. Research has showed that comorbidity is significantly higher in clinical samples like the present compared to community and epidemiological samples (Kessler et al. 2006). Secondly the samples consisted of patients assessed not only at the psychiatric clinic but also at a specialized out-patient clinic for SUD and a clinic for congenital neuropsychiatric disorders. A third reason may be the method of collecting data from the medical records. The medical records contained for most patients abundant information collected during several years of treatment and from various sources. Compared to a cross-sectional interview or self-rating inventory the detection rate of comorbid disorders may be higher with this methodology. Previous research has showed that the combined subtype of ADHD is related to functional

impairment and comorbidity (Molina et al. 2009), and in our samples the combined subtype dominated.

Barkley and colleagues compared in their book "ADHD in adults. What the science says" a sample of children with ADHD followed to adulthood with a sample of self-referred adults with ADHD. The results indicated that children with ADHD as adults had more comorbid SUD and ASPD compared with self-referred adults, but less anxiety and depression (Barkley et al. 2008b). The present samples cannot exactly be classified into one of these groups; the majority of the patients were self-referred as adults, but a substantial number was first diagnosed with ADHD as children, or was identified as children with mental problems in child and adolescence psychiatry.

The prevalence of dissocial personality disorder according to ICD-10 Criteria for research in Paper I was twice as high as reported for DSM-IV ASPD in most other studies (Mannuzza et al. 1993;Mannuzza et al. 1998). Further, the prevalence for dissocial personality disorder was higher in Paper I than the prevalence for ASPD presented in Paper II-IV. This may be due to the lack of concordance between the criteria for the two diagnoses (Ottosson et al. 2002;Sara et al. 1996;Starcevic et al. 1997). Another reason may be the small numbers in Paper I which may cause large effects on prevalence. The relationship between ADHD combined type and ASPD is consistent with findings from previous studies on children and adults (Murphy et al. 2002). The very high prevalence of dissocial personality disorder in Paper I may reflect a genuine high level of this disorder among the ADHD patients seeking CS treatment the first years after CS treatment was allowed for adults in 1997.

4.2.2 Functional impairment

Many previous studies have shown significant educational and occupational impairment in samples of adult ADHD (Biederman et al. 1993;Mannuzza et al. 1993;Murphy and Barkley 1996;Murphy et al. 2002;Rasmussen and Gillberg 2000), and even worse in the presence of comorbid psychiatric disorders (Jensen et al. 1997;Sobanski et al. 2007). The present samples of predominantly self-referred adults with ADHD had a very high degree of educational and occupational impairment. The rate of current employment ranged between 16 and 22 %, in contrast to the overall employment rate in the general adult population in Norway which is about 70 % (Statistics Norway 2005). These findings may indicate that our sample is more impaired than is typical of most US studies (Barkley et al. 2008d), but major differences in the social welfare system between the countries may explain lower employment figures in patient populations in Norway as compared to the US. The number of patients having junior high school as their highest degree of education ranged between 48 % in Paper IV to 80 % in Paper I-III, as compared to 30 % in the general Norwegian population in 2009 (Statistics Norway 2010). Thus a majority of the sample had an educational level not suited for most domains in the labor-market. In Paper IV only 8.9 % reported having a college or university degree, compared to 20.8 % in the general Norwegian population at the time of data collection (Statistics Norway 2010).

Barkley and colleagues (Barkley et al. 2008d) have compared samples of self-referred adults with ADHD to children with ADHD growing up and showed that the latter group is more adversely affected in their educational career. This may seem like a contradiction to our findings of very impaired self-referred adults with ADHD. A possible explanation is that the self-referred adults assessed for ADHD in Norway the first years after CS was allowed in 1997 probably are more severely affected by their ADHD than is typical of US studies

(Barkley et al. 2008d). Previous findings also suggest that unemployment might be related to other symptoms, deficits and comorbid disorders than what is accounted for by ADHD alone (Sobanski et al. 2007;Young et al. 2003).

One might speculate that the severe impairment seen in our samples in terms of educational and occupational functioning could be due to lack of proper recognition and treatment in childhood ADHD. The design of the present study does not allow for any conclusions regarding this question. There are, however, some arguments for this view. Alcohol use disorders and SUD are by themselves unfavourable indices for functional impairment. ADHD is a risk factor for drug abuse (Biederman et al. 1997;Mannuzza et al. 1991), and recent studies indicate that CS treatment in childhood may reduce the risk for later adult SUD, especially in adolescence but also in adulthood (Biederman et al. 2008a;Wilens et al. 2003). There are many theories why CS treatment reduces the risk for SUD, and one is that CS indirectly reduces the risk by diminishing conduct symptoms, as CD and later ASPD are predictors of SUD (Klein et al. 1997). Another possible explanation is that CS treatment reduces ADHD symptoms, demoralization, poor self-esteem, academic and occupational failure; factors associated independently with risk for SUD (Brook et al. 1995;Crum et al. 1992;Kandel and Logan 1984). A review by Hechtman and Greenfield (Hechtman and Greenfield 2003) found that children treated with CS for 2 years showed improvement in ADHD symptoms, comorbid ODD, and academic and school functioning. Follow-up periods into adulthood showed that CS treatment in childhood also was beneficial for social skills and self-esteem. Higher doses and longer treatment period predicted less comorbidity and better social functioning (Hechtman and Greenfield 2003). A Norwegian study by Halmøy and colleagues found that early recognition and treatment of ADHD was a strong predictor of being in work as an adult, independently of comorbidity, substance abuse, and current treatment (Halmoy et al. 2009).

An issue related both to ASPD and functional impairment is criminality. In Paper I we showed that half of the patients (47 %) had one or more criminal sentences, and 24 % had at least 2 types of sentences (violence, theft, drug-related crime and drunk driving). A substantial number of studies have shown that ADHD is a predictor for criminal activity itself, although comorbidity with CD and ASPD is the major cause of criminality in the ADHD population (Barkley et al. 2008c).

4.2.3 Variables predicting long-term (> 3 years) CS treatment

The primary aim of Paper II was to investigate the duration of CS treatment in a naturalistic and unselected sample of highly comorbid self-referred adults with ADHD. Despite the high levels of comorbidity and functional impairment the patients had a median duration of CS treatment of 33.0 months. This is comparable to an Italian study of CS treatment in children showing 46 % persistent use after 36 months (Atzori et al. 2009). We have found no other studies of adult ADHD showing duration of CS treatment as long as the present study. A systematic long-term follow-up study from Sweden showed that 50% of the patients continued CS treatment for 24 months or more (Bejerot et al. 2010). This study had excluded patients with major comorbidities like SUD and severe personality disorders. A report to Norwegian Health authorities on all adult ADHD patients treated with CS in Norway in the period 1997–2003 (1328 patients), showed that only 20% were still in treatment after 24 months (Aanonsen NO 2004). In an open study of treatment with mixed amphetamine salts (MAS) in a selected US sample of adult ADHD patients, only 34 % of the patients were still using MAS after 24 months (Biederman et al. 2005). Studies of US pharmacy claim data

bases show duration of CS treatment for only a few months in adult ADHD (Hodgkins et al. 2011;Olfson et al. 2007).

The reasons for the long duration of CS treatment in the present sample are unknown. The hospital had a policy of following the patients a long time before transferring the responsibility for treatment to the general practitioner. These circumstances, and the fact that the clinic was the only psychiatric clinic diagnosing and treating ADHD in the area, may have resulted in more stable and prolonged contact between the clinician and the patient. Results from the MTA study have indicated that treatment by specialists in ADHD treatment give better results than community treatment in children and adolescents (Molina et al. 2009). Olfson and colleagues also showed an association between longer duration and treatment by a psychiatrist (Olfson et al. 2007). In addition, the population in the catchment area, which is made up of rural districts and small towns, is quite homogeneous and stable. This could contribute to longer duration of treatment, although research has revealed conflicting results about the significance of urban versus rural districts on duration of CS treatment (Cox et al. 2003).

A number of studies from different countries have shown large geographical differences in prevalence of CS treatment in both children and adults with ADHD, without having been able to identify the causes of these geographical variations (Aanonsen NO 2004;Cox et al. 2003;Janols et al. 2009;Prosser and Reid 2009). Nord-Trøndelag county, were the present study took place, are among the counties in Norway with the highest prevalence of CS treatment in Norway (The Norwegian Institute of Public Health 2010). Bejerot and colleagues (Bejerot et al. 2010) discusses the importance of skillful, understanding and supportive clinicians to achieve high compliance rates. Other authors have discussed the importance of enthusiastic physicians for CS treatment prevalence and duration (Cox et al. 2003).

Another major finding in the present study is the positive prediction of CS treatment duration ≥36 months by the use of MPH ER in a severely impaired and comorbid sample like the present. This finding adds to other studies indicating an association between ER formulations and longer duration of CS treatment in adult ADHD (Kemner and Lage 2006;Olfson et al. 2007;van den Ban et al. 2010). A Spanish study based on chart reviews also found that a switch from MPH IR to MPH ER was associated with both a significant reduction of ADHD symptoms, longer treatment duration and better compliance (Ramos-Quiroga et al. 2008). There is reason to believe that superiority in efficacy and more convenient medication of ER formulations may contribute to longer duration and better compliance. However, two recent meta-analyses have given conflicting results about the superiority in efficacy of ER formulations over IR formulations in controlled studies (Faraone and Glatt 2009;Peterson et al. 2008).

Comorbid ASPD predicted CS treatment duration negatively, and there are several possible explanations for this finding. ASPD has a strong association to SUD, and information from the medical records revealed that problems related to SUD were important reasons for discontinuation of CS treatment in Paper II (23.1 %). In Table 2 of Paper II we showed that comorbid Any SUD (includes amphetamine, cannabis and/or opiates), comorbid cannabis abuse and comorbid opiate abuse were significantly more prevalent in the group with less than 3 years of treatment. However, when entered into the logistic regression model none of the comorbid SUD variables were significant predictors, while ASPD was a significant predictor ($p=0.001$). Based on various data from this study it is still reason to believe that comorbid SUD is related to shorter duration of CS treatment. Criminal activity, which is often associated to ASPD, is also difficult to combine with stable medical follow-up.

The finding that contact with PPS in school predicted long duration negatively is of uncertain importance. At the time the patients in the present study were children, the interest

in and knowledge of ADHD was sparse in Norway. Most likely contact with PPS in school reflects severity of the condition in childhood, and comorbidity with conduct disorders and learning disabilities.

The present study showed that it is possible to treat adult ADHD patients with high levels of comorbidity and functional impairment for many years. Because of the methodological deficiences of the study we could not show improvement in ADHD symptoms, comorbidity, quality of life or functional outcomes. A key issue regarding duration of CS treatment in adult ADHD is whether the efficacy shown in short-term studies is maintained during long-term treatment. In other words; do we know that long-term CS treatment is necessary and desirable in adult ADHD? A few long-term studies in children of functional outcomes indicates sustained effects of CS treatment on ADHD symptoms over years, and even some effect on functional outcomes (Biederman et al. 2009;Hechtman et al. 1984;Hechtman and Greenfield 2003;Powers et al. 2008). The MTA study showed initially that 14 months of intensive CS treatment in a large sample of ADHD children was superior to behavioral treatment and community treatment (The MTA Cooperative Group 1999), but later follow-up studies of this sample showed that type or intensity of the 14 months treatment did not predict functioning 6 to 8 years later (Molina et al. 2009). Instead they found that early ADHD symptoms regardless of treatment type was prognostic, and that children with the combined subtype of ADHD exhibited significant impairment in adolescence regardless of treatment (Molina et al. 2009).

Very few studies of CS treatment in adult ADHD have lasted more than a year. A naturalistic Swedish study showed that 50 % of adult ADHD patients remained in CS treatment after 2 years, and the effect on ADHD symptoms was good and the adverse effects mild (Bejerot et al. 2010). Biederman and colleagues found similar results in an open-label 24-months study of mixed amphetamine salts in adult ADHD, but in this study only 36 %

continued treatment for 2 years (Biederman et al. 2005). In a recently published open-label trial by Wender and colleagues, patients continuing 12 months of MPH immediate release (IR) treatment showed significant improvement on both symptoms and social functioning (Wender et al. 2010). Based on the limited research available we may conclude that CS treatment in adult ADHD has long-term beneficial effects for many patients.

4.2.4 Prevalence of SUD during long-term CS treatment

To our knowledge the present study is the first to explore this clinically important and controversial issue. The present study could not detect any onset of SUD during CS treatment in the group of patients who did not have comorbid SUD at baseline despite a very long treatment period (mean 41.1 months). This finding indicates that CS treatment in adult ADHD patients with no previous SUD does not precipitate onset of SUD. The results are in line with the Swedish study by Bejerot (Bejerot et al. 2010) on long-term CS treatment in ADHD. Their study excluded patients "without obvious drug or alcohol abuse or dependence", and found that only 2 out of 133 patients had to terminate CS treatment because of SUD during a 2 years follow-up period. Previous studies have showed that CS treatment in children may reduce the risk for SUD in adult life (Wilens et al. 2008). However, some research has indicated that initiation of treatment with CS in adolescence and young adults is linked to increased risk of poly-drug use and non-medical stimulant use (Kollins 2008). The mean age in the present study and in the study by Bejerot (Bejerot et al. 2010) was 28.6 and 31.1 years respectively, and this may represent an age group with low risk for debut of SUD.

The study revealed that among patients with Comorbid SUD at baseline a majority (58.5%) had one or more relapses during the CS treatment period. When interpreting these results we have to consider that SUD is a chronic relapsing disorder. Present research data

indicates that up to 90 % of patients who go into remission from SUD relapse over time (Sellman 2010). Compared to the high relapse rate in SUD patients the relapse rate in the present group of ADHD patients with Comorbid SUD may not be high. However, the lack of a proper control group makes it impossible to conclude about the protective or causative effects of CS treatment when it comes to relapse of SUD in adult patients with ADHD and comorbid SUD.

A relapse of SUD during CS treatment is challenging for the treatment of ADHD. Previous research have showed no or very sparse effects of CS treatment in controlled studies of adult ADHD with current comorbid SUD, both on ADHD symptoms and SUD (Konstenius et al. 2010;Wilens 2009). More important than lack of efficacy of the treatment is the possible increased risk for health damage when CS treatment is combined with SUD. The NICE guidelines recommend CS treatment for adults with ADHD who also misuse substances only when the clinician is an appropriately qualified healthcare professional with expertise in managing both ADHD and SUD (National Institute for Health and Clinical Excellence 2008). CS treatment of ADHD patients with comorbid SUD is associated with an increased risk for misuse, abuse and diversion of the CS drugs (Kaloyanides et al. 2007;McCabe et al. 2006;Wilens et al. 2006). The clinician should take precautions like obtaining urine toxicology screens, prescribing long-acting CS drugs or non-stimulant drugs, put more emphasis on psychotherapeutic approaches and focus strongly on the importance of taking medications regularly (Mariani and Levin 2007;Upadhyaya 2007)

The decision to terminate CS treatment or not when a patient experience a relapse of SUD will be an individual assessment in each case, depending on a number of factors. In the present sample 71.1 % of the patients with comorbid SUD had to terminate CS treatment because of SUD, and this is an important reason for the significantly reduced treatment length in the Relapse of SUD group (19.3 vs. 40.0). The treatment length in the No relapse of SUD

group was almost identical with the treatment length in the No comorbid SUD group (40.0 vs. 41.1).

4.2.5 Variables predicting relapse of SUD during CS treatment

The findings in the present study that ASPD are related to relapse of SUD are not surprising, but to our knowledge this has not been documented before in the context of CS treatment in adult ADHD with comorbid SUD. Studies from populations of patients with SUD have showed that comorbid PD predicts relapse (Thomas et al. 1999). Some studies indicate that the increased rates of SUD in populations with ADHD are mostly accounted for by the presence of comorbid CD (Harty et al. 2011).

Previous research in populations with SUD have documented that the risk for relapse is highest during the first period after cessation, and more specifically the first 100 days (Dekel et al. 2004;Gedaly et al. 2008;Kirshenbaum et al. 2009;Nides et al. 1995;Plebani et al. 2009). The finding that more than 12 months abstinence from cannabis was a significant negative predictor of relapse of SUD may be clinically important, but due to the naturalistic approach and small numbers the results must be interpreted with caution. The finding that cannabis is stronger related to relapse than the other substances must be further examined in larger and more controlled studies and may be due to the small numbers in the present study.

4.2.6 Variables predicting occupational outcome in adult ADHD

The present study showed that older age when CS treatment was initiated and inattentiveness as measured by ASRS was significantly negatively correlated with the degree of occupational participation in adulthood, expressed by number of months in work the last

year. The regression analysis showed that early CS treatment was a significant positive predictor of occupational participation. Recent studies suggest that CS treatment is beneficial for adult function in general (Spencer et al. 2008), thus possibly a predictor of occupational function. A Norwegian study found that childhood diagnosis and treatment with CS might have a beneficial effect on adult occupational outcome as measured by being in work or not (Halmoy et al. 2009).

We also found that ASRS inattentiveness negatively predicted the degree of occupational participation. This is in line with a recent study showing that inattention was associated with the greatest loss of income and disadvantage in a sample of Australian adult ADHD patients (Ebejer et al. 2012). Research has further documented that childhood inattention persists to a higher degree into adulthood than hyperactivity/impulsivity (Kessler et al. 2010). A study by Mannuzza and colleagues reported a strong relationship between number of ADHD symptoms and degree of general impairment, including work functioning (Mannuzza et al. 2010). A comprehensive review of follow-up and cross-sectional studies concluded that no other identified factor than ADHD alone predicted occupational outcome in adults with ADHD (Barkley et al. 2008d). The finding from the present study that symptoms of inattentiveness predict occupational participation adds to these results. Contrary to what has been reported in some previous studies (Halmoy et al. 2009;Sobanski et al. 2007) we found no effect from comorbidity on occupational participation, and our findings are more in line with those of Barkley and colleagues (Barkley et al. 2008d).

Compared with age- and gender-matched controls ADHD in adults is associated with occupational under attainment relative to what may be expected according to their intellectual potentials (Biederman et al. 2008b). A large-scale prevalence study among workers showed that ADHD was significantly associated with decrements in both quantitative and qualitative role performance in work (de et al. 2008). Compared with other workers those with ADHD

had more days out of work-role, being less productive, and having reduced work performance quality (de Graaf et al. 2008). Cross-sectional studies have shown lower occupational functioning in adults with ADHD compared with controls (Barkley et al. 2008d). This indicates that the symptoms of ADHD play an important role in occupational functioning. This is supported by a recent study reporting associations between the severity of ADHD symptoms and work impairment (Safren et al. 2010b). Being in work seems to include the ability to perform several skills and strategies relevant to most functional domains. Executive function deficits such as problems with self-management of time, self-motivation, and self-discipline are found to contribute to occupational problems in adults (Barkley and Murphy 2010).

5. Conclusions

-Adults with ADHD had far lower levels of education and employment compared to the general population.

-Adults with ADHD had high levels of psychiatric comorbidity, especially alcohol and substance use disorders and antisocial personality disorder

-Most adults with ADHD received treatment with central stimulants for several years, and treatment duration for more than 3 years was predicted positively by the use of extended release formulations of methylphenidate, and negatively by comorbid antisocial personality disorder

-In adult ADHD without comorbid substance use disorder central stimulant treatment does not precipitate new onset of substance abuse, and in adults ADHD with substance use disorder the

relapse rate is not higher than in substance use disorder alone during central stimulant treatment

- Later age of first central stimulant treatment and higher inattentiveness ratings were associated with lower level of employment in adulthood

6. Future perspectives

The present thesis emphasizes the high rates of comorbidity between adult ADHD and other psychiatric disorders like SUD and ASPD. Despite a fair amount of research on the nature of the relationship between these disorders there are still many unanswered questions concerning issues like shared etiology and genetics, prevalence, and the importance of comorbidity on treatment of adult ADHD. The possibility that the triad consisting of ADHD, SUD and ASPD constitutes a separate entity with specific etiologic and clinical characteristics must be explored further. This question is even more relevant when DSM-V in 2013 probably rejects the use of the 3 subgroups introduced in DSM-IV. In an even longer perspective the designation ADHD may be replaced by new designations with stronger scientific and biological basis.

In addition to a further emphasis on the impact of comorbidity on the course of ADHD future research should explore the functional impairment following ADHD in all ages, and identify treatment which is capable of reducing impairment.

Further research should also focus on the treatment providing systems and investigate factors that could enhance CS treatment effectiveness such as adherence and compliance.

The relationship between duration of CS treatment in adulthood and improvement in symptoms and functional impairment should be investigated in studies with more controlled design.

A longer period of abstinence from SUD before CS treatment may reduce the risk for relapse. However, trial derived evidence is lacking and it needs to be examined in a study with a prospective, controlled design.

Early detection and treatment of ADHD is shown in the present and some other long-term studies to have a positive effect with regards to adult functional impairment. However, most long-term studies are open-label extensions or naturalistic studies, with several methodological limitations. Efforts should be made to initiate larger, scientifically more stringent and multisite naturalistic studies to investigate the impact of different treatments on adult functional outcomes.

Reference List

1. Aanonsen NO LMPR (2004) Utproevende behandling med sentralstimulerende legemidler til voksne med hyperkinetisk forstyrrelse/ADHD. Oslo: Ullevaal University Hospital

2. Amen DG (1997) General Adult ADD symptom checklist. In: Clark CG (ed) ADHD throughout the life span. NV: Random Clark, Las Vegas

3. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). American Psychiatric Association, Washington

4. American Psychiatric Association (2012) DSM-V development . Available at www.dsm5.org

5. Asherson P, Adamou M, Bolea B, Muller U, Morua SD, Pitts M, Thome J, Young S (2010) Is ADHD a valid diagnosis in adults? Yes. BMJ Mar 26;340:c549

6. Atzori P, Usala T, Carucci S, Danjou F, Zuddas A (2009) Predictive factors for persistent use and compliance of immediate-release methylphenidate: a 36-month naturalistic study. J Child Adolesc Psychopharmacol 19:673-681

7. Bagoien G, Morken G, Zahlsen K, Aamo T, Spigset O (2009) Evaluation of a urine on-site drugs of abuse screening test in patients admitted to a psychiatric emergency unit. J Clin Psychopharmacol 29:248-254

8. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, Danckaerts M, Dopfner M, Faraone SV, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke EJ, Taylor E (2006) Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 15:476-495

9. Barkley RA (1997) Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr 18:271-279

10. Barkley RA, Fischer M (2010) The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. J Am Acad Child Adolesc Psychiatry 49:503-513

11. Barkley RA, Fischer M, Edelbrock CS, Smallish L (1990) The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 29:546-557

12. Barkley RA, Fischer M, Smallish L, Fletcher K (2003) Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. Pediatrics 111:97-109

13. Barkley RA, Murphy KR (2010) Impairment in occupational functioning and adult ADHD: the predictive utility of executive function (EF) ratings versus EF tests. Arch Clin Neuropsychol 25:157-173

14. Barkley RA, Murphy KR, Fischer M (2008a) ADHD in adults. What the science says. The Guilford Press, New York

15. Barkley RA, Murphy KR, Fischer M (2008b) Comorbid psychiatric disorders and psychological maladjustments. ADHD in adults; what the science says. The Guildford Press, New York, pp 205-244

16. Barkley RA, Murphy KR, Fischer M (2008c) Drug use and antisocial behavior. ADHD in adults. What the science says. The Guilford Press, New York, pp 291-329

17. Barkley RA, Murphy KR, Fischer M (2008d) Educational and Occupational Functioning. ADHD in adults. What science says. The Guilford Press, New York, pp 245-290

18. Bejerot S, Ryden EM, Arlinde CM (2010) Two-year outcome of treatment with central stimulant medication in adult attention-deficit/hyperactivity disorder: a prospective study. J Clin Psychiatry

19. Biederman J (2003) Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. J Clin Psychiatry 64 Suppl 11:3-8

20. Biederman J, Faraone SV, Monuteaux MC, Bober M, Cadogen E (2004) Gender effects on attention-deficit/hyperactivity disorder in adults, revisited. Biol Psychiatry 55:692-700

21. Biederman J, Faraone SV, Spencer T, Wilens T, Mick E, Lapey KA (1994) Gender differences in a sample of adults with attention deficit hyperactivity disorder. Psychiatry Res 53:13-29

22. Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman BK, Doyle A (1993) Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 150:1792-1798

23. Biederman J, Mick E, Faraone SV (2000) Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 157:816-818

24. Biederman J, Monuteaux MC, Spencer T, Wilens TE, Faraone SV (2009) Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. Pediatrics 124:71-78

25. Biederman J, Monuteaux MC, Spencer T, Wilens TE, Macpherson HA, Faraone SV (2008a) Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. Am J Psychiatry 165:597-603

26. Biederman J, Petty CR, Fried R, Kaiser R, Dolan CR, Schoenfeld S, Doyle AE, Seidman LJ, Faraone SV (2008b) Educational and occupational underattainment in adults with attention-deficit/hyperactivity disorder: a controlled study. J Clin Psychiatry 69:1217-1222

27. Biederman J, Spencer TJ, Wilens TE, Weisler RH, Read SC, Tulloch SJ (2005) Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. CNS Spectr 10:16-25

28. Biederman J, Wilens T, Mick E, Faraone SV, Weber W, Curtis S, Thornell A, Pfister K, Jetton JG, Soriano J (1997) Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 36:21-29

29. Biederman J, Wilens T, Mick E, Milberger S, Spencer TJ, Faraone SV (1995) Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric comorbidity. Am J Psychiatry 152:1652-1658

30. Brook JS, Whiteman M, Cohen P, Shapiro J, Balka E (1995) Longitudinally predicting late adolescent and young adult drug use: childhood and adolescent precursors. J Am Acad Child Adolesc Psychiatry 34:1230-1238

31. Carpentier PJ, de Jong CA, Dijkstra BA, Verbrugge CA, Krabbe PF (2005) A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. Addiction 100:1868-1874

32. Christensen L, Sasane R, Hodgkins P, Harley C, Tetali S (2010) Pharmacological treatment patterns among patients with attention-deficit/hyperactivity disorder: retrospective claims-based analysis of a managed care population. Curr Med Res Opin 26:977-989

33. Clarke S, Heussler H, Kohn MR (2005) Attention deficit disorder: not just for children. Intern Med J 35:721-725

34. Cox ER, Motheral BR, Henderson RR, Mager D (2003) Geographic variation in the prevalence of stimulant medication use among children 5 to 14 years old: results from a commercially insured US sample. Pediatrics 111:237-243

35. Crum RM, Bucholz KK, Helzer JE, Anthony JC (1992) The risk of alcohol abuse and dependence in adulthood: the association with educational level. Am J Epidemiol 135:989-999

36. Cumyn L, French L, Hechtman L (2009) Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatry 54:673-683

37. de Beaurepaire R, Lukasiewicz M, Beauverie P, Castera S, Dagorne O, Espaze R, Falissard B, Giroult P, Houery M, Mahuzier G, Matheron I, Niel P, Padovani P, Poisson N, Richier JP, Rocher J, Ruetsh O, Touzeau D, Visinoni A, Molimard R (2007) Comparison of self-reports and biological measures for alcohol, tobacco, and illicit drugs consumption in psychiatric inpatients. Eur Psychiatry 22:540-548

38. de Graaf R, Kessler RC, Fayyad J, ten HM, Alonso J, Angermeyer M, Borges G, Demyttenaere K, Gasquet I, de GG, Haro JM, Jin R, Karam EG, Ormel J, Posada-Villa J (2008) The prevalence and effects of adult attention-deficit/hyperactivity disorder (ADHD) on the performance of workers: results from the WHO World Mental Health Survey Initiative. Occup Environ Med 65:835-842

39. Dekel R, Benbenishty R, Amram Y (2004) Therapeutic communities for drug addicts: prediction of long-term outcomes. Addict Behav 29:1833-1837

40. DeRogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L (1974) The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 19:1-15

41. Ebejer JL, Medland SE, van der Werf J, Gondro C, Henders AK, Lynskey M, Martin NG, Duffy DL (2012) Attention deficit hyperactivity disorder in Australian adults: prevalence, persistence, conduct problems and disadvantage. PLoS One 7:e47404

42. Faraone SV, Biederman J, Mick E (2006a) The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med 36:159-165

43. Faraone SV, Biederman J, Spencer TJ, Aleardi M (2006b) Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed 8:4

44. Faraone SV, Glatt SJ (2009) A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry Jun;71(6):754-63

45. Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J (2004) Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 24:24-29

46. Fayyad J, de GR, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, de GG, Haro JM, Karam EG, Lara C, Lepine JP, Ormel J, Posada-Villa J, Zaslavsky AM, Jin R (2007) Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 190:402-409

47. Fischer M, Barkley RA, Edelbrock CS, Smallish L (1990) The adolescent outcome of hyperactive children diagnosed by research criteria: II. Academic, attentional, and neuropsychological status. J Consult Clin Psychol 58:580-588

48. Flory K, Malone PS, Lamis DA (2011) Childhood ADHD symptoms and risk for cigarette smoking during adolescence: School adjustment as a potential mediator. Psychol Addict Behav 25:320-329

49. Flovig JC, Vaaler AE, Morken G (2009) Substance use at admission to an acute psychiatric department. Nord J Psychiatry 63:113-119

50. Gedaly R, McHugh PP, Johnston TD, Jeon H, Koch A, Clifford TM, Ranjan D (2008) Predictors of relapse to alcohol and illicit drugs after liver transplantation for alcoholic liver disease. Transplantation 86:1090-1095

51. Gibson AP, Bettinger TL, Patel NC, Crismon ML (2006) Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. Ann Pharmacother 40:1134-1142

52. Goodman DW, Thase ME (2009) Recognizing ADHD in adults with comorbid mood disorders: implications for identification and management. Postgrad Med 121:20-30

53. Greydanus DE, Pratt HD, Patel DR (2007) Attention deficit hyperactivity disorder across the lifespan: the child, adolescent, and adult. Dis Mon 53:70-131

54. Haavik J, Halmoy A, Lundervold AJ, Fasmer OB (2010) Clinical assessment and diagnosis of adults with attention-deficit/hyperactivity disorder. Expert Rev Neurother 10:1569-1580

55. Halmoy A, Fasmer OB, Gillberg C, Haavik J (2009) Occupational outcome in adult ADHD: impact of symptom profile, comorbid psychiatric problems, and treatment: a cross-sectional study of 414 clinically diagnosed adult ADHD patients. J Atten Disord 13:175-187

56. Hansen SS, Munk-Jorgensen P, Guldbaek B, Solgard T, Lauszus KS, Albrechtsen N, Borg L, Egander A, Faurholdt K, Gilberg A, Gosden NP, Lorenzen J, Richelsen B, Weischer K, Bertelsen

A (2000) Psychoactive substance use diagnoses among psychiatric in-patients. Acta Psychiatr Scand 102:432-438

57. Harty SC, Ivanov I, Newcorn JH, Halperin JM (2011) The impact of conduct disorder and stimulant medication on later substance use in an ethnically diverse sample of individuals with attention-deficit/hyperactivity disorder in childhood. J Child Adolesc Psychopharmacol 21:331-339

58. Hechtman L, Greenfield B (2003) Long-term use of stimulants in children with attention deficit hyperactivity disorder: safety, efficacy, and long-term outcome. Paediatr Drugs 5:787-794

59. Hechtman L, Weiss G, Perlman T (1984) Young adult outcome of hyperactive children who received long-term stimulant treatment. J Am Acad Child Psychiatry 23:261-269

60. Hodgkins P, Sasane R, Christensen L, Harley C, Liu F (2011) Treatment outcomes with methylphenidate formulations among patients with ADHD: retrospective claims analysis of a managed care population. Curr Med Res Opin 27 Suppl 2:53-62

61. Janols LO, Liliemark J, Klintberg K, von Knorring AL (2009) Central stimulants in the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents. A naturalistic study of the prescription in Sweden, 1977-2007. Nord J Psychiatry 63:508-516

62. Jensen P (2002) Longer term effects of stimulant treatments for Attention-Deficit/Hyperactivity Disorder. J Atten Disord 6 Suppl 1:S45-S56

63. Jensen PS, Martin D, Cantwell DP (1997) Comorbidity in ADHD: implications for research, practice, and DSM-V. J Am Acad Child Adolesc Psychiatry 36:1065-1079

64. Kaloyanides KB, McCabe SE, Cranford JA, Teter CJ (2007) Prevalence of illicit use and abuse of prescription stimulants, alcohol, and other drugs among college students: relationship with age at initiation of prescription stimulants. Pharmacotherapy 27:666-674

65. Kandel DB, Logan JA (1984) Patterns of drug use from adolescence to young adulthood: I. Periods of risk for initiation, continued use, and discontinuation. Am J Public Health 74:660-666

66. Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ (2005) Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: a population-based, birth cohort study. J Child Adolesc Psychopharmacol 15:764-776

67. Kemner JE, Lage MJ (2006) Impact of methylphenidate formulation on treatment patterns and hospitalizations: a retrospective analysis. Ann Gen Psychiatry 5:5

68. Kessler RC, Adler L, Ames M, Barkley RA, Birnbaum H, Greenberg P, Johnston JA, Spencer T, Ustun TB (2005a) The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. J Occup Environ Med 47:565-572

69. Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE (2005b) The World Health Organization Adult ADHD Self-

Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med 35:245-256

70. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM (2006) The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 163:716-723

71. Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM (2005c) Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol Psychiatry 57:1442-1451

72. Kessler RC, Green JG, Adler LA, Barkley RA, Chatterji S, Faraone SV, Finkelman M, Greenhill LL, Gruber MJ, Jewell M, Russo LJ, Sampson NA, Van Brunt DL (2010) Structure and diagnosis of adult attention-deficit/hyperactivity disorder: analysis of expanded symptom criteria from the Adult ADHD Clinical Diagnostic Scale. Arch Gen Psychiatry 67:1168-1178

73. Kirshenbaum AP, Olsen DM, Bickel WK (2009) A quantitative review of the ubiquitous relapse curve. J Subst Abuse Treat 36:8-17

74. Klein RG, Abikoff H, Klass E, Ganeles D, Seese LM, Pollack S (1997) Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. Arch Gen Psychiatry 54:1073-1080

75. Koesters M, Becker T, Kilian R, Fegert JM, Weinmann S (2009) Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. J Psychopharmacol 23:733-744

76. Kollins SH (2008) A qualitative review of issues arising in the use of psycho-stimulant medications in patients with ADHD and co-morbid substance use disorders. Curr Med Res Opin 24:1345-1357

77. Konstenius M, Jayaram-Lindstrom N, Beck O, Franck J (2010) Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: a pilot study. Drug Alcohol Depend 108:130-133

78. Kooij JJ, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CA, Hodiamont PP (2005) Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. Psychol Med 35:817-827

79. Kousha M, Shahrivar Z, Alaghband-Rad J (2012) Substance use disorder and ADHD: is ADHD a particularly "specific" risk factor? J Atten Disord 16:325-332

80. Kringlen E, Torgersen S, Cramer V (2001) A Norwegian psychiatric epidemiological study. Am J Psychiatry 158:1091-1098

81. Lahey BB, Applegate B, McBurnett K, Biederman J, Greenhill L, Hynd GW, Barkley RA, Newcorn J, Jensen P, Richters J, . (1994) DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. Am J Psychiatry 151:1673-1685

82. Lange KW, Reichl S, Lange KM, Tucha L, Tucha O (2010) The history of attention deficit hyperactivity disorder. Atten Defic Hyperact Disord 2:241-255

83. Lara C, Fayyad J, de GR, Kessler RC, Aguilar-Gaxiola S, Angermeyer M, Demytteneare K, de GG, Haro JM, Jin R, Karam EG, Lepine JP, Mora ME, Ormel J, Posada-Villa J, Sampson N (2009) Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. Biol Psychiatry 65:46-54

84. Levin FR, Evans SM, Brooks DJ, Garawi F (2007) Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend 87:20-29

85. Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV (2006) Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend 81:137-148

86. Mannuzza S, Castellanos FX, Roizen ER, Hutchison JA, Lashua EC, Klein RG (2010) Impact of the Impairment Criterion in the Diagnosis of Adult ADHD: 33-Year Follow-Up Study of Boys With ADHD. J Atten Disord Feb;15(2):122-9

87. Mannuzza S, Klein RG, Addalli KA (1991) Young adult mental status of hyperactive boys and their brothers: a prospective follow-up study. J Am Acad Child Adolesc Psychiatry 30:743-751

88. Mannuzza S, Klein RG, Bessler A, Malloy P, Hynes ME (1997) Educational and occupational outcome of hyperactive boys grown up. J Am Acad Child Adolesc Psychiatry 36:1222-1227

89. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M (1993) Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Arch Gen Psychiatry 50:565-576

90. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M (1998) Adult psychiatric status of hyperactive boys grown up. Am J Psychiatry 155:493-498

91. Mannuzza S, Klein RG, Konig PH, Giampino TL (1989) Hyperactive boys almost grown up. IV. Criminality and its relationship to psychiatric status. Arch Gen Psychiatry 46:1073-1079

92. Mannuzza S, Klein RG, Truong NL, Moulton JL, III, Roizen ER, Howell KH, Castellanos FX (2008) Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry 165:604-609

93. Mariani JJ, Levin FR (2007) Treatment strategies for co-occurring ADHD and substance use disorders. Am J Addict 16 Suppl 1:45-54

94. Matte B, Rohde LA, Grevet EH (2012) ADHD in adults: a concept in evolution. Atten Defic Hyperact Disord 4:53-62

95. Mattes JA, Boswell L, Oliver H (1984) Methylphenidate effects on symptoms of attention deficit disorder in adults. Arch Gen Psychiatry 41:1059-1063

96. Maughan B, Rowe R, Messer J, Goodman R, Meltzer H (2004) Conduct disorder and oppositional defiant disorder in a national sample: developmental epidemiology. J Child Psychol Psychiatry 45:609-621

97. McCabe SE, Teter CJ, Boyd CJ (2006) Medical use, illicit use and diversion of prescription stimulant medication. J Psychoactive Drugs 38:43-56

98. McCarthy S, Asherson P, Coghill D, Hollis C, Murray M, Potts L, Sayal K, de SR, Taylor E, Williams T, Wong IC (2009) Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. Br J Psychiatry 194:273-277

99. McGough JJ, Barkley RA (2004) Diagnostic controversies in adult attention deficit hyperactivity disorder. Am J Psychiatry 161:1948-1956

100. McGough JJ, Smalley SL, McCracken JT, Yang M, Del'Homme M, Lynn DE, Loo S (2005) Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. Am J Psychiatry 162:1621-1627

101. Mick E, Byrne D, Fried R, Monuteaux M, Faraone SV, Biederman J (2011) Predictors of ADHD persistence in girls at 5-year follow-up. J Atten Disord. 2011 Apr;15(3):183-92.

102. Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Gibbons RD, Hur K, Houck PR (2009) The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 48:484-500

103. Moncrieff J, Timimi S (2010) Is ADHD a valid diagnosis in adults? No. BMJ Mar 26;340:c547

104. Montano CB, Weisler R (2011) Distinguishing symptoms of ADHD from other psychiatric disorders in the adult primary care setting. Postgrad Med 123:88-98

105. Mordal J, Holm B, Morland J, Bramness JG (2010) Recent substance intake among patients admitted to acute psychiatric wards: physician's assessment and on-site urine testing compared with comprehensive laboratory analyses. J Clin Psychopharmacol 30:455-459

106. Murphy K, Barkley RA (1996) Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr Psychiatry 37:393-401

107. Murphy KR, Barkley RA, Bush T (2002) Young adults with attention deficit hyperactivity disorder: subtype differences in comorbidity, educational, and clinical history. J Nerv Ment Dis 190:147-157

108. National Institute for Health and Clinical Excellence (2004) National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. Pediatrics 113:754-761

109. National Institute for Health and Clinical Excellence (2008) Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults. Available at http://publications.nice.org.uk/attention-deficit-hyperactivity-disorder-cg72

110. Newcorn J, Halperin JM, Miller CJ (2009) ADHD with oppositionality and aggression. In: Brown TE (ed) ADHD comorbidities. Handbook for ADHD complications in children and adults. American Psychiatric Publishing, Inc., Arlington, pp 157-176

111. Newcorn JH (2008) Nonstimulants and emerging treatments in adults with ADHD. CNS Spectr 13:12-16

112. Newcorn JH, Miller SR, Ivanova I, Schulz KP, Kalmar J, Marks DJ, Halperin JM (2004) Adolescent outcome of ADHD: impact of childhood conduct and anxiety disorders. CNS Spectr 9:668-678

113. Nides MA, Rakos RF, Gonzales D, Murray RP, Tashkin DP, Bjornson-Benson WM, Lindgren P, Connett JE (1995) Predictors of initial smoking cessation and relapse through the first 2 years of the Lung Health Study. J Consult Clin Psychol 63:60-69

114. Nutt DJ, Fone K, Asherson P, Bramble D, Hill P, Matthews K, Morris KA, Santosh P, Sonuga-Barke E, Taylor E, Weiss M, Young S (2007) Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 21:10-41

115. Olfson M, Marcus SC, Zhang HF, Wan GJ (2007) Continuity in methylphenidate treatment of adults with attention-deficit/hyperactivity disorder. J Manag Care Pharm 13:570-577

116. Ottosson H, Ekselius L, Grann M, Kullgren G (2002) Cross-system concordance of personality disorder diagnoses of DSM-IV and diagnostic criteria for research of ICD-10. J Pers Disord 16:283-292

117. Perwien A, Hall J, Swensen A, Swindle R (2004) Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder. J Manag Care Pharm 10:122-129

118. Peterson K, McDonagh MS, Fu R (2008) Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. Psychopharmacology (Berl) 197:1-11

119. Plebani JG, Kampman KM, Lynch KG (2009) Early abstinence in cocaine pharmacotherapy trials predicts successful treatment outcomes. J Subst Abuse Treat 37:313-317

120. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164:942-948

121. Polanczyk G, Rohde LA (2007) Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry 20:386-392

122. Powers RL, Marks DJ, Miller CJ, Newcorn JH, Halperin JM (2008) Stimulant treatment in children with attention-deficit/hyperactivity disorder moderates adolescent academic outcome. J Child Adolesc Psychopharmacol 18:449-459

123. Prosser B, Reid R (2009) Changes in use of psychostimulant medication for ADHD in South Australia (1990-2006). Aust N Z J Psychiatry 43:340-347

124. Ramos-Quiroga JA, Bosch R, Castells X, Valero S, Nogueira M, Gomez N, Yelmo S, Ferrer M, Martinez Y, Casas M (2008) Effect of switching drug formulations from immediate-release to extended-release OROS methylphenidate : a chart review of Spanish adults with attention-deficit hyperactivity disorder. CNS Drugs 22:603-611

125. Rasmussen K, Levander S (2009) Untreated ADHD in adults: are there sex differences in symptoms, comorbidity, and impairment? J Atten Disord 12:353-360

126. Rasmussen P, Gillberg C (2000) Natural outcome of ADHD with developmental coordination disorder at age 22 years: a controlled, longitudinal, community-based study. J Am Acad Child Adolesc Psychiatry 39:1424-1431

127. Reimherr FW, Marchant BK, Strong RE, Hedges DW, Adler L, Spencer TJ, West SA, Soni P (2005) Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry 58:125-131

128. Robison RJ, Reimherr FW, Marchant BK, Faraone SV, Adler LA, West SA (2008) Gender differences in 2 clinical trials of adults with attention-deficit/hyperactivity disorder: a retrospective data analysis. J Clin Psychiatry 69:213-221

129. Rucklidge JJ (2008) Gender differences in ADHD: implications for psychosocial treatments. Expert Rev Neurother 8:643-655

130. Safren SA, Otto MW, Sprich S, Winett CL, Wilens TE, Biederman J (2005) Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. Behav Res Ther 43:831-842

131. Safren SA, Sprich S, Mimiaga MJ, Surman C, Knouse L, Groves M, Otto MW (2010a) Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with ADHD and persistent symptoms: a randomized controlled trial. JAMA 304:875-880

132. Safren SA, Sprich SE, Cooper-Vince C, Knouse LE, Lerner JA (2010b) Life impairments in adults with medication-treated ADHD. J Atten Disord 13:524-531

133. Sara G, Raven P, Mann A (1996) A comparison of DSM-III-R and ICD-10 personality disorder criteria in an out-patient population. Psychol Med 26:151-160

134. Schachter HM, Pham B, King J, Langford S, Moher D (2001) How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. CMAJ 165:1475-1488

135. Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, Edwards A, Donlin J, Pihlgren E (2002) Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol 10:286-294

136. Schuckit MA (2006) Comorbidity between substance use disorders and psychiatric conditions. Addiction 101 Suppl 1:76-88

137. Sellman D (2010) The 10 most important things known about addiction. Addiction 105:6-13

138. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20:22-33

139. Smith BH, Waschbusch DA, Willoughby MT, Evans S (2000) The efficacy, safety, and practicality of treatments for adolescents with attention-deficit/hyperactivity disorder (ADHD). Clin Child Fam Psychol Rev 3:243-267

140. Sobanski E, Banaschewski T, Asherson P, Buitelaar J, Chen W, Franke B, Holtmann M, Krumm B, Sergeant J, Sonuga-Barke E, Stringaris A, Taylor E, Anney R, Ebstein RP, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV (2010) Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (ADHD): clinical correlates and familial prevalence. J Child Psychol Psychiatry 51:915-923

141. Sobanski E, Bruggemann D, Alm B, Kern S, Deschner M, Schubert T, Philipsen A, Rietschel M (2007) Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 257:371-377

142. Sobanski E, Bruggemann D, Alm B, Kern S, Philipsen A, Schmalzried H, Hesslinger B, Waschkowski H, Rietschel M (2008) Subtype differences in adults with attention-deficit/hyperactivity disorder (ADHD) with regard to ADHD-symptoms, psychiatric comorbidity and psychosocial adjustment. Eur Psychiatry 23:142-149

143. Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S (1996) Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolesc Psychiatry 35:409-432

144. Spencer T, Biederman J, Wilens TE, Faraone SV (1998) Adults with attention-deficit/hyperactivity disorder: a controversial diagnosis. J Clin Psychiatry 59 Suppl 7:59-68

145. Spencer TJ, Landgraf JM, Adler LA, Weisler RH, Anderson CS, Youcha SH (2008) Attention-deficit/hyperactivity disorder-specific quality of life with triple-bead mixed amphetamine salts (SPD465) in adults: results of a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 69:1766-1775

146. Sprafkin J, Gadow KD, Weiss MD, Schneider J, Nolan EE (2007) Psychiatric comorbidity in ADHD symptom subtypes in clinic and community adults. J Atten Disord 11:114-124

147. Starcevic V, Bogojevic G, Kelin K (1997) Diagnostic agreement between the DSM-IV and ICD-10-DCR personality disorders. Psychopathology 30:328-334

148. Statistics Norway (2005) Labour Force Survey. Updated January 15, 2008. Available at http://www.ssb.no

149. Statistics Norway (2010) Education statistics. Population's level of education. Available at http://www.ssb.no/utniv_en/

150. Stevenson CS, Whitmont S, Bornholt L, Livesey D, Stevenson RJ (2002) A cognitive remediation programme for adults with Attention Deficit Hyperactivity Disorder. Aust N Z J Psychiatry 36:610-616

151. Szatmari P, Boyle M, Offord DR (1989) ADDH and conduct disorder: degree of diagnostic overlap and differences among correlates. J Am Acad Child Adolesc Psychiatry 28:865-872

152. Thapar A, Langley K, Asherson P, Gill M (2007) Gene-environment interplay in attention-deficit hyperactivity disorder and the importance of a developmental perspective. Br J Psychiatry 190:1-3

153. Thapar A, van den Bree M, Fowler T, Langley K, Whittinger N (2006) Predictors of antisocial behaviour in children with attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry 15:118-125

154. The MTA Cooperative Group (1999) A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry 56:1073-1086

155. The Norwegian Directorate of Health (2004) IS-1244 National Guidelines for Diagnosing Lifespan ADHD.

156. Norwegian Prescription Database (2011). The Norwegian Institute of Public Health; Updated October 10, 2011. Available at http://www.reseptregisteret.no

157. Thomas VH, Melchert TP, Banken JA (1999) Substance dependence and personality disorders: comorbidity and treatment outcome in an inpatient treatment population. J Stud Alcohol 60:271-277

158. Upadhyaya HP (2007) Managing attention-deficit/hyperactivity disorder in the presence of substance use disorder. J Clin Psychiatry 68 Suppl 11:23-30

159. van den Ban E, Souverein PC, Swaab H, van EH, Egberts TC, Heerdink ER (2010) Less discontinuation of ADHD drug use since the availability of long-acting ADHD medication in children, adolescents and adults under the age of 45 years in the Netherlands. Atten Defic Hyperact Disord 2:213-220

160. Verbeeck W, Tuinier S, Bekkering GE (2009) Antidepressants in the treatment of adult attention-deficit hyperactivity disorder: a systematic review. Adv Ther 26:170-184

161. Verstraete AG (2004) Detection times of drugs of abuse in blood, urine, and oral fluid. Ther Drug Monit 26:200-205

162. Ward MF, Wender PH, Reimherr FW (1993) The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 150:885-890

163. Weiss G, Hechtman L, Milroy T, Perlman T (1985) Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Psychiatry 24:211-220

164. Weiss MD, Gadow K, Wasdell MB (2006) Effectiveness outcomes in attention-deficit/hyperactivity disorder. J Clin Psychiatry 67 Suppl 8:38-45

165. Wender PH, Reimherr FW, Marchant BK, Sanford ME, Czajkowski LA, Tomb DA (2010) A One Year Trial of Methylphenidate in the Treatment of ADHD. J Atten Disord

166. Wender PH, Reimherr FW, Wood DR (1981) Attention deficit disorder ('minimal brain dysfunction') in adults. A replication study of diagnosis and drug treatment. Arch Gen Psychiatry 38:449-456

167. Wilens TE (2008) Effects of methylphenidate on the catecholaminergic system in attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 28:S46-S53

168. Wilens TE (2009) ADHD with Substance Use Disorders. In: Brown TE (ed) ADHD comorbidities. Handbook for ADHD complications in children and adults. American Psychiatric Publishers, Inc., Arlington, pp 249-264

169. Wilens TE, Adamson J, Monuteaux MC, Faraone SV, Schillinger M, Westerberg D, Biederman J (2008) Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. Arch Pediatr Adolesc Med 162:916-921

170. Wilens TE, Biederman J, Faraone SV, Martelon M, Westerberg D, Spencer TJ (2009) Presenting ADHD symptoms, subtypes, and comorbid disorders in clinically referred adults with ADHD. J Clin Psychiatry 70:1557-1562

171. Wilens TE, Biederman J, Mick E, Faraone SV, Spencer T (1997) Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. J Nerv Ment Dis 185:475-482

172. Wilens TE, Faraone SV, Biederman J, Gunawardene S (2003) Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 111:179-185

173. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J (2006) Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. J Am Acad Child Adolesc Psychiatry 45:408-414

174. Wilens TE, Monuteaux MC, Snyder LE, Moore H, Whitley J, Gignac M (2005a) The clinical dilemma of using medications in substance-abusing adolescents and adults with attention-deficit/hyperactivity disorder: what does the literature tell us? J Child Adolesc Psychopharmacol 15:787-798

175. Wilens TE, Monuteaux MC, Snyder LE, Moore H, Whitley J, Gignac M (2005b) The clinical dilemma of using medications in substance-abusing adolescents and adults with attention-deficit/hyperactivity disorder: what does the literature tell us? J Child Adolesc Psychopharmacol 15:787-798

176. Wilens TE, Morrison NR, Prince J (2011) An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. Expert Rev Neurother 11:1443-1465

177. Wilens TE, Spencer TJ, Biederman J (2002) A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. J Atten Disord 5:189-202

178. Willcutt EG, Nigg JT, Pennington BF, Solanto MV, Rohde LA, Tannock R, Loo SK, Carlson CL, McBurnett K, Lahey BB (2012) Validity of DSM-IV Attention Deficit/Hyperactivity Disorder Symptom Dimensions and Subtypes. J Abnorm Psychol

179. Witkiewitz K, King K, McMahon RJ, Wu J, Luk J, Bierman KL, Coie JD, Dodge KA, Greenberg MT, Lochman JE, Pinderhughes EE (2012) Evidence for a Multi-Dimensional Latent Structural Model of Externalizing Disorders. J Abnorm Child Psychol

180. Woo BS, Rey JM (2005) The validity of the DSM-IV subtypes of attention-deficit/hyperactivity disorder. Aust N Z J Psychiatry 39:344-353

181. World Health Organization (1992) The International Classification of Disease, 10th revision. Geneva, Switzerland: World Health Organization

182. Young S, Toone B, Tyson C (2003) Comorbidity and psychosocial profile of adults with attention deficit hyperactivity disorder. Personality and Individual Differences 35:743-755

183. Zoega H, Rothman KJ, Huybrechts KF, Olafsson O, Baldursson G, Almarsdottir AB, Jonsdottir S, Halldorsson M, Hernandez-Diaz S, Valdimarsdottir UA (2012) A population-based study of stimulant drug treatment of ADHD and academic progress in children. Pediatrics 130:e53-e62

Paper I-IV

Paper I

Is not included due to copyright

Paper II

Is not included due to copyright

Paper III

Is not included due to copyright

Paper IV

Is not included due to copyright

Attachment I

Procedures published by Expert Committees of Hyperkinetic Disorders/ADHD

Regional sikkerhets- og kompetansesenter Brøset
Sakkyndig team for helseregion Midt- og Nord-Norge
Postboks 1803 Lade
7440 Trondheim

Skjema/huskeliste for supplerende medisinsk utredning ved utprøvende behandling av hyperkinetisk forstyrrelse/ADHD med sentralstimulerende midler.

Pasientens navn , Fødselsdato, Journalnummer fra Sakkyndig Team, Dato for utfylling av skjema

⇒ Somatisk klinisk undersøkelse	
⇒ Blodtrykk og puls	
⇒ Blodprøver	
senkning	
hemoglobin	
hvite blodlegemer	
differensialtelling	
kreatinin	
urea	
ASAT	
ALAT	
GT	
LD	
ALP	
FT4	
TSH	
⇒ orienterende nevrologisk undersøkelse	
⇒ EKG	
☒ Psykiatrisk vurdering av :	
tidligere psykosetilbøyelighet	
depresjon, bipolar lidelse	
angstforstyrrelse, tvangslidelser	
atferdsforstyrrelse	
stoff/alkoholavhengighet	
☒ Annen medikamentell behandling	
☒ Røkevaner	

Attachment II

The International Classification of Disease, 10th revision, research criteria

Hyperkinetisk forstyrrelse – ICD-10 forskningskriteriene

Diagnosen krever klare tegn på sviktende oppmerksomhet, unormalt aktivitetsnivå og rastløshet som forekommer på tvers av situasjoner og som vedvarer over tid, og som ikke er forårsaket av noen annen lidelse som for eksempel autisme og affektive lidelser.

G1. *Svikt i oppmerksomhet.* Minst seks av symptomene på sviktende oppmerksomhet må ha vedvart i minst 6 måneder, og i en grad som hindrer adekvat tilpasning, og som ikke er aldersadekvat.

(1) er ofte ikke oppmerksom på detaljer, eller gjør feil på grunn av skjødesløshet, i skolearbeid, arbeid, eller i andre aktiviteter

(2) klarer ofte ikke å fokusere oppmerksomhet over tid i forhold til arbeidsoppgaver eller lek

(3) hører ofte tilsynelatende ikke på hva som blir sagt til ham/henne

(4) klarer ofte ikke å følge instrukser eller å gjøre ferdig skolearbeid eller arbeidsoppgaver (ikke på grunn av uvilje eller manglende forståelse av instruksjon)

(5) har ofte vansker med å organisere oppgaver og aktiviteter

(6) prøver ofte å unngå, eller misliker sterkt, oppgaver som for eksempel hjemmelekser som krever vedvarende konsentrasjon

(7) roter ofte bort eller mister ting som er nødvendig for visse aktiviteter som hjemmelekser, for eksempel blyanter, bøker, leker eller verktøy

(8) blir lett distrahert av ytre stimuli

(9) er ofte glemsom gjennom daglige aktiviteter

G2. *Hyperaktivitet.* Minst tre av symptomene på hyperaktivitet må ha vært til stede i minst 6 måneder, og i en grad som hindrer normal tilpasning og som ikke er aldersadekvat.

(1) er ofte rastløs med hender eller føtter eller vrir seg i stolen

(2) forlater plassen sin i klasserommet eller i andre situasjoner hvor det er forventet at han/hun skal sitte stille

(3) løper ofte omkring eller klatrer rundt i situasjoner hvor det ikke er passende (hos ungdom og voksne finnes kanskje bare en følelse av rastløshet)

(4) er ofte unødig støyende under lek eller har vanskeligheter med å involvere seg stille i fritidsaktiviteter

(5) viser vedvarende økt motorisk aktivitet som ikke i særlig grad lar seg modifisere av sosial sammenheng eller krav.

G3. *Impulsivitet.* Minst ett av symptomene har vedvart gjennom minst 6 måneder, og i en grad som hindrer normal tilpasning og som ikke er aldersadekvat.

(1) buser ut med svaret før spørsmålet er ferdigstilt

(2) mestrer dårlig å stå i kø eller vente på tur i lek/spill eller gruppesituasjoner

(3) avbryter eller forstyrrer andre (for eksempel bryter inn i andres samtaler eller lek)

(4) snakker ofte ustoppelig uten å ta hensyn til sosiale begrensninger.

G4. Plagene skal ha startet før fylte 7 år.

G5. *Utbredt.* Kriteria bør være oppfylt i mer enn enkelt situasjon, for eksempel bør kombinasjon av uoppmerksomhet og hyperaktivitet viser seg både hjemme og på skolen, eller både på skolen og i en annen situasjon hvor vedkommende

blir observert, for eksempel i klinikken. (Holdepunkter for utbredthet må vanligvis komme fra flere kilder; foreldres utsagn om klasseromatferd vil for eksempel neppe være tilstrekkelig).

G6. Symptomene under G1-G3 forårsaker betydelige plager eller svekkelse i sosial, utdannings- eller yrkesmessig funksjon.

G7. Tilstanden fyller ikke kriteria for gjennomgripende utviklingsforstyrrelse (F84.-), manisk episode (F30.-), depressiv episode (F32.-) eller angstlidelse (F41.-)

Attachment III

Data collecting form for screening of medical records

Versjon 16.01.09

Variabler: ADHD hos voksne; forløpsstudien

1.0 **Demografiske data:**

1.1 Kjønn Mann 0 Kvinne 1

1.2 **Punkt 3.5** Alder ved inklusjon (behandlingsstart med sentralstimulerende medikamenter (SSM)) _____

2.0 **Bakgrunnsdata fra før fylte 18 år:**

2.1 Kontakt Pedag.-Psykol. Tjeneste (PPT) 0 1

2.2 Kontakt Barne- og ungdomspsykiatri (BUP) 0 1

2.3 Diagnoser fra BUP

ADHD 0 1

Atferdsforstyrrelse 0 1

Lærevansker 0 1

Annet _____ 0 1

2.4 Behandling i BUP

SSM 0 1

Hvis ja;

Hvilket medikament _____

Alder ved behandlingsstart _____

Varighet (måneder) _____

2.5 Negative livshendelser i barndom (<18 år):

Dødsfall nær slektning/venn 0 1

Alvorlig somatisk sykdom (egen) 0 1

	Alvorlig ulykke/brann (selvopplevd)	0	1
	Forårsake alvorlig skade/død	0	1
	Utsatt for vold utenfor hjemmet	0	1
	Utsatt for vold i hjemmet	0	1
	Psykisk sykdom hos foreldre	0	1
	Rusmisbruk hos foreldre	0	1
	Utsatt for seksuelt overgrep	0	1
	Alvorlig/langvarig mobbing	0	1
	Opplevd foreldres skilsmisse	0	1
	Barnevernstiltak	0	1
	Fosterhjemsplassert	0	1
	Adoptert	0	1
	Annet_____	0	1
	Sumscore	____	

2.6	Livstidsforekomst allergi, atopi, astma		0	1
	Hvis ja, hvilken:	Allergi	0	1
		Atopi	0	1
		Astma	0	1

3.0 **Kontakt med Voksenpsykiatri (VOP) før behandling med SSM**

3.1 Alder første kontakt med VOP (år) _____

3.2 Tidspunkt (år)_____

3.3 Alder ADHD diagnose i VOP _____

3.4 Tidspunkt (år)_____

3.5 Alder oppstart SSM i VOP _____

3.6 Tidspunkt (år)_____

3.7 Varighet fra første kontakt VOP til ADHD diagnose (mndr)_____

Henvist til ADHD-utredning fra:

3.8	I VOP før ADHD-utredning	0	1
3.9	Overført fra BUP	0	1

3.10	Henvist fra fastlege	0	1
3.11	Henvist fra andre_____	0	1
	Psykiatrisk behandling i VOP før ADHD-utredning		
3.12	Poliklin. konsultasjoner (antall)	_____	
3.13	Innleggelser (uker)	_____	

ICD-10 diagnoser satt i VOP før ADHD-diagnose (PAS-koder/benevnelser)

3.2.1	**Psykisk utviklingshemming**	0	1
3.2.2	Alvorlighetsgrad	_____	
	Læringsforstyrrelser		
3.2.3	Leseforstyrrelser	0	1
3.2.4	Regneforstyrrelse	0	1
3.2.5	Skriveforstyrrelse	0	1
3.2.6	Uspesifiserte lærevansker	0	1
	Gjennomgripende utviklingsforstyrrelser		
3.2.7	Autisme		
3.2.8	Aspergers syndrom	0	1
3.2.9	Tourette syndrom	0	1
	Substansbrukslidelser		
3.2.10	Alkoholavhengighet/misbruk	0	1
3.2.11	Amfetaminavhengighet/misbruk	0	1
3.2.12	Cannabisavhengighet/misbruk	0	1
3.2.13	Opiatavhengighet/misbruk	0	1
3.2.14	Sedativa-, hypnotika- og anxiolytikaavh/misbruk	0	1
3.2.15	Blandingsavhengighet	0	1
	Stemningslidelser		
3.2.16	Alvorlig depressiv episode, aktuell	0	1
3.2.17	Alvorlig depressiv episode, tidligere	0	1
3.2.18	Alvorlig depressiv episode, tilbakevendende	0	1
3.2.19	Bipolar lidelse, aktuell	0	1

3.2.20	Bipolar lidelse type I	0	1
3.2.21	Bipolar lidelse type II	0	1
	Angstlidelser		
3.2.22	Panikklidelse	0	1
3.2.23	Sosial fobi	0	1
3.2.24	OCD	0	1
3.2.25	PTSD	0	1
3.2.26	GAD	0	1
	Personlighetsforstyrrelser		
3.2.27	Antisosial	0	1
3.2.28	Ustabil	0	1
3.2.29	Unngående	0	1
3.2.30	Avhengig	0	1
3.2.31	**Spiseforstyrrelser**	0	1
3.2.32	**Andre psykiatriske lidelser_____**	0	1

4.0 Utredning av ADHD før behandlingsstart

4.1 Journalinformasjon

Antall løpende journalsider _____

4.2 Utredet hvor?

Psykiatrisk poliklinikk	0	1
Habiliteringstjenesten.	0	1
Ruspoliklinikk	0	1
Psykiatrisk sengepost	0	1
Annet _____	0	1

4.3 F90.0 Hyperkinetisk forstyrrelse; forskningskriteriene

ADHD kombinert type	1
ADHD hovedsakelig Oppmerksomhetssvikt	2
ADHD hovedsakelig Hyperaktivitet-Impulsivitet	3

4.4	Strukturert klinisk intervju:		
	SPIFA	0	1
	MINI	0	1
	SCID	0	1
4.5	Nevropsykologisk undersøkelse		
	WAIS	0	1
	Utvidet testbatteri	0	1
4.6	Cerebral CT/MR _____	0	1
	Normale funn	0	1
4.7	EEG _____	0	1
	Normale funn	0	1
4.8	Blodprøver	0	1
	Normale funn	0	1
4.9	Komparentopplysninger	0	1
	Hvem_____		
4.10	MMPI	0	1

5.0 **Funksjonsnivå ved behandlingsstart**

5.1	Sivilstatus	
	Ugift	0
	Samboende	1
	Gift	2
	Separert	3
	Skilt	4

	Enke/enkemann		5
5.2	Bosituasjon		
	Bor alene		0
	Bor sammen med foreldre		1
	Bor sammen med bare barn		2
	Bor sammen med ektefelle/samboer (og evt barn)		3
	Bor sammen med andre		4
5.3	Barn		
	Har ikke barn		0
	Har egne barn, men andre har omsorgen		1
	Har omsorg for egne barn (<18 år)		2
5.4	Utdanning		
	Ikke fullført grunnskole		0
	Fullført grunnskole		1
	Fullført videregående skole		2
	Fullført universitet eller høgskole		3
5.5	Arbeid/sysselsetting		
	Lever av sosial stønad		0
	Uførepensjon		1
	Rehabiliteringspenger		2
	Sykemeldt		3
	Yrkesrettet attføring		4
	Arbeidsledighetstrygd		5
	Under ordinær utdanning		6
	I lønnet arbeid		7
5.6	Kriminalitet før behandling (domfelt):		
	Vold	0	1
	Vinning	0	1

	Narkotika	0	1
	Promilledom	0	1

6.0 **<u>Komorbiditet etter DSM-IV vurdert ved behandlingsstart med SSM</u>**

(Oppfyllelse av diagnosekriteriene klart dokumentert i journal)

	Ingen sikker komorbiditet	0	1
	<u>Hvis 0, hvilke diagnoser</u>		
6.1	**Psykisk utviklingshemming**	0	1
6.2	Alvorlighetsgrad	_____	
	Læringsforstyrrelser		
6.3	Leseforstyrrelser	0	1
6.4	Regneforstyrrelse	0	1
6.5	Skriveforstyrrelse	0	1
6.6	Uspesifiserte lærevansker	0	1
6.7	Atferdslidelse	0	1
6.8	Trasslidelse	0	1
	Gjennomgripende utviklingsforstyrrelser		
6.9	Autisme	0	1
6.10	Aspergers syndrom	0	1
6.11	Tourette syndrom	0	1

	Substansbrukslidelser		**PÅGA**	**TDR**	**TFR**	**VDR**	**VFR**	
6.12	Alkoholavhengighet/misbruk	0	1	0	1	2	3	4
6.13	Amfetaminavhengighet/misbruk	0	1	0	1	2	3	4
6.14	Cannabisavhengighet/misbruk	0	1	0	1	2	3	4
6.15	Opiatavhengighet/misbruk	0	1	0	1	2	3	4
6.16	Sedativa-, hypnotika- og anx	0	1	0	1	2	3	4
6.17	Blandingsavhengighet	0	1	0	1	2	3	4

Forløpsspesifikasjon ved oppstart sentralstimulerende medikamenter

Pågående	PÅGÅ
Tidlig delvis remisjon	1<TDR<12 måneder

	Tidlig full remisjon	1<TFR<12 måneder	
	Vedvarende delvis remisjon	12<VDR	
	Vedvarende full remisjon	12<VFR	

	Stemningslidelser		
6.18	Alvorlig depressiv episode, aktuell	0	1
6.19	Alvorlig depressiv episode, tidligere	0	1
6.20	Alvorlig depressiv episode, tilbakevendende	0	1
6.21	Bipolar lidelse, aktuell	0	1
6.22	Bipolar lidelse, tidligere	0	1
6.23	Bipolar lidelse type I	0	1
6.24	Bipolar lidelse type II	0	1
	Angstlidelser		
6.25	Panikklidelse	0	1
6.26	Sosial fobi	0	1
6.27	OCD	0	1
6.28	PTSD	0	1
6.29	GAD	0	1
	Personlighetsforstyrrelser		
6.30	Antisosial	0	1
6.31	Ustabil	0	1
6.32	Unngående	0	1
6.33	Avhengig	0	1
6.34	**Spiseforstyrrelser**	0	1
6.35	**Andre psykiatriske lidelser_____**	0	1
	Andre tilstander beskrevet i journal		
6.36	Muskel- og skjelettplager ina	0	1
6.37	Søvnforstyrrelser ina	0	1

7.0	**Symptomnivå ved behandlingsstart**		
7.1	SCL-90	0	1

7.2	GSI	_____		
7.3	Hyperkinetisk sjekkliste	0	1	
7.4	HS Score	_____		
7.5.1	ASRS	0	1	Del A___Del B____

8.0 Medikamentell behandling (SSM)

8.1 Førstevalg

Metylfendidat IR (Ritalin tabletter)	0	1
Metylfendidat SR (Concerta/Ritalin SR)	0	1
Amfetamin IR	0	1
Annet_____	0	1

8.2	Maksimal dose	_____	
8.3	Vedlikeholdsdose	_____	
8.4	Skifte av sentralstimulerende medikament	0	1
	Fra Metylfenidat til Deksamfetamin	0	1
	Fra Deksamfetamin til Metylfenidat	0	1
	Fra IR til SR (Metylfenidat)	0	1
	Fra SR til IR (Metylfenidat)	0	1
	Begrunnelse for skiftet_____		

8.5	Skiftet skjedde etter (måneder)	_____
8.6	Varighet av ny medikasjon	_____
8.7	Pauser i behandlingen mer enn 3 måneder	_____
8.8	Total behandlingstid med SSM	_____

8.9 Registrerte bivirkninger

Redusert matlyst	0	1
Vekttap	0	1
Løs mage/diare	0	1
Kvalme/uvelhet	0	1
Magesmerter	0	1

	Svimmelhet	0	1
	Munntørrhet	0	1
	Tretthet	0	1
	Nervøs/urolig	0	1
	Hodepine	0	1
	Hjertebank/økt puls	0	1
	Innsovningsproblemer	0	1
	Søvnproblemer, andre	0	1
	Irritabilitet	0	1
	Angst	0	1
	Depresjonsfølelse	0	1
	Andre_____	0	1

8.10 ”Serious adverse events” under behandling med SSM 0 1

Hvis 1, hvilke_____

8.11 ”Serious adverse events” etter avsluttet behandling med SSM

0 1

Hvis 1, hvilke_____

9 **<u>Ikke-medikamentell behandling 1. år</u>**
Hovedbehandlers profesjon

9.1	Legespesialist	0	
9.2	Psykologspesialist	1	
9.3	Lege	2	
9.4	Psykolog	3	
9.5	Høyskoleutdannet	4	
9.6	Antall polikliniske konsultasjoner	_____	
9.7	Innlagt (evt. antall uker_____)	0	1
9.8	Ansvarsgruppe etablert	0	1
9.9	Individuell plan	0	1

9 Behandlingseffekt etter 6 uker vurdert fra skjema eller tekst

10.1	Hyperaktivitet	0	1	2	3	4
10.2	Impulsivitet	0	1	2	3	4
10.3	Irritabilitet	0	1	2	3	4
10.4	Oppmerksomhet	0	1	2	3	4
10.5	Struktur/organisering	0	1	2	3	4
10.6	Uro/rastløshet	0	1	2	3	4
10.7	Distraherbarhet	0	1	2	3	4
10.8	Annet_____	0	1	2	3	4

11 Status ved oppfølgingstidspunktet 31.12.2008

11.1	Total varighet behandlingskontakt VOP (mndr)		_____	
11.2	**Punkt 8.8** Total behandlingstid med SSM		_____	
	< 3 måneder			0
	3 måneder-1 år			1
	1-2 år			2
	2-3 år			3
	> 3 år			4
11.3	Fortsatt medikamentell behandling	0		1
11.4	Avsluttet medikamentell behandling	0		1

Hvis avsluttet, hvorfor?

Pasientens valg pga:

Bivirkninger	0	1
Manglende effekt	0	1
Rusmisbruk	0	1
Annet	0	1
Ukjent årsak	0	1

Behandlers valg pga:

Bivirkninger	0	1

	Manglende effekt	0	1
	Rusmisbruk	0	1
	Annet	0	1
	Ukjent årsak	0	1
11.5	Fortsatt behandling i VOP	0	1
11.6	Overført 1. linje for med. behandling	0	1
11.7	Arbeid/sysselsetting		
	Lever av sosial stønad		0
	Uførepensjon		1
	Rehabiliteringspenger		2
	Sykemeldt		3
	Yrkesrettet attføring		4
	Arbeidsledighetstrygd		5
	Under ordinær utdanning		6
	I lønnet arbeid		7
11.8	Endring i Arbeid/trygdestatus		
	Uendret		0
	Bedring		1
	Forverring		2
11.9	Ved tidl. rusmisbruk; tilbakefall	0	1

Attachment IV

Self-Report Questionnaire

Spørsmål om behandlingstilbudet du har mottatt ved Psykiatrisk klinikk på Sykehuset Levanger:

Sett ring rundt tallet for det svaret du synes passer best. Kun ett tall for hvert spørsmål.

Har det vært viktig for deg å få diagnosen ADHD?

Ikke i det hele tatt	0
Litt viktig	1
Ganske viktig	2
Veldig viktig	3

Hvis du har prøvd medisiner mot din ADHD, synes du at medisinene har vært nyttige for deg?

Ikke i det hele tatt	0
Litt nyttig	1
Ganske nyttig	2
Veldig nyttig	3

Hva synes du om det tilbudet Psykiatrisk klinikk gir til voksne pasienter med ADHD?

Dårlig	0
Litt bra	1
Ganske bra	2
Veldig bra	3

Hva synes du mangler ved det tilbudet Psykiatrisk klinikk gir til voksne pasienter med ADHD?

Svar:

Bruker du for tiden medisiner mot din ADHD (Ritalin, dexedrine, concerta, strattera, og lignende)?

0 Nei
1 Ja

Hvis nei, har du brukt det tidligere og sluttet med det selv?

0 Nei

1 Ja

Spørsmål om din nåværende situasjon:

Sett ring rundt tallet for det svaret du synes passer for deg. Kun ett tall for hvert spørsmål.

Sivilstatus

0 Jeg er ugift
1 Jeg er samboende
2 Jeg er gift
3 Jeg er separert
4 Jeg er skilt
5 Jeg er enke/enkemann

Bosituasjon

0 Jeg bor alene
1 Jeg bor sammen med foreldre
2 Jeg bor sammen med bare barn
3 Jeg bor sammen med ektefelle/samboer (og evt. barn)
4 Jeg bor sammen med andre enn de som er nevnt over

Utdanning

0 Ikke fullført grunnskole

1 Fullført grunnskole

2 Fullført videregående skole

3 Fullført universitet eller høgskole

Arbeid/sysselsetting

0 Lever av sosial stønad

1 Uførepensjon

2 Rehabiliteringspenger

3 Sykemeldt

4 Yrkesrettet attføring

5 Arbeidsledighetstrygd

6 Under ordinær utdanning (ikke attføring)

7 I lønnet arbeid

Hva er din nåværende arbeids-/studiesituasjon?

0 Jeg er skoleelev/student
1 Jeg er hjemmearbeidende/husmor)
2 Jeg er i arbeid, ca. 100 % (sett ring rundt selv om du for tiden er sykemeldt)
3 Jeg er i arbeid, ca. 50 % (sett ring rundt selv om du for tiden er sykemeldt)
4 Jeg er uføretrygdet
5 Jeg er arbeidsløs (sett ring rundt selv om du for tiden er under rehabilitering)

Er du for tiden under attføring?

0 Nei
1 Ja, ca. 50 % attføring
2 Ja, ca. 100 % attføring
3 Ja, annen gradering

Arbeid/studier

Hvor mange måneder har du arbeidet eller studert minst halv tid (50% eller mer) i løpet av de siste 12 måneder? (Regn ikke med tiden du har vært sykemeldt)

Svar:_____