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ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PRISON INMATES

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'If one is truly to succeed in leading a person towards a specific goal,
one must first and foremost meet him where he is and start from there.
This is the secret in the entire art of helping.'

Søren Kierkegaard, 1813-1855

ABSTRACT

Background: Attention deficit hyperactivity disorder (ADHD) is an inherited developmental disorder with early onset, chronically persisting in the vast majority of cases. ADHD is associated with pervasive cognitive, emotional and functional impairments, as well as an increased rate of coexisting disorders. ADHD in the presence of early disruptive behaviours increase the risk for later delinquency. ADHD is estimated to be present in about 25-45% of adult prison inmates, thus 10-times increased relative to the general population. Despite this, pharmacological treatment for ADHD has not previously been evaluated in prison inmates.

Aims: The aims of the present thesis were to characterise symptoms and impairments of adult male long-term prison inmates with ADHD, and to evaluate the efficacy, safety and tolerability of osmotic release oral system methylphenidate (OROS-MPH) provided to adult male prison inmates with ADHD and coexisting disorders as compared to placebo. An additional aim was to evaluate the long-term effectiveness of OROS-MPH when delivered alongside regularly provided psychosocial interventions within a prison setting.

Methods: Following an initial screening procedure at Norrtälje Prison, Sweden, extensive diagnostic evaluations were undertaken in 34 inmates indicating ADHD by the screening. Subsequently, 30 inmates out of 34 that confirmed ADHD and coexisting disorders were enrolled to a 5-week randomised, double-blind, placebo-controlled, fixed-dose trial of OROS-MPH followed by a 47-week open-label, flexible-dosing extension.

Results: ADHD was estimated to be present in about 40% of adult male long-term inmates of Norrtälje Prison. Inmates with ADHD were severely symptomatic and functionally impaired when compared to psychiatric outpatients with ADHD and with controls. OROS-MPH was highly effective and overall safe, both in the short-term relative to placebo (Cohen's $d=2.17$; Number needed to treat=1.1), and in the long-term when provided alongside psychosocial interventions.

The placebo response was non-significant. By the primary end-point, 87% of participants receiving OROS-MPH had achieved $\geq 30\%$ improvement in ADHD symptoms evaluated by the investigator-rated CAARS: O-SV scale, thus defined as treatment responders. On the other hand, 40% were defined to be in full remission by achieving normalisation of CAARS: O-SV scores when compared to a norm population without ADHD. Overall, symptomatic improvements translated into functional improvements. A few predictors of treatment response are suggested.

Conclusions: ADHD is a prevalent, persistent and impairing disorder in adult male long-term prison inmates. Treatment with OROS-MPH appears to be associated with a robust positive response in this specific group of long-term prison inmates with ADHD and coexisting disorders.

LIST OF PUBLICATIONS

This thesis is based on the following scientific papers, which will be referred to in the text by their corresponding Roman numerals:

- I. Ginsberg Y, Hirvikoski T, Lindefors N (2010).
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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ADOS	Autism diagnostic observation schedule
AMP	Amphetamine
ANOVA	Analysis of variance
AE	Adverse event
APA	American psychiatric association
ASD	Autism spectrum disorder
ASPD	Antisocial personality disorder
ASRS	Adult ADHD self-report scale
ASSQ	Asperger syndrome screening questionnaire
ATX	Atomoxetine
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BPD	Borderline personality disorder
Bpm	Beats per minute
BPR	Bupropion
CAARS: O-SV	Conners' adult ADHD rating scale-observer screening version
CBT	Cognitive behavioural therapy
CD	Conduct disorder
CGI-S	Clinical global impression severity of illness scale
CI	Confidence interval
Conners' CPT II	Conners' continuous performance test II
COMT	Catechol-O-methyltransferase
CPT	Continuous performance test
CU	Callous and unemotional
DA	Dopamine
DAT	Dopamine transporter
DBT	Dialectic behavioural therapy
DCD	Developmental coordination disorder
DEX-AMP	Dextroamphetamine
DIVA	Diagnostic interview for ADHD in adults

DISCO	Diagnostic interview for social and communication disorders
DRD2	Dopamine receptor D2
DRD4	Dopamine receptor D4
DSM-IV-TR	Diagnostic and statistical manual of mental disorders, fourth edition, text revision
E	Environmental factor
EEG	Electroencephalogram
ER	Extended release
ERP	Event-related potentials
ESSENCE	Early symptomatic syndromes eliciting neurodevelopmental clinical examinations
ETS	Enhanced thinking skills
FSIQ	Full scale intelligence quotient
FTF	Five to fifteen questionnaire
GAF	Global assessment of functioning scale
GCP	Good clinical practice
GxE	Gene by environmental interaction
GxG	Gene by gene interaction
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD-10	International classification of diseases, tenth revision
IQ	Intelligence quotient
IR	Immediate release
ITT	Intention-to-treat population
LD	Learning disability
LDX	Lisdexamfetamine dimesylate
LOCF	Last observation carried forward
MAO-A	Monoamine oxidase A
MPH	Methylphenidate
MRI	Magnetic resonance imaging
MTA	Multimodal treatment for ADHD
NE	Norepinephrine
NET	Norepinephrine transporter
NICE	National institute for health and clinical excellence

NNT	Number needed to treat
NVLD	Non-verbal learning disability
ODD	Oppositional defiant disorder
OROS	Osmotic release oral system
PCL-R	Psychopathy check list-revised
PD	Personality disorder
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder, not otherwise specified
PET	Positron emission tomography
PPV	Positive predictive value
PRISM	Program for reducing individual substance misuse
QOLI	Quality of life inventory
R-fMRI	Resting-state functional magnetic resonance imaging
rmANOVA	Repeated measures analysis of variance
ROS	Relations and companionship program
R&R	Reasoning and rehabilitation program
SAE	Serious adverse event
SCID-I	Structured clinical interview for DSM-IV axis I disorders
SCID II PQ	Structured clinical interview for axis II disorders, patient questionnaire
SD	Standard deviation
SLI	Specific language impairment
SUD	Substance use disorder
WAIS	Wechsler adult intelligence scale
WHO	World health organization
WURS	Wender Utah rating scale

1 INTRODUCTION

1.1 ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly established neurodevelopmental disorder of childhood, with an estimated worldwide prevalence rate of 5% to 10%, depending on the use of diagnostic criteria (Faraone et al., 2003). Over the past decades, the persistence of impairing symptoms of ADHD into adulthood has been increasingly acknowledged. In a meta-analysis by Faraone and colleagues it was suggested that about 15% of those diagnosed in childhood retain the full diagnosis by age 25 years in consistence with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) published by the American Psychiatric Association (APA) (APA, 2000) and with a further 50% in partial remission (Faraone et al., 2006). The prevalence rate of adult ADHD in the United States is estimated at 4.4% (Kessler et al., 2006), whereas a recent meta-analysis of population-based studies across several countries estimated the pooled prevalence of adult ADHD at 2.5% (Simon, 2009). The DSM-IV-TR defines ADHD as persistent and developmentally inappropriate symptom levels of inattention, hyperactivity and impulsivity, resulting in clinically significant impairment in social or academic-occupational functioning that is pervasive over situations. Further, DSM-IV-TR requires an onset of symptoms by the age of 7 years.

However, to better reflect the characteristics of ADHD and avoid missed diagnoses in adolescents and adults, the new proposal for DSM-5 (expected release in May 2013) increases the age of onset to 12 years (APA, 2012a).

Presently, the same diagnostic criteria and cut-off levels for ADHD are applied for both children and adults. However, an age-dependent decline in symptoms has been reported, with a more rapid decline in symptoms of hyperactivity and impulsivity by age, than inattentive symptoms (Biederman et al., 2000; Faraone et al., 2006). To better reflect the characteristics and natural course of ADHD and to avoid underdiagnosis of ADHD, it is suggested that DSM-5 will require 4 symptoms out of 9 for older adolescents and adults (ages 17 and older) of inattention and hyperactivity-impulsivity, respectively (APA, 2012a).

Originally, the symptom criteria of DSM-IV-TR were based on children and adolescents in the ages of 4-17 years, and they preferably included boys. The wording of symptoms may therefore not reflect the presentation of symptoms in male and female adults, thus making the diagnostic evaluation of adult ADHD more difficult.

The gross motor overactivity as commonly observed in children has been reported to change to a sense of inner restlessness as reported in adults with ADHD. However, increased levels of motor activity have recently been observed in adults with ADHD by means of objective measurements, thus challenging the view of motor overactivity not being a concern in adults (Lis et al., 2010).

Three different subtypes of ADHD are defined by DSM-IV-TR; inattentive, hyperactive-impulsive and combined subtype. However, the relative distribution

of ADHD subtypes is reported to vary as a function of methods used to combine information from different informants, thus questioning the validity and reliability of this subgrouping system (Rowland et al., 2008; Valo and Tannock, 2010).

Further, it is suggested that these subtypes of ADHD are temporally unstable (Lahey et al., 2005) and cannot be differentiated reliably with respect to cognitive correlates or treatment response (Baeyens et al., 2006; Solanto et al., 2009). Thus, it is proposed that DSM-5 replaces the categorical subtype classification with dimensional measures of the severity of inattention and hyperactivity, and the resultant impairment. Also, new criteria for impulsivity are proposed for DSM-5, which is important considering the relationship between ADHD and delinquency.

In total, four specifiers of current presentations are proposed (APA, 2012a):

- 1) Combined presentation of both inattention and hyperactivity-impulsivity; meeting the criteria for inattention (4 or 6 depending on the age) and hyperactivity-impulsivity (4 or 6 depending on the age), respectively.
- 2) Predominately inattentive presentation by meeting the inattention criteria, but not reaching the cut-off level for the hyperactivity-impulsivity criterion. However, more than 2 but less than 4 or 6 symptoms (depending on the age) of hyperactivity-impulsivity must have been present for the past 6 months.
- 3) Predominately hyperactive-impulsive presentation by meeting the criterion of hyperactivity-impulsivity but not the inattention criterion;
- 4) Inattentive presentation (restrictive) by meeting the inattention criterion but \leq 2 symptoms of hyperactivity-impulsivity for the past 6 months. By this procedure, those who only present symptoms of inattention will be divided from those who were combined from the beginning but later became predominately inattentive when symptoms of hyperactivity and impulsivity diminished with age.

Further, ADHD will be conceptualised as a disorder with both behavioural and cognitive dimensions (APA, 2012a). Multiple cognitive deficits are suggested to be associated with ADHD, supported by the observed heterogeneity of cognitive impairments seen in ADHD (for a review, see Swanson et al., 2011).

DSM-IV-TR precludes the simultaneous presence of autism spectrum disorder (ASD) and ADHD. However, research has established the coexistence of both disorders, and studies have suggested shared genes to be involved in some cases. Thus, it is proposed that DSM-5 will allow a simultaneous presence of ADHD and ASD (APA, 2012a).

The clinical presentation of ADHD symptoms in adults comprise difficulty to sustain attention in reading, paperwork, or at meetings, and also presenting insufficient listening skills, difficulties in finishing complex tasks and sitting through meetings, making careless mistakes, being easily distracted and forgetful, as well as having a low frustration tolerance (Kooij et al., 2010).

The associated functional impairments of ADHD in adults affect various aspects of daily functioning, including education, work performances, social relationships and quality of life (Kooij et al., 2010). Underperforming relative to the person's own ability, as well as having difficulties in finding and maintaining employment is

common. Symptoms of hyperactivity might present by working more than one job, working long hours, or by self-selecting a very active job to compensate for the need of stimulating activity, motion and change. Also, impulsive and frequent job changes without considering the long-term consequences are often seen.

With respect to daily functioning in the family environment, adults with ADHD are often easily distracted, forgetful, disorganised, misplace items, and experience difficulties in establishing and maintaining daily routines at home as well.

Together with poor listening skills, a tendency to interrupt others, being in constant activity and easily frustrated, these difficulties can lead to tensions in relationships with family members and significant others.

When exploring the economic impact of ADHD, it has become evident that adults with ADHD utilise medical services 50% more than controls, in addition to the costs associated with ADHD treatment itself (Wasserstein, 2005). In part this was related both to an increased number and higher costs of accidents. For instance, adolescents and younger adults are involved in more traffic accidents related to driving impairments than those without ADHD (Barkley, 2004; Fried et al., 2006).

Further, estimates of lost work days were comparably higher in adults with ADHD (Secnik et al., 2005), and they were also less likely to be full time employed (Biederman et al., 2006). Not surprisingly, household income for adults with ADHD, aged 25 years or older, was lower compared to controls (Biederman and Faraone, 2006). The overall health-related quality of life is reported to be compromised as a result of the personal, social and economic impairments related to adult ADHD, particularly when ADHD is neither recognised nor treated (Coghill, 2010; Able et al., 2007).

1.2 THE GENETICS AND NEUROBIOLOGY OF ADHD

1.2.1 Genetic findings

The heritable component of ADHD is well established; ADHD tends to aggregate within families, and ADHD is more commonly observed among monozygotic twins than in dizygotic twins. Based on twin studies it is estimated that about 70-80% of the variation seen in ADHD symptoms (phenotypic variance) can be explained by genetic factors (the heritability estimate). Despite the evidence of a strong genetic contribution to ADHD, identifying the genes involved in ADHD by genetic studies has been difficult (for a review, see Plomp et al., 2009). A hypothesis of a catecholamine dysregulation as the underlying mechanism of ADHD has been supported by the observations of stimulants improving ADHD symptoms, as well as by the findings from neuroimaging studies suggesting deficits in prefrontal-striatal circuits that are closely related to the catecholamine system, mainly the dopamine (DA) system. Thus, candidate gene studies have so far mainly focused on dopamine (DA) genes e.g., the dopamine receptor D4 (DRD4) gene and the dopamine transporter (DAT) 1 gene, although other monoamine candidates e.g., serotonin genes have also been suggested. However, since individual risk genes only appear to explain about 1-3% of the phenotypic variance, thus indicating very small effects, the role of environmental factors (E), as well as gene by gene

(GxG) and gene by environmental (GxE) interactions have been explored. Several E risk factors e.g., exposure to adverse circumstances pre-, peri-, and post-natally have been identified. However, most of these studies were confounded as they did not control for genetic influences. Further, it has been suggested that a simultaneous occurrence of polymorphisms in DRD4 and DAT1 genes (GxG interactions) would produce an increased risk for ADHD. Moreover, recent studies have explored the role of environmental factors as mediators or moderators of genetic effects (GxE interactions). However, results have so far been inconsistent (Plomp et al., 2009).

1.2.2 Neurobiological findings

Previous neuroimaging studies using magnetic resonance imaging (MRI) indicated smaller volumes of prefrontal areas, caudate nucleus and the pallidum, as well as reduced cortical thickness in children and adults with ADHD supporting the prefrontal-striatal model as mentioned above. Further, a delay in cortical maturation was reported, most prominent in prefrontal regions (for a review, see Cherkasova and Hechtman, 2009).

However, based on findings from resting-state functional MRI (R-fMRI), an extension of the prefrontal-striatal model to include other circuits and their interrelationships, was recently suggested. A recent review reported the findings so far (Castellanos and Proal, 2012). This review will be summarised as follows (for specific references, please see the review):

By the use of R-fMRI, seven major intrinsic connectivity networks have been identified; sensorimotor and primary visual cortex, limbic, dorsal attention, ventral attention, frontoparietal control and default networks.

So far, the most studied functional connectivity system is the default network. Fluctuations of this network decrease during cognitive tasks and increase during rest, thus representing the physiological baseline of the brain. The fluctuations are 180 degrees out of phase (anticorrelated) with fluctuations of the task-mode network, thought to be reflective of a competition between opposing processes for processing of resources. A diminished suppression of the default mode network has been associated with attentional lapses. It was proposed that ADHD might be viewed as a default mode network disorder and also suggested that the network might be refractory to regulation by other neural systems, thus intruding ongoing cognitive activation. This intrusion would lead to periodic lapses of performance, as often observed in ADHD. Further, decreased default network coherence was reported in ADHD, as well as an association between decreased suppression of the default network and increased intra-individual variability in children with ADHD (Castellanos and Proal, 2012).

An aim of the studies herein was to explore cognition-related effects of MPH in individuals with ADHD. In addition, we aimed at evaluating aspects of cognitive functioning in more detail by a range of diverse assessments with the purpose of generating hypotheses to be tested in future research.

1.3 COEXISTING DISORDERS IN ADHD

Coexistence is the rule rather than the exception in both children and adults with ADHD. There is a considerable overlap in the presentation of symptoms between ADHD and several syndromes that are referred to as discrete and separable entities in the categorical diagnostic systems of both the DSM-IV-TR (APA, 2000), and the current tenth version of the International classification of diseases (ICD) system, published by the World Health Organization (WHO), called ICD-10 (WHO, 1993). Although ADHD sometimes presents as an isolated disorder, it is much more often associated with several other disorders that in many cases probably are reflective of the same underlying brain dysfunctions.

DSM-IV and ICD-10 are indeed useful as diagnostic tools. However, we need to remind us that they are artificial constructs, thus not necessarily reflecting reality. Dividing disorders into discrete entities may give an impression of isolated disorders even when they are not exclusive and separable.

1.3.1 Coexisting disorders in children

Recently, the acronym ESSENCE referring to Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations was coined (Gillberg, 2010).

Major impairing symptoms in at least one ESSENCE domain before the age of 5 years strongly predict major impairments in the same or overlapping domains several years later. The ESSENCE domains refer to general development, communication and language, social inter-relatedness, motor coordination, attention, activity, behaviour, mood and (or) sleep.

Major impairing symptoms that signal ESSENCE in the first 4 years of life include developmental coordination disorder (DCD), general developmental delay, speech and language delay, social interaction-communication problems, behaviour problems, hyperactivity-impulsivity, hypoactivity, inattention, sleep problems, as well as feeding difficulties.

Syndromes included under the ESSENCE acronym include ASD-Pervasive developmental disorder (PDD), ADHD, oppositional defiant disorder (ODD), specific language impairment (SLI), learning disability (LD), non-verbal learning disability (NVLD), tic disorders, Tourette syndrome, bipolar disorder, behavioural phenotype syndromes (e.g., 22q11 deletion syndrome), rare epilepsy syndromes and reactive attachment disorder. The sum prevalence rate of these ESSENCE syndromes is estimated to be about 10% in the general population of children.

The concept of ESSENCE suggests that a child presenting with an ESSENCE problem is at risk for having complex problems and should, as early as possible, be provided a multidisciplinary assessment to identify all the child's different needs. Individually tailored interventions should then be provided in a holistic approach. Recognising and intervening early for e.g. ADHD and ODD has the potential of improving the prognosis and may prevent children from later ending up in prison.

Coexistent disorders of ADHD are also frequently present in the general population (Kadesjö and Gillberg, 2001). The most commonly reported coexisting

disorders are ODD, conduct disorder (CD), DCD, depression, anxiety disorder, ASD and substance use disorder (SUD).

1.3.2 Coexisting disorders in adults

In addition to overlapping neurodevelopmental disorders, studies have estimated the rate of lifetime coexisting psychiatric disorders of both Axis I and Axis II in adults with ADHD at about 80% (Sobanski, 2006; Jacob et al., 2007).

The most common Axis I disorders were depression, dysthymia, anxiety disorders (e.g., generalised anxiety disorder, social phobia, specific phobias, and panic disorder), SUD including nicotine dependence, and eating disorders (anorexia, bulimia) (Cumyn et al., 2009). Some gender differences have been reported; females were more likely to have eating disorders, panic disorder, depression and dysthymia, whereas males more often had SUD. According to most studies, the combined subtype is more often associated with coexisting disorders than the inattentive subtype (Sprafkin et al., 2007).

The most commonly reported personality disorders (PDs) were borderline personality disorder (BPD), antisocial personality disorder (ASPD), histrionic and narcissistic traits (Sobanski, 2006). Further, BPD was more common in females, whereas ASPD was more common in males (Cumyn et al., 2009).

However, the coexistence is bi-directional, as ADHD is frequently observed among patients with e.g., affective disorders, anxiety disorders, PDs, and SUD.

Recently, a meta-analysis reported ADHD to be present among 23% of SUD populations comprising adolescents and adults with a variety of SUDs (nicotine dependence excluded). Cocaine dependence was less associated with ADHD than alcohol dependence, opioid dependence and other addictions (van Emmerik-van Oortmerssen et al., 2012). ADHD is reported to have a negative effect on the course of SUD. In ADHD, the onset of SUD is earlier and they become more easily addicted, have lower remission rates and are more often hospitalised as compared to those with SUD without ADHD (Arias et al., 2008; Schubiner, 2005).

1.4 ADHD AND DELINQUENCY

1.4.1 The antisocial trajectory

There has been an ongoing controversy whether ADHD by itself constitutes a risk factor for later antisocial behaviour and delinquency, or if the developmental trajectory is mediated by coexisting disruptive symptoms of ODD and (or) CD.

ODD is defined as a pattern of negativistic, hostile, and defiant behaviour directed at authority figures (Hazell, 2010; Connor et al., 2010; Steiner and Remsing, 2007). DSM-IV-TR requires that at least 4 out of 8 oppositional symptoms are present for a period of at least 6 months, and that symptoms cause severe impairment in social and academic functioning (APA, 2000). In the proposed revisions for the DSM-5, the same 8 symptom criteria of ODD are being allocated to three diagnostic subgroups; angry-irritable mood, defiant-headstrong behaviour, and

vindictiveness. Further, a diagnosis of CD or ASPD will no longer be excluding for a diagnosis of ODD. Also, only one setting for the presence of disruptive behaviour will be required, and a frequency criterion will be included. ODD usually has its onset before 8 years of age, but a second wave of onset in early adolescence has also been reported. The prevalence rate of ODD in the general population is estimated at a median of 3% in boys and 1.4% in girls (Hazell, 2010; Maughan et al., 2004). ODD is even more frequently observed in clinical samples, probably related to referral bias. In a selective review by Biederman, ODD was reported to occur in about 30-60% of those with ADHD (Biederman, 2005).

Children with ADHD + ODD (or ADHD + CD) were more likely to be placed in special education, and to have received pharmacological treatment for ADHD than those with 'pure' ADHD (Steiner and Remsing, 2007). Disruptive behaviour is often seen as the driving force when parents seek professional help for their children, which could explain the higher rates of treatment in this group (Connor and Doerfler, 2008).

Twin studies have found that ODD, just as ADHD, has both shared and unique genetic influences, with a modest contribution of shared environment to the aetiology (Dick et al., 2005).

The prevalence rate of CD in the general population is estimated at a median of about 2% in boys and 0.8% in girls (Hazell, 2010; Larson et al., 2011; Maughan et al., 2004). CD is reported to be coexistent with ADHD in about 20% of cases (Biederman, 2005; Larson et al., 2011). According to DSM-IV-TR, a diagnosis of CD requires repeated violation of the basic rights of other individuals.

It is required to meet at least three out of 15 diagnostic criteria, including overt aggression toward people or animals, property destruction, theft and deceitfulness, and serious violations of rules and laws (APA, 2000).

In the proposed revision for DSM-5, the value and accuracy of the current definition is emphasised. Further, a 'Callous and Unemotional (CU) Specifier for Conduct Disorder' has been proposed, defined as meeting at least two characteristics of CU behaviour over at least 12 months, apart from CD (APA, 2012b). In an initial field trial, those with CD and CU traits were considered to have more severe symptoms of CD, such as aggression and cruelty (Scheepers et al, 2011).

Currently, there is a controversy as to whether oppositional symptoms in the context of ADHD truly represent a distinct diagnosis of ODD or CD, or if these oppositional symptoms should be viewed as a component of ADHD by itself (Connor et al., 2010). Further, there is a debate whether ODD and CD should be seen as being on the same continuum, with CD encompassing ODD and being treated as a more severe or progressed form of ODD. The temporal relationship between ODD and CD might not always be clear. One longitudinal study suggested that two different subtypes of ODD were coexistent with ADHD; one ODD subtype appearing to be prodromal to CD, and the other subtype subsyndromal, less likely progressing to CD (Biederman et al., 1996). DSM-IV-TR established a hierarchical relationship between ODD and CD, meaning that the presence of ODD and CD are mutually exclusive and that ODD precedes CD. In contrast to the DSM-IV-TR, the ICD-10 (WHO, 1993) differentiates between ADHD, and ADHD with CD, by

defining a category of hyperkinetic disorder of social behaviour (F 90.1). Interpretation of research data regarding the complex relationships between ADHD, oppositional symptoms, ODD and CD are difficult, especially considering that many previous studies did not differentiate between ODD and CD when comparing groups of ADHD with groups of ADHD and coexisting disruptive behaviours of ODD and CD. Also, many previous studies did not differentiate between different subtypes of ADHD in their statistical analyses (Connor et al., 2010). These issues need to be resolved in the future in order to find the optimal treatment approach for ADHD with coexisting oppositional symptoms, and to evaluate if early treatment for ADHD + ODD could reduce the risk for developing CD, and later on ASPD.

In a recent review by von Polier and colleagues (von Polier et al., 2012), they reported the most relevant findings regarding the association between ADHD and later delinquency and the impact of coexisting disruptive symptoms. They also provided an insight into the developmental trajectory from childhood until adult antisocial behaviours. The review by von Polier and colleagues is summarised as follows (for specific references, see von Polier et al., 2012):

Most authors agree on two distinct trajectories that lead to later antisocial behaviour as delineated in the DSM-IV-TR; the 'early starter' type with onset in early childhood before the age of 10 years that tends to be more chronic, than the 'late starter' type with onset in late childhood or early adolescence, suggested having an episodic course.

In the longitudinal Dunedin Study, Moffitt and colleagues recognised four developmental subtypes of conduct problems:

- 1) *Childhood onset type/life-course persistent type*, which showed high levels of aggression throughout development with continuation of violence in adulthood. This group experienced the worst health burdens and economic problems. Although they constituted only 10% of the original male birth cohort, by the age of 32 they were attributed about 70% of the months spent in prison and about 30% of the days spent in psychiatric hospitals. In this group, 38% were diagnosed with ADHD, which was the highest prevalence rate of ADHD among the different subtypes.
- 2) *Adolescent-onset type* which also showed continued offending behaviour, although to a lesser degree than the life-course persistent type. Also, they experienced severe mental and physical health problems. About 6% had ADHD in this group.
- 3) *Childhood-limited type* which showed similar severity of conduct problems at the age of seven, but did well at the age of 32. Their health outcomes did not differ from the cohort norm group. That is, childhood CD does not always predict a poor outcome as an adult, especially when there are few risk factors. A total of 12% of participants suffered from ADHD in this subtype.
- 4) *Low-trajectory type*. Only 3% in this subgroup had ADHD, which was the lowest prevalence rate of ADHD among subtypes.

The researchers of the Dunedin Study follow a birth cohort of 1,037 children born in 1972 from the age of three years. The cohort has been evaluated at several time points, most recently when the participants are at the age of 32. Children with CD and ADHD, especially the combined subtype of ADHD, had an increased genetic, neurocognitive and psychosocial burden as compared to healthy control children:

Antisocial behaviour among children with CD and ADHD is heritable, but also influenced by environmental factors. It is reported that parents of children with ADHD and antisocial behaviour often are affected by schizophrenia, substance abuse, depression (mothers preferably) or ASPD (fathers preferably).

A highly heritable general liability to externalising psychopathology was reported, manifested by inattention, hyperactivity, oppositional, defiant and conduct symptoms in offspring. In genetic association studies, both the dopamine receptor D2 (DRD2) and DRD4 have repeatedly been associated with CD and antisocial behaviour. Environmental risk factors include low parental intelligence, drug availability, and poor parenting. Poor parenting is found in parents with ADHD, and parents may also be models of violence and antisocial behaviour, or reward aggressive behaviour, particularly in families of young children developing CD. The few studies exploring gene-environment interactions have suggested antisocial behaviour to be increased in boys with low monoamine oxidase A (MAO-A) activity that had experienced childhood maltreatment.

Further, an interaction was found between the catechol-O-methyltransferase (COMT) Val 108/158Met polymorphism and maternal cigarette smoking during pregnancy, which predicted later aggressive behaviour of the child.

Poor educational achievement, learning disabilities and low intelligence have consistently been recognised as risk factors for antisocial and criminal behaviour. Several studies have established a specific linkage between difficulties in reading comprehension and antisocial behaviour. In a recent study exploring learning disabilities and ADHD among prison inmates, strong links were found between ADHD and early school termination, as well as between learning disabilities and younger age of onset of criminal activity.

Children with ADHD are more rejected by peers, being perceived as less socially competent, have fewer friends and more frequently show aggressive interactions predicting social exclusion. At baseline in the Multimodal Treatment for ADHD (MTA) study, children with ADHD were more aggressive, had reduced social skills and were more rejected by peers as compared with a healthy control group.

At the same time, they tended to overestimate their competences in social and behavioural areas. Over time, there were vicious cycles among problems; peer rejection was related to impaired social skills, which in turn predicted later peer rejection. Overestimation of competences at baseline predicted aggressive and antisocial behaviour three years later. Further, children with ADHD and coexisting ODD/CD presented worse social functioning than children with ADHD alone. Also, poor social functioning and internalising problems was reported to be associated in children with ODD/CD (von Polier et al., 2012).

As mentioned previously, multiple widespread neural systems are considered to be involved in ADHD. These systems seem to be associated with cognitive control or the capacity to suppress inappropriate thoughts and behaviours and initiate

more appropriate ones (Nigg and Casey, 2005). Of special interest with respect to delinquency is the involvement of the motivational system in the form of delay aversion, meaning that those with ADHD often prefer a small immediate reward to a large delayed reward, as well as a positive reaction to a high-intensity reward. However, neuroimaging studies exploring antisocial individuals have so far not controlled for coexisting ADHD, thus limiting the conclusions to be made regarding ADHD versus CD. However, data from adult ASPD samples indicate changes mainly in the fronto-limbic system (Huebner et al., 2008; Raine, 2011). Dysfunctions of the amygdala (which is closely connected and modulated by the prefrontal cortex) may contribute to antisocial development through deficient emotion processing (Fairchild et al., 2011; Raine, 2011).

Children with ADHD are at increased risk for SUD, anxiety, depression, and possibly also for bipolar disorder (Fayyad et al., 2007). Those following an adverse trajectory were more likely to have the combination of ADHD and ODD (Biederman et al., 2008; Harpold et al., 2007). It is well established that SUD by itself increases the risk for delinquency (Brook et al., 1996), academic failure (Lewinsohn et al., 1995) and coexisting psychiatric disorders (Kandel et al., 1999). A recent meta-analytic review reported that children with ADHD more likely developed SUD in the presence of CD (Charach et al., 2011).

There are several long-term investigations following children with ADHD until adulthood. A few of these studies excluded children with ADHD + CD in order to evaluate the influence of ADHD, by itself or in combination with other disorders, on the risk for later delinquency (Gittelman et al., 1985; Mannuzza et al., 1991). According to these studies, also children with ADHD without CD symptoms were more likely diagnosed with ASPD in adulthood as compared to children without ADHD. However, these prospective studies did not control for childhood ODD, which is known to precede CD in some cases. In summary, most studies so far suggest early CD/ODD in individuals with ADHD to moderate the risk of antisocial development. Additionally, in a recent Norwegian study, a group of child psychiatric inpatients were followed up after 19-41 years to evaluate the risk for adult delinquency (Mordre et al., 2011). CD and hyperkinetic conduct disorder as defined by ICD-10 (WHO, 1993) increased the risk for delinquency in adulthood as opposed to ADHD alone. This finding was consistent with a previous 30-year-follow-up study that could not confirm hyperactive boys without CD to be at increased risk for developing criminality in adulthood (Satterfield et al., 2007).

A Swedish controlled, longitudinal, community-based study of children with ADHD ± DCD at age 7 years were compared with age-matched controls without neurodevelopmental disorders by the age of 22 years (Rasmussen and Gillberg, 2000). Blinded assessments revealed that 58% of the collapsed ADHD/DCD group had a poor outcome relative to 13% of the comparison group. Persistence of ADHD symptoms, ASPD, alcohol abuse, criminal offences, reading disorders and a low educational level were more frequently observed in the ADHD/DCD group. None of the participants had been treated with stimulants at any time. ASD was only observed in the ADHD + DCD group; 15% of them confirmed ASD by the age of 22 years. The strongest predictor of a poor outcome was childhood

ADHD + DCD. Criminal offence was recorded in 19% of index cases (all males) as compared to 0% of the comparison group and female index cases.

Several trials of stimulants; methylphenidate (MPH) or dextroamphetamine (dex-AMP), as well as of the non-stimulant atomoxetine (ATX) conducted in children with ADHD alone and in children with ADHD and coexisting ODD of mild to moderate severity, suggested that treatment was equally effective in improving core symptoms of ADHD in both groups of children (Biederman et al., 2007; Hazell et al., 2006; Swanson et al., 2001). However, one ATX trial suggested a potential need for higher dosages in children with ADHD + ODD as compared to children with ADHD alone (Newcorn et al., 2005). The MTA study suggested that both symptoms of ADHD and ODD were equally improved over 14 months by treatment with either medication alone, or with medication combined with behavioural interventions in children aged 7 to 10 years (Jensen et al., 2001). However, treatment did not prevent children from developing delinquent behaviour in the long term. It was suggested that participants would have needed a more prolonged and intensive multimodal treatment with extension into adolescence than the 14 months provided by the MTA-study to prevent the negative developmental trajectory (von Polier et al., 2012).

1.4.2 ADHD in adult prison inmates

It is recognised that a disproportionately high number of prison inmates suffer from ADHD as compared to the general population. Reported prevalence rates of ADHD among inmates varies (Vermeiren et al., 2003), which could be related to differences in criminal law systems across countries, different methodologies used, and differences in study populations with respect to age, gender and type of offences (Young et al., 2011). However, most studies have estimated the prevalence of ADHD at about 45% of youth offenders (Rösler et al., 2004) and about 30% of adult offenders (Young et al., 2009; Young and Goodwin, 2010). Female offenders have been less explored than males; a German study reported a 10% prevalence of ADHD among adult female offenders (Rösler et al., 2009) as opposed to two Swedish studies that estimated the prevalence to be about 30% (Edvinsson et al., 2010; Konstenius et al., 2010, retrievable report at www.kriminalvarden.se/sv/publikationer). Youth offenders are costly to manage (Young and Goodwin, 2010; Chitsabesan et al., 2006; Barrett et al., 2006). Offenders suffering from ADHD are considered to cost comparably more than those without ADHD, because of earlier and repeated contact with the criminal justice system and more frequent and severe institutional aggression among offenders with ADHD (Young et al., 2003; Young et al., 2009; Young and Goodwin, 2010).

Young and colleagues and Gudjonsson and colleagues have reported from a series of studies conducted at a Scottish prison, exploring the characteristics of male inmates with ADHD (Young et al., 2009; Young et al., 2011; Gudjonsson et al., 2008, 2009, 2011, 2012). To summarise their findings; compared with other offenders, those with ADHD had a comparably younger onset of offending by about 2.5 years, higher rates of re-offending and a larger number of property and

violent offences. Also, they were more often coexistent with ASPD and had greater use of heroin prior to incarceration. Further, offenders with ADHD were more symptomatic and impaired, although the key predictor of ADHD was a chaotic-disorganised personality style rather than a PD. Notably, ADHD symptoms during childhood, as well as currently persisting symptoms were the strongest predictors of violent offending, even over and above substance misuse.

The absence of routine screening for ADHD in offender facilities was noted, and that very few offenders were previously diagnosed with ADHD. It was suggested, that if ADHD is left untreated there is a serious risk of maintained SUD as well as of consolidated antisocial attitudes and lifestyles, thus reducing the potential for rehabilitation (Young and Goodwin, 2010).

In a large German study of young male offenders, a younger onset of offending was found in inmates with ADHD and coexistent CD as compared to a CD group without ADHD (Rösler et al., 2004). In addition, inmates with ADHD + CD had significantly more relatives that were previously imprisoned due to severe crimes, than inmates with CD without ADHD. In a subsequent study of incarcerated adult women, a comparably younger age of first conviction was observed in female inmates with ADHD and CD (Rösler et al., 2009).

Recently, Rösler provided an overview regarding functional impairment, conduct problems and criminality in adult ADHD (Rösler, 2010) which will be summarised and referred to in the following part (please see the overview for specific references). The prevalence rate of ADHD appears to differ between offender types with the highest ADHD rates observed in sexual offenders, whereas property-related crimes had slightly increased prevalence rates of childhood ADHD. On the contrary, ADHD was not overrepresented among inmates convicted of fraud. When violence was dichotomised into reactive-impulsive and affective violence versus proactive-predatory and instrumental violence, ADHD was considered to be a moderator of reactive but not of proactive aggression in children with CD. Further, reactive antisocial behaviour was found to be more related to ADHD than proactive antisocial behaviour in a study of children between 7 and 15 years of age. Likewise, a strong association between present ADHD and reactive violence was found when exploring male violent offenders. Proactive violence appeared to be more related to offenders without ADHD. The relationship between ADHD and reactive violence might be explained by the characteristics of reactive violence, as a spontaneous and impulsive reaction to a provocation or a conflict, driven by affective outbursts, without planning or organisation. Further, reactive violence is short-lived and with no other finalistic target than reducing tension and agitation. This definition of reactive violence seems to overlap considerably with the psychopathology of ADHD. Moreover, it is well established that ADHD and ASPD often coexist. In fact, in forensic psychiatric populations, the combination of ADHD + ASPD was observed to be at least 100 times more prevalent than if the disorders were occurring independently. However, the association between ADHD and the concept of psychopathy is less well explored. Psychopathy can be assessed by the Psychopathy Check List (PCL-R) as defined by Hare (Hare et al., 1991, 2000). The psychopathology of psychopathy is characterised by shallow affects, superficial charm, and absence of

feelings of guilt and remorse, and manipulativeness. Psychopaths comprise a small but severely affected population, and psychopathy is associated with persistence and a poor treatment response. Recently, single increased psychopathic traits were observed in adolescents with ADHD. However, PCL-R scores were below the range of typical psychopathy.

Rösler and colleagues explored the overlapping psychopathology between ADHD and psychopathy by conducting a factor analysis. The solution with seven factors accounted for 60% of the variance and included 3 'pure' ADHD and 4 'pure' psychopathy factors. Thus, ADHD and psychopathy seemed to be two different and unrelated concepts (Rösler, 2010).

Further, previous studies from forensic populations reported a 10-fold increased risk for ASD (Anckarsäter et al., 2007, 2008). Despite the assumed similarities between forensic populations and prison populations, we are not aware of any studies evaluating the prevalence of ASD among prison inmates.

Overall, studies exploring the risk factors for criminal behaviour in ASD have been scarce (Bjørkly, 2009). Many of them were case studies comprising small samples, while prospective studies have been few. As previously mentioned, a follow-up study of children with ADHD reported those coexistent with ASD (and DCD) to be at increased risk for antisocial behaviour by the age of 22 (Rasmussen and Gillberg, 2000). Further, in a retrospective survey of a young Swedish forensic population (aged 15-22 years) referred for pre-trial forensic psychiatric investigations, the total prevalence of ASD was estimated at 15%; the criteria for PDD-NOS were considered to be met by 12% ,and 3% met the criteria for Asperger syndrome (Siponmaa et al., 2001).

Moreover, a Swedish register based study explored sociodemographic and clinical characteristics of hospitalised individuals with ASD as risk factors for violent convictions, by comparing a group of violent offenders with ASD with a group comprising ASD individuals without violent convictions. Violent offenders with ASD were more often male, established with Asperger syndrome rather than autism, and more often coexistent with psychotic disorders and SUD. Notably, these risk factors were similar to those previously identified in violent offenders without ASD (Långström et al., 2009).

In a recent report, a late initial ASD diagnosis and a history of neglect and physical abuse significantly predicted criminal behaviour in individuals with ASD. The rate of sexual misconduct was relatively high in the study population and the criminal behaviours were repeated.

It was suggested that restricted activities and interests might have contributed to the observed re-offending (Kawakami et al., 2012).

The authors suggested that earlier diagnosis of ASD and early educational interventions, aiming at increasing the acquirement of social skills and adaptation to society might prevent from a criminal trajectory of these children.

1.5 DIAGNOSTIC ASSESSMENT OF ADHD IN ADULTS

Considering the substantial overlap in symptoms, as previously discussed (1.3), an integrative evaluation process is suggested (Kooij et al., 2010; Haavik et al., 2010).

The evaluation should comprise a clinical interview for ADHD, e.g., the Diagnostic Interview for ADHD in adults (DIVA), which was recently developed by Francken and Kooij (Kooij, 2010). The DIVA is based on the DSM-IV-TR criteria and was recently translated into several European languages by members of the European Network Adult ADHD. A Swedish, not yet validated version of DIVA, is freely available at www.divacenter.eu. The Wender Utah Rating Scale (WURS) may be used for screening of childhood symptoms of ADHD (Ward et al., 1993).

The World Health Organization Adult ADHD Self-Report Scale (ASRS) may be used for screening of present symptoms in adulthood, as well as for evaluation of treatment effects (Adler et al., 2006).

The ASRS comprises 18 items that correspond to the 18 DSM-IV-TR criteria but are re-worded to better reflect the presentation of ADHD in adults.

There is a Swedish, not yet validated, version of the ASRS freely available at <http://www.hcp.med.harvard.edu/ncs/asrs.php>. The ASRS-Screener, a 6-item short version of the ASRS is available at the same website (Kessler et al., 2005, 2007). Notably, rating scales are generally not sufficient to use as diagnostic tools.

Further, collateral information from multiple informants should be obtained whenever possible to gain insights of the developmental history including e.g., the age of onset of ADHD symptoms, overlapping developmental symptoms, the trajectory of symptoms and impairments, as well as to provide information regarding current symptoms and the level of impairment in different settings.

In addition to the core symptoms of ADHD as defined by the DSM-IV-TR criteria, adults with ADHD often report associated symptoms that may be more impairing in their daily life than the 'classical' core symptoms. These associated symptoms comprise e.g., emotional over-reactivity, temper outbursts, irritability, poor motivation, as well as affective instability with mood shifts that usually last for hours to a few days, thus not fulfilling the criteria for mood disorders.

In spite the categorical classifications of both DSM-IV-TR and ICD-10, ADHD represents from a dimensional point of view, the tail (or the extreme end) of a trait that is normally distributed within the general population.

Thus, to be assigned a diagnosis of ADHD, symptoms need to be chronically persistent and, which is important, also associated with functional impairments. However, impairments may occasionally be difficult to recognise in adults, especially in those with a high intellectual capacity who have acquired compensatory strategies that could mask for underlying impairments, and (or) in those who receive much support from significant others.

Further, coexisting psychiatric (including other neurodevelopmental disorders) disorders need to be evaluated, preferably by the use of standard structured clinical interviews.

A medical assessment is important for differentiating between ADHD and somatic conditions that could 'mimic' ADHD symptoms, e.g., neurological, endocrine and

metabolic disorders. The assessment usually comprises a full medical history, physical examination and laboratory measures. Urine drug screening for illicit drugs is strongly recommended considering the high rates of SUD within ADHD. Also, eligibility for subsequent pharmacological treatment needs to be ensured.

Although there is currently no objective, laboratory-based test or biomarker available that can establish ADHD within the individual, performance-based measures e.g., neuropsychological tests provide additional information regarding cognitive functions that may facilitate in the understanding of the complex clinical picture, as well as in the treatment planning.

1.6 TREATMENT FOR ADHD

The increased recognition of ADHD persisting across the lifespan for about two-thirds of the cases means, that ADHD has to be conceptualised as a chronic disorder.

Analogous to other chronic medical disorders which begin in childhood and cause ongoing impairment into adulthood, e.g., asthma, diabetes, cerebral palsy and autism, there is a need for a longitudinal, developmental approach toward recognition and management of ADHD (Turgay et al., 2012).

By optimally treating ADHD across the lifespan from childhood through adulthood, there is also the potential of increasing treatment persistence during key life transitions and minimising adult psychopathology (Simon et al., 2009; Polanczyk et al., 2007).

Application of such conceptual framework might hopefully also prevent children with ADHD and disruptive behaviours from entering the antisocial path leading towards imprisonment.

A Life Transition Model has been proposed as a step toward developing criteria to optimise recognition and management of ADHD across the lifespan and across various medical subspecialties (Turgay et al., 2012).

The Life Transition Model describes the change in clinical presentation of ADHD over time, defines patient needs in different developmental stages, barriers to treatment and clinical goals, as well as suggests solutions for effective management of ADHD across the lifespan, through multidisciplinary interventions (pharmacological as well as non-pharmacological), intensive education of psychiatrists and mental health professionals regarding evidence-based practices, as well as involvement of stake holders, ranging from patients to policy makers, aiming at system-wide changes in care (Dixon et al., 2010; Brown, et al., 2008; Turgay et al., 2012).

Future research needs to evaluate the costs, benefits and long-term outcomes if these interventions are to be implemented in clinical practice.

As mentioned previously, ADHD is associated with functional impairments in several domains of life. A functional impairment in a specific area indicates that

available resources are inadequate to meet the functional demands of this area; thus conceptualised as a *resource-demand imbalance*.

Environmental demands include academic, occupational, financial, and social activities and functions. They tend to increase in number, scope and complexity with increasing age and level of independence.

Available resources to meet these demands comprise:

- *Internal resources*; e.g., working memory, ability to wait one's turn, sustain focus, plan and prioritise, complete tasks for reaching future goals
- *External resources*;
 - People (e.g., parents, siblings, teacher, school nurse, paediatrician, family practitioner, child psychiatrist, friends, spouse, colleagues, social worker, substance abuse counsellor, psychiatrist, psychologist, occupational therapist, prison staff, program leader)
 - Objects (e.g., alarm clocks, medication, calendars, reminders)

Generally, internal resources develop gradually with age as the environmental demands increase. At the same time, the initially intense external support provided by parents and teachers decrease over time to permit increased levels of independence. As long as the available resources of the individual are sufficient to meet the increasing environmental demands, functional impairments will not emerge.

However, in case of ADHD, functional impairments emerge in several areas, as previously outlined in detail.

Optimal management of ADHD should therefore address the resource-demand imbalance by strengthen internal and external resources, in consistence with the identified needs of each individual, as part of a comprehensive treatment plan (personalised treatment).

Further, an optimal management of ADHD requires an understanding of the change in presentation of symptoms and impairments within the different developmental phases, as well as changing of the environmental demands during sensitive transitional periods.

The Life Transitional Model identified three key developmental transitions; from childhood into adolescence; from adolescence into young adulthood; and from young to older adulthood or receiving the first diagnosis in later adulthood. During these sensitive periods, health professionals have to proactively anticipate additional need for support, patient education, development of patient-defined goals and self-management skills. The transition from child & adolescent psychiatry to general psychiatry needs special consideration for ensuring access to continued treatment in adulthood (Turgay et al., 2012).

1.6.1 Multimodal treatment in adults

The European Network Adult ADHD, which comprises several Swedish members, recently published a consensus document addressing diagnosis and treatment of adult ADHD (Kooij et al., 2010).

According to the guidelines published by the British National Institute for Health and Clinical Excellence (NICE), pharmacological treatment with MPH should be the first-line treatment and ATX the second line treatment for adults with ADHD of moderate or severe levels of impairment, unless the person would prefer a psychological approach (NICE, 2008). However, these guidelines emphasise that pharmacological treatment should always form part of a more comprehensive treatment program addressing psychological, behavioural, educational and occupational needs.

However, there are yet no official Swedish guidelines for assessment and treatment of ADHD available. Instead, there are a few regional guidelines, e.g., the guidelines published by the Stockholm County Council, freely available at www.vardsamordning.sll.se/Global/Vardsamordning/Dokument/Publikationer/Vardprogram/RV_ADHD_webbversion.pdf.

To date, studies evaluating psychological treatment of ADHD in adults are limited, although in increasing number. Data strongly suggest the effectiveness of ADHD-specific, skill-based, structured and brief psychological interventions (Young and Amarasinghe, 2010; Weiss et al., 2008). Interventions based on cognitive behavioural therapy (CBT) or dialectic behavioural therapy (DBT) are delivered either individually or in group settings; preferably as an adjunct to pharmacological treatment. Medication is considered to reduce symptom levels of ADHD rather than improving functional impairments related to executive dysfunction. Psychotherapy on the other hand, is mainly considered to target behavioural, social, cognitive or other functional impairments of ADHD, as well as coexisting disorders.

Other components of the multimodal treatment approach include coaching, psychoeducational and psychosocial interventions, as well as family therapy (Kooij et al., 2010).

Neural based interventions such as working memory training, and neurofeedback or electroencephalographic (EEG) biofeedback have shown promising results in children with ADHD. However, in the absence of well-designed, controlled studies in adults with ADHD, these interventions are considered as experimental (Bidwell et al., 2011).

1.6.2 Pharmacological treatment in adults

Coexistent disorders of ADHD have to be accounted for in the integrated treatment plan. The type and severity of coexistent disorders should decide the order of pharmacological treatment. Generally, severe mental disorders should be adequately treated first (e.g., in-patients with psychosis, major depression, mania

or SUD) followed by additional or combined treatment for ADHD (NICE, 2008; Kooij et al., 2010).

Milder symptoms of depression and anxiety may be secondary to untreated ADHD, thus possibly resolved when ADHD is successfully addressed. However, more severe cases of affective disorders require appropriate treatment with e.g. antidepressants or mood stabilisers before initiation of ADHD treatment.

PHARMACOLOGY

Pharmacological treatment for ADHD and related symptoms has been explored for more than 50 years, with the first controlled stimulant trials conducted in children in the early 1960s (Eisenberg et al., 1963; Conners and Eisenberg, 1963). Over the years, hundreds of randomised controlled studies conducted in children and adolescents have demonstrated stimulants, and recently also the non-stimulant ATX to improve core symptoms of ADHD relative to placebo.

Following the increased recognition of ADHD as being persistent across the lifespan, clinical trials have increasingly been conducted in adults with ADHD, although much fewer in numbers than trials conducted in children. Clinical trials of adults with ADHD have established efficacy of both stimulants and ATX although stimulants appear to be more effective than ATX in adults (indirect comparisons). However, we are not aware of any directly comparative studies of stimulants and ATX in adults with ADHD.

As mentioned previously, the NICE guidelines consider stimulants, specifically MPH as the pharmacotherapeutic principle of choice for adult ADHD (NICE, 2008). MPH facilitates striatal dopamine neurotransmission by inhibiting the reuptake of DA via blockade of presynaptic DAT protein (Zetterström, 1988; Volkow et al., 2001). Positron emission tomography (PET) imaging shows MPH doses of 0.25 mg/kg to result in 50% occupancy of DAT in striatum of individuals with ADHD (Volkow et al., 1998). Further, clinically relevant doses of MPH result in increased extracellular DA levels as shown by PET (Volkow et al., 2002; Villemagne et al., 1999). In addition, MPH may exert some effect through blockade of the norepinephrine transporter (NET). A recent PET study reported therapeutic doses of MPH to result in 70-80% occupancy of NET, thus suggesting MPH to have an even greater affinity for NET than for DAT (Hannestad et al., 2010).

On the other hand, the non-stimulant ATX that specifically inhibits presynaptic norepinephrine (NE) reuptake, resulted in increased extracellular levels of NE and DA in the prefrontal cortex (Bymaster et al., 2002). In a recent PET study, it was concluded that DA enhancement in ventral striatum (the brain region involved with reward and motivation) was associated with therapeutic response to MPH, which further supported the relevance of a DA reward-motivation circuitry in ADHD (Volkow et al., 2012).

TRIALS AND RECOMMENDATIONS

Wilens and colleagues (Wilens et al., 2011) recently conducted a systematic search of pharmacological trials evaluating stimulants (MPH, amphetamine (AMP), lisdexamfetamine dimesylate (LDX) and non-stimulants (ATX, antidepressants and other substances) in adults with ADHD; both shorter-term (<12 weeks) controlled efficacy trials and long-term (>12 weeks) effectiveness trials (both controlled and open-label trials) were included.

Results of this review will be summarised as follows (Wilens et al., 2011):

A total of 25 short-term controlled trials (24 double-blind, 1 single-blind) of stimulants comprising a total of 2804 participants (ranging 15-420 in each study) were identified. Of these trials, 19 evaluated MPH, 4 AMP and 2 evaluated LDX. The duration of the trials was 2-11 weeks, and the total mean dose of MPH was 10-90 mg/day; AMP 20-60 mg/day; LDX 30-70 mg/day.

A total of 15 long-term stimulant trials were identified (7 double-blind, 8 open trials, usually following upon short-term controlled trials) comprising a total of 1989 participants (range 12-359). Of these trials, 10 evaluated MPH, 5 AMP, and 1 trial evaluated LDX (one study evaluated both MPH and AMP). The duration of the trials was 12 weeks to 12 months. The total mean dose of MPH was 10-100 mg/day; AMP 5-75 mg/day; LDX 30-70 mg/day.

1.6.2.1.1 Variable results and trial inconsistencies

In contrast to the more than 300 controlled trials of stimulants conducted in paediatric populations with ADHD that reported a consistent response rate of about 70%, the response rate of adults with ADHD has been variable. The response rates of reviewed trials ranged between 25% and 78%, with a short-term controlled weighted mean of 60%; long-term weighted mean of 74%; similar response rate between AMP and MPH was reported. Several factors were suggested to account for the differences observed in response rates, including different used diagnostic criteria for establishment of ADHD, differences in study populations with respect to psychopathology and coexisting disorders, inconsistencies in defining treatment response, and varying doses of stimulants. It appears that higher immediate release (IR) MPH dosing (≥ 1.0 mg/kg/day) (Spencer et al., 1995) resulted in superior outcomes than lower MPH dosing (< 0.7 mg/kg) (Mattes et al., 1984; Wender et al., 1981). A similar pattern was observed in studies of AMP (Taylor, 2000; Spencer et al., 2001). Notably, an inconsistent dose-response relationship has been reported in several stimulant trials of adults (Medori et al., 2008; Spencer et al., 2007; Adler et al., 2008).

However, transferring results from clinical trials presented as mean values, obtained at a group level within a selected study population, into treatment of individual patients in clinical practice is not always straight forward and easily applied. Within a group there is a wide range of doses to which individual patients

may respond. In clinical practice it is apparent that some patients respond to lower doses and others require relatively higher doses to respond.

The causes for variable responses in adults with ADHD are not fully understood. Identification of clinical predictors of responsiveness may lead to a more effective treatment regimen, accounting for the likelihood of effectiveness at the individual level. To date, most studies exploring treatment predictors have been conducted in children and adolescents with ADHD. Several pharmacogenetic studies reported genetic moderators of treatment response to stimulants in children with ADHD, including specific genotypes of the DAT gene and the DRD4 genes, but results have been inconsistent (Kirley et al., 2003; Roman et al., 2004; Hamarman et al., 2004).

Studies that investigated differences in EEG between good and poor responses to MPH and dextro-amphetamine (dex-AMP) within children of the combined subtype of ADHD, suggested that good responders to MPH had EEG profiles indicating more cortical hypoarousal than poor responders. In contrast, good responders to dex-AMP appeared to be more maturationally lagged than poor responders (Clarke et al., 2002). Taken these data together, useful clinical predictors for treatment response remain to be further explored, especially in adults with ADHD.

The short-term trials reviewed by Wilens and colleagues displayed efficacy in reducing ADHD symptoms as compared to placebo. However, there is a paucity of long-term data related to stimulant treatment for adults with ADHD.

Nevertheless, the 15 long-term stimulant trials included in the review, supported the long-term effectiveness as well as maintenance of response to stimulants at the 24-72 week follow-up endpoints (Wilens et al., 2011).

ADVERSE EVENTS AND OUTCOME MEASURES

The most frequently observed adverse events (AEs) of both short-term and long-term trials were dry mouth, insomnia, edginess, loss of appetite, weight loss, dysphoria, obsessiveness, tics and headaches. AEs were rated as mild- to-moderate in severity. Stimulant trials of adults have not reported any stimulant-related psychosis at therapeutic levels, and cardiovascular effects have been reported as small but significant with a mean increase in systolic and diastolic blood pressures (3-5 mm Hg) and heart rate (5 beats per minute, bpm). Recently, a retrospective, population-based cohort study could not confirm an association between current use of MPH, AMP or ATX prescribed for treatment of ADHD in adults aged 25 through 64 years, and increased risk of serious cardiovascular events (Habel et al., 2011). Further, no laboratory abnormalities were reported in stimulant treated adults, including complete blood counts, renal or liver function tests.

The review by Wilens and colleagues also included 47 non-stimulant trials (23 double-blind, 1 single-blind, 23 open trials) comprising a total of 4069 participants (range 6-536). Of these trials, 14 evaluated ATX (8 controlled and 6 open trials comprising 2938 participants), 10 evaluated bupropion (BPR), and 23 other agents including clonidine, guanfacine, tricyclic antidepressants, monoamine oxidase inhibitor, modafinil, and different amino acids. Trial duration

was 2 weeks to 1 year. The total mean dose of ATX was 25-320 mg/day; BPR 100-450 mg/day.

ATX significantly improved symptoms of inattention and hyperactivity-impulsivity, as well as ADHD related emotional dysregulation. Improvements were evident both in the short-term and in the long-term. However, ATX seems slightly less effective than MPH in adults, when indirectly comparing the reported effect sizes of ATX and MPH trials. While the response to stimulants has an immediate onset, ATX and antidepressants have a delayed onset of full therapeutic action of up to 4 weeks.

Despite the notion of ADHD being coexistent with other psychiatric disorders in almost 80% of adults, very few studies have evaluated pharmacological treatment for those with ADHD and coexisting disorders. In addition to having lower rates of lifetime coexisting disorders, participants of clinical trials typically demonstrate less functional impairments, and higher occupation and socioeconomic status as compared to adults with ADHD seen in the general population. These observations suggest that results from many clinical trials may be difficult to generalise to a broader population, thus implying the need for clinical trials evaluating treatment for individuals with ADHD and coexisting disorders that experience the most severe complications of ADHD (Surman et al., 2010).

Among the few studies that evaluated treatment for adults with ADHD and coexisting disorders, there is one study of ATX in adults with ADHD and coexistent social anxiety disorder that reported significant reductions of both ADHD symptoms and anxiety (Adler et al., 2009). Another controlled trial of ATX in recently abstinent alcoholics reported improvements in ADHD and reduced drinking, although not affecting the absolute abstinent rates (Wilens et al., 2008). Moreover, studies that have evaluated treatment with MPH in adults with ADHD and SUD could not establish efficacy as compared to placebo in improving ADHD symptoms (for a review, see Koesters et al., 2009). Importantly, there was no worsening of substance abuse or misuse of study drugs reported during the study (Wilens et al., 2011).

In clinical practice, extended release (ER) formulations of MPH are often preferred compared to IR formulations for increased protection against substance misuse. This preference is related to reports of lower likeability ratings with ER formulations than with IR formulations (Spencer et al., 2006). It was suggested that the rate of increase in MPH levels in the brain and the level of saturation of DAT protein is related to the abuse liability; a slower increase as in ER formulations is related to a lower likeability of the stimulant. Other reasons favouring ER formulations in clinical practice are adherence to treatment, less rebound of symptoms, safer driving and increased coverage throughout the day without the need for multiple dosing.

Further, most pharmacological trials of adults with ADHD have primarily evaluated the effectiveness on core symptoms of ADHD and global functioning, with limited information regarding cognition related effects. As mentioned previously, there is a substantial clinical and neuropsychological heterogeneity among individuals with ADHD, considered to reflect combined effects from

weaknesses of several cognitive domains (Nigg and Casey, 2005; Pennington, 2006; Sonuga-Barke, 2005; Sonuga-Barke and Sergeant, 2005).

Interestingly, cognition-related outcomes of stimulant trials were addressed already in the 1960s (Conners and Eisenberg, 1963; Conners et al., 1969).

Recent reviews have addressed the effects of stimulants on a broad range of cognitive functions associated with ADHD, primarily in children (Pietrzak et al., 2006; Advokat, 2010; Swanson et al., 2011; Bidwell et al., 2011). These reviews reported the absence of evidence for stimulants fully correcting any ADHD related cognitive deficit. Broadly, the effects on attentional and executive processes have been inconsistent. Although significant improvements were observed on tasks without an executive component (complex reaction time, reaction time variability, sustained attention, spatial recognition memory reaction time, and delayed matching-to-sample), performance on tasks with increased attentional or executive demands were inconsistently improved by stimulants (inhibition, working memory, planning, and set-shifting). Further, the optimal stimulant dose appears to vary across individuals, as suggested by dose-response studies, as well as being related to the functional domain, with increased doses improving some domains (e.g., attention, vigilance, memory and working memory) more than others (e.g., planning, cognitive flexibility, inhibitory control, naming and motor speed). In a recent study, MPH was reported to normalise deactivation of the default mode network ('task negative' network) while improving activation of a 'task positive' network during performance of an inhibitory control task, in children with ADHD as compared to controls (Liddle et al., 2011).

Moreover, while studies have suggested short-term improvements by stimulants on academic performance in children with ADHD, stimulants have not confirmed long-term academic achievement (Jensen et al., 2007).

Also, studies suggested that stimulants did not restore deficits in social cognition, although treatment normalised neuronal activity measured by event-related potentials (ERPs) (Williams et al., 2008).

Furthermore, although amelioration of symptoms is important to achieve, translation of symptomatic improvement to increased daily functioning and enhanced quality of life should be the aim targets of treatment. To date, only a few stimulant trials have evaluated the association between symptomatic and functional improvements in adults with ADHD. A relationship was suggested by these studies, but more research is warranted to clarify this issue (Wender et al., 2011; Rösler et al., 2011; Fallu et al., 2006; Buitelaar et al., 2012).

1.6.3 Treatment of offenders with ADHD

Despite the recognition of high prevalence rates of ADHD in adult prison inmates, treatment with stimulants had not previously been evaluated in this population. This lack of treatment could be related to concerns regarding the use of controlled substances within prison settings as well as concerns regarding the potential for diversion of medication.

However, the idea of treating delinquents with stimulants is not entirely new. As early as 1963 Eisenberg and colleagues reported a double-blind controlled 10-

week dex-AMP trial that was conducted within a group of delinquent boys aged 11-17 years, institutionalised at a training school (Eisenberg et al., 1963). The 21 most troublesome boys were chosen to participate. Dex-AMP significantly reduced disturbed behaviour as rated by parents, teachers and peers when compared to placebo and controls (no treatment). Weight loss was the only observed AE on the highest dosage (40 mg). Subsequent to treatment discontinuation, behaviour and weight returned to pre-treatment levels.

The authors concluded: ‘...If the delinquent youngster can be helped to diminish his disturbing behavior in the institution, personnel may be enabled to respond to him in a more positive fashion. If he has a more satisfactory experience in the training school, we might hope for a more constructive outcome of his period of commitment than is customarily the case. But drugs will not in any way diminish the necessity for more and better trained personnel and well-conceived programs of rehabilitation if any advantage is to be taken of the amelioration of behavior produced by medication...’ (Eisenberg et al., 1963).

The Swedish Prison and Probation Service is part of the criminal justice system. Their primary aims are both to reduce recidivism in offences and to increase safety in society. In order to reduce recidivism, they provide various accredited, evidence based treatment programs, preferably addressing offending in general, violence and addiction. Inmates are also provided work, vocational training and educational programs aiming at increasing their chances of obtaining a job after conditional release. The educational programs aim at increasing basic skills of reading, writing and mathematics in consistence with the Swedish curriculum, mainly at the primary school level.

At present, no treatment program is available in Sweden that specifically addresses symptoms and impairments of ADHD and ASPD in offenders.

Once imprisoned, individuals with ADHD are considered costly and difficult to manage due to their aggressive behaviour (Young et al., 2011; Young et al., 2009; Young and Thome, 2011). As mentioned previously, studies consistently reported ADHD to coexist with personality disorders, especially ASPD in the vast majority of prison inmates (Gudjonsson et al., 2009, 2011, 2012; Rösler et al., 2004).

A Scottish prison cohort study reported inmates with ADHD to account for eight times more aggressive behavioural disturbances (critical incidents) than other inmates, and six times more critical incidents when controlling for coexistent ASPD (Young et al., 2009). Aggressive incidents were predicted by persistence of ADHD symptoms, impulsivity, mood instability, low frustration tolerance, and a disorganised-chaotic personality style.

Therefore, a comprehensive treatment approach is warranted for prison inmates with ADHD. Goals for treatment would be to reduce symptoms, improve behavioural control, affect regulation and prosocial skills in order to reduce critical incidents, improve adherence to provided treatment, educational and vocational programs, with the final aim of reducing re-offending (Young and Goodwin, 2010; Young and Thome, 2011).

As mentioned previously, the NICE guidelines recommend multimodal treatment that combines medication with non-pharmacological interventions (NICE, 2008).

The Reasoning and Rehabilitation (R&R) program is one of the most widely used cognitive skills programs delivered in a group setting, aiming at changing the criminogenic thinking of offenders. A recent meta-analysis reported significant decreases in re-offending for R&R participants in both institutional and community settings when compared to controls. Both low and high risk offenders, as well as volunteers and non-volunteers improved from the R&R program (Tong and Farrington, 2008).

However, a high dropout rate of 50% was reported from a randomised controlled trial of the R&R program with mentally disordered offenders (Cullen et al., 2012). Dropout was predicted by traits of both psychopathy and antisocial personality, as well as by violent behaviour. Completion of program interventions appears to be critical as non-completers were reported to re-offend more often than program completers (McMurran and Theodosi, 2007; Palmer et al., 2007).

Thus, a shorter version (R&R2 ADHD) of the R&R program was recently developed for youths and adults with ADHD (Young and Ross, 2007, retrieved from www.cognitivecentre.ca/rr2adhd). It integrates group and individual treatment by supplementation of guided individual mentoring between group sessions in order to consolidate learning and maintain engagement. The R&R2 ADHD program comprises 15 structured and manualised 90-min sessions aiming at increasing neurocognitive abilities, problem solving, emotional control, prosocial skills and critical reasoning.

A randomised controlled trial of this program conducted in a non-offending adult Icelandic ADHD population was recently reported (Emilsson et al., 2011).

This study reported a 26% dropout rate, medium to large effect sizes in reducing ADHD symptoms and antisocial behaviour. At 3-month follow-up outcomes were further improved in addition to improvements of anxiety, depression, emotional control, global and social functioning. Recently, R&R2 ADHD was reported to be effective in a small sample of severely personality-disordered offenders (Young et al., 2012). However, R&R2 ADHD needs to be further evaluated under controlled conditions within prison populations affected by ADHD.

2 AIMS

The general aims of this thesis were to characterise ADHD and to evaluate OROS-MPH as treatment in adult male long-term prison inmates with ADHD hosted at Norrtälje Prison. Specific aims of each study are specified in the following part.

2.1 STUDY I

- To characterise ADHD in adult male long-term inmates of Norrtälje Prison, a Swedish high-security correction facility.

We hypothesised that ADHD would be more frequently observed in this highly specific prison population relative to the general population. Further, we hypothesised that a group of long-term inmates comprehensively assessed for ADHD and coexisting disorders would be more symptomatic and functionally impaired from ADHD across the lifespan, presenting with more coexisting disorders, and demonstrating poorer cognitive abilities, compared with a group of adult males confirmed with ADHD at a psychiatric outpatient clinic, and with a group of healthy controls.

2.2 STUDY II

- To evaluate the efficacy of osmotic release oral system (OROS)-MPH compared with placebo, as treatment for ADHD in a group of adult male long-term prison inmates with ADHD and coexisting disorders.

We hypothesised that OROS-MPH would outperform placebo in reducing symptoms and impairments of ADHD and increasing the global functioning, in a 5-week randomised, double-blind, placebo-controlled trial.

- To evaluate the long-term effectiveness and maintenance of achieved improvements from treatment with OROS-MPH provided alongside psychosocial interventions in the same study population, with respect to ADHD symptoms and global functioning.

We hypothesised that the therapeutic effect of interventions would continue and that achieved improvements would be maintained throughout the cumulated 52-week study period.

- To evaluate the safety and tolerability of treatment with OROS-MPH during the cumulated 52-week trial.

We hypothesised that treatment would be both tolerable and safe.

2.3 STUDY III

- To evaluate the long-term effectiveness and maintenance of achieved improvements within participants of the cumulated 52-week trial that evaluated OROS-MPH as treatment for ADHD in adult male long-term prison inmates alongside psychosocial interventions, with respect to aspects of cognition, motor activity, institutional behaviour and quality of life.

We hypothesised that interventions would improve these outcomes and that achieved improvements would be maintained over time.

- To explore the associations between ratings of symptoms and daily functioning, as well as between investigators' and self-ratings of ADHD symptoms.

We hypothesised that ratings of symptoms and functional outcomes, as well as investigators' and self-ratings of ADHD symptoms, would be significantly associated.

2.4 STUDY IV

- To evaluate the predictive value of pre-existing psychopathology, coexisting disorders, neuropsychological performances, psychosocial factors and treatment variables, on both short-term and long-term treatment response to OROS-MPH within participants of the cumulated 52-week trial that evaluated OROS-MPH as treatment for ADHD in adult male long-term prison inmates.

We hypothesised that lower educational achievement, more severe symptoms of ADHD assessed at baseline, and higher delivered dosages of OROS-MPH during the open-label extension, would predict a superior treatment response.

3 METHODS

To provide an overview of methods that we used in the studies of the present thesis, the common or overlapping elements of study populations, assessments and interventions will be presented, instead of divided by each separate study.

3.1 STUDY POPULATIONS

All prison inmates participating in the studies of this thesis were hosted at Norrtälje Prison, a high-security prison that serves the entire country and is located north of Stockholm, Sweden. This correction facility hosts about 200 adult males in the ages of 18 years and above. Norrtälje Prison primarily hosts long-term inmates convicted of drug-related or violent offences. However, there is also a wing that exclusively hosts sexual offenders. In addition, Norrtälje Prison hosts offenders that are to be deported from Sweden after served conviction.

3.1.1 Screening survey

During the study period, between December 2006 and April 2009, a total of 589 inmates were hosted at Norrtälje Prison. We aimed at approaching as many inmates as possible during this period. In accordance with the study protocol, recruitment continued until all participants that were required for the subsequent OROS-MPH trial had been randomised, which occurred in April 2009.

Inmates were invited to participate in the screening survey with few exceptions. These exceptions either related to practical issues of performing the screening survey, or to ethical reasons that will be further discussed under the section of Ethical considerations (3.5).

Of 589 inmates, 315 were invited to take part in the screening survey. Of the remaining 274 inmates, 74 were not invited of practical reasons, whereas 200 inmates were not approached of ethical reasons. The response rate of the screening survey was 62%. That is, of 315 inmates approached, 194 were defined as responders. Overall, responders were slightly older ($P=0.028$) and served longer convictions ($P=0.030$) than non-responders.

3.1.2 Diagnostic assessments

A total of 34 prison inmates that indicated ADHD by the screening survey and were considered probably not fulfilling exclusion criteria for the subsequent clinical trial in case of ADHD, consented to take part in the comprehensive diagnostic evaluations for ADHD and coexisting disorders.

Diagnostic assessments confirmed ADHD in 30 out of 34 participants. Thus, the prison group comprised the 30 adult male long-term inmates with ADHD.

The psychiatric outpatient study group comprised 20 adult males, established with ADHD by diagnostic assessments performed between 2004 and 2006 at the

Neuropsychiatric Unit at Karolinska University Hospital; a psychiatric outpatient unit, specialised in assessments of adult ADHD. Participants of this group differed somewhat from the prison inmate group, as they were primarily recruited to another study. These participants were required to present an intelligence quotient (IQ) > 85, not allowed to receive treatment for coexisting psychiatric disorders during the study, or being established with ASD or ASPD. However, we controlled for differences in IQ levels between groups in the statistical analyses of executive functions.

The control group comprised 18 adult males, age-matched with the psychiatric outpatient group described above. Participants were either recruited from fitness training centres in the city of Stockholm by advertisement, or among friends of staff members. Participants had to be healthy, not requiring psychiatric care during the study, or during childhood. It was also required, that they were not assessed for learning disabilities or required educational support during childhood.

3.1.3 Clinical trial

The clinical trial was conducted between 2007 and 2010; the study population comprised 30 males, aged 21-61 years, primarily registered in the Stockholm County, with conditional releases after study completion.

Two out of 30 participants were diagnosed with ADHD before the age of 18, whereas seven inmates were diagnosed with ADHD during adulthood, prior to the present study. Our assessments confirmed ADHD in consistence with DSM-IV-TR criteria. Of nine inmates with a previous diagnosis of ADHD, five had received treatment with MPH prior to conviction for periods lasting a few months at the most; only one of them had received treatment for ADHD during childhood. None of the participants were known to be non-responsive or intolerant to treatment with MPH. All 30 participants reported lifetime SUD and AMP was the most frequently reported preferred drug of choice. We considered all 30 participants to retrospectively fulfill the criteria for ODD and CD before the age of 18, and all but one to confirm ASPD in adulthood. Almost one participant out of four was established with concomitant ASD. Participants were not allowed to suffer from chronic psychoses. However, previous drug-elicited episodes of psychosis did not exclude from taking part. Almost three out of four participants reported lifetime mood and (or) anxiety disorders, and almost half of them received pharmacological treatment for coexisting psychiatric disorders at study entry. Concomitant treatment was allowed during the study, as long as it did not interfere with MPH and doses were kept stable for at least one month at the baseline visit. Any interfering treatment had to be tapered off in advance of the baseline visit. To be eligible for the trial, participants had to agree not to behave violently during the study, against study staff, correctional officers or other inmates. Participants were informed that if they behaved violently, that would be a cause for discontinuation. Further, supervised urine drug screenings had to confirm that participants were without substance misuse up to three months before the baseline visit. Also to be eligible, participants had to present an IQ>70, and be absent from serious medical conditions. However, hepatitis C was allowed.

3.2 ASSESSMENTS

3.2.1 Screening survey

In the screening survey, we used the self-reported 61-item WURS to rate childhood symptoms and behaviours retrospectively (Ward et al, 1993). More specifically, we used the subscale WURS-25 comprising the 25 items out of 61 suggested to best differentiate between ADHD and controls. We defined childhood ADHD as scoring ≥ 36 on WURS-25.

Current symptoms of ADHD in adulthood were assessed by the self-reported ASRS-Screener. This 6-item rating scale comprises the 6 out of 18 items of the ASRS that are considered to best predict adult ADHD, by requiring fulfilment of at least 4 out of 6 significant items (Kessler et al., 2005, 2007).

Both WURS-25 and ASRS-Screener are widely used as standard tools in clinical practice, despite the lack of Swedish validations.

In the present study, we required the fulfilment of both childhood ADHD by WURS-25 (≥ 36) and adult ADHD by ASRS-Screener (≥ 4 significant items) to be defined as having *adult ADHD*, thus aiming at increasing the specificity of the screening procedure.

3.2.2 Diagnostic assessments

Board certified psychiatrists and clinical psychologists well experienced in assessments of adult ADHD, performed the diagnostic evaluations of all participants in this study.

However, the contents of the assessment procedures were not identical between study populations. Differences will be outlined in the following part.

PRISON INMATE GROUP

In the prison inmate group, ADHD was established by a semi-structured clinical diagnostic interview for ADHD, confirming the presence of symptoms and impairments of ADHD during both childhood and adulthood in consistence with the DSM-IV-TR criteria.

Current symptom severity of ADHD was evaluated by the 18-item ASRS (Adler et al., 2006). Whenever possible, evaluations also included obtainment of collateral information by both questionnaires and interviews, including the Five to Fifteen questionnaire (FTF) (Kadesjö et al., 2004; Trillingsgaard et al., 2004) and the Conners' Brief Parent Rating Scale- Conners' Hyperactivity Index (Conners, 1969; Conners et al., 1998), assessing the developmental history, current symptoms and impairments. We also obtained school reports and records from health services and the Prison and Probation Service, providing additional information of symptoms, behaviours and previous diagnostic assessments.

Coexisting disorders were evaluated by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) (Lobbestael et al., 2011), the PCL-R (Hare et al., 2000) and the SCID II Patient Questionnaire (SCID II PQ), a self-rated version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (Ekselius et al., 1994). When we estimated the frequencies of PDs based on the results of the self-reported SCID II PQ, we increased the screening cut-off level for each PD by one score, aiming not to overestimate the frequencies by using a self-report instead of interviews. This procedure of increasing the cut-off level has shown acceptable agreement with results obtained by the SCID II interview (Ekselius et al., 1994).

Additional assessments included obtainment of a medical history, a physical examination, routine laboratory tests, and supervised urine drug screening.

The purpose of these additional assessments was to ensure participants to be eligible for the subsequent clinical trial, but also to rule out other explanations to the observed symptoms and impairments than ADHD.

When clinical observations or the developmental history indicated a possibility of concomitant ASD, defined as Autistic syndrome, Asperger syndrome or PDD, not otherwise specified (PDD-NOS), we extended the assessments to include the Asperger syndrome screening questionnaire (ASSQ) (Ehlers et al., 1999), the Autism diagnostic observation schedule (ADOS) module 4 (Lord et al., 1989) and in some cases also the Diagnostic interview for social and communication disorders (DISCO) (Leekam et al., 2002; Wing et al., 2002). ASD were established in consistence with the DSM-IV-TR criteria (APA, 2000).

Neuropsychological assessments were conducted, and tests were selected with the aim of requiring a minimum of reading, writing or mathematical skills, considering the previous observations of frequent learning disabilities among prison inmates (Rasmussen et al., 2001).

Assessments included an estimation of IQ by a dyadic short form of the Wechsler Adult Intelligence Scale (WAIS) comprising the sub tests of Vocabulary and Block Design. This short form is highly correlated (0.92) with the WAIS-III full scale IQ (FSIQ) (Wechsler, 1997; Ringe et al., 2002). Verbal working memory was assessed by the Digit Span (Wechsler, 1997) and visuo-spatial working memory by the Span Board test (Kaplan et al., 1991). Cognition related measures of basic reaction time, variability and accuracy were evaluated by a computerised visual continuous performance test (CPT), the Conners' Continuous Performance Test II (Conners' CPT II) (Conners, 2002).

PSYCHIATRIC OUTPATIENT GROUP

The diagnostic assessments in the psychiatric outpatient group differed somewhat from the assessments performed in the prison inmate group.

Medical records provided information of previous coexisting psychiatric disorders. In contrast to the prison inmate group, present symptoms were evaluated by the self-rated Beck Depression Inventory (BDI) (Beck et al., 1961), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and the Current ADHD

Symptom Scale –Self-Report Form (Barkley and Murphy, 1998). On the other hand, SCID-I, SCID-II PQ, and PCL-R were not assessed in the psychiatric outpatient group. Finally, the neuropsychological assessments were similar to those performed in both the prison inmate group and in the control group.

HEALTHY CONTROL GROUP

The diagnostic assessments as well as the neuropsychological assessments of the control group were almost identical to those of the psychiatric outpatient group. In addition, participants of the control group were confirmed to be healthy, not assessed for learning disabilities or requiring educational support during childhood.

3.2.3 Outcome measures of the clinical trial

THE CONNERS' ADULT ADHD RATING SCALE: OBSERVER-SCREENING VERSION

The Conners' Adult ADHD Rating Scale-Observer version (CAARS: O-SV), rated by a masked assessor, comprises 18 items corresponding to the 18 DSM-IV criteria of ADHD (Rösler et al., 2010). CAARS: O-SV can be further divided into the subscales of inattention and hyperactivity-impulsivity, respectively. Change in the total sum-score of ADHD symptom frequencies, as measured by CAARS: O-SV from baseline until the end of week 5 was the primary outcome measure of this trial.

Secondary outcome measures were changes in the total sum-scores of CAARS: O-SV from study week 6 until the end of week 52, as well as ratings of both the inattention and the hyperactivity-impulsivity subscales that were used in *post hoc* analyses exploring the associations between ratings of symptoms and functioning, as well as between investigators' and self-ratings of ADHD symptoms. Change in the total sum-scores of CAARS: O-SV was also used in *post hoc* analyses of numbers needed to treat, treatment response rates, and normalisation rates, respectively, as well as in prediction analyses conducted *post hoc*.

THE ADULT ADHD SELF-REPORT SCALE

In the ASRS the participant rates 18 items that correspond to the 18 ADHD symptom criteria of DSM-IV-TR and are worded to be more reflective of the expression of ADHD symptoms in adulthood (Adler et al., 2006; Rösler et al., 2010). ASRS can be further divided into the subscales of inattention and hyperactivity-impulsivity, respectively. Secondary outcome measures were changes in the total sum-scores of ASRS, from baseline until the end of week 5, and from week 5 until the end of week 52, respectively, as well as ratings of both the inattention and the hyperactivity-impulsivity subscales that were used in *post hoc* analyses exploring the associations between ratings of symptoms and functioning, as well as between investigators' and self-ratings of ADHD symptoms.

The sum-score of ASRS assessed at baseline was also used in prediction analyses conducted *post hoc*.

CLINICAL GLOBAL IMPRESSION SEVERITY OF ILLNESS SCALE

The investigator-rated Clinical Global Impression Severity of Illness Scale (CGI-S) was used to rate the participant's global symptom severity of ADHD (Guy, 1976).

Secondary outcome measures were changes in CGI-S scores, from baseline until the end of week 5, and from week 5 until the end of week 52, respectively, as well as ratings of CGI-S used in *post hoc* analyses exploring the associations between ratings of symptoms and functioning. The CGI-S score assessed at baseline was also used in prediction analyses conducted *post hoc*.

GLOBAL ASSESSMENT OF FUNCTIONING SCALE

The investigator-rated Global Assessment of Functioning Scale (GAF) was used to evaluate the participants' level of global functioning. This visual analogue scale ranges between 0 and 100 (Ramirez et al., 2008). A higher value indicates an increased level of functioning as compared to a lower value.

Secondary outcome measures were changes in GAF scores, from baseline until the end of week 5, and from week 5 until the end of week 52, respectively, as well as ratings of GAF used in *post hoc* analyses exploring the associations between ratings of symptoms and functioning. The GAF score assessed at baseline was also used in prediction analyses conducted *post hoc*.

THE DIGIT SPAN AND THE SPAN BOARD

Changes in verbal working memory capacity during the course of the study were measured by the Digit Span (Wechsler, 1997) whereas changes in visuo-spatial working memory were measured by the Span Board (Kaplan et al., 1991).

Changes in both tasks, from baseline until study week 16, as well as from week 16 until week 52, were used as secondary outcome measures. Baseline scores of both tasks were also used in prediction analyses conducted *post hoc*.

SIMILARITIES

The WAIS-III test Similarities measures abstract verbal reasoning (Wechsler, 1997). This task is not expected to show learning effects from repeated testing, especially not with the long test-retest intervals as in the present study.

Further, we did not expect the capacity of abstract verbal reasoning to improve from MPH treatment. Therefore, we decided to use Similarities as a specificity measure for the assessments performed during this study.

It was assessed at baseline and at study week 52. Baseline scores of Similarities were used in prediction analyses conducted *post hoc*.

THE CONNERS' CONTINUOUS PERFORMANCE TEST II

Changes in cognition-related measures of basic reaction time, variability and accuracy were evaluated by the Conners' CPT II (Conners, 2002) assessed at baseline, study week 16, and at week 52. Changes from baseline until study week 16, as well as from week 16 until the end of week 52, were used as secondary outcome measures.

THE QBTEST

The QbTest combines a simultaneous delivered computerised visual CPT with a high-precision infrared motion tracking device (provided by Qbtech, Stockholm, Sweden; www.qbtech.se/products/qbtest; Qb Test technical manual, Fredrik Ulberstad, Rev E, January 2012).

Changes in cognition-related measures and motor activity measured by QbTest, from baseline until study week 16, and from week 16 until the end of week 52, respectively, were secondary outcome measures. Baseline assessments of area, commission error and reaction time variability, were also used in prediction analyses conducted *post hoc*.

INSTITUTIONAL BEHAVIOUR

Information regarding participation in accredited treatment programs and educational activities, results of urinary drug screenings, and reported critical incidents were recorded throughout the 52-week study period.

THE QUALITY OF LIFE INVENTORY

Self-reported quality of life was assessed by a validated Swedish version of the general 32-item Quality of Life Inventory (QOLI) (Paunovic and Öst, 2004).

Changes in the 16 domains of QOLI, from baseline until study week 16, and from week 16 until week 52, were secondary outcome measures. Ratings of QOLI domains were also used in *post hoc* analyses exploring the associations between ratings of symptoms and functioning. Also, the global index score of QOLI assessed at baseline was used in prediction analyses conducted *post hoc*.

VITAL SIGNS

Systolic and diastolic blood pressure, heart rate and body weight were recorded regularly throughout the 52-week study period.

To ensure eligibility for study entrance, blood samples were drawn for quantification of liver enzymes and complete blood count prior to randomisation, and then repeated at study weeks 16 and 44, respectively.

ADVERSE EVENTS (AEs)

Treatment emergent AEs were collected by the investigator at each visit throughout the 52-week study period by open questioning. The investigator rated the severity and recorded any action taken with respect to each reported AE.

TREATMENT COMPLIANCE

Correctional officers at the wing supervised and documented delivery of the study drug at each occasion. All packages, documentation and remaining study drugs were returned to the primary investigator at the end of the study for evaluation of treatment compliance.

3.3 INTERVENTIONS

3.3.1 Pharmacological intervention

RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Following written informed consents, 30 participants were consecutively, equally and randomly assigned to treatment with placebo or OROS-MPH for 5 weeks under double-blind conditions. The study drug was titrated from 36 mg delivered once daily for 4 days, to 54 mg once daily for 3 days, and then to 72 mg once daily for the remaining 4 weeks.

OPEN-LABEL EXTENSION

All participants that completed the initial 5-week trial were eligible to enter the subsequent 47-week open-label extension without comparator, which started the day after completion of the double-blind phase.

During the open-label extension, OROS-MPH was individually titrated from 36 mg daily to an optimal dose, on the basis of response and tolerability, with a maximum daily dose of 1.3 mg/kg body weight. In case of AEs, downward titration was allowed, followed by upward titration once the AE was resolved.

3.3.2 Psychosocial interventions

As part of regular prison routines, inmates are obliged to take part in scheduled programs during daytime, comprising activities such as vocational training, educational programs, and participation in evidence based treatment programs, accredited by the Swedish Prison and Probation Service. These programs aim at increasing the chances of obtaining a job, as well as preventing from continued substance abuse or recidivism in crime after served conviction.

During the present study, participants were alongside pharmacological treatment, provided general offending programs (One to one, ETS – Enhanced thinking skills), program for violence prevention (Aggression replacement training),

substance abuse programs (Dare to choose, PRISM – Program for reducing individual substance misuse, Twelve step program), sexual offending program (ROS - Relations and companionship) and motivational program (Behavior–talk–change) (www.kriminalvarden.se). Neither of these programs specifically addresses symptoms and associated impairments of ADHD.

Participants were also provided educational programs adhering to the Swedish curriculum. The main purpose of educational activities was to increase basic skills such as reading, writing and mathematics, mainly at the primary school level.

3.4 STATISTICAL ANALYSES

Generally, descriptive statistics summarised demographics, clinical characteristics and outcome scores at baseline. For inferential statistics, the alpha-level was set at $P=0.05$ with two sided significance; analyses were based on the intention-to-treat population (ITT) including all randomised participants, if nothing else is specified.

Last observation carried forward (LOCF) was used for imputation of drop-outs. Single missing values were handled conservatively by substituting the missing value with the higher value from the preceding or following visit, aiming not to overestimate observed improvements.

In Paper I, analyses of variance (ANOVA), Student's t-test or Mann-Whitney U test were used for continuous variables, and chi-square test or Fisher's exact test for categorical variables. We used series of ANOVA with Bonferroni corrected *post hoc* analyses, in case of significant differences in the main analyses. We also controlled for differences in IQ levels between groups by using ANCOVA analyses, entering the dyadic estimated IQ as a covariate.

In Paper II, we performed paired t-tests for changes within participants over time, and mixed between-within participants ANOVA for changes from baseline until the end of the double-blind phase. We also used non-parametric statistics for outcomes measured by Likert scales. As results of the parametric and non-parametric tests were similar, only parametric statistics were presented.

The sample size calculation was based on CAARS: O-SV, the primary outcome measure of this trial. The effect size was analysed using Cohen's *d* for outcome measures of the initial double-blind phase. *Post hoc* analyses explored treatment response rate and number needed to treat (NNT).

In Paper III, we employed repeated measures analysis of variance (rmANOVA) for changes within participants. Tests of within-subjects contrasts with simple contrasts using the last (third) assessment as the reference level were employed to evaluate changes between the second and third assessment. We presented results of both the ITT-population and the per-protocol-population (completers). LOCF was used for drop-outs during the open-label extension phase.

The effect sizes were presented by partial eta squared. In the multiple testing of the QOLI domains, significance levels and confidence intervals were adjusted with Bonferroni corrections (0.05/16).

Post hoc analyses explored the associations between rating scales by the determination of Pearson's Product Moment correlation coefficients (r).

In Paper IV, we conducted preliminary analyses before multivariate regression analyses were undertaken *post hoc*. First, univariate analyses comprising visual inspection to ensure normal distribution of data, as well as absence of influential outliers were performed. Subsequently, we explored the associations between potential predictors and each of the dependent variables.

Scatterplots were checked for linearity, absence of influential outliers, homoscedasticity, as well as the direction of the relationship, before Pearson's Product Moment correlation coefficients (r) were determined.

All potential predictors that correlated at least 0.3 ($r \geq 0.3$) were checked for acceptable collinearity before introduced either into a standard multiple linear regression model by forced entry, or into a logistic regression model.

Both regression models were used to identify predictors of treatment outcome.

3.5 ETHICAL CONSIDERATIONS

The Ethical Board of Stockholm (2006/1141-31/3) and the Swedish Medical Products Agency (EudraCT-nr 2006-002553-80) approved the studies of this thesis. Written informed consents were obtained from participants after they had received a thorough description of the study. Study related procedures were not undertaken until obtainment of informed consents.

In case prison inmates were substantially mentally unstable from e.g., psychosis, severe depression or overly aggressive behaviour; they were not approached for taking part in the initial screening survey. We considered it unethical to approach an inmate for participation, if we were unsure of the inmate's capability of providing an informed consent statement.

Further, for several reasons, we did not approach inmates that were to be deported from Sweden after served conviction. We considered it unlikely that we would be able to refer these inmates for, either a diagnostically evaluation of ADHD, or for continued treatment of ADHD.

Therefore, we considered it unethical to raise the question of a potential diagnosis of ADHD within the inmate, when we were not able to take care of the long-term consequences of a diagnosis.

There are many ethical aspects to take into consideration when conducting a clinical trial of a controlled substance within a vulnerable study population of prison inmates. Advantages and disadvantages had to be carefully considered in detail. We considered, if inmates with ADHD would benefit from treatment, it would from one perspective be unethical not to provide treatment, in view of their severely disabling disorder.

However, we had to apply the highest ethical standards of the Helsinki declaration, and to follow the regulations of Good Clinical Practice (GCP) very carefully, always setting the highest priority to the safety and will of the study participant. The safety and need of the participant will always overrule the needs

of research. Further, we had to assure that the study drug was delivered under strictly controlled conditions, thus minimising the risk for diversion of the drug among other inmates than study participants.

This trial was independently monitored by the Karolinska Trial Alliance, and inspected by the Swedish Medical Products Agency, to validate adherence to GCP and the Declaration of Helsinki.

4 RESULTS

4.1 CHARACTERISTICS OF ADHD IN ADULT LONG-TERM PRISON INMATES OF NORRTÄLJE PRISON (STUDY I)

4.1.1 Screening survey

The total response rate of the screening survey was 62%. A total of 88 out of 194 respondents (45%) indicated the presence of adult ADHD by reaching the cut-off levels for both WURS-25 and ASRS-Screener. However, subsequent diagnostic assessments for ADHD in 34 inmates indicating ADHD by the screening survey, confirmed ADHD in 30 of them. Thus, the positive predictive value (PPV) of the screening procedure was 88% (30/34). By assuming the same PPV for the remaining 54 (88-34) inmates that were not assessed for ADHD, we may expect a total of 77 (30 + 47) out of 194 respondents (40%) to have confirmed ADHD by diagnostic assessments. Hence, we may cautiously suggest ADHD to be present in about 40% of adult male long-term inmates hosted at Norrtälje Prison.

4.1.2 Diagnostic assessments of long-term prison inmates

The prison inmate group comprised 30 adult men, aged 21-61 years (mean age 34.4 years, standard deviation (SD) =10.7). Almost all participants (28 out of 30) confirmed ADHD of the combined subtype according to the DSM-IV-TR criteria.

The educational level was low in this group; the vast majority of 83% had achieved 9 year of compulsory school or less. Learning disabilities and emotional and (or) externalising symptoms were recognised early; 80% of participants were provided educational support during childhood and 60% reported previous requirement of health care from school health services and (or) from child and adolescent psychiatry.

In spite the early recognition of symptoms and impairments, only two out of 30 participants were assessed for and diagnosed with ADHD before the age of 18.

One of them received pharmacological treatment for ADHD during childhood, but only for a few months. According to his medical records, he dropped out from treatment, as he did not show up for scheduled appointments.

The other boy was assessed at a regional center for neurodevelopmental disorders. After establishment of ADHD, he was referred back to the local outpatient clinic, and was strongly recommended to be provided pharmacological treatment for ADHD. He was considered to be at high risk for developing antisocial personality disorder otherwise. However, he did not receive the recommended treatment.

During adulthood, before taking part in the present study, another seven participants were diagnosed with ADHD. Four out of seven participants had prior to the present conviction been treated with MPH for periods lasting a few months at the most.

Further, all 30 participants reported lifetime SUD and AMP was reported as the most preferred drug of choice in almost two thirds of cases, thus being the most frequent drug of abuse. The onset of substance misuse and antisocial behaviour was early in general. Following, we retrospectively considered all 30 participants to have fulfilled the criteria of ODD and CD before the age of 18.

Further, 30% (9/30) of participants were, based on the physical examination as part of the diagnostic assessments and collateral information regarding the developmental history, considered to confirm DCD according to the DSM-IV-TR criteria.

Moreover, almost three quarters reported lifetime mood and (or) anxiety disorders, and almost half of participants had pharmacological treatment for mood and (or) anxiety disorders by the time of assessments.

Further, almost one quarter was established with ASD in addition to ADHD, primarily PDD-NOS. Psychopathy on the other hand, was confirmed in one tenth.

According to the self-reported SCID II PQ, all but one participant (22/23) presented ASPD. In addition, borderline, paranoid, narcissistic, and obsessive-compulsive traits were commonly reported. However, the purpose of screening for PDs in this study mainly aimed at getting an impression of the extent and diversity of symptoms as expressed by participants. Therefore, we did not formerly diagnose participants with PDs. Also, in many cases we considered ADHD and (or) ASD to better account for the reported and observed symptoms and impairments than diagnoses of PDs.

4.1.3 Comparisons of long-term prison inmates with other groups

Participants of the three different study populations comprised adult males of similar age. Long-term prison inmates with ADHD from Norrtälje Prison had a much lower educational level than psychiatric outpatients with ADHD and healthy controls.

Also, long-term prison inmates rated more severe ADHD related symptoms and behaviours during both childhood and adulthood, as compared to psychiatric outpatients. However, retrospective ratings of childhood symptoms by parents of both groups did not confirm the observed differences in self-report.

Further, the dyadic estimation of IQ was similar between psychiatric outpatients and controls. However, long-term prison inmates displayed a substantially lower IQ than the other groups. When we controlled for the lower IQ among inmates in statistical analyses, long-term prison inmates and psychiatric outpatients performed almost similar on both verbal and visuo-spatial working memory tasks. However, both ADHD groups were outperformed by the control group.

On the Conners' CPT II, controls and psychiatric outpatients performed almost similar; both groups outperformed the prison inmate group on all four *accuracy-dependent* measures, as well as in three out of seven *variability-dependent* measures, also when controlled for differences in IQ levels between groups. The prison group deviated considerably from both other groups on *perseverations*,

thought to primarily be reflective of impulsivity (reacting too fast to the presented stimuli). However, the *reaction time* was similar between groups.

4.2 EFFICACY OF OROS-METHYLPHENIDATE COMPARED WITH PLACEBO (STUDY II)

4.2.1 Primary outcome measure

The primary outcome measure was investigator-rated ADHD symptoms by CAARS: O-SV (the total sum-score). Mean scores were significantly reduced by 19.6 units (95% confidence interval (CI) 14.7 to 24.5) in the OROS-MPH group ($P<0.001$) compared with a negligible reduction of 1.9 units in the placebo group (95% CI -0.4 to 4.2), from baseline until the end of week 5. The effect size was exceptionally large, Cohen's $d=2.17$.

4.2.2 Secondary outcome measures

Treatment with OROS-MPH significantly outperformed placebo also on self-rated ADHD symptoms by ASRS ($P=0.003$, $d=1.67$), investigator-rated global symptom severity of ADHD by CGI-S ($P<0.001$, $d=2.36$), and the participant's level of global functioning by investigator-rated GAF ($P=0.004$, $d=1.62$). Effect sizes (Cohen's d) were all exceptionally large.

Treatment response was defined by the study protocol as $\geq 30\%$ decrease in the total sum-score of CAARS: O-SV, from baseline until the end of week 5. When we applied this definition in analyses performed *post hoc*, 87% of participants in the OROS-MPH group were defined as treatment responders, as opposed to 0% in the placebo group. Correspondingly, NNT was 1.1 (95% CI 1 to 2).

Further, *post hoc* analyses revealed an excellent adherence to treatment (99%) during this initial double-blind, placebo-controlled phase.

4.3 LONG-TERM EFFECTIVENESS OF INTERVENTIONS (STUDY II-III)

Scores of investigator-rated ADHD symptoms by CAARS: O-SV, self-rated ADHD symptoms by ASRS, investigator-rated global symptom severity of ADHD by CGI-S, and the participant's level of global functioning by investigator-rated GAF improved in both groups over time in the subsequent 47-week open-label extension, during which all participants received OROS-MPH without comparator.

However, when considering the cumulated 52-week study period, participants who received OROS-MPH from the start improved the most.

Both verbal and visuo-spatial working memory and abstract verbal reasoning improved significantly over participants, as well as several cognition-related measures and motor activity assessed by computerised CPTs.

Outcomes, calculated by repeated measures ANOVA, mainly improved from baseline until study week 16, with maintained or further improvements observed until the end of study week 52.

A majority of participants took part in accredited treatment programs and educational activities as part of regular prison routines. The self-reported quality of life domains of Goals and values, and Learning improved significantly within participants over time.

4.4 SAFETY AND TOLERABILITY OF TREATMENT WITH OROS-METHYLPHENIDATE (STUDY II)

4.4.1 Adverse events (AEs)

During the randomised, double-blind, placebo-controlled trial, mucosal dryness was the only AE more frequently observed in the OROS-MPH group. There was no serious adverse event (SAE) recorded during this phase.

During the open-label extension, one SAE of unknown cause occurred, which justified discontinuation from the study. The most frequent AEs considered as related to OROS-MPH were abdominal discomfort, headache, dry mouth, loss of appetite, anxiety, diarrhoea, sweating, interrupted sleep, fatigue, and dysphoric mood.

The severity of AEs was usually rated as mild to moderate and not a reason for discontinuation.

4.4.2 Vital signs

During the initial placebo-controlled phase there were no significant changes in systolic or diastolic blood pressure, heart rate or body weight, either within groups, or between those who received OROS-MPH and those who received placebo.

When considering the entire 52-week trial, the group that received OROS-MPH from baseline onwards significantly increased both the systolic blood pressure (21.5 mmHg; 95% CI 4.9–17.1) and the diastolic blood pressure (11.0 mmHg; 95% CI 4.9–17.1). However, there were no significant changes in heart rate or body weight during this period.

On the other hand, the group that received placebo during the initial 5-week period presented a significant increase in heart rate during the cumulated 52-week study period (13.2 beats per minute; 95% CI 7.0–19.4).

However, body weight, systolic and diastolic blood pressure remained almost unchanged during the same study period. Regularly performed supervised urinary drug screenings did not detect any substance abuse during the entire course of the study.

There were no treatment-related changes of liver enzymes or blood cells count during the course of the study, although about a third of participants were infected by hepatitis C virus (HCV) and (or) human immunodeficiency virus (HIV).

4.5 ASSOCIATIONS BETWEEN SYMPTOMATIC AND FUNCTIONAL IMPROVEMENTS (STUDY III)

ADHD symptoms measured by both the inattention and the hyperactivity-impulsivity subscales of the investigator-rated CAARS: O-SV, as well as the self-rated ASRS associated negatively with the global level of functioning as measured by GAF.

Associations determined by Pearson's Product Moment correlation coefficients (r), were evident from study week 16 onwards, and strongest by open-label endpoint at study week 52 ($r = -0.736$, $P < 0.001$).

The inattention subscales of CAARS: O-SV and ASRS were both more strongly associated with GAF than were their corresponding hyperactivity-impulsivity subscales.

The global symptom severity of ADHD by investigator-rated CGI-S was significantly negatively associated with GAF from baseline onwards ($r = -0.486$, $P = 0.006$). Convergence increased over time to be most consistent by open-label endpoint at study week 52 ($r = -0.885$, $P < 0.001$).

However, domains of self-reported quality of life by QOLI correlated weaker with symptomatic improvements measured by CAARS: O-SV, ASRS, and CGI-S, than did GAF. Goals and values was the only quality of life domain that correlated significantly with symptomatic improvements, and did so only by open-label endpoint.

At study week 52, the domain of Goals and values was significantly related to improvements in attention subscales of both CAARS: O-SV and ASRS.

4.6 ASSOCIATIONS BETWEEN INVESTIGATORS' AND SELF-RATINGS OF ADHD SYMPTOMS (STUDY III)

Investigator-rated ADHD symptoms by the total sum-score of CAARS: O-SV correlated strongly with self-reported ADHD symptoms by the total sum-score of ASRS, at all assessments during the course of the study.

The Pearson's Product Moment correlation coefficients (r) increased over time, from baseline onwards, with increased convergence until open-label endpoint at study week 52, ranging from 0.473 to 0.730 (all P s < 0.01).

4.7 PREDICTORS OF TREATMENT RESPONSE (STUDY IV)

We explored potential predictors for superior treatment response to OROS-MPH, both in the short-term (5 weeks) and in the long-term (52 weeks), measured both relatively by changes in investigator-rated ADHD symptoms by CAARS: O-SV, and absolutely as being rated as normalised in ADHD symptoms by achieving a CAARS: O-SV score within the normal range.

By the primary end-point, 87% of participants receiving OROS-MPH during the initial 5 weeks had achieved $\geq 30\%$ improvement in ADHD symptoms, thus defined as treatment responders.

On the other hand, 40% of participants receiving OROS-MPH had achieved CAARS: O-SV scores within the normal range thus defined as being in full remission.

The placebo response was non-significant, thus no participants receiving placebo during the initial controlled phase were defined as either responder or remitter to treatment.

By the open-label endpoint, 53% of participants had achieved full remission. Study participants were according to the study protocol, required to achieve treatment response during the open-label extension, otherwise they had to be discontinued from the study. However, no participants were discontinued because of non-responding. Thus, 100% were defined as treatment responders.

In the final multivariate regression models, a history of parental substance abuse increased the likelihood by almost 8 times to be rated as a short-term treatment responder.

Further, the likelihood of being in full remission after 5 weeks of treatment was increased by almost 15 times in case of a concomitant ASD.

On the other hand, relative long-term treatment response was best predicted by a high dosage of OROS-MPH delivered at week 52, and by elevated CAARS: O-SV scores assessed at baseline.

Finally, the likelihood of being in full remission after the cumulated 52 weeks of treatment increased by almost 20 times if the participant had been provided educational support during childhood, and by almost 15 times in case of a history of parental substance abuse during childhood.

5 GENERAL DISCUSSION

5.1 INTERPRETATION OF RESULTS AND LIMITATIONS

In *Study I*, our hypothesis of ADHD being more frequently observed within long-term prison inmates of Norrtälje Prison relative to the general population was confirmed. With the requirement of reaching the predefined cut-off levels for both childhood ADHD and present symptoms of ADHD according to rating scales, we estimated adult ADHD to be present in 45% of long-term inmates hosted at Norrtälje Prison. This is in line with a previous study of male offenders, although they were younger than participants of the present study (Rösler et al., 2004).

However, the PPV of the screening procedure was 88%. Accordingly, we correspondingly adjusted the estimated rate of adult ADHD in this group to be 40%, thus aiming to avoid inflated rates of adult ADHD.

There are several **limitations** of the screening survey to address that call for a very cautious interpretation of results.

First, the attrition rate of the screening survey was 38%. Further, it must be emphasised that this study population was highly specific as it comprised adult male long-term inmates convicted of crimes related to violence and (or) drugs. Results may therefore not translate to other prison populations of other ages, gender and types of offences.

Selection of participants for the present screening survey was previously discussed (3.5). The selection of participants due to ethical considerations strongly restricted the number of participants to approach for the screening procedure, thus contributing to a substantial selection bias.

However, in this considerably vulnerable study population of long-term prison inmates, we decided to strictly prioritise the ethics although it compromised the results of the screening survey. In addition, the aim of the present study was not to estimate the prevalence of ADHD in prison inmates overall, but rather to gain insight into how frequent and impairing ADHD was in this specific study population comprising long-term inmates of a high-security prison, as well as to aid in the recruitment of participants for the subsequent clinical trial.

Studies are indeed warranted to find out the prevalence of ADHD in Swedish prison inmates, though by the use of other methods than in the present study, e.g., random sampling of participants across various prison facilities.

Further hypotheses of *Study I*, that long-term prison inmates with ADHD hosted at Norrtälje Prison would be severely disabled and more symptomatic and impaired when compared to males with ADHD assessed at a psychiatric outpatient clinic, and with healthy controls, were confirmed with few exceptions.

This group of long-term prison inmates reported more severe ADHD symptoms and related functional impairments across the lifespan.

However, parental retrospective ratings of childhood pathology were similar between both ADHD groups, thus not confirming the observed differences in self-

reports. This was an unexpected finding considering impairments of the prison inmate group that had called for educational support and health care services during childhood. Neither of the questionnaires used for parental retrospective ratings in this study, FTF and Conners' Brief Parent Rating Scale- Conners' Hyperactivity Index were designed for retrospective evaluations of adults, thus possibly limiting their usefulness in the present context.

Future studies exploring the validity of these questionnaires as tools in assessments for ADHD in adults are warranted.

The long-term prison inmate group displayed a lower estimated IQ compared with both other groups, which in part could be explained by somewhat diverging inclusion criteria between the different study populations.

However, when we controlled statistically for differences in IQ levels, both ADHD groups performed similar on working memory tasks, but poorer compared to healthy controls.

This finding is in line with reports suggesting that lower IQ does not account for the key cognitive problems observed in ADHD (Wood et al., 2010, 2011).

In Conners' CPT II, the group of long-term prison inmates performed much poorer on accuracy- and variability-related measures than the other groups. Increased intra-individual variability in reaction times is one of the most consistent findings of children with ADHD (Swanson et al., 2011).

The more objective findings by CPT II of larger impairments within the group of long-term prison inmates lend support to their self-reported increased severity of ADHD symptoms.

The finding of a normal mean reaction time in this group of long-term inmates is supported by previous studies performed in children with ADHD (Epstein et al., 2003).

Coexisting ODD, CD, ASPD, lifetime SUD, early onset of drug misuse and offending were commonly observed in the long-term prison inmate group, as were learning disabilities, early drop-out from school and a very low educational level.

These findings are in line with prospective longitudinal studies, as well as with retrospective case-control studies observing an increased risk for delinquency, especially in children and adolescents with a combination of ADHD, ODD/CD, SUD and early drop-out from school (von Polier et al., 2012).

Anxiety disorders, depression and traits of various PDs were evident in the vast majority of these long-term inmates, consistent with previous reports of prison inmates with ADHD presenting a higher rate of coexisting psychiatric disorders of Axis I and Axis II including ASPD than other inmates without ADHD (Einarsson et al., 2009; Gudjonsson et al., 2009, 2011, 2012).

By contrast, psychopathy was established in only one tenth of participants in the present study. This finding was expected and consistent with a previous report suggesting ADHD and psychopathy to be viewed as two different and unrelated concepts (Rösler, 2010).

Further, ASD was confirmed in almost one fourth of participants. To the best of our knowledge, previous data are absent regarding the prevalence rate of ASD within prison facilities.

However, studies conducted in forensic populations report a 10-fold increased risk for ASD in these populations, and the coexistence between ASD and ADHD was substantial (Anckarsäter et al., 2007, 2008).

Findings from forensic psychiatry and from the present study signal a substantial overrepresentation of severe mental health problems in institutionalised individuals that call for immediate attention.

Notably, neither of the participants in the present study was previously assigned a diagnosis of ASD. Although symptoms of ADHD may be ameliorated by stimulants, core symptoms of ASD including impairments in social interaction and communication skills could not be expected to improve from treatment.

Thus, identifying ASD (with or without coexistent ADHD) in institutionalised individuals is important of several reasons. Individuals with ASD have special rights according to the Swedish legislation and they may also have the right to social insurance benefits.

Further, the impairments in social interaction and communication skills could easily be misinterpreted as intentional actions, thus leading to formal sanctions. Also, individuals with ASD could be at risk for becoming bullied by other inmates. Thus, studies exploring the prevalence of ASD among prison inmates are urgent.

If the results of the present study would be confirmed, that would signal the need for increasing the awareness of ASD within the criminal justice system overall, as well as to ensure access to adequate support for this group.

Correctional officers need to be educated in symptoms and impairments of ASD and learn how to successfully meet this specific prison population. Environmental adjustments may also be beneficial ('ASD-friendly') considering the common perceptual problems. Finally, programs aiming at improving meta-cognition and adaptation to society may also need to be developed.

Although being severely affected by ADHD and in many cases also by ASD, none of the participants were recognised prior to this study, in spite having received mental health services from childhood onwards. This observation calls for attention. Early recognition of symptoms, immediately followed by appropriate interventions may prevent children from later ending up in prison.

Implementation of the previously (1.3.1) introduced ESSENCE concept might be very useful in this sense (Gillberg, 2010).

There are **limitations** to consider regarding the diagnostic assessments of long-term prison inmates. There might have been a selection bias towards more motivated inmates when recruiting for the assessments. The prison wing designated for this study had a reputation of being a 'psych wing' which may have limited its attraction, especially since inmates were provided less time for physical exercise and restricted access to vocational training as long as they were hosted at the 'ADHD wing'. This wing was apart from other wings to reduce the risk for exposure to illicit drugs.

However, the strengths of this study were the comprehensive evaluations including self-report, parental report, review of medical records, physical examination, lab measures, neuropsychological assessments, structured diagnostic interviews for ADHD and psychopathy, assessments of both Axis I and Axis II disorders, and extended assessments for ASD whenever needed. Other strengths were the comparisons of results with a psychiatric outpatient group with ADHD and with healthy controls.

In **Study II**, our hypothesis of OROS-MPH outperforming placebo in reducing symptoms and impairments of ADHD, as well as increasing the global functioning in the initial 5-week double-blind phase was confirmed. Although our finding of efficacy is in accordance with previous studies of MPH (Koesters et al., 2010), the large effect size has to be emphasised.

The effect size of Cohen's $d=2.17$ points to a very large benefit from treatment. In fact, this is the largest effect size reported to date of MPH treatment. This value corresponds to a NNT of only 1.1; meaning that you need to treat 1.1 individuals to receive one responder.

How could this apparently large effect size be explained?

First, the effect size depends on a) the treatment response of participants receiving active treatment during the double-blind phase. A large response will *increase* the effect size and b) the treatment response of participants receiving placebo treatment during the double-blind condition. A large placebo response will *decrease* the effect size.

In the present study, a large treatment response was achieved by active treatment, while the placebo response was negligible, thus optimising the effect size.

Second, what factors could explain the superior treatment response seen in this study as compared to previous studies?

Recently, a study investigated if adults with ADHD taking part in clinical trials are representative of adults with ADHD in the community (Surman et al., 2010). The authors found that 61% of the ADHD community sample was unlikely to meet the restricted eligibility criteria for participation in clinical trials.

Compared to the community sample, trial participants had lower rates of lifetime psychopathologies (major depression, anxiety disorders and SUD), higher current and past GAF scores and higher occupational and socioeconomic statuses.

This finding implies several things; results from clinical trials may not generalise to community samples as typical eligibility criteria exclude the large population of adults with ADHD that carries the greatest burden of coexistent disorders; clinical trials exclude participants who have the greatest need for treatment, thus possibly individuals who would improve the most from treatment.

The findings of our study are in support of the suggestions by Surman and colleagues (Surman et al., 2010). When we designed the present study, we decided to use less restrictive inclusion criteria, aiming at recruiting participants that were reflective of long-term prison inmates with ADHD.

We argued that if results were to be significant, they would also be possible to

generalise. However, as this was the first controlled trial of MPH conducted within a prison setting, there was an uncertainty whether long-term inmates would benefit from treatment, especially considering the anticipated spectrum of coexisting disorders, also including a lifetime history of SUD that usually precludes from trial participation.

In hindsight, we suggest that the use of less restrictive inclusion criteria, apart from increasing the external validity of results, contributed to the superior treatment response. Participants had elevated baseline ratings of ADHD symptoms and global severity, as well as low ratings of global functioning, thus leaving a large window for improvement by treatment.

In addition, all participants were male and had a history of poor academic achievement; factors that all predicted superior treatment response to MPH in a previous study (Buitelaar et al., 2011).

Third, what factors could explain the non-significant placebo response observed in the present study as compared to previous studies?

In a recent review, adults with ADHD overall presented a placebo response of 26% in short-term trials as compared to 34% in longer-term controlled trials (Wilens et al., 2011).

To date, very little attention has been paid to factors predicting placebo response in stimulant trials, especially with regard to treatment of adults with ADHD (Waxmonsky et al., 2011; Buitelaar et al., 2011; Newcorn et al., 2009).

A recent study that explored predictors of placebo response in a LDX trial of adults, reported greater symptom severity of ADHD at baseline to be associated with reduced placebo response. However, previous stimulant treatment did not predict response to placebo (Waxmonsky et al., 2011).

It was suggested that individuals with milder symptoms may be amenable to placebo treatment, whereas those seriously impaired less likely would remit without active treatment. Milder cases of ADHD enrolled to clinical trials may also increase the risk of 'false-positive' diagnoses, thus explaining their apparent 'remission' from treatment, as compared to more severe cases.

Further, there was a slower onset of response for placebo than for active treatment.

In conclusion, it was suggested that placebo response may be minimised by including more severe cases of ADHD into short-term trials. However, the impact of coexistent psychiatric disorders on response to placebo remains to be explored.

The results of the present thesis support the findings by Waxmonsky and colleagues; participants were severely affected by ADHD at baseline; the duration of the double-blind phase was five weeks; participants were comprehensively assessed, thus probably minimising the number of 'false-positives'.

Other factors possibly contributing to the very large effect size of $d=2.17$ comprise the excellent treatment adherence, absence of drug misuse during the study, as well as absence of dropouts during the controlled phase which preserved the statistical power.

Further in **Study II**, our hypotheses of treatment with OROS-MPH being tolerable and safe, were confirmed with few exceptions. AEs and vital signs were similar to those previously reported (Wilens et al., 2011).

In **Study II**, our hypotheses that treatment with OROS-MPH provided alongside psychosocial interventions would demonstrate long-term effectiveness on ADHD symptoms, global severity and global functioning, as well as maintenance of achieved improvements were confirmed and also in accordance with previous studies (Buitelaar et al., 2011; Wilens et al., 2011; Bejerot et al., 2010; Adler et al., 2009; Rösler et al., 2009).

In **Study III**, our hypotheses that treatment with OROS-MPH provided alongside psychosocial interventions would demonstrate long-term effectiveness on outcomes of cognition, motor activity, institutional behaviour and quality of life were overall confirmed.

As previously mentioned, increased reaction time variability as measured by CPTs is one of the most consistent findings in ADHD, suggested to be related to insufficient suppression of the default mode network (task negative network) during task performance (Swanson et al., 2011; Bidwell et al., 2011).

A recent study proposed stimulants to improve symptoms of inattention by facilitating deactivation of the default mode network (Liddle et al., 2011). Our findings of OROS-MPH improving sustained attention and reaction time variability while improving ADHD symptoms support these observations.

Participants in this study improved both the verbal and visuo-spatial working memory over time, which is in line with a previous study (Fallu et al., 2006).

Further, the considerable motor hyperactivity objectively quantified among participants in the present study at baseline, decreased significantly over time although not reaching normalisation as compared to the norm.

This finding is consistent with a previous report on MPH (Vogt and Williams, 2011).

The observations of treatment improving cognition as measured by objective tools, suggest a broadening of outcome measures in future studies by including objective measurements such as CPTs, preferably with tracking of motor activity.

During the present study, we observed a decrease of critical incidents as compared with the year before. However, because of methodological considerations (e.g., change of report system, transferrals between correction facilities) we did not employ inferential statistics.

The vast majority of participants took part in scheduled treatment programs, educational activities and vocational training; for some of them it was the first time of success in attending and completing programs and educational activities.

The significant improvements over time of the quality of life domains Goals and values, and Learning were especially encouraging.

We suggest based upon our findings that symptomatic and functional improvements together with new experiences of succeeding at school and in treatment programs, as well as being able to control behaviour instead of

repeatedly being reported for critical incidents, contributed to increased self-respect and an improved sense of internal locus of control.

When a life situation becomes possible to change, it brings hope; goals in life that previously seemed out of reach might become important to strive for.

Also, improvements in capacities of working memory and abstract verbal reasoning might have facilitated in this change of view.

In **Study III**, our hypothesis of ADHD symptom ratings being significantly associated with ratings of daily functioning was confirmed in part.

The *post hoc* analysis implying translation of ADHD symptoms into functional improvements measured by GAF was in line with previous reports (Wender et al., 2011; Buitelaar et al., 2012; Rösler et al., 2011).

However, most of the quality of life domains measured by QOLI were weaker associated with symptomatic improvements than GAF, as Goals and values was the only significant domain.

Also in **Study III**, our hypothesis of a significant association between investigators' and self-ratings of ADHD symptoms was supported and in line with a previous study (Adler et al., 2008).

The high correlation between investigators' and self-reported ADHD symptoms, and between symptom ratings and functional outcomes, imply that self-reported ADHD symptom scales might be reliable.

We suggest that an increased use of self-ratings in the future, preferably together with easy assessed clinical rating scales e.g., CGI-S might simplify monitoring of pharmacological treatment, and be cost-saving as well.

However, future studies will need to explore if an increased use of self-rating scales would be sufficient.

In **Study IV**, our hypotheses of higher baseline scores of ADHD symptoms and high dosages of OROS-MPH by open-label endpoint predicting a superior treatment response were confirmed and consistent with previous studies (Newcorn et al., 2009; Buitelaar et al, 2011).

However, the hypothesis of lower educational achievement predicting superior treatment outcome was not confirmed.

On the other hand, those who received educational supports at school during childhood were more likely to be in full remission by the open-label endpoint.

Apart from the predefined hypotheses, the present study suggested that a history of parental substance abuse predicted short-term response, whereas concomitant ASD predicted short-term remission.

Identification of predictors of treatment may lead to a more rational treatment regimen accounting for the likelihood of effectiveness at the individual level.

The results of the present clinical trial are indeed encouraging.

However, since this is the first trial evaluating stimulant treatment for ADHD within a prison setting, the results need to be confirmed by other research groups.

There are **limitations** of *Study II-IV* to discuss. First, the sample size was small. However, results of the double-blind trial were highly significant and the effect size was very large, implying a well powered study.

Further, larger effects are to be expected from an open-label extension trial, in the absence of a comparator controlling for non-specific treatment effects.

On the other hand, results of the neuropsychological tests were compared to norm group data. However, the small study sample limited the range of statistical analyses to be employed.

Results of this clinical trial comprising a highly specific study population may not generalise to other populations. However, inclusion of participants suffering from, and being treated for, coexisting disorders increased the generalisability of results, as most adults with ADHD are affected by coexisting disorders.

Finally, this is the first study to evaluate OROS-MPH as treatment for prison inmates with ADHD and coexisting disorders, and it is so far one of few long-term studies of adults with ADHD that observed a robust treatment response, in the short-term as well as in the long-term.

6 CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis lends further support to the observed enrichment of ADHD among prison inmates. Further, this thesis suggests that adult male long-term prison inmates with ADHD hosted at Norrtälje Prison were severely symptomatic and functionally impaired when compared to psychiatric outpatients with ADHD and with controls. This specific group of inmates also presented high rates of coexisting disorders including lifetime SUD and ASD. Further, this thesis provides new evidence of OROS-MPH being highly effective and overall safe for this group of long-term inmates with ADHD and coexisting disorders, both in the short-term relative to placebo (Cohen's $d=2.17$; $NNT=1.1$), and in the long-term when provided alongside regularly provided psychosocial interventions within a prison setting. Overall, symptomatic improvements translated into functional improvements, and investigators' and self-ratings of ADHD symptoms were significantly related. Also, new information of predictors for treatment response, as well as for treatment remission of OROS-MPH is suggested by this thesis.

The high prevalence of ADHD within prison inmates, as demonstrated by studies across several countries, its documented relationship with violent offences and persistence of offending leads to the conclusion that we could not afford to ignore ADHD any longer. Studies suggest ADHD to be a serious public health concern. Individuals affected by ADHD have a quality of life between 1.5 and 2 SD below the population norms, with the strongest impact on psychosocial and achievement-related measures, comparable to that seen for many physical disorders (Coghill, 2010). An even stronger impact on quality of life would be expected in prison inmates with ADHD experiencing the worst outcomes, which might be comparable to individuals suffering from serious and life-threatening disorders.

In addition to the personal impact of ADHD, the societal costs associated with ADHD are considerable, especially with regard to ADHD and offending.

Offenders are in general costly to manage; the broad cost of care per annum for the 'average' youth offender in prison in the UK is estimated to be about 600 000 SEK (Young and Goodwin, 2010). However, offenders with ADHD are even more costly, considering their early onset of offending, increased re-offending and increased rates of critical incidents related to institutional aggression.

Considering ADHD within prison inmates in a larger, international perspective, the size of the problem is obvious. The prison populations of the Scandinavian countries, UK, the Netherlands, Belgium, France, Italy and the US comprise about 2.5 million individuals in total (International Center for Prison Studies, University of Essex). Assuming a conservative prevalence of 25% ADHD, the potential target population for treatment would be more than 630 000 individuals (1.1 million individuals if 45% ADHD is assumed). A cautious assumption that almost all of these prison inmates with ADHD are untreated, and about half of them (315 000 individuals) would respond favourably to treatment, to the point that they would not be re-convicted, this would lead to annual savings of about 189 billion SEK. Of course, this is purely speculative and simplified, and does neither include costs for assessment and treatment, nor other savings that might follow from successful treatment such as productive work from employment in society.

The purpose of this example was to put the problem with untreated ADHD in prison inmates in proportion, and to give an impression of the sums involved.

Given that ADHD is treatable also in prison inmates, as suggested by this thesis, we consider it unacceptable to continue ignoring ADHD. For every offender that benefits from treatment the potential gains will be significant at the individual level. Given the large numbers of offenders that might benefit and the total potential gains, it further implies that ADHD must be appropriately identified and managed within the criminal justice systems, thus providing better justice for both offenders and society.

Based upon our findings in the present thesis, we suggest that screening and diagnostic evaluation for ADHD, followed by MPH treatment in combination with rehabilitation programs are feasible and effective interventions to provide within a prison setting. Treatment improved ADHD symptoms, global functioning, executive functioning, behaviour control and quality of life.

Participants took better advantage of educational activities, offender treatment programs, educational activities and vocational training aiming at reducing re-offending and increasing re-integration into society.

If these interventions will reduce re-offending and be cost-saving needs to be explored. At the moment, we are following participants of the present study in a prospective observational study. Data from the 24-month follow-up assessment are under preparation, whereas the 48-month follow-up study is ongoing.

Concerns have been raised regarding the use of controlled substances such as stimulants within prison inmates, as well as concerns regarding the potential for diversion of substances. As always, the potential benefits of treatment have to be weighed against the potential risks, both in the short-term and in the long-term. Benefit is assessed in terms of effects from treatment as well as the outcome in the absence of treatment. If ADHD is left untreated, the ability to alter the behaviour will be reduced, thus maintaining the antisocial behaviour. The abuse potential for stimulants has been evaluated in long-term follow-up studies. These studies could not confirm an overall increase in drug abuse for ADHD children treated with stimulants (Wilens et al., 2011). Diversion of drugs within prison facilities should not be a problem considering the already existent programs for e.g., methadone maintenance. However, stimulant treatment requires careful supervision and should not be provided unless the inmate is appropriately diagnosed with ADHD. Overall, the potential benefits of treating these highly impaired inmates with ADHD appear by far to outweigh the potential risks of treatment.

However, since this study is the first controlled trial of MPH conducted in prison inmates with ADHD within a prison setting, our results need to be confirmed in future studies. Other substances such as ATX could also be trialled in prison populations.

According to treatment guidelines, pharmacological treatment should always form part of a multimodal treatment approach addressing psychological, behavioural, educational and occupational needs (NICE, 2008). Preferably, treatment starts with medication to ameliorate symptoms of inattention, motor restlessness and impulsivity, and is then followed by behavioural and psychosocial interventions.

In the Swedish Prison and Probation Service there is a need for programs based on CBT that are adjusted to fit inmates with ADHD and antisocial behaviour. CBT programs developed for adults with ADHD usually target ADHD symptoms and executive functions. However, relative to non-offending individuals with ADHD, treating offenders with ADHD may require more complex and comprehensive interventions. In addition to improving ADHD symptoms and executive functioning, antisocial attitudes and thinking styles also need to be addressed e.g., developing insight into offending and empathy for victims. The R&R2 ADHD is an example of a CBT program comprising these comprehensive components. However, it is not yet available in Sweden. Thus, a CBT program for ADHD inmates urgently needs to be evaluated in the Swedish Prison and Probation Service, preferably as an add-on to medication.

In consistence with the recommendations of a multimodal treatment approach, we are presently planning for a randomised controlled trial evaluating computerised working memory training as treatment for adult prison inmates with ADHD, in collaboration with the Swedish Prison and Probation Service.

Overall, the awareness about adult ADHD, its detection, assessment, treatment and management need to be raised within all parts of the criminal justice system. Recently, a consensus statement from the Adult ADHD Network in the UK and criminal justice agencies was published (Young et al., 2011). Although this statement applies to the UK, it should be possible to adapt it for the Swedish criminal justice system.

In summary, the consensus statement provides recommendations for a continuous, integrated multimodal care pathway that follows the offender with ADHD (or suspected ADHD) from the initial police contact through all stages in the criminal justice system. The statement emphasises the importance of health and criminal justice agencies working together to find 'win-win' solutions for managing the individuals and their care, also after conditional release. The transition to general psychiatry could be critical and needs special consideration for ensuring access to continued treatment.

If the previously (3.1) discussed Life Transition Model (Turgay et al., 2012) was to be adopted by the general psychiatry, it would probably facilitate transitions from the criminal justice system, and ensure that inmates with ADHD will have access to optimal multimodal treatment also after being conditionally released.

Therefore, we need to put effort in developing treatment protocols comprising e.g., pharmacological, psychological (CBT/DBT) and neuro-modulation interventions as part of a multimodal approach, for the benefit of all individuals with ADHD, offenders as well as non-offenders.

As a consequence of the studies that form the basis of this thesis, routines are now being developed aiming at implementing assessment and treatment for ADHD as part of regular prison routines within the Swedish Prison and Probation Service.

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