A controlled trial of clonidine in hyperkinetic children

De toepassing van clonidine bij kinderen met een hyperkinetisch syndroom:
Een gecontroleerd klinisch-farmacologisch onderzoek.

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ABBREVIATIONS

ADHD	Attention-deficit Hyperactivity Disorder	(31)
BMDP 5V	Programme for repeated measures analysis of variance (RM ANOVA)	(109)
CAS	Child Assessment Schedule	(29)
CBCL	Child Behavior Checklist	(36)
CTRS	Conners Teacher Rating Scale	(40)
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised	(14)
FDF	Freedom from distractibility factor	(43)
GBO	Groninger Basisschool Observatielijst (Groningen Behavior Observation scale,teacher version)	(37)
GGBS	Groninger Gedragslijst Basisschool (Groningen Behavior Checklist: School Situation, abbreviated version)	(39)
GGGS	Groninger Gedragslijst Gezinssituatie (Groningen Behavior Checklist Family Situation, abbreviated version)	(39)
GOO	Groninger Ouder Observatielijst (Groningen Behavior Observation scale, parent version)	(37)
GPO	Groninger Psychodiagnostische Observatielijst (Groningen Behavior Observation scale, laboratory version)	(37)
GTS	Gilles de la Tourette Syndrome (Tourette's Disorder)	(49)
HPLC	High-performance liquid chromatography	(130)
MHPG	3-methoxy-4-hydroxyphenylglycol	(124)
PDD-NOS	Pervasive Developmental Disorder Not Otherwise Specified (DSM-III-R)	(49)
PMA	Primary Mental Ability test	(44)
PPCT	Paper and Pencil Cancellation Test	(43)
RT	Reaction Time Experiments	(41)
TRF	Teacher's Report Form	(36)
Trial groups	Definition of trial groups	(49)

NB: The figures in parentheses refer to the pages where the terms are defined in more detail.

Chapter 1

CHAPTER 1 INTRODUCTION

1.1 Background of the study

It is important to develop effective treatment strategies for children with the hyperkinetic syndrome, also called hyperkinesis, because this disorder is usually accompanied by impairment of social and school functioning and in the majority of cases persists throughout childhood. Moreover, prospective longitudinal studies of hyperkinetic children indicate that a substantial proportion retains hyperkinetic symptoms and go on to antisocial disorders (Klein & Mannuzza, 1989; Barkley et al., 1990b).

Stimulants (primarily methylphenidate) are currently considered the first-line drugs for children with hyperkinetic syndrome (Rapport, 1990). While in Europe drug treatment is seldom applied, it is widely used in North America (Sergeant & Steinhausen, 1992). A trial of stimulant medication should be considered for children with marked inattention and restlessness, severe enough to impede development (Taylor et al., 1987). Over the past 25 years, there have been many controlled studies demonstrating the short-term efficacy of stimulants in hyperkinesis (Jacobvitz et al., 1990). The short-term effects include: increased attention span, decreased impulsivity and a reduction in socially maladjusted behavior.

About 75% of hyperkinetic children show a beneficial response to stimulants (Barkley, 1977; Klein, 1987; Jacobvitz et al., 1990). Both aggressive and nonaggressive children with hyperkinesis responded similarly to methylphenidate (Barkley et al., 1989). In her review of follow-up studies Weiss (1984) concluded that children treated with stimulants had the same long-term outcome as untreated controls. However, the evaluation of the long-term efficacy of stimulant medication is fraught with methodological difficulties, such as the selection of control groups, compliance, age of initiation of treatment, attrition rate (Hinshaw, 1989). In their 10-year prospective follow-up study from childhood to young adulthood, Hechtman et al. (1984) found that stimulant-treated hyperactives functioned significantly worse than matched normal controls, and similar to untreated hyperactives. However, stimulant-treated hyperactives did better than their untreated counterparts in some areas, e.g., car accidents, positive view of childhood, delinquency, social skills, and self-esteem.

If psychological treatment was as effective as drug treatment, it would probably be preferred on grounds of safety (Taylor et al., 1987). Behavior therapy, however, has not been shown to induce clinically meaningful behavioral changes (Klein & Abikoff, 1989). Behavior treatment invariably fails to affect settings outside the ones in which treatment is instituted, and the effects of treatment are maintained only as long as it is taking place; the development of internalized self-regulation skills often fails. Cognitive

training has been promoted as a promising intervention for hyperkinetic children. The central aim of this approach is the development of self-control skills and reflective problem-solving strategies, both of which are presumed deficient in hyperkinetic children. Yet findings from controlled studies do not indicate that the behavior of hyperkinetic children improves with cognitive training, either in school or at home. Neither do studies indicate that cognitive training enhances the beneficial effects of stimulants (Klein & Abikoff, 1989).

Klein et al. (1980) found that the addition of behavior therapy to stimulant medication led to accrued improvement. Horn et al. (1991) investigated the effects of methylphenidate treatment alone and in combination with behavioral parent training plus child self-control instruction. They found no evidence of to the superiority of the combined conditions relative to medication alone. However, some limited support was found for the hypothesis that the effects of a high dose of stimulant medication (0.8 mg/kg/day) could be achieved by combining a low dose (0.4 mg/kg/day) with a behavioral intervention.

Multimodality treatment (MMT) has been recommended for hyperkinetic children. MMT includes an individualized comprehensive treatment plan which usually includes methylphenidate (Satterfield, 1990). Kelly et al. (1989) found that MMT in hyperkinetic children did not significantly improve initially low self-esteem after one month of treatment, despite significant behavioral responses to medication. After a 16-month follow-up, however, self-esteem had improved significantly. Thus far, there is no evidence that MMT might ameliorate the poor adolescent and adult prognosis consistently reported in most long-term follow-up studies (Satterfield, 1990).

Although stimulants help many children with hyperkinesis, in 25% of them symptoms either remain unchanged or become worse (Jacobvitz et al., 1990). Common undesired adverse effects associated with stimulant medication include decreased appetite, insomnia, stomachaches, and headaches (Barkley, 1990). These are generally transient and decrease with time (Calis et al., 1990). Increased sensitivity and emotionality are also highly distressing to families (Brown & Borden, 1989).

Besides children who do not benefit from stimulants, there are other children for whom this treatment is contraindicated: children with autism, children with tics, and children with epilepsy. In autistic children an increase in stereotype movements, and irritability were reported in several studies, although other studies showed meaningful effects without major side effects or worsening of stereotype movements (Birmaher et al., 1988). In children with tics there might be a link between stimulant treatment and either the onset or exacerbation of tics (Jacobvitz et al., 1990; Golden, 1988). Children with epilepsy should not be given methylphenidate because animal research and histories of amphetamine intoxication suggest that methylphenidate may lower seizure thresholds (Gilman et al., 1985). The relative contraindication of stimulants in children with autism, tics, or epilepsy, is a problem in clinical practice, because poor attention span, and overactivity are common problem behaviors in children with these disorders (Wing, 1988; Comings & Comings, 1988; Barkley, 1990).

Finally, there is little information about possible long-term side effects of stimulants, such as growth suppression and substance abuse (Jacobvitz et al., 1990).

In conclusion, there were two groups of hyperkinetic children, who were in need of an alternative drug:
(1) children who did not benefit from stimulant medication, or developed persistent undesired adverse effects during treatment with stimulants; and
(2) hyperkinetic children with comorbid conditions in which the use of stimulants was relatively contraindicated.

In the past few years new medicines for hyperkinesis have been explored: monoamine oxidase inhibitors, tricyclic antidepressants, bupropion, and clonidine (Campbell & Spencer, 1988). Tricyclic antidepressants (imipramine, desipramine) are less effective and may produce more serious adverse effects than stimulants and are therefore considered second-line agents for the treatment of hyperkinesis (Pliszka, 1987). Monoamine oxidase inhibitors, and the antidepressant bupropion have not yet been tested in controlled trials in hyperkinetic children (Wender & Reimherr, 1990).

1.2 Noradrenergic involvement, clonidine

In the late 1970s, noradrenergic involvement in Tourette's Disorder (GTS) was suggested because of two findings:
(1) Cohen et al. (1979a) found an elevated CSF level of 3-methoxy-4-hydroxyphenylglycol (MHPG) in a child with GTS; and
(2) GTS is exacerbated by stress and anxiety, and studies had reported that stress did enhance the activity of norepinephrine (NE) neurons in the locus coeruleus (Antelman & Caggiula, 1977).

Studies using iontophoretic and microelectrical techniques, reported that the α_2-noradrenergic agonist clonidine in low doses diminishes the endogenous NE production by activating autoinhibitory effects of the presynaptic receptors in cell bodies concentrated in the locus coeruleus (Svensson et al., 1975; Cedarbaum & Aghajanian, 1977). It was also found that when given as a single challenge dose, clonidine stimulates growth hormone (GH) release, inhibits NE release, and diminishes plasma concentrations of the major NE metabolite, MHPG (Lal et al., 1975).

These findings led Cohen and co-workers to test clonidine in the treatment of GTS (Cohen et al., 1979b, 1980). Cohen et al. (1980), in open treatment gave clonidine to 25 GTS patients who could not tolerate or did not benefit from treatment with haloperidol. Clonidine was observed to ameliorate the disorder in 70% of patients. Not only tics, but also hyperactive and obsessive-compulsive behaviors appeared responsive to treatment. GTS children demonstrated improved calmness and attention on clonidine. GTS patients have a high prevalence of comorbid hyperkinesis (approximately 50%; Comings & Comings, 1988).

Hunt et al. (1984) measured GH and MHPG response following an acute single-dose

of clonidine in hyperkinetic children, before and during treatment with methylphenidate (MPH). They found that MPH treatment strongly diminished the GH response to clonidine. The pretreatment GH response of these children was greater than the response found in a comparative group of children with short stature, and was also higher than the pretreatment GH peak in patients with GTS. This indicated that untreated hyperkinetic children might have an augmented sensitivity to noradrenergic stimulation and that this hypersensitivity was diminished by MPH treatment. This finding suggested that hyperkinetic symptoms might be responsive to treatment with clonidine.

Cohen et al.'s (1980) findings, and Hunt et al.'s (1984) findings led Hunt et al. (1985) to try clonidine in hyperkinetic patients without tics. Ten hyperkinetic children were treated in a double-blind placebo-crossover trial, consisting of clonidine 4-5 µg/kg/day for 8 weeks, and placebo for 4 weeks. Parents' behavior ratings showed that 7 of the 10 children clearly benefited from clonidine. Of the 8 children on whom teachers' ratings were completed, 7 improved with clonidine. Upon tapering off clonidine and returning to placebo, behavioral control quickly deteriorated to pretreatment levels. Clonidine's major side effect was sleepiness which occurred about 1 hour after administration of the drug and lasted about 30-60 minutes. This sedation decreased to minimal levels or disappeared within three weeks in all but one child. Blood pressure was reduced by about 10%, and was clinically nonsignificant. One child with prior symptoms of depression became more depressed on clonidine; children who had no prior symptoms of depressive disorder did not exhibit emergent symptoms on treatment. It was concluded that clonidine appeared to be a safe and effective medication for hyperkinetic children. Klein's (1987) critique on Hunt et al.'s (1985) study was that treatment possibly was not blind because all children were on clonidine after two weeks into the trial. We then reread another publication of the study (Hunt et al., 1986) in which it is reported that parents, teachers, children, and one clinician remained blind to the study design, but that two clinicians, blind to the treatment condition, rated the children every month using a scale quantitatively scoring hyperactive symptoms. Therefore, as not all evaluating clinicians were blind to the study design the study was possibly not double-blind.

In 1984, clonidine was introduced in the treatment of GTS children and hyperkinetic children at the Sophia Children's Hospital, Rotterdam (department of Child and Adolescent Psychiatry; Minderaa, 1987). Open treatment experiences with hyperkinetic children were encouraging (Gunning et al., 1990). After at least three months of open treatment with clonidine 4 µg/kg/day a clinically significant improvement of hyperactivity was seen in 72% of the hyperkinetic Gilles de la Tourette patients (n=43), 65% of the hyperkinetic patients (n=26), and 63% of the hyperkinetic children with Pervasive Developmental Disorders (n=16). The major adverse effect was sleepiness, which occurred in 64% of the children in the first month. Five weeks after dosage was installed 21% of the patients still complained of adverse effects.

Hunt (1987) compared the clinical response of hyperkinetic children to clonidine and methylphenidate. A population of 10 hyperkinetic children was openly treated with clonidine, methylphenidate and placebo in random sequence. It was found that clonidine

(5 µg/kg/day) and methylphenidate (0.3 mg/kg/day, and 0.6 mg/kg/day) were equally effective and significantly better than placebo as rated by parents and teachers. Teachers expressed a slight preference for methylphenidate, perhaps reflecting its preferential effect on distractibility. Parents rated a nonsignificant preference for clonidine, indicating that it improved hyperactivity, impulsivity, cooperation, and oppositionality during the weekends and in the evenings.

Based on the reported small sample size, open and controlled trials and on their own clinical experience, Hunt et al., (1991a) conclude that clonidine is effective in hyperkinesis, although it is slightly less effective than methylphenidate. However, clonidine is often preferred to methylphenidate by parents for its stabilizing effect, lack of evening and weekend withdrawal and its absence of anorectic or insomniac effects. Teachers showed slight preference for the effects of methylphenidate. A similar pattern and incidence of side effects was noted during treatment with clonidine and methylphenidate.

With the low doses generally used in child psychiatry (i.e., 3-5 µg/kg/day), clonidine reduces the NE release in the cells of the locus coeruleus. The locus coeruleus fires during transition states requiring arousal, such as awakening. Continuous firing of the locus coeruleus produces a state of vigilant arousal (Everitt et al., 1990). . Excessive NE firing may erroneously label routine stimuli as significant, thereby increasing the amount of information requiring active processing and diminishing selective attention (Hunt et al., 1988). In children with immature behavioral inhibition systems, this increase in unbalanced arousal systems may result in excessive, poorly directed activity. The diffuse neuroanatomical distribution of NE suggests it functions as a neuromodulator of many integrative cortical processes, rather than as a discrete neurotransmitter for highly specific actions (Hunt et al., 1991b). Vocci and Deutsch (1990) suggest that the insistence on sameness, avoidance of novelty, and aggressive and explosive behaviors in autistic children might result from a disturbance of the locus coeruleus, which may function as a novelty detector and differential amplification system for noxious stimuli. An abnormally sensitive differential amplifier might process stimuli as noxious, that a normal individual would process at low-level novelty, resulting in an activation for fight or flight recognized by the individual as somatic anxiety, fear, panic, or life-threatening terror. It was hypothesized that an α_2-agonist (clonidine) might have beneficial effects in autistic patients as a dampening agent of the differential amplifier system.

Clonidine and methylphenidate have very different neurochemical mechanisms of action (Hunt et al., 1991a). Methylphenidate releases presynaptically stored dopamine (DA) and NE, producing an increase in basal brain arousal, evident by increase in blood pressure and pulse, and decrease in appetite and sleep. However, methylphenidate also facilitates improved behavioral inhibition and cognitive selective attention, probably by activation of cortical dopaminergically mediated inhibition systems. Clonidine, through presynaptic inhibition of locus coeruleus firing, reduces basal brain arousal. Reduced arousal can diminish the background "noise" and reduce the amount of stimuli that must be processed (improved signal to noise ratio).

Clonidine's major clinical use is to treat hypertension. Clonidine is also used in migraine, and in postmenopausal flushing (Frisk-Holmberg, 1986). It is also used for inhibiting the rush of NE released in the locus coeruleus when opiate or alcohol addicts are undergoing withdrawal (Golds et al., 1978). It has been used to treat the symptoms of withdrawal from cigarette smoking (Glassman et al., 1984). It was also demonstrated that clonidine has short-term anxiolytic effects in patients with panic disorder (Uhde et al., 1989). Clonidine in low doses produces sedation in rats. However, high doses produced hyperactivity and aggression in reserpinized rats, suggesting an activation of postsynaptic α_1-adrenoreceptors (Heal, 1990). Rats which had been exposed to clonidine in the neonatal period were reported to show behavioral abnormalities. This effect was probably due to REM sleep suppression through clonidine. Because clonidine used to be the drug of choice for severe hypertension in pregnancy, the finding in rats led Huisjes et al. (1986) to investigate children who prenatally had been exposed to clonidine. It was found that these children showed a marginal excess of hyperactivity and an excess of sleep disturbances when compared with normal controls.

The effectiveness of clonidine in GTS still remains controversial, with some well-controlled, double-blind clinical trials supporting its use (McKeith et al., 1981; Borison et al., 1983; Leckman et al., 1991), while others do not (Dysken et al., 1981; Goetz et al., 1987). The waxing and waning course of GTS makes it difficult to demonstrate clonidine's effectiveness. In their recent 12-week, parallel-group, double-blind, placebo-controlled clinical trial in 40 children and adults with GTS, Leckman et al. (1991) found that motor tics showed a 35% improvement in the clonidine group, compared with an 8% improvement with placebo. Based on parental reports and self-reports, it was found that clonidine was more effective than placebo in reducing symptoms of impulsivity and hyperactivity. The effect of clonidine on impulsivity and hyperactivity seemed to be independent of its effects on tic behaviors.

To conclude: The effect of clonidine in hyperkinesis has thus far only been tested in one controlled trial (Hunt et al., 1985) with a small sample size, and that possibly was not double-blind. In their review of psychopharmacology in child and adolescent psychiatry, Campbell and Spencer (1988) called the results of the Hunt et al. (1985) study promising, although inconclusive. Nevertheless, the Hunt et al. (1985) study has been mentioned in each recent review of child psychopharmacology (Klein, 1987; Zametkin & Rapoport, 1987a; Campbell & Spencer, 1988; Weizman et al., 1990). Klein (1987) considered the clinical efficacy of clonidine in hyperkinesis to be of considerable interest because of the markedly different neuropharmacological profile of clonidine compared with the stimulants. Therefore, a large and controlled trial was needed to further substantiate the therapeutic benefit of clonidine in hyperkinesis, and to compare its effect with methylphenidate. These findings led us to formulate the aims of the study as follows.

1.3 Aims of the study

(A) A comparison of clonidine with placebo with respect to efficacy and safety concerning short term effects on hyperactivity in subgroups of hyperkinetic children:

(1) subjects, meeting the DSM-III-R criteria for Attention-deficit Hyperactivity Disorder (ADHD), who in addition met the DSM-III-R criteria for Pervasive Developmental Disorder (PDD);
(2) subjects, meeting both the DSM-III-R criteria for ADHD and the criteria for Tic Disorder (but not PDD);
(3) subjects, meeting the DSM-III-R criteria for ADHD, but not the criteria for PDD or Tic Disorder.

(B) A comparison of clonidine with placebo and methylphenidate with respect to safety and efficacy concerning short term effects on hyperactivity in trial group (3).

The primary aim of the study was to demonstrate whether clonidine was effective on hyperactivity in subgroups of hyperkinetic children. The secondary aim was to investigate the effects of medication on three levels: behavioral, neuropsychological and neurochemical. As measures on the behavioral level we used the parents' and teacher's global judgment of the child's behavior, behavior rating scales, and ethological techniques. As measures on the neuropsychological level we used reaction-time experiments and the Bourdon-Wiersma paper-and-pencil cancellation task (the latter was used for the diagnostic assessment only). As measures on the biochemical level we used plasma and 24-hours urine levels of 3-methoxy-4-hydroxyphenylglycol (MHPG).

This approach corresponds with Rose's (1976) hierarchical levels of explanation. Rose (1976) arranged the biological explanations of brain phenomena in a diagram with the sociological and psychological descriptions at the top, the physiological descriptions in the middle, and the anatomical-biochemical descriptions at the bottom. It was hypothesized that points on each level correspond to points on levels both below and above. If attempts are made to cross the levels of the hierarchies of explanation, one is sometimes attributing a causal relationship between the point-set on one level and that on another, whereas usually no more than a correlative relationship is legitimated.

In this thesis the relationship between the behavioral level and the neuropsychological level with regard to the diagnostic assessment of hyperkinetic children will be described in section 4.6.4. The relationship between the behavioral level and the biochemical level with regard to medication effects (i.e., clonidine and methylphenidate versus placebo) will be described in Chapter 6. The investigations using ethological techniques and reaction-time tasks will not be reported in this thesis.

1.4 Structure of the report

In chapter 2, a survey is presented of recent research findings in hyperkinesis. In chapter 3, the methods employed in the diagnostic assessment and the medication trial are described. The results of the diagnostic assessment are presented in chapter 4, and the results of the medication trial in chapter 5.

A 109 hyperkinetic children entered the 8-weeks, double-blind, placebo-controlled, parallel-group clinical trial. Hyperkinetic children, who also had a diagnosis of pervasive

developmental disorder (n=5), or a diagnosis of tic disorder (n=32), were treated with either clonidine or placebo. Hyperkinetic children without an additional diagnosis of pervasive developmental disorder, or tic disorder (n=72), were treated with clonidine, placebo, or methylphenidate.

Chapter 6 deals with the neurochemical aspects of hyperkinesis. It also contains a report on the differential effects of clonidine and methylphenidate on plasma and urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) that were found during the medication trial. In chapter 7 the total study is evaluated.

Chapter 2

CHAPTER 2 HYPERKINESIS

2.1 Terminology

Taylor (1986) distinguishes between "hyperactivity" and "hyperkinesis". Hyperactivity is used to classify behaviors. Hyperactivity is characterized by a disorganized and chaotic style of behavior, including restlessness and inattention in a degree that is inappropriate to the child's age. Hyperkinesis (or "hyperkinetic syndrome") is the name for a hyperactivity syndrome and is used to classify individual cases. The DSM-III-R category Attention-deficit Hyperactivity Disorder (ADHD; APA, 1987), and the ICD-9 category Hyperkinetic Syndrome (World Health Organization, 1978) are the current diagnostic labels for children showing significant problems with attention, impulse control, and overactivity. DSM-III-R's predecessor, DSM-III (APA, 1980), used the term Attention Deficit Disorder with Hyperactivity (ADDH) to label children with hyperkinesis.

Hyperkinesis is a chronic, heterogeneous disorder of unknown etiology, usually first evident in childhood, and affecting approximately 6% of children and youths. In general population studies ADDH was found to be the most common diagnosis (Offord et al., 1987). Hyperactive symptoms account for the impairment of emotional, academic, and social development, commonly observed in patients with this disorder (Calis et al., 1990). Hyperactivity is a common cause of referrals to pediatricians, neurologists, and child psychiatrists. Because symptoms of the syndrome are distressing to the environment (to parents and to teachers) and also sufficiently distressful to the child, such affected children are likely to come to the attention of health professionals (Cantwell, 1986). Despite substantial progress in the detection and management of hyperkinesis, questions regarding the etiology and pathophysiology of the disorder have remained unanswered.

2.2 Diagnostic classification

The main scientific purpose of a syndromic classification is to enable sharp conclusions to be drawn about the causes, pathogenesis, and course of a disorder that distinguish it from other disorders (Taylor, 1988a). The clinical acceptance of a hyperkinetic syndrome has gone far ahead of its scientific status (Taylor, 1989a). Barkley (1981) in his review concluded that "hyperactivity" was used to refer to the behavior of a relatively heterogeneous group of children who did not necessarily share a common set of characteristics; however, most of these children appeared to have primary deficiencies in their attention span, impulse control, and rule-governed behavior.

The history of the conceptualizations of the hyperkinetic syndrome has been turbulent. First, the concept of Minimal Brain Dysfunction (MBD) was abandoned in the 1960s, because biological findings failed to establish the nosological validity of a MBD syndrome (Taylor, 1986). By the early 1970s, the defining features of the hyperkinetic syndrome had been broadened to include what were previously felt to be only associated characteristics, including impulsivity, short attention span, low frustration tolerance, distractibility, and aggressiveness (Barkley, 1990). Then, Douglas (1972) argued that deficits in sustained attention and impulse control were more likely to account for the difficulties seen in these children than hyperactivity. This led to a shift of focus to problems of inattention, a shift reflected in the American Psychiatric Association renaming the syndrome Attention Deficit Disorder (1980). Recently the evidence supporting an attentional-process dysfunction in hyperactive children has been seriously questioned, and it has been suggested that hyperactive children are suffering from a disorder in energetical regulation mechanisms (Van der Meere et al., 1991).

All general population and clinical studies have underlined how highly overactivity and inattention are associated with other psychiatric problems (Barkley, 1981; Taylor, 1989). In particular, there is a very large overlap with aggressive and delinquent behaviors, and with learning disabilities. Taylor (1986) hypothesized an hierarchical classification of overactive states based on Foulds' hierarchical approach to illness. The basic idea is that a condition high in the hierarchy will include the symptoms of lower conditions, but higher disorders are not included in lower diorders. It offers a means to test rational grounds for inclusion and exclusion criteria. Foulds' hierarchical approach can easily be applied in the case of an overactive autistic person, but application becomes quite controversial in other areas, such as the relationship of affective disturbance and conduct disorder. Taylor cautions not to adopt any such scheme in its entirety but test its predictions in clinical research. To test the validity of the hypothesized attention-deficit / hyperactivity syndrome, we need to turn to studies that have compared the syndrome (however defined) with other psychiatric disorders in terms of some criterion that is external to the behavioral definition of the diagnostic groups being examined (Rutter, 1989).

Taylor et al. (1986ab, 1987) used a controlled trial of methylphenidate as a diagnostic discriminator in a group of boys referred to a psychiatric clinic for antisocial, disruptive, or overactive behavior. A good response, as defined by a difference between reactions to methylphenidate and placebo, was predicted by higher levels of inattentive and restless behavior, impaired performance on tests of attention, clumsiness, younger age and by the absence of overt anxiety as shown at school. Interestingly, neither DSM-III (ADD) nor ICD-9 diagnoses (Hyperkinetic Syndrome) were good predictors. DSM-III was not a good predictor because the ADD diagnostic category included many children who responded poorly to medication and ICD-9 was poor because Hyperkinetic Syndrome failed to include many children who responded well to drugs. The findings suggested that the syndrome may be best conceptualized in terms of both the severity and pervasiveness of hyperactivity and inattention. The presence of disruptive behavior did

not differentiate responders and non-responders to stimulants. Taylor et al.'s study (1986a) showed that the association with cognitive impairment serves to divide the group of children with disruptive behavior in much the same way as does the response to stimulants: Cluster analysis served to identify a group of pervasively hyperkinetic children who were characterized by hyperactivity that had an onset before the age of 5 years, a lower IQ, more neurodevelopmental abnormalities, a high frequency of language impairment or other forms of developmental delay, accident prone behavior and markedly poor peer relationships, as well as a good response to stimulant medication.

At the time the study was planned, two diagnostic classification systems were available: The ninth edition of the International Classification of Diseases (ICD-9; World Health Organization, 1978), and the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987).

The ICD-9 includes a disorder, "Hyperkinetic Syndrome", whose essential feature is poor concentration and with which extreme overactivity is associated. For a ICD-9 diagnosis of "Hyperkinetic Syndrome" not only the presence of hyperactivity is required, but also the absence of any other condition that could give rise to this behavior. If, for instance, both hyperactive and aggressive behaviors are present, one needs to judge which is primary and make one diagnosis only.

The DSM-III-R includes a disorder, "Attention-deficit Hyperactivity Disorder" (ADHD), whose essential features are developmentally inappropriate degrees of inattention, impulsiveness, and hyperactivity. DSM-III-R states: "People with the disorder generally display some disturbance in each of these areas, but to varying degrees". The criteria for ADHD (see appendix 3.2.3) form an index of symptoms of which a certain number, but no single one, is required to make the diagnosis. DSM-III-R states, that this polythetic format is likely to enhance diagnostic reliability, in contrast to a monothetic format in which each of several criteria must be present for the diagnosis to be made. In the DSM-III-R ADHD forms a subclass of disorders with Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). DSM-III-R states: "This subclass of "disruptive behavior disorders" is characterized by behavior which is socially disruptive and is often more distressing to others than to the people with the disorders. Studies have indicated that in both clinic and community samples, the symptoms of these disorders covary to a high degree. In psychiatric literature the behaviors that these disorders encompass have been referred to as "externalizing" symptoms". Spitzer et al. (1990) performed a field trial of the DSM-III-R criteria for ADHD, ODD and CD, using as a standard the diagnosis of these disorders made by expert clinicians with experience of these disorders. The DSM-III-R criteria for ADHD, ODD and CD demonstrated high sensitivity, specificity, and internal consistency.

In this study a patient is considered "hyperkinetic" when its symptoms satisfy the DSM-III-R criteria of ADHD. There were two reasons for choosing the DSM-III-R and not the ICD-9 in our study:

(1) Hyperactivity so often overlaps other forms of psychiatric disturbance. The DSM-

III-R has the advantage over the ICD-9 in that it does not force the clinician to give preference to any one set of symptoms (e.g., "hyperkinetic syndrome" or "disturbance of conduct"), but makes multiple diagnoses possible (e.g., ADHD and Conduct Disorder). In our study we wanted to include "all" hyperkinetic children, including conduct disordered and children with autistic-like symptoms. In The Netherlands, this approach was best linked on to clinical practices concerning medication for hyperactivity. It made study results suitable to be generalized; and
(2) At the department the DSM-III-R, and not the ICD-9, is in use. In the study four child psychiatrists had to make classification ratings. It was most appropriate to use the classification system that these child psychiatrists were accustomed to.

2.3 Prevalence of hyperkinesis

Estimates of the prevalence of "hyperactivity"/"hyperkinesis" in the general population vary widely from less than 0.09% (Isle of Wight Study; Rutter et al., 1970) to 14.3% (Trites et al., 1979). In their review of epidemiological studies, Szatmari et al. (1989a) mention five factors that appear to be responsible for this variation:
(1) the symptoms used to define the disorder: there have been studies that, in addition to symptoms such as restlessness and inattention, included symptoms such as low frustration tolerance, irritability, and poor peer relationships;
(2) the method that was used to collect information: questionnaires, clinical interviews, or direct observation;
(3) the source of information: parents, teachers, clinicians, children;
(4) the criteria or threshold score used to make a diagnosis: studies that use a scale may simply require a score in excess of 1.5 SD above the mean to make a diagnosis, while other studies consider a child hyperkinetic only in the absence of comorbid conduct disorder or neurotic disorder;
(5) differences in the sample characteristics: rural/urban, socioeconomic class, clinic-based (referral bias).

In order to obtain precise estimates of the prevalence of ADDH, the Ontario Child Health Study (Szatmari et al., 1989a) used a checklist, covering DSM-III criteria for conduct disorder, emotional disorder, ADDH, and somatization. This checklist was made available for parents, teachers and youths aged 12-16. Threshold scores for a disorder were established on the basis of their ability to discriminate in the best possible way the presence or absence of a DSM-III diagnosis made by a child psychiatrist. These threshold scores had been determined on the basis of an earlier measurement-development study. It was found that the overall prevalence of ADDH for males and females aged 4-16 was 6.3%. The rate for males was 9.0%, and for females 3.3%. Of the ADDH males aged 4-11 only 15.5% was pervasive ADDH (i.e., parent and teacher agreed upon ADDH). Among the girls there were no cases of pervasive ADDH. Teachers identified many more boys and girls as ADDH than parents.

2.4 Pervasive and situational hyperactivity

In the U.K., clinicians have a tendency to reserve the diagnosis of hyperkinetic syndrome for the very few children who show severe overactivity and inattentiveness in nearly all situations (pervasive hyperactivity). In North America, clinicians include in the category hyperkinetic syndrome children with conduct problems, many of whom are indeed markedly overactive or inattentive in some but not all situations (situational hyperactivity). Previous research, both clinical and epidemiological, has shown that pervasively hyperactive children, compared with situationally hyperactive children, differ in the following areas (Costello et al., 1991): (1) they show more symptoms of hyperactivity, impulsivity, and inattention; (2) they have more symptoms of other disruptive behaviors; (3) they have more "internalizing" symptoms (i.e., anxiety or depression); (4) they are more likely to come from disadvantaged families; (5) they function at a lower level in the home and at school; (6) they show a higher persistence of overall disorder; and (7) they respond relatively well to stimulant medication.

Goodman and Stevenson (1989a) surveyed a general population sample of 570 13-year-old twins, using parent and teacher questionnaires (Rutter scales), to identify pervasively and situationally hyperactive or antisocial groups of children. They found that higher hyperactivity scores from parent and teacher ratings were associated with male sex, lower intelligence, inattention, specific learning problems, and behavioral deviance (mainly antisocial). This pattern of correlates also characterized all three hyperactivity categories: to a marked degree in pervasive hyperactivity; less marked in school hyperactivity; and the least marked in home hyperactivity. Children with pervasive hyperactivity had more attentional and educational problems than non-hyperactive children who were pervasively antisocial. By contrast, children with school or home hyperactivity resembled non-hyperactive children who were situationally antisocial. Goodman and Stevenson's (1989a) findings cast doubt on the validity of combining situational and pervasive hyperactivity into a single diagnostic category such as DSM-III-R Attention-deficit Hyperactivity Disorder.

2.5 Sex differences

Estimates of sex ratios for hyperactivity have ranged from 3:1 to 10:1 with higher rates for boys (McGee et al., 1987). There is a similar sex difference for aggression and learning disorders. The higher rates of accidents and lethal accidents in boys suggests a male tendency to impulsiveness. Rutter (1989) suggested that possibly in hyperkinesis the same genetic factors that might operate within a multifactorial framework are also responsible for the sex difference.

McGee et al. (1987) suggested that perhaps the sex difference is artificial: In most studies the same cut-off on a rating scale that is recommended to identify hyperactive

boys is used to identify hyperactive girls. In their general population survey (N=925, aged 9 and 11), McGee et al. (1987) identified 10% of the boys and 2% of the girls as inattentive, when they used the same cut-off. When they compared boys with a top 10% score on the inattentive scale with girls with a top 10% score, both inattentive boys and girls showed the same pattern of deficits on measures of IQ, verbal comprehension, reading, spelling, speech articulation, and tapping speed. Assuming that the higher inattentiveness scores attributed to boys might be a function of their associated hyperactivity and antisocial behavior ("halo effect"), inattentive ratings of boys and girls were examined, controlling for hyperactivity and antisocial behaviors. It was found that the sex difference in inattentive score disappeared then. It was concluded that problems relating to inattention are equally prevalent in both sexes and the associated cognitive features are the same for boys and girls.

Some studies have suggested that hyperactive boys are more aggressive and impulsive than hyperactive girls, but girls have more problems of language development, enuresis, family psychopathology and a higher frequency of mental retardation. Other studies, however, have suggested limited gender differences in hyperactive children (Taylor, 1986; Breen, 1989).

2.6 Related psychiatric conditions

Most epidemiological studies found a considerable degree of overlap between hyperkinesis and other disorders. In the Ontario Child Health Study (Szatmari et al., 1989a), 40% of the ADDH children aged 4-16 also had a conduct disorder, whereas the proportion of ADDH children who also had an emotional disorder varied with gender and age (males 4-11 21%, females 4-11 17%, males 12-16 24%, females 12-16 50%).

In an epidemiological study in London, Taylor (1989b) used threshold scores on parent and teacher scales to classify subjects as "hyperactive" or "conduct disordered". A child was considered "pervasively hyperactive" if he was classified "hyperactive" on both parent and teacher scales. In a general population sample of boys aged 6-7, 9% were found to be "pervasively hyperactive". Of these boys 58% were also "conduct disordered".

In the DSM-III-R field trial of disruptive behavior disorders (Spitzer et al., 1990) 550 children were evaluated by 72 clinicians from 10 child psychiatry clinics in the USA. The DSM-III-R subclass disruptive behavior disorders includes ADHD, Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). As expected, a high degree of comorbidity was found within the group of disruptive behavior disorders. Of the 311 children diagnosed ADHD, 35% had a diagnosis of ADHD only, 53% also had a diagnosis of either ODD or CD, and 12% had a nondisruptive mental disorder (e.g., specific developmental, major depression, overanxious disorder). Similarly, 55% of the cases of CD also had a diagnosis of ADHD, and 67% of the cases of ODD also had a diagnosis of ADHD. Although the degree of comorbidity may represent referral biases

to the particular clinics that were involved, the results suggest that each of these disruptive disorders (particularly ODD) are usually seen in association with another disruptive behavior disorder.

Barkley et al. (1989) selected children diagnosed ADHD according to DSM-III-R criteria based on either parent or teacher reports. These subjects were then subdivided into aggressive and nonaggressive ADHD children (taking as a cut-off the 90th percentile of the Aggressive scale on the Child Behavior Checklist). Aggressive ADHD children differed little from nonaggressive ADHD children except that nonaggressives displayed more problems with inattentiveness at school than aggressives, while mothers of aggressives reported more symptoms of psychopathology in themselves than mothers of nonaggressives. In their stimulant drug responses, aggressives and nonaggressives were quite similar. The few exceptions were from the measures of conduct. The aggressives were initially rated as more extreme and subsequently showed the greater degree of improvement from medication than nonaggressives.

Szatmari et al. (Ontario Child Health Study, 1989a) compared children with ADDH with children diagnosed Conduct Disorder (CD) and children diagnosed both ADDH and CD. Pure groups of ADDH and CD differed in a variety of ways. In general, ADDH children were younger and had experienced more developmental delays and less psychosocial disadvantage than the CD children. Children with both ADDH and CD appeared to represent a true hybrid disorder rather than the one or the other diagnosis.

Hyperactivity and Learning Disabilities

A significant number of hyperactive children are academic underachievers and meet criteria for learning disabilities (Anderson et al., 1987; McGee et al., 1988).

Lambert and Sandoval (1980) found that nearly half of their hyperactive subjects could be identified as "learning disabled", defined in terms of a discrepancy between actual achievement and expected ability based on IQ.

Anderson et al. (1987) investigated the prevalence of DSM-III disorders in a general population sample of children aged 11, using child interviews, parent and teacher questionnaires. Six percent of the children were identified as having "pervasive" ADD. Of the pervasive ADD children 80% had learning difficulties in reading, spelling, mathematics, or written language skills.

August and Garfinkel (1989) surveyed a nonreferred elementary school population using the Conners Teacher Rating Scale (CTRS), teacher based DSM-III-R ratings on ADHD and Conduct Disturbances (CD), and tested for specific reading/spelling disability (RD). Nine percent of the pupils had a score on the Hyperactivity Index of the CTRS above a cut-off defined as 2 SD's above the population mean. The ADHD group consisted of 20% children who were both ADHD and RD, 46% who had both ADHD and CD, 2% who had ADHD + CD + RD, and 32% who had ADHD without CD or RD. It was concluded that there seems to be a cognitive subtype of ADHD, characterized by

information processing deficits that involve inadequate encoding and retrieval of linguistic information, characteristic of reading disabilities.

2.7 Long-term outcome

The long-term outcome of hyperkinesis has been studied in retrospective and prospective studies. Because retrospective studies have many methodological shortcomings, ideally, follow-up studies should be prospective. Even if an "hyperactive syndrome" was diagnosed in childhood, it is difficult in retrospective studies to select a homogeneous clinical sample since the standards for diagnosis are likely to have been inconsistent. Moreover, retrospective studies that rely on the recollections of informants at "follow-up" are susceptible to selective forgetting, selective recall, and memory distortions. Klein and Mannuzza (1989) consider a study prospective if: (1) The diagnosis of a hyperactivity syndrome was made in childhood, and (2) The diagnosis was based on relatively uniform clinical standards for assessment or on specified clinical criteria. Prospective studies should include appropriate controls, have adequate sample size and follow-up duration, obtain data from multiple sources, show low attrition, and rely on assessments that are conducted blind to group membership.

An example of an excellent prospective investigation is Klein and Mannuzza's 17-year follow-up study of 101 white males, whose conditions had been diagnosed as DSM-II Hyperkinetic Reaction in childhood (mean age 9 years). They were reassessed as adolescents (mean age 18 years), and recently were examined as young adults (mean age 26). Table 2.7 shows the follow-up data in the hyperactive group, and in a sample of 100 nonhyperactive male controls (Klein et al., 1985, Klein & Mannuzza, 1991).

Table 2.7 Rates of ADDH (a), antisocial disorders (b), and drug use disorders (c) in Klein and Mannuzza's (1991) New York follow-up study of 101 boys, who had been diagnosed hyperactive in childhood, and 100 nonhyperactive controls.

	Adolescence			Adulthood		
	a	**b**	**c**	**a**	**b**	**c**
Hyperactive children:	31%	27%	16%	8%	18%	16%
Controls:	3%	8%	3%	1%	2%	4%

When the boys were examined as adolescents it was found that the full ADDH syndrome persisted in 31% of the probands vs. in 3% of the controls. Both antisocial disorders and substance use disorders (other than alcohol) aggregated significantly among the probands with continued ADDH. No excess of any other disorder (e.g., affective or anxiety disorders) was found among the former hyperactive children. The children who had retained the ADDH syndrome were much more likely to have developed antisocial disorders than those whose ADDH had remitted (48% vs. 13%); moreover, substance use disorders had developed consistently after the onset of an antisocial personality disorder (Klein et al., 1985). Recently the boys were examined as young adults (Klein & Mannuzza, 1991). Compared to the controls, the cases showed a weak trend for an excess of ADDH (8% vs. 1%), but a significantly higher rate of antisocial personality disorder (18% vs. 2%) and substance use disorder (16% vs 4%). Once again, the risk for other psychopathology, such as affective or anxiety disorders, was not increased (at least in males). It was concluded that there is a high comorbidity for continued ADDH, antisocial personality disorder, and substance use disorder both in adolescence and in adulthood.

Klein et al.'s follow-up findings in late adolescence have been replicated in another group of 94 children (Mannuzza et al., 1991). Barkley et al. (1990b) and McGee et al. (1991) reported similar findings. Weiss and Hechtman (1986) followed a group of hyperactive children into adulthood (ages 21 to 33) and found that many more probands (66%) than controls (7%) reported that symptoms of either inattention, impulsivity, or hyperactivity were mildly to severely disabling.

Follow-up data of hyperactive girls are scarce. Preliminary results suggest that girls are as vulnerable as boys to the maintenance of ADDH and to the development of conduct disorders (Klein & Mannuzza, 1991).

The cognitive performance of hyperactive children has systematically been assessed in the prospective study by the Montreal group (Weiss & Hechtman, 1986). The adolescent status of hyperkinetic children is characterized by impaired cognitive test performance and poor scholastic achievement. In adulthood the results show a normalization of cognitive performance. However, work functioning seems negatively affected. In their review of prospective studies of hyperkinetic children Klein and Mannuzza (1989) conclude that the major predictor of poor outcome appears to be childhood aggression. Other predictors of outcome include social factors (disrupted families), and neurological findings (perinatal complications, abnormal childhood EEG).

We found only one longitudinal prospective study investigating differences in outcome between ADDH patients who had symptoms of hyperactivity in multiple settings (school and home: pervasive hyperactivity) and ADDH patients who had symptoms in only one setting (situational hyperactivity). In their longitudinal study into adulthood Klein and Mannuzza (1991) found that the rate of psychiatric diagnosis in early adulthood differs little between children reported hyperactive in school only and pervasively hyperactive children. In contrast, the children who were reported to be

hyperactive at home only had a much lower rate of ADDH and conduct disorder at the follow-up than the children with pervasive hyperactivity or than those reported hyperactive in school only.

2.8 Genetic factors

Because families share genes and environment, a family study can support a genetic hypothesis but cannot confirm it. In Biederman et al.'s (1990) family study, family-genetic risk factors for hyperkinesis were evaluated among the first-degree relatives of hyperkinetic children. It was found that relatives of hyperkinetic probands had a higher morbidity risk for hyperkinesis, antisocial disorders, and mood disorders, compared with psychiatric and normal controls. These results were in accordance with earlier findings.

In twin studies, a comparison of monozygotic and dizygotic co-twin concordance for hyperkinesis allows a test of a genetic hypothesis: To the extent that hyperkinesis is inherited, the concordance rate would be higher in the monozygotic than in the dizygotic co-twins. In their twin study, Goodman and Stevenson (1989a,b) found that monozygotic pairs were more alike than same-sex dizygotic pairs on objective measures of attentiveness and on parent and teacher ratings of hyperactivity. Comparisons of monozygotic and dizygotic twins suggested that genetic effects accounted for roughly half of the explainable variance in trait measures of hyperactivity and inattentiveness. Family resemblances on these measures appeared to owe more to shared genes than shared environment. Although this study is persuasive in suggesting an important genetic component, a disadvantage is that most hyperkinetic subjects were also diagnosed conduct disorder.

Twin studies still confound genes and environment. Adoption studies provide the most convincing demonstration of genetic components to psychiatric disorders. Among the biological parents and siblings of non-adopted hyperkinetic children a higher rate of hyperkinesis has been found than among the adoptive parents and siblings of adoptive hyperkinetic children (Deutsch & Kinsbourne, 1990a). Within this design, common postnatal environment is assumed to be held constant, but genetic relatedness is varied as an independent variable. Therefore, Deutsch and Kinsbourne's (1990) finding seems to support a genetic hypothesis. Rutter et al. (1990), however, suggested that the low rate of hyperkinesis in the adopting families that is found in several studies, could reflect no more than the result of selection policies for parents who wish to adopt (as they tend to be screened for absence of serious psychiatric disorder).

The family, twin, and adoption studies provide convergent support for a genetic hypothesis for hyperkinetic symptomatology. To be able to answer questions like "what might be transmitted, and by what mode of inheritance?", one possibility is to seek biological correlates that reveal homogeneous subgroups (Deutsch & Kinsbourne, 1990a).

Comings and Comings (1984) have suggested that Tourette's syndrome (GTS) and hyperkinesis are possibly due to the same underlying genetic factor(s). However, in their GTS family study, Pauls et al. (1986) found a higher frequency of (DSM-III) ADDH among the relatives with both disorders (GTS+ADDH) than among the relatives with pure GTS (GTS-ADDH). This suggests that GTS and ADDH are genetically unrelated or that GTS+ADDH and TS-ADDH are etiologically distinct syndromes. In addition, an independent segregation of ADDH and GTS was found in the relatives of probands with GTS+ADDH. This argues against genetic commonality. There was no difference between the frequencies of ADDH among the relatives of GTS probands compared with the population prevalence of ADDH. A genetic association would predict an increased frequency among the relatives of GTS probands.

2.9 Prenatal and perinatal adversity

Based on retrospective data Pasamanick and Knobloch (1966) postulated a direct relationship between moderate perinatal adversity and later hyperactivity. Afterwards Sameroff and Chandler (1975) found, that the environment in which the child grows up can minimalize or maximalize the effect of perinatal complications. Prospective studies showed that prenatal and perinatal adversity are only weak predictors of later psychological problems (Taylor, 1986). In her prospective study of children who had been hospitalized in a neonatal intensive care unit Schothorst (1990) found that both family factors and neonatal/postnatal factors had a predictive value with regards to later neuropsychological, cognitive and psychiatric functioning. In their study of a representative sample of 570 13-year-old twins Goodman and Stevenson (1989b) found no relation between perinatal adversity and later hyperactivity.

Several studies found a significant relationship between intra-uterine exposure to alcohol and both dysmorphic signs (fetal alcohol syndrome) and hyperactivity/ distractibility at school age (Spohr & Steinhausen, 1987).

2.10 Overt brain disease

The role of overt brain disease in the development of psychiatric disturbances is best seen in terms of an increased vulnerability to the whole range of psychiatric disorders (Rutter, 1977). Children with acquired brain damage are more likely to be hyperactive than other children; but they are also more likely to show underactivity and overpersistence in their attention than controls (Rutter et al., 1970). Evidence suggests that hyperkinesis is related to intellectual retardation rather than per se brain injury (Taylor, 1986). Children with pervasive hyperactivity of early onset tend to have more neurodevelopmental immaturities and have a high prevalence of delays in language or motor development, as well as a lower mean IQ.

The influence of blood-lead levels on children's behavior has recently been investi-

gated by Thomson et al. (1989). Lead in water, and lead in dust are important sources of exposure. The children were recruited for the study from an area of Edinburgh, selected to include the older houses in the city, some of which had retained their original lead plumbing. A significant relation was found between measures of deviant behavior (aggressive/antisocial score and hyperactive score) and blood-lead when confounding variables were taken into account (more deviant behavior was found when: male sex; the mother's performance on a mathematical test was poor; there was a positive history of family disruption; and when more cigarettes were smoked in the household). It was concluded that lead at low levels of exposure probably has a small but harmful effect on children's behavior. Therefore, all reasonable attempts to eliminate sources of environmental lead should be encouraged.

2.11 Minor neurological dysfunction

The routine neurological examination is frequently normal in hyperkinetic children (Barkley, 1990). Neurological "soft" signs are defined as an abnormal motor or sensory performance without localizable neurological disorder (Shaffer et al., 1984). Examples of "soft" signs are choreiform movements, delayed laterality development, fine or gross motor incoordination, and dysdiadochokinesis. Several studies found that children with "soft" signs more frequently display behavioral and learning problems than children without "soft" signs (Pincus, 1991). Touwen (1979) introduced the term "minor neurological dysfunction" (MND) to classify "soft" signs on the basis of a standardized neurological examination. Hadders-Algra et al. (1986; Groningen Perinatal Project) examined a group of children aged six, who neonatally had been neurologically abnormal, and compared these children with a control group of neonatally normal children. It was found that children with an abnormal neonatal neurological condition are, as a group, more at risk of deviant neurological development. Children with MND were found to be more vulnerable with regard to behavioral development and school achievement than neurologically normal children. It was concluded that at any age the mildly impaired brain is apparently more vulnerable to adverse environmental influences than the intact brain.

Hyperkinetic children display a greater prevalence of neurological "soft" signs. However, "soft" signs are nonspecific for hyperkinesis and can often be found in learning-disabled, conduct disordered, autistic, and emotional disordered children, and even a small minority of normal children (Vitiello et al., 1989). Claims have been made that hyperkinetic children respond better to stimulant treatment if they have "soft" signs. However, other studies have not confirmed this relationship (Halperin et al., 1986). Barkley (1990) states that the importance of finding "soft" signs in hyperkinetic children is that the child possibly requires more thorough testing by occupational or physical therapists and may be in need of some assistance in school with fine motor tasks or adaptive physical education.

2.12 Adverse family factors

Several studies found that low socioeconomic status, family dysfunction, marital discord, and psychosocial adversity such as overcrowding and poverty were equally associated with conduct disturbance and both situational and pervasive hyperactivity. The most conservative interpretation of these results is that no specific relationship of hyperkinesis and psychosocial dysfunction has been discovered (Schachar, 1991). Barkley et al. (1991) performed an 8-year follow-up study of hyperkinetic and normal control children. Direct observations of mother-child interactions were taken in childhood and again at adolescent follow-up. Observations of mother-adolescent interactions at outcome found the hyperkinetic dyads displaying more negative and controlling behaviors and less positive and facilitating behaviors towards each other than in the normal dyads. These interaction patterns were significantly related to similar patterns in mother-child interactions observed 8 years earlier. Mothers of hyperkinetic children also reported more personal psychological distress than mothers of normal children at outcome. Further analysis of subgroups of hyperkinetic children at outcome, formed on the presence or absence of (DSM-III-R) ADHD and Oppositional-defiant Disorder (ODD), indicated that the presence of ODD accounted for most of the differences between hyperkinetic and normal children on the interaction measures, ratings of home conflicts, and ratings of maternal psychological distress.

Schachar and Wachsmuth (1990) explored the association of child hyperkinesis and parental psychopathology by establishing lifetime DSM-III diagnoses and histories of childhood hyperactivity among the parents of boys, aged 7-11, in five diagnostic groups: ADDH, conduct disorder (CD), ADDH+CD, emotional disorder (ED), and no disorder (NC). It was found that ADDH+CD, CD, and ED groups all had significantly higher rates of parental psychopathology than the ADDH and NC groups, for which rates were similar. Significantly more boys in the ADDH, CD, and ADDH+CD groups had family histories of parental childhood hyperactivity than did boys in the ED and NC groups.

2.13 Conclusion

This chapter confined itself to a review of the literature on the symptomatology of hyperkinesis, related child psychiatric conditions, the course of hyperkinesis, and possible causes of the disorder. Recent research on hyperkinesis has primarily been engaged in the development of more satisfactory diagnostic criteria. The discrimination between hyperkinesis and other child psychiatric disorders is still problematic. More sensitive and discriminating measures are needed. Rutter (1989) has noted that questionnaires and highly structured interviews requiring "yes" and "no" answers to closed questions are of limited value, and that naive raters are not very good at making the kind

of discriminations that are crucial in the understanding of hyperkinesis. He suggested that, instead, there needs to be greater reliance on investigator-based standardized interviews that require descriptions of actual behavior, on standardized observational methods, on mechanical means of recording, and on psychological testing. Longitudinal research is needed to identify the risk factors for poor peer relationships, antisocial behavior, and personality difficulties in adolescence and early adult life, and how factors in the child combine or interact with psychosocial adversities and family influences.

The main aim of the study was to investigate the effects of clonidine on hyperactivity in subgroups of hyperkinetic children. In addition, the effects of clonidine on ethological, neuropsychological (i.e., reaction-time experiments), and neurochemical parameters have been investigated. This thesis confines itself to a report on the behavioral and neurochemical drug effects. The ethological and reaction-time experiments are not reported in this thesis and the concerning literature has therefore not been reviewed in this thesis.

To attain the aims of the study, the diagnostic classification (DSM-III-R) was taken as the independent variable, and both the behavioral and neurochemical measures as the dependent variables. The literature on the diagnostic classification of hyperkinesis has been reviewed in Chapter 2. A review of the behavioral effects of clonidine and methylphenidate has been given in Chapter 1. The literature on the neurochemical effects will be reviewed in Chapter 6. Chapter 3 will describe the methods of the child psychiatric assessment and diagnostic classification and will outline the behavioral measures used in the study.

Chapter 3

CHAPTER 3 METHODS OF THE DIAGNOSTIC ASSESSMENT AND MEDICATION TRIAL

3.1 INTRODUCTION

A categorical diagnostic approach (DSM-III-R, ICD-9) may be simultaneously too broad and too narrow to identify underlying neurobiological processes. The cardinal behaviors of hyperkinesis may be due to distinct underlying mechanisms predominantly altered in subtypes of hyperkinesis. Hunt et al. (1991b) suggested that a detailed assessment (on a dimensional level) of patients who have common characteristics that cross individual (DSM, ICD) diagnoses may be the wave that reflects the underlying homogeneous current of neurobiological dysfunction. Hunt et al.'s (1991b) approach corresponds to Van Praag's (1991) thesis that "two-tier diagnosing" is the most productive way to systematize abnormal behavior in order to study its biological roots: Tier one comprises the nosological diagnosis (DSM, ICD), and tier two a detailed depiction of the component psychological dysfunctions (a functional organization of psychopathology).

This chapter describes the methods of the study. The aim of the study was to investigate the effects of clonidine on hyperactivity in hyperkinetic children. Hyperkinetic symptoms were assessed both in categorical and in dimensional terms. The former approach (DSM-III-R) was used as the independent variable (section 3.2). The latter approach was used as the dependent variable and included medical examinations, behavior rating scales, psychological tests, and direct behavioral observations (section 3.3). Finally, this chapter will describe the methods of the medication trial (section 3.4). The methods of the neurochemical part of the study will be outlined in Chapter 6.

3.2 THE INDEPENDENT VARIABLES (DSM-III-R CLASSIFICATION)

3.2.1 Introduction

Obtaining information from multiple sources (e.g., parents, teachers, children, clinicians and peers) can contribute to a comprehensive picture of a child. However, different informants having different relations to the child and seeing the child under different conditions often disagree about the presence and severity of problem behaviors (Achenbach et al., 1987a; Verhulst & Akkerhuis, 1989). Landau et al. (1991) made an attempt to determine if the child is a reliable informant regarding those symptoms that serve as diagnostic criteria for DSM-III Attention Deficit Disorder (ADD) classification. They

obtained information from standardized interviews of 76 clinic-referred boys using the child and the parent versions of the Diagnostic Interview for Children and Adolescents (DICA; Herjanic & Reich, 1982). It was found that the children were unwilling or unable to admit to as many ADD symptoms as their mothers reported about. ADD children appear to deny their symptomatology. This finding suggests that data obtained from parent interviews may be more useful in ruling out the presence of ADD than data from child interviews.

Clinical psychiatric assessment procedure

For our study we decided to base child psychiatric diagnoses on both child and parent interviews. After children were referred for potential inclusion in the trial, they were seen in order to inquire about all problem behaviors for which help was sought. This was followed by a comprehensive child psychiatric assessment, including a clinical child psychiatric examination and taking a case history from both parents and teacher. A provisional descriptive diagnosis was made, and it was checked if the child fulfilled the inclusion criteria for the trial. Then the parents were given a comprehensive treatment advice, informed consent was obtained, and appointments were made for further investigations:

(1) Standardized interviews of the child and of the parents.
(2) A medical examination (see section 3.3.3).
(3) Psychological testing (see section 3.3.5).

Subsequently a summarizing report was made, based on both all the nonstandardized and all the standardized information (see appendix 3.2.2). Then, the project-leader and two child psychiatrists made a DSM-III-R classification, independent of one another (see section 3.2.3).

3.2.2 Instruments

Standardized interview of the child

We used the Dutch translation of the Child Assessment Schedule (CAS; Hodges et al., 1982; Verhulst, 1985; Verhulst et al., 1987). The CAS is a semistructured diagnostic interview for children aged 7-12. It consists of two parts. In the first part, the child is asked about several content areas, including school, friends, activities and hobbies, family, fears, worries, self-image, mood (especially sadness), somatic concerns, expression of anger, and thought disorder symptomatology. The responses are coded yes/no/ambiguous/no response/not applicable. The questions and response items on the CAS were developed so as to solicit information about the diagnostic criteria for major childhood diagnoses given in DSM-III (APA, 1980). In addition, inquiry is made about many areas that do not bear directly to the diagnosis but are relevant to clinical treatment planning (e.g., feelings toward parental figures). The second part provides a format for the interviewer to record observations and judgments after the completion of the interview.

Items in this section inquire about the following areas: insight, grooming, motor coordination, activity level (including attention span and impulsivity), other spontaneous physical behaviors, estimate of cognitive ability, quality of verbal communications (speech and logic of thought), quality of emotional expression, and impressions about quality of interpersonal interactions. It takes from 45 min to one hour to interview a patient.

Several studies support the reliability and validity of the CAS (Hodges & Saunders, 1989). In Verhulst et al.'s (1987) study, the CAS classified 76% of a sample of 116 children correctly as either disturbed or non-disturbed. Of the disturbed children 35% were falsely labelled normal, whereas 18% of the non-disturbed children were incorrectly classified as disturbed. Edelbrock and Costello (1988b), in their review of structured interviews for children state that a considerable degree of clinical judgment and inference is required in administering and scoring CAS items. Symptom coverage is somewhat narrower than other interviews. They conclude that the CAS can be tentatively recommended as a descriptive tool and diagnostic aid.

We followed Verhulst et al. (1987), who introduced two breaks during the interview, because when interviewing clinically referred children they found that these children had difficulties in sustaining attention. We certainly expected similar problems in hyperkinetic children. In the first break the child was asked to make two drawings ("a human being", and "free"). In the second, the child was asked to arrange a standardized playset of dolls, blocks and other objects (Sceno-test; Altmann-Herz, 1990). Both the drawings, and the Sceno-test, were used for child psychiatric judgment, and to observe the child's behavior during the tests, but not as psychological tests. Important information not scorable in the CAS was written down in the margin. The child psychiatrists, who later made a DSM-III-R classification, had access to all the information from the CAS, including the scores on content areas, the records of observations and clinical judgment, and all the notes.

Standardized interview of the parents

For the assessment of the parents of the subjects we used the semistructured interview developed by Graham and Rutter (1968) modified by Richman et al. (1982). This interview comprises questions on: family background, the child's physical health, the child's functioning at home, at school and in his peergroup, parent-child relationship, child-sibling relationship, marital relationship, stress on the family, and problem behaviors (appetite, encopresis, enuresis, antisocial behavior, concentration, activity level, tics and habits, motor coordination, speech, sleeping problems, level of independence, mood, worries, compulsions and obsessions, fears). The parent is asked for recent concrete descriptions of behavior during the past 6 months, rather than for attitude or opinions. The interviewer makes notes of all answers. When sufficient information has been obtained, the interviewer scores each item according to operationally defined criteria.

We used the Dutch version, which was employed by Verhulst et al. (1987) in their

assessment of 8- and 11-year-old children selected from a general population sample. This version includes the "Malaise Inventory" (Rutter et al., 1970), which comprises questions concerning physical and psychological symptoms of mother and father (physical health, hypochondria, worries, fears, panic, depressive symptoms, alcohol consumption, medication, medical help, absenteeism through illness). Rutter et al. (1970) reported that the "Malaise Inventory" differentiated moderately well between parents with and without psychiatric disorder.

Verhulst et al. (1987) used both the CAS and the Graham and Rutter Parent Interview in their assessment of 8- and 11-year-old children from a general population sample and found a moderately high agreement between both interviews (i.e., r=0.58 between total scores on both interviews).

The child psychiatrists, who later made a DSM-III-R classification, were provided with all the information from the parent interview, including the scores and notes.

3.2.3 DSM-III-R classification

The DSM-III-R states: "The essential features of ADHD are developmentally inappropriate degrees of inattention, impulsiveness, and hyperactivity. People with ADHD generally display some disturbance in each of these areas, but to varying degrees. Manifestations of the disorder usually appear in most situations, including at home, in school, at work, and in social situations, but to varying degrees. Some people, however, show signs of the disorder in only one setting, such as at home or at school". The criteria for ADHD are listed in descending order of discriminating power, based on data from the USA field trial of DSM-III-R criteria for Disruptive Behavior Disorders (Spitzer et al., 1990).

In our study the DSM-III-R diagnosis ADHD was made on the basis of the information concerning ADHD symptoms obtained from parents, teacher, and playroom observation. The DSM-III-R items for ADHD were scored by the project-leader on a ADHD Rating Scale (DuPaul; Barkley, 1990; see appendix 3.2.3). When we started the study we had a first draft of this scale at our disposal, with definitions for the 4-point scale: 1 not at all = not present; 2 just a little = few, if any symptoms, only minimal or no impairment in school and social functioning; 3 pretty much = symptoms or interference with functioning between "mild" and "severe"; 4 very much = many symptoms, significant, pervasive or widespread impairment in functioning at home and school and with peers. The scale provides a direct rating of the essential symptoms of ADHD from both parents and teachers. Recently normative data were published and cutoff points chosen (Barkley, 1990; sensitivity/specificity figures have not yet been published). The scale has been shown to discriminate ADHD children from learning-disabled and normal children (Barkley, 1990). The cutoff points are as follows (Barkley, 1990): (1) Scores of 3 or higher are considered to be "inappropriate for a child's developmental level"; (2) A count of the number of items with such scores determines whether the child meets

the DSM-III-R criteria for ADHD: at least 10-out-of-14 are required for boys, and 8-out-of-14 for girls. For our study we did not have these recently published norms at our proposal. Our draft of the DuPaul scale still stated that scores of 2 ("just a little") had to be included in the count of items required for the ADHD DSM-III-R criteria and stated in accordance with DSM-III-R that ≥ 8-out-of-14 items were required for a diagnosis ADHD. Information with respect to the child's behavior on the 14 ADHD items, and the count of items on the ADHD Rating Scale, was supplied for the DSM-III-R rating.

Based on both the standardized child and parent interviews and the summarizing report, a DSM-III-R classification was made by the project-leader, and subsequently (and independently) by two other child psychiatrists (GB, FV and/or PW). In addition, the raters had access to videotapes of the children's behavior during psychological testing and standardized playroom observation (see section 3.3.6). The instruction for the DSM-III-R rating was as follows. Raters were referred to the DSM-III-R instructions. Raters were first asked to make a descriptive diagnosis (to be used for consensus diagnostic case conferences), and then a DSM-III-R classification. It was agreed upon that the categories "Mental Retardation"/"Borderline Intellectual Functioning", and "Specific Developmental Disorders", did not need to be considered. With respect to these categories the subjects were characterized according to the results of the psychological and medical examination.

Because the DSM-III-R criteria for Pervasive Developmental Disorder NOS can be polyinterpretable, boundaries were agreed upon before the diagnostic assessment started, using the following articles: Cohen et al. (1987), Provence and Dahl (1987), Wing and Attwood (1987), Bemporad et al. (1987), and Tantam (1988). The DSM-III-R criteria for PDD NOS run as follows: "This category should be used when there is a qualitative impairment in the development of reciprocal social interaction and of verbal and nonverbal communication skills, but the criteria are not met for Autistic Disorder, Schizophrenia, or Schizotypal or Schizoid Personality Disorder. Some people with this diagnosis will exhibit a markedly restricted repertoire of activities and interests, but others will not". It was agreed upon to interpret the clause "a qualitative impairment in the development of reciprocal social interaction and of verbal and nonverbal communication skills" as follows: this criterion was met if a child fulfilled at least one item of Autistic Disorder heading A ("Qualitative impairment in reciprocal social interaction"), as well as at least one item of Autistic Disorder heading B ("Qualitative impairment in verbal and nonverbal communication, and in imaginative activity"). The publications mentioned were given to the raters as background-information containing recent scientific opinions with respect to the continuum of conditions surrounding this issue (including case reports). Bemporad et al. (1987) give a definition of "Borderline Child Syndrome" and make a clear distinction between Pervasive Developmental Disorder and Borderline Child Syndrome (the latter diagnosis is not a DSM-III-R category, if one has a patient with "Borderline Child Syndrome" one has to check if the criteria for some DSM-III-R category are met): "These children differ from those with Pervasive Developmental Disorders by their ability to relate to others, their fuller range of affects,

and their greater ability to withstand changes in the environment. Borderline children also do not demonstrate oddities of movement, abnormalities of speech, or peculiarities of sensation typical of children with PDDs. The greatest distinction between these two conditions is the fluctuation of functioning found in borderline children so that they, at times of emotional security, may appear neurotic or even normal". With respect to DSM-III-R category PDD NOS the instruction to the raters was summarized: Classify according to DSM-III-R, while interpreting "qualitative impairment" as "the child must meet criteria for items from Autistic Disorder headings A and B".

According to the DSM-III-R convention a diagnosis of Conduct Disorder preempts a diagnosis of Oppositional Defiant Disorder. In the DSM-III-R field trial of disruptive behavior disorders (Spitzer et al., 1990) as many as 84% of children with Conduct Disorder also had the symptomatic features of Oppositional Defiant Disorder. This supported the decision in the DSM-III-R for a diagnosis of Conduct Disorder to preempt the diagnosis of Oppositional Defiant Disorder, and is consistent with previous findings that Conduct Disorder most often evolves along with or is a later developmental stage of Oppositional Defiant Disorder.

Those DSM-III-R classification(s) were chosen for each subject which were diagnosed by at least two of the three raters. In the case that not even two raters could agree on a classification, a diagnostic case conference was held to make a consensus decision. Interrater reliability was determined before a consensus decision was made. The degree of correspondence between raters was determined by computing kappa coefficients of agreement (kappa) and interrater correlation coefficients (Φ). Kappa is a measure of agreement with desirable properties (Fleiss, 1981): If there is complete agreement, then kappa = +1; if observed agreement is greater than or equal to chance agreement, then kappa $\geq$ 0, and if observed agreement is less than or equal to chance agreement, then kappa $\leq$ 0. Interrater correlation coefficient Φ is another widely used measure of interrater reliability. Φ is defined as: $\Phi = \sqrt{(X^2/N)}$. Kappa is identical to Φ if $k_1/k_2 = r_1/r_2$ (k_1 and k_2 are sums of columns, r_1 and r_2 are sums of rows).

3.3 THE DEPENDENT VARIABLES

3.3.1 Introduction

The above section described the independent variables by which the criterium groups ("trial groups") were formed. The dependent variables will now be described. They fall into five groups: symptom severity scores (section 3.3.2), the medical examination (section 3.3.3), behavior rating scales (section 3.3.4), psychological assessment (section 3.3.5), and direct behavioral observation (section 3.3.6).

3.3.2 Symptom severity scores

For each child a global clinical judgment was made by the project-leader by scoring the severity of symptoms on each of the following three dimensions (according to Taylor et al., 1987): "hyperactivity" (inattentive, restless, impulsive behavior), "conduct disorder" (antisocial, aggressive behavior) and "emotional disorder" (overt symptoms of anxiety, misery or obsessionality). For each of these dimensions a 4 point rating scale was used (0="absent", 1="mild", 2="moderate", or 3="severe"). Information from parental and teacher accounts and from clinic observation was integrated for these ratings. We did not succeed in organizing an independent rating of these dimensions by a second child psychiatrist. As a consequence we could not calculate interrater reliability.

3.3.3 The medical examination

The medical examination included:
(1) A physical examination;
(2) The assessment of minor physical anomalies; and
(3) A developmental neurological examination.

Physical examination

The physical examination included: measurement of head circumference, length and weight, including a comparison with standardized graphs; observation of the nutritional state, and skin anomalies (particularly café-au-lait spots); measurement of sitting blood pressure and heart rate; an examination of lungs and heart; screening of hearing and vision; and attention for symptoms suggestive of hyper- or hypothyroidism.

Assessment of minor physical anomalies

Minor physical anomalies (MPAs) are slight deviations in the outward appearance of the child. Examples of MPAs are wideset eyes, a curved fifth finger, and a single transverse palmar crease. Sometimes they indicate specific malformation syndromes or classes of altered morphogenesis (Deutsch et al., 1990). Some studies have found a relationship between number of MPAs and ADHD, other studies have not (Barkley, 1990). We decided to assess MPAs in order to select subjects with a high MPA score. For these children we regarded a consultation of a clinical geneticist indicated to rule out possible specific malformation syndromes.

The examination for MPAs was as described by Waldrop and Halverson (1971). This list has been used in the majority of studies of dysmorphology in psychiatric disorders (Firestone & Peters, 1983). Fifteen possible anomalies (e.g., large head, hypertelorisme, low set ears) are scored present or absent and then given a weighted score of 0-2 according to their severity (see Appendix 3.3.3a). In accordance with earlier studies

(Firestone & Peters, 1983; Reeves et al., 1987) a weight score of 5 or more was chosen as indicating a high anomaly score.

Developmental neurological examination

We used the neurological examination according to Touwen (Touwen, 1979). This examination focuses on minor neurological dysfunction (MND). The principal features of Touwen's examination technique are: (1) Standardization, meaning that a sign is considered to be a sign only when it is clearly observable and repeatedly elicitable; and (2) age-specific, taking into account properties of the developing brain. The results of the neurological examination are summarized for each child in a cluster profile (Hadders-Algra, 1987; see appendix 3.3.3b). The cluster profile helps to classify the neurological findings as "normal", MND-1 (one or two deviant clusters), MND-2 (more than two deviant clusters) or "abnormal". MND signifies the presence of minor neurological signs which do not lead to an overt handicap and can not be admitted into a traditional neurological diagnosis. Abnormal means that a neurological disorder has been diagnosed which has resulted in a handicapping condition (e.g., cerebral palsy).

3.3.4 Behavior rating scales

3.3.4.1 The use of rating scales in this study

The DSM-III-R states: "Manifestations of ADHD usually appear in most situations (home, school, social situations), but to varying degrees. Signs of the disorder may be minimal or absent when the person is receiving frequent reinforcement or very strict control, or is in a novel setting or a one-to-one situation (e.g., being examined in the clinician's office, or interacting with a videogame)". Both for diagnostic assessment and for drug effect evaluation we needed information on the child's behavior in his natural environment (home, school).

Barkley (1990) mentioned the many problems inherent in the use and interpretation of rating scales when evaluating ADHD children. For instance: (1) are the scale items worded so that it is clear to the respondent what is being rated; (2) does the scale actually assess the construct of interest (construct validity); (3) does the scale discriminate ADHD groups from normal and from non-ADHD clinical samples (discriminant validity); (4) taking into consideration that ADHD symptoms are both relatively stable and chronic over a period of time, does the rating scale have an acceptable test-retest reliability; (5) can two raters, assessing the person at the same time, agree on the presence and degree of the behavior or construct being rated (interrater reliability). Even when the mentioned conditions are met, one must realize that informant and clinician, because their perceptions are sometimes so different, will differ in their scoring of items on a rating scale. Clinicians should weigh and balance information obtained from different sources

and informants.

We applied rating scales in the following way:

(1) We wanted to compare our subjects with clinical norms.

(2) By obtaining ratings on hyperactivity from both parents and teachers we wanted to quantify the pervasiveness of the children's hyperactivity.

(3) We needed both the parents and the teacher as informants for drug efficacy measurements, because we were interested in the effects of clonidine and methylphenidate during both school time, and at home (in the afternoon and evening, during the weekend). Rating scales offer a means of repeatedly measuring specific dimensions of the children's behavior both at home and at school. The effect of methylphenidate ceases after approximately four hours, whereas clonidine has a longer duration of action (elimination half-time 8-12 hours). As a consequence the peak therapeutic effects of methylphenidate occur during school hours, whereas clonidine has a more equable effect during the course of the day. In addition, methylphenidate gives rebound effects in some children (in the afternoon, at home). As a consequence it often occurs that parents see no effect at all (or even deterioration), although the teacher experiences obvious beneficial effects during school time.

3.3.4.2 Diagnostic assessment using the CBCL and TRF

The Child Behavior Checklist (CBCL) is a standardized questionnaire designed to obtain parents' reports of behavioral / emotional problems and competencies of children aged 4-16 (Achenbach & Edelbrock, 1983). The teacher version of the CBCL, the Teacher's Report Form (TRF), is a questionnaire designed to obtain teachers' reports of children's behavioral / emotional problems and adaptive functioning (Achenbach & Edelbrock 1986). Research has shown the CBCL as well as the TRF to discriminate ADHD from normal and other psychiatric groups of children (Barkley, 1990).

Our study focused on the behavioral/emotional problem sections in CBCL and TRF. The behavioral/emotional problem items on both are scored as follows: 0 = not true of the child; 1 = somewhat or sometimes true; 2 = very true or often true. Achenbach and Edelbrock (1983, 1986) have constructed empirically derived syndromes for Child Behavior Checklist (CBCL, parents) and Teacher's Report Form (TRF, teacher) by factor analyzing ratings of large samples of children referred to mental health agencies. For each age- and sex-group, Achenbach and Edelbrock computed several narrow-band factors and two broad-band factors 'Externalizing' and 'Internalizing' (relevant for our study are the age groupings 6-11 and 12-16). Internalizing problems mainly involve internal conflicts and distress, whereas externalizing problems mainly involve conflicts with other people and their expectations of the child.

CBCL and TRF have been translated into Dutch. The reliability and validity of CBCL and TRF have been thoroughly documented in the USA and in Holland (Achenbach & Edelbrock, 1983, 1986; Verhulst & Akkerhuis, 1986; Verhulst et al., 1990). The

applicability of the instruments in the U.S.A. and Holland was tested by comparing the prevalence rates of 118 behavioral / emotional problems reported for large samples of American and Dutch children by their parents and teachers (Achenbach et al., 1987bc). Very few differences were found between American and Dutch prevalence rates despite differences in culture and language.

For comparisons of our CBCL/TRF data with norms for nonreferred children we used USA factors and norms (Achenbach & Edelbrock, 1983, 1986), because complete Dutch norms (including TRF factorscores) were not available. Studies by Achenbach and Verhulst demonstrated high USA-Dutch correlations and found no significant differences between normative samples of American and Dutch children for CBCL and TRF (Achenbach et al., 1987abc; Verhulst et al., 1988, 1990).

For comparisons of our CBCL/TRF data with norms for clinically referred children we also used USA norms (Achenbach & Edelbrock, 1983, 1986), because complete Dutch norms (including TRF norms) were not yet available. We made this choice although Verhulst et al. (1989) found small but significant differences in parent reported (CBCL) total; externalizing; and internalizing problems between children seen in American and Dutch mental health services. American children obtained somewhat higher total problem scores than Dutch children, and American children obtained higher scores on more externalizing items than Dutch children. Our choice to compare with USA norms is not a serious disadvantage, because: (1) our study is not an epidemiological research project aiming at finding differences between populations; and (2) for our study it seemed appropriate to limit ourselves to a rough comparison between our sample of subjects and normative samples.

3.3.4.3 The Groninger Behavior Observation scales

The Groningen Behavior Observation scale is a Dutch scale, focusing on a hyperactivity / poor-taskorientation aspect. The scale was developed from the Groningen Behavior Checklist for selection purposes, and consists of 15 items covering behavior regarding activity, attention, impulsivity, rapidly changing task orientation and talkativeness. Three versions have been developed (Vaessen & Van der Meere, 1990):
(1) The parent version for the home situation (Groninger Ouder Observatielijst, GOO; Boorsma, 1990). The GOO is shown in English in appendix 3.3.4.3a.
(2) The teacher version for the behavior of children at school (Groninger Basisschool Observatielijst, GBO; Vaessen, 1990). The GBO is shown in English in appendix 3.3.4.3b.
(3) The laboratory version for standardized laboratory situations (Groninger Psychodiagnostische Observatielijst, GPO; Van Hoeken, 1990). The GPO consists of similar items as the GOO and the GBO.

GOO: Boorsma (1990) investigated the reliability of the GOO using principal component analysis and found a stable two-factor solution ("activity" and "attention").

However, the subscales were found to be less reliable than the total scale. The internal consistency of the total scale in terms of Cronbach's α was .80 in a normative group of 220 children aged 7-10 (children from a follow-up study, who had been judged as neurologically normal immediately after birth). The intercorrelations of the GOO sum score with age and sex were small enough ($\leq$.12) to leave the percentile points of the sum score uncorrected for age and sex (sum score 90th percentile: 42). The concurrent validity of the GOO sum score was investigated using the CBCL. GOO sum scores correlated high with the CBCL Hyperactive scale (boys .88, girls .81), but also moderately high with the CBCL Aggressive scale (boys .78, girls .72). The high correlation with the Hyperactive scale corroborates the validity of the GOO sum score as an index of ADHD symptomatology.

GBO: Vaessen (1990) investigated the reliability of the GBO using principal component analysis and found a one-factor solution ("lack of task orientation"). The internal consistency of the scale in terms of Cronbach's α was .95 in a normative group of 1436 children aged 6-13 (a regular school population). Sex and age were found to have a significant effect on the GBO sum score. Therefore the percentile points have to be adapted for age and sex effects (90th percentile points for boys and girls respectively: 6 years 43/35; 7 years 44/43; 8 years 47/42; 9 years 45/39; 10 years 40/36; 11 and 12 years 49/36). The concurrent validity of the GBO has not yet been investigated.

GPO: The GPO has been tested in a sample of children who were preselected for ADHD according to teacher and parent ratings (GBO and GOO respectively). For this group the GPO was rated by six independent raters during two diagnostic situations (Bourdon-Wiersma paper-and-pencil-cancellation test, and Motor Impairment Test). Van Hoeken (1990) found correlations between pairs of raters ranging from .63 to .91. Some raters had practiced evaluating children with the GPO in pairs. Correlations were higher for these pairs (from .85 upward) than for the others. Van Hoeken also determined the stability of the GPO and found correlations between the original and the repeated evaluations ranging from .80 to .92. For research purposes a minimum interrater agreement of .80 is necessary. In Van Hoeken's (1990) study this level was reached only for those pairs of raters who had practiced together. Therefore Van Hoeken advised to develop a videotape to provide a standard "practice partner". Such a standard tape may also be used to check and correct rater drift during the course of a study.

In our study we used GOO, GBO and GPO as follows:

(1) GOO and GBO were used for a comparison of our sample with Vaessen and Van der Meere's (1990) normative sample (see section 4.5.2).

(2) GOO, GBO, and GPO of the child's behavior during psychological testing were used to classify the subjects in proportion to their degree of pervasiveness (see section 4.6.4).

(3) GOO, GBO, and GPO of the child's behavior during a standardized playroom session were used for evaluation of drug effects (see section 5.3). These rating scales had not been used for this purpose before.

3.3.4.4 Groningen Behavior Checklists

The Groningen Behavior Checklists comprise the Groningen Behavior Checklist School Situation (Groninger Gedragslijst Basisschool, GGBS), and the Groningen Behavior Checklist Family Situation (Groninger Gedragslijst Gezinssituatie, GGGS). The Groningen Behavior Checklists are Dutch checklists for the description of children's behavior by parents (GGGS) and teachers (GGBS). They have been developed by Schaefer and Kalverboer, and were applied in studies of children with learning and behavioral problems as well as in studies of normal children (Kalverboer et al., 1990). The GGGS and GGBS cover a broad range of behaviors in the social-emotional domain. In various studies, three factors have been consistently found (Kalverboer et al., 1990). They can be labeled as: Good versus Poor Task Orientation, Extroversion versus Introversion, and Social Negative versus Social Positive.

Kalverboer (1988) found that not only inattentiveness, impulsivity and motor restlessness, but also a number of social negative behaviors (irritability, covert hostility, tending to tease, and suspiciousness) had moderate to high loadings on the negative pole of the task orientation factor, suggesting a connection between target signs of hyperactivity and negative social behavior. Recently, Kalverboer et al. (1990), using the GGGS and GGBS, found that children who had been selected solely on the basis of ADHD target phenomena also differed from control cases with respect to various aspects of their social behavior.

For our study we were interested in the GGGS and GGBS as a means to compare changes (due to medication) appearing in the hyperactivity/task-orientation with changes in other behavior clusters. Because of the danger of overloading parents and teachers with our rating scales, we decided to use the abbreviated versions of the GGGS and GGBS, consisting of 32 and 30 items respectively, instead of the 90-item versions. The abreviated versions have the same factor solution as the 90 item versions. A four-point scale is used for each item. GGGS and GGBS have the following factors:

GGGS:
factor 1: Social Positive
factor 2: Extrovert
factor 3: Hyperactive
factor 4: Social Negative
factor 5: Introvert

GGBS:
factor 1: Extrovert
factor 2: Introvert
factor 3: Social Negative
factor 4: Taskorientation Good
factor 5: Taskorientation Poor

The GGGS and GGBS are used in our study in the drug efficacy measurement, using repeated measures ANOVA.

3.3.4.5 The Conners Teacher Rating Scale

Developed to assess the effects of stimulant drugs in hyperactive children and to aid in differentiating hyperactive from nonhyperactive children, the original version of the Conners Teacher Rating Scale (CTRS; 39 items) has become the most widely used rating scale in research and clinical practice to date (Barkley, 1990). The CTRS items particularly cover externalizing problems. Coverage for internalizing problems is weak. Blöte and Curfs (1986) translated the partially reworded 39-item NIMH version of the CTRS (Werry et al., 1975) into Dutch and investigated reliability and validity. In our study we used this Dutch version (the Werry et al.'s English version is showed in Appendix 3.3.4.5). Each of the 39 items is rated on a 4-point scale.

Blöte and Curfs (1986) tested the psychometric properties of the CTRS using principal component analysis and varimax rotation. They found a five factor solution. The factors are: 1. Acting-out; 2. Anti-social; 3. Hyperactivity; 4. Anxiety-Withdrawal; and 5. Social Isolation. The internal consistency of the five subscales in terms of Cronbach's α was satisfactory with α's reaching from .66 (factor Social Isolation) to .93 (factor Acting-out). The stability of the subscales was satisfactory. All subscales except factor 3 discriminated between schooltypes (MANOVA, $p<0.01$). The factors 1, 2, and 3 discriminated between sexes (MANOVA, $p<0.01$). Different norms for boys and for girls as well as for children of different types of schools appeared necessary.

"Those wishing to use the scale to assess treatment effects should be cautious of practice effects, scores being significantly lower at the second administration compared to the first, particularly over short periods" (Barkley, 1990). For that reason we applied the CTRS for the first time before the child's first visit to the clinic, and for the second time as a baseline rating for pre-post treatment effects.

In our study we compared CTRS sum and factor scores of subjects with Blöte and Curfs' (1986) normative data derived from a sample of regular school children (449 children aged 6-13). The distribution of factor scores in the normative sample is skewed (to the right), especially in the sample of regular school children. We chose 90th percentile points.

3.3.5 Psychological assessment

3.3.5.1 Introduction

In research as well as in clinical practice one is in need of more objective means of assessing hyperkinetic symptoms. Tests of vigilance and sustained attention, and direct, systematic behavioral observations of hyperkinetic symptoms are at present considered to be the most useful laboratory measures available in the assessment of hyperkinesis (Barkley, 1990). Barkley (1990) recommends these measures as components of a

multimethod assessment battery in hyperkinesis. In section 3.3.6 the methodology of direct observations is dealt with. In this section we consider the application of vigilance and sustained attention tests. These tests have the advantage of being less tainted by biases that can arise in the use of methods relying on personal opinions (i.e., interviews and rating scales). Barkley (1990) considers the following tests the most promising among the tests of vigilance and sustained attention:
(1) Continuous-performance tests (CPT);
(2) Paper-and-pencil cancellation tasks (PPCT); and
(3) Freedom from Distractibility Factor of the WISC-R (FDF).

Continuous-performance tests (CPT)

In vigilance and reaction-time (RT) tasks subjects are required to pay close attention to relatively simple visual or auditory stimuli, often over extended periods of time, so that they will be able to respond in a designated manner to certain stimuli or configurations of stimuli when they appear. An additional requirement involves withholding responses to nonsignal stimuli. Because of the extended and constant nature of the demands made on subjects, the tasks are referred to as CPTs. The scores derived from CPT are: (1) the mean latencies; (2) the number of correct responses; (3) the number of target stimuli missed (omission errors); and (4) the number of responses following nontarget or incorrect stimuli (commission errors). Presumably, omission and commission errors are respectively indicative of attentional and impulsivity problems. Hyperactives generally have been found to have slower mean latencies, more errors of omission and more errors of commission than normal controls (Douglas, 1984). In several studies it was found that methylphenidate improved both speed and accuracy in hyperkinetic children (Klorman et al., 1988; Rapport, 1990).

The aims of the RT experiments in our study were:
(1) a comparison between ADHD subjects and controls in order to investigate the relation between a response selection deficiency (suggested in earlier studies) and an inability to program and to inhibit a response set in aid of an optimal task performance in ADHD children;
(2) testing if this inability in ADHD children is removed or reduced by clonidine and/or methylphenidate.
The RT experiments do not form a part of this thesis and are reported elsewhere (Van der Meere, Gunning, et al., in preparation).

Paper-and-pencil cancellation tasks (PPCT)

PPCTs are CPTs used as methods of assessing attention (Barkley, 1990). In the Netherlands the Bourdon-Wiersma PPCT is frequently used for this purpose (Boeke, 1962; de Zeeuw, 1986). Hyperactive children have been found to make more omission and commission errors than controls on PPCTs (Aman et al., 1986). PPCTs typically involve having the child scan a series of symbols (letters, numbers, shapes) presented in rows on sheets of paper. The child is required to draw a line through or under the target

stimulus with a pencil. PPCTs differ from RT tasks in task structure: RT tasks are paced (by the experimenter), PPCTs are self-paced (by the subject).

Using the Bourdon-Wiersma paper-and-pencil cancellation test (PPCT), Van der Meere et al. (1991; Wekking, 1986) investigated if hyperactive children showed a sustained attention deficit. A sustained attention deficit was defined as a significant decrement in task performance with task duration (task-on-time effect). The subjects in this study were pervasively hyperactive (i.e., they scored high on both parent and teacher reported hyperactivity ratings), but differed in their degree of pervasiveness (according to if they scored high on hyperactivity ratings during 1, 2, or 3 psychological tests: WISC-R, a test of motor impairment, and the Bourdon-Wiersma PPCT). It was found that task inefficiency was most pronounced in the most pervasively hyperactive children (i.e.: the more pervasively hyperactive the child, the slower and more variable the PPCT cancellation time was). However, no differences were found between controls and subgroups of hyperactive children in the decline in task efficiency. Therefore, no evidence was found in favour of a sustained attention deficit in hyperactivity. This result corroborated prior findings (see Sergeant & Van der Meere, 1990, for review).

Freedom from Distractibility Factor of the WISC-R (FDF)

Kaufman (1975), in his factor analysis of the WISC-R (Wechsler, 1974), demonstrated that the 12 subtests can be reduced to three factors: Verbal, Spatial Construction, and Freedom from Distractibility (FDF). The FDF factor includes the subtests arithmetic, digit span, and coding. The FDF score has been found to correlate to a low but significant degree with other tests of attention. Evidence is conflicting, however, as to whether the test can adequately discriminate groups of hyperkinetic from normal and reading-disabled children (Barkley, 1990). The subtests of the FDF appear to assess short-term memory, facility with numbers, perceptual-motor speed, visual-spatial skills, and arithmetic calculation. Barkley (1990) emphasizes that he does not recommend this factor in assessing attention or in establishing evidence for or against a diagnosis of ADHD.

Van der Meere et al. (1991) used the FDF and found differences in FDF between controls (mean FDF-score 115) and subgroups of pervasively hyperactive children (mean FDF-scores between 87 and 94).

Learning disabilities

Many hyperkinetic children are at the same time learning disabled (LD; Lambert & Sandoval, 1980; Barkley, 1990). LD is generally defined as a significant discrepancy between intelligence and academic achievement. The prevalence rates of LD can vary greatly depending on how this "significant discrepancy" is defined. The most rigorous approach is to define LD as both a score below a cut-off on an achievement test and a significant discrepancy between IQ and achievement.

Using the Additive Factor Method (Sternberg, 1969), Van der Meere et al. (1989) found a slow task performance in both hyperactive and LD children as compared to

controls. LD and hyperactives did not significantly differ from one another in slowness. The Additive Factor Method assumes that task performance is the sum of sequential and independent processes. Van der Meere et al. (1989) studied the duration of the central processes (memory search and decision) and the motor decision process in hyperactive and learning disabled children under so-called divided attention and S-R compatibility conditions. It was found that LD were impaired in the memory search and decision processes whereas hyperactives were impaired in their motor decision process.

Van der Meere et al. (1989) used the Primary Mental Ability test (PMA; Kema, 1978) to diagnose LD. In another study (Koldijk & Borger, 1990) the PMA was used to validate teachers' ratings of learning disability in a sample of both hyperactive and nonhyperactive children, attending regular schools. Teacher's ratings of hyperactivity (GBO) correlated highly with teacher's ratings of LD. In this group of children, suspected of LD, however, only 16 percent showed LD, and these were all nonhyperactive children.

We wanted to classify LD in our subjects in order to be able to compare our results with the prevalence rates of LD in hyperkinetic children, reported in earlier studies. Secondly, a classification of LD was needed for the analyses of the RT test results.

3.3.5.2 Psychological tests

Paper-and-pencil cancellation task (PPCT)

The Bourdon-Wiersma paper-and-pencil-cancellation test was used in our study (Boeke, 1962). The test consists of 50 consecutive lines. Each line consists of groups of three, four and five dots. The subject is instructed to cross out groups of four dots as quickly and as accurately as possible. The task has a continuous character and is self-paced (by the subject). The dependent variables are the mean cancellation time (in seconds), the within-subject variability in cancellation time, and the error percentage. Error percentage is defined as the sum of target omissions and false alarms, divided by the total number of targets (i.e., 231 targets for 25 lines). Just as Wekking (1986) we did not use all 50 lines of the original test, but only the first 25 (administration takes approximately 10 minutes). This was because taking all 50 lines usually makes the test too difficult to perform for young, hyperactive children. We considered that only 25 lines was justified, because we compared the test results with a control sample (with identical test procedure). In addition, the Bourdon-Wiersma PPCT has an excellent internal consistency between the test lines (Cronbach's α .988). Unlike Wekking (1986) we did not introduce an additional task during the last 6 lines (Van der Meere et al. asked the children to react to high or low tones during the last 6 lines).

Freedom from Distractibility Factor (FDF) of the WISC-R

Bearing in mind Barkley's caution (1990) that there is no straightforward way in which poor performances on this factor indicate that deficits in attention account for them, we used the FDF: (1) for a comparison of FDF-score between the subjects and nonhyperactive

controls (i.e., the group of children who were tested with PPCT); (2) to control for differences in FDF-score between the subjects and the controls, when analysing PPCT performance; and (3) for a GPO-rating during FDF.

Primary Mental Ability test (PMA)

As an instrument to diagnose learning disability (LD), we chose the PMA, because it is an accepted test for LD and includes an index of intelligence ("PMA-score"). In accordance with Koldijk and Borger (1990) we defined LD as specific language or arithmetic problems combined with an intelligence in the normal range.

To be able to classify a subject as LD, a child had to obtain:

(1) a PMA-score ≥ 90; and

(2) a score ≥ 5 on the PMA subtests vocabulary, sorting figures, dictation, and arithmetic skill; and

(3) a Brus normscore ≥ 4. The Brus one-minute-reading-test is a measure for technical reading skill (Brus & Voeten, 1972). "Language dysfunction" was scored when a child obtained a score below the cutoff point for vocabulary, or dictation, or Brus score. "Arithmetic dysfunction" was scored when a child obtained a score below the cutoff point for sorting figures, or arithmetic skill. Subjects were classified as having:

(1) language dysfunction;

(2) arithmetic dysfunction;

(3) both language and arithmetic dysfunctions;

(4) normal (no language or arithmetic dysfunctions); or

(5) PMA-score < 90.

Because the PMA has norms for the age range 7 to 12, we did not obtain PMA test results for subjects aged 13 and older.

3.3.5.3 Procedure

The procedure included, that a subject was tested successively on PPCT, FDF, and Brus during one session, and on the PMA test in another. The research-assistant who did the psychological assessment (IH) was supervised by two psychologists with respect to test procedures. Notes were made on the subjects's behavior and cooperation during psychological testing.

3.3.6 Direct behavioral observations

3.3.6.1 Introduction

Van der Meere et al. (1991) tested hyperactive and control children using the Bourdon-Wiersma paper-and-pencil cancellation test (PPCT), the WISC-R, and a test for measuring motor abilities. Hyperactives and controls had been selected on the basis of

parent and teacher ratings. The children's behavior during testing was rated on the GPO. Low correlations were found between parents' / teacher's hyperactivity ratings and GPO ratings. It was concluded that hyperactivity ratings during structured tests help to form more homegeneous subgroups of hyperactive and control children.

The behavior of a child with hyperkinesis in the clinical setting has often been shown to be quite atypical of the child's behavior with other caregivers in natural settings (Kalverboer, 1988; Barkley, 1990). Making the clinic situation analogue to natural settings maximizes the likelihood of observing behavior typical of the child's behavior in more natural settings. Barkley sums up what helps to make the clinic situation "analogue":

(1) furnishing the clinic room so that it looks similar to an average home family room;
(2) the nature of the tasks assigned to the children should approximate those given at home or school that typically elicit the hyperactivity symptoms or other behaviors of interest to the clinician;
(3) when the purpose is to assess hyperactive behaviors, it is recommended to place the child in the room alone, to see how well the child works without supervision;
(4) where defiant and oppositional behavior are of interest, having the mother present in the room with the child and requiring her to give the instructions or tasks to the child is essential;
(5) allowing the child adequate time to get accustomed to the room can help to enhance the child's comfort with the surroundings and hence to increase the likelihood that more typical behaviors will be observed.

Research suggests that where such steps are taken, the behaviors recorded do correlate to a significant and meaningful degree with behavioral observations and ratings taken in the natural environment. However, the degree of relationship still remains low to moderate (r=.20 to .50; Barkley, 1990).

3.3.6.2 Instruments

GPO ratings were made of the children's behavior during psychological assessment (PPCT and FDF), and during standardized playroom sessions. GPO sum scores were used.

We chose GPO ratings during PPCT and FDF for the following reason. In Wekking's (1986) study children demonstrated more hyperactive symptoms during WISC-R than during PPCT. A moderate correlation was found between GPO rating during WISC-R and GPO rating during PPCT (.36 approximately). Wekking (1986) suggested that this probably was because the test situation is more structured during PPCT than during WISC-R. For ratings of behavior during standardized test situations we decided to choose the FDF as a probable less structured test situation, and the PPCT as a more structured test situation.

GPO ratings of the child's behavior during playroom sessions, before and in the

seventh week of treatment, were used as a measure of drug efficacy. GPO ratings have not been used for this purpose before. The children's behavior during the playroom sessions was registered on videotape. Afterwards these videotapes have been used for an ethological study. This ethological study does not form a part of this thesis and is reported elsewhere (Dienske & Gunning, in preparation). Personal and financial limitations caused that only the subjects of trial group 3 were seen in playroom sessions.

We standardized the 30 minutes, semistructured playroom sessions as follows: A clinic playroom was used, equipped with a one-way mirror and a video monitoring system from behind the mirror. After entering the playroom the child and the examiner sat down respectively behind and beside a table, which was placed in front of the one-way mirror. The session started with a chat of a few minutes to explain the procedure and to familiarize the child to the room and the examiner. The child was instructed to perform each task as well as possible, to fulfil each task completely, and not to make haste. Then, the child was asked to perform the following tasks:

(1) A paper-and-pencil task: copying ten figures (Gesell-Santucci test of visual-motor functioning; Njiokiktjien & Gobin, 1981). Then the child was asked to write his name and the date on the sheet.

(2) The examiner laid out 106 "memory" cards "open" on the table. The child was instructed to sort the pairs of cards as fast as possible, while remaining seated.

(3) The child was asked to stage a puppet-show. He had to choose one of the following themes: Little Red Riding-hood, The Pied Piper of Hamelin, Sleeping Beauty, or Hansel and Gretel. The child was told that sometimes there exist more versions of a particular fairy-tale. The child was free to choose which story or to make his own version of one of the stories. After the puppet-show the child was asked to sit down at the table again.

(4) The child was asked to build a Lego-car, using a catalogue picture as a model.

(5) The child was asked to put domino-stones in a row, alternating his stones with those of the examiner.

The videocamera-man was instructed to film the child with hands and feet visible as long as the child sat at the table. In his second playroom session the child had to choose another fairy-tale and was given a different Lego-car model.

In order to improve interrater agreement, a glossary was written with instructions on GPO scoring. The videotape of trial subject No. 5 during PPCT, FDF, and playroom session was used as a "practice partner" to standardize GPO scoring. This videotape was used by the research-assistants to check and correct rater drift every three to four months, and anyhow when a new research-assistant was introduced.

3.3.6.3 Procedure

With respect to GPO-PPCT and GPO-FDF the procedure included, that a subject was tested successively on PPCT, FDF, and Brus during one session. The GPO was rated by the test leader immediately after the tests, and afterwards independently by another

research-assistant from videotape. All subjects were tested by the same test leader (IH).

With respect to GPO-play the procedure included, that the GPO was rated by the test leader immediately after the playroom session, and afterwards independently by another research-assistant from videotape. All playroom sessions were performed by the same test leader (IH), in the same playroom, and the same research-assistant rated all the videotapes of one subject (PPCT, FDF, and playroom sessions).

3.4 THE METHODS OF THE TRIAL

3.4.1 Trial design

We have explained the background and aims of the study in Chapter 1. We now call to mind the objectives:

(A) A comparison of clonidine with placebo with respect to efficacy and safety concerning short term effects on hyperactivity in subgroups of hyperkinetic children:
(1) subjects, meeting the DSM-III-R criteria for Attention-deficit Hyperactivity Disorder (ADHD), who in addition met the DSM-III-R criteria for Pervasive Developmental Disorder (PDD);
(2) subjects, meeting both the DSM-III-R criteria for ADHD and the criteria for Tic Disorder (but not PDD);
(3) subjects, meeting the DSM-III-R criteria for ADHD, but not the criteria for PDD or Tic Disorder.

(B) A comparison of clonidine with placebo and methylphenidate with respect to safety and efficacy concerning short term effects on hyperactivity in trial group 3.

We created subgroups for the following reasons:
(1) The possibility of finding different effects of clonidine vs placebo in samples with different diagnoses. We decided not to finish the trial until enough subjects were able to enter the combination of trial groups 1 and 2: enough (see "calculation trial size") for a separate statistical analysis to assess the efficacy of clonidine in the treatment of "ADHD children, for whom methylphenidate was relatively contraindicated". In addition, we planned a pooled statistical analysis for trial groups 1+2+3 to assess the efficacy of clonidine in "ADHD patients in general, including ADHD children with PDD or Tic Disorder".
(2) Methylphenidate is relatively contraindicated in patients with PDD or Tic Disorder. Trial group 3, consisting of subjects for whom methylphenidate was allowed, was created as a construction to test clonidine against both placebo and methylphenidate.

In order to attain our aims we chose for a balanced, parallel-group, double-blind, placebo-controlled clinical trial with random assignment to clonidine or placebo (or -trial group 3- methylphenidate).

Parallel-group design

We chose a parallel-group design, implying a between-patients comparison of treatments, and not a crossover design. A crossover design, implying a within-patient comparison of treatments, is only applicable if:
(1) the disease condition remains sufficiently stable, and
(2) there are no long-term carry-over effects of the first treatment into the second period (Pocock, 1983).

Provided that the treatment periods are well chosen (i.e., excluding holidays and other potential interfering events), the disease condition (ADHD) is expected to remain sufficiently stable to perform a trial with respect to short-term effects (8 weeks) on hyperactivity. Unfortunately, however, long-term carry-over effects have been described both for clonidine and for methylphenidate. We review the following findings:
(a) Hunt et al. (1984) found that hyperkinetic children exhibited increased growth hormone response to a challenge dose of clonidine. It was suggested that this observation indicated a possible supersensitivity to noradrenergic stimulation (i.e., a combination of diminished presynaptic norepinephrine production and increased postsynaptic responsivity). It was found that chronic methylphenidate treatment (12 weeks) reduced the growth hormone response to acute stimulation with clonidine, which may indicate a normalization of the noradrenergic postsynaptic receptor in methylphenidate-treated ADHD children.
(b) The urinary excretion of MHPG was reported to be reduced, unaltered, or increased in hyperkinesis (Weizman et al., 1990). Prior use of stimulants may account for the reduction in MHPG excretion in hyperkinetic children. Zametkin et al. (1985b) reported that urinary MHPG remained depressed for at least 2 weeks after treatment with d-amphetamine, whereas deviant behavior returned immediately.
(c) Leckman et al. (1986) studied the behavioral, cardiovascular, and neurochemical effects of abrupt clonidine withdrawal in seven children with Tourette's syndrome. Five patients showed marked worsening of tics. After reinitiation of clonidine therapy, the time required for patients to return to prewithdrawal levels of tic symptoms ranged from two weeks to four months. Increases in motor restlessness, blood pressure, and pulse rate were also observed over a 72-hour period following abrupt withdrawal of clonidine. Plasma levels of free MHPG, homovanillic acid, and urinary excretion of norepinephrine and epinephrine increased during the withdrawal period.
(d) Psychopharmacological treatment can sometimes break vicious circles with a durable improvement even when treatment is not reinstituted (Loonen & Zwanikken, 1987).

Although a crossover design did not suit our purposes, a parallel-group design, however, also had disadvantages: Patients may vary much in their initial level of functioning and in their response to therapy (Pocock, 1983). This means that one needs substantial groups of patients on each treatment in order to make a reliable estimation of the magnitude of any treatment difference.

We judged the disadvantages of a parallel-group design to be fewer than the drawbacks

of a crossover design, and hence chose the former.

Trial assignment and randomization

The three trial groups were formed on the basis of the subject's DSM-III-R diagnoses after this diagnosis had been established by at least two of the three experienced clinicians:

(1) subjects, meeting DSM-III-R criteria for ADHD, but classified as Pervasive Developmental Disorder (i.e., Autistic Disorder or Pervasive Developmental Disorder NOS). According to DSM-III-R a diagnosis of ADHD is preempted in PDD children, who at the same time meet the criteria for ADHD;

(2) subjects, meeting both DSM-III-R criteria for ADHD and criteria for Tic Disorder (but not PDD). Tic Disorder included: Tourette's Disorder, Chronic Motor or Vocal Tic Disorder, or Transient Tic Disorder;

(3) subjects, meeting DSM-III-R criteria for ADHD, but not PDD or Tic Disorder.

Table 3.4.1 Trial groups and treatment

Trial group 1 (ADHD + PDD NOS):	clonidine or placebo.
Trial group 2 (ADHD + Tic Disorder):	clonidine or placebo.
Trial group 3 (ADHD):	clonidine, placebo, or methylphenidate.

For trial groups 1 and 2, the experimental treatment was clonidine (see table 3.4.1). For trial group 3 the experimental treatment was either clonidine or methylphenidate. After the diagnostic assessment and informed consent procedure, subjects of the treatment groups 1 and 2 were randomly assigned by a research pharmacist to clonidine or placebo, and subjects of treatment group 3 to clonidine, placebo or methylphenidate.

In our study we applied a stratified randomization. In any randomized trial it is desirable that the treatment groups should be similar as regards certain relevant patient characteristics (Pocock, 1983). We considered the following factors relevant with respect to trial outcome: (1) a distinction between the children with disorders, for whom methylphenidate was relatively contraindicated (trial groups 1+2) and the children for whom methylphenidate was not contraindicated (trial group 3); (2) within trial 1+2: Pervasive Developmental Disorder; a stratified randomization could help to guard against the possibility of all the PDD patients coming in the placebo group, or in the clonidine group.

Trial groups 1+2 on the one hand, and trial group 3 on the other hand were already two separate trials (trial 1+2: clonidine versus placebo; trial 3: clonidine versus methylphenidate versus placebo). As a consequence we chose two strata for trial 1+2: PDD + and PDD -.

The statistician sent randomization lists for each trial, and within trial 1+2 for both

strata, to the pharmacist. In addition we anticipated the following problem: In our study, the project-leader was at the same time the attending physician. We planned for the project-leader to get the medication code after each of the subjects had completed his or her treatment period. We wanted to blind the project-leader as much as possible. This we realized by applying randomization blocks of at random a length of 2 or 4 subjects (e.g., BABA BBAA AB AB ABBA, etc.). Because trial group 3 implicated 3 treatments, the length of the randomization blocks was here at random 3 or 6 subjects (e.g., BCA ABC BAC CBCAAB, etc.).

Calculation of the size of the trial

Estimating the future "patient-stream" to our out-patient clinic with respect to ADHD patients eligible for inclusion in the trial, we expected more children in "trial groups 1 and 2" (PDD and tics) than in "trial group 3". Therefore we calculated a size for trial groups 1+2, that was large enough to attain our aim of assessing the efficacy (with respect to hyperactivity) and safety of clonidine in the treatment of "ADHD children for whom methylphenidate was relatively contraindicated". In addition we calculated the size for a trial (based on a pooled analysis of trial 1+2+3) to attain our aim of assessing the efficacy of clonidine in "ADHD patients in general, including ADHD children with PDD or Tic Disorder".

To calculate the trial size, we formulated the following parameters (Pocock, 1983):
(1) The main purpose of the trial was to assess the efficacy of clonidine compared to placebo (parallel-group design);
(2) The principal measure of patient outcome relevant for the power calculation was "respondership" (see section 3.4.5).
(3) What type of results were anticipated with standard treatment (placebo) and what type of results with the drug under investigation?
(a) In Taylor et al.'s (1987) methylphenidate placebo-controlled crossover trial of 38 boys aged 6-10, referred because of antisocial, disruptive or overactive behavior, 26% of the children were "somewhat" to "much" improved at the end of placebo treatment, and 69% were "somewhat" to "much" improved at the end of methylphenidate treatment. Taylor et al.'s (1987) definition of respondership was similar to our own.
(b) In order to calculate an expected percentage of responders on clonidine, we checked retrospectively the response to clonidine for ADHD patients in open treatment (Gunning et al., 1990). At our out-patient clinic 54 DSM-III ADDH and DSM-III-R ADHD children had been treated with clonidine between 1984 and 1987. Retrospectively these children were classified according to DSM-III-R as Tourette's Disorder + ADHD (n=35), Pervasive Developmental Disorder NOS + at the same time meeting criteria for ADHD (n=6), and ADHD "only" (n=13; in fact some of these children had comorbid Oppositional Defiant Disorder or Conduct Disorder, just as many of the Tourette patients had). According to our judgment, clonidine gave a clinically significant improvement

of hyperactivity symptoms in 74.1% (n=40) of the children during open treatment. The respondership percentages in children with Tourette Syndrome + ADHD or PDD + ADHD were slightly better than in children with "only" ADHD (74.3%, "100%", and 61.5% respectively). We chose the following expected percentages of responders:
(a) placebo (p_1): 26%; (b) clonidine (p_2): We chose 74% for trial group 1+2, and 61.5% for pooled trial groups 1+2+3; and (c) methylphenidate (p_2): 69%.
(4) We chose $\alpha = 0.05$. α is the level of the X^2 test used for detecting a treatment difference. Alpha is commonly called the type I error: the probability of detecting a "significant difference" when the treatments are really equally effective (i.e., α represents the risk of a false-positive result).
(5) We chose $ß = 0.1$. ß is called the type II error: the probability of not detecting a significant difference when there really is a difference of magnitude $p_1 - p_2$ (i.e., ß represents the risk of a false-negative result). "1 - ß" is called the power to detect a difference of magnitude $p_1 - p_2$.
(6) We chose an expected percentage of withdrawals: 10%. Based on the open treatment results, we estimated 14% of the children to show drowsiness after 7 weeks of treatment.

The statistician calculated the sizes of the trials using the calculation after Casagrande et al. (1978). We found the following:
(1) In order to find a statistically significant effect for trial groups 1+2 ("ADHD children for whom methylphenidate was relatively contraindicated") two groups of 31 patients each were needed.
(2) In order to find a statistically significant effect for the pooled (1+2) + 3 trial groups ("ADHD patients in general, including ADHD children with PDD or Tic Disorder") two groups of 43 patients each were needed. Moreover, we desired 3x15 subjects for trial group 3 in order to perform the reaction-time experiments. Our calculation produced the following number of patient, minimally required:
Trial groups 1+2: two parallel groups of 31 patients each.
Trial group 3: three parallel groups of 15 patients each.
Total number of patients required for the trial: 107.

We expected to obtain the required number of patients in the course of two years (1989-1990). In trial group 3 we compared the effects of clonidine with the effects of placebo and methylphenidate (three parallel groups of at least 15 patients each). As a consequence of the choices we had made, we did not aim at finding a significant effect of clonidine compared to placebo separately for trial 3, but were primarily interested in a qualitative (hypotheses finding) comparison of the effects of clonidine, placebo and methylphenidate, using ethological, neuropsychological (reaction time experiments), and neurochemical measures.

3.4.2 Patient selection criteria

In order to be able to generalize the findings of our study, we required the trial patients to be representative of those ADHD patients we subscribe medication to in child psychiatric practice. Many clinicians in the Dutch mental health services and in pediatric/ child neurological practice seem to consider a "hyperactivity medication try" when:
(1) a child shows moderate to severe chronic impairment in social, emotional and/or cognitive functioning; and
(2) hyperactivity symptoms determine this functional impairment considerably, and both clinical experience and study findings with respect to "hyperactivity medication" support expectations that children with these symptoms have a reasonable chance to benefit from medication; and
(3) other sorts of treatment have proved to have insufficient effect, or are not available within reasonable time.

In clinical practice, the physician with "hyperactivity medication" (i.e., mostly stimulants or clonidine) aims at setting "afloat" a child's compromised development by ameliorating target symptoms (hyperactivity, or symptomatology indirectly facilitated by hyperactivity symptoms). Drugs do not reverse any specific pathology. However, if they are beneficial for target symptoms without at the same time giving too many adverse effects, they form a stepping-stone, which helps to get other (non-drug) treatments rooted. After some time (mostly one to two years, occasionally even three to four years) the child does not need this stepping-stone anymore as a help, and the medication can be stopped. During the course of the drug treatment it is important to keep sight on both the efficacy and safety of the drug, and on the extent to which the child still "needs" the drug (taking into account the contributions of maturation, and of any other treatments), or whether the child can possibly already make it on a lower dosage.

In clinical practice, the children for whom we considered a medication try meaningful, mostly met ADHD criteria. It was only on extremely rare occasions that we gave stimulants or clonidine to children, who did not meet the DSM-III-R criteria for ADHD. These non-ADHD children, however, showed moderate to severe functional impairment caused by a few ADHD symptoms. Therefore, the DSM-III-R criteria for ADHD seemed to be appropriate as a threshold for inclusion of patients in our study.

We decided to include in the trial those children, who:
(1) met ADHD criteria; and (2) for whom it was clinically considered meaningful by both the parents and the attending physician to try "hyperactivity medication".

Taking into account the many factors, which unnecessarily might interfere with the medication effect or with a solid measurement of efficacy and safety, we formulated the following inclusion and exclusion criteria:

Table 3.4.2 Trial inclusion criteria

1. boys and girls, aged 6-15, IQ > 70.
2. living in a family home, and attending school.
3. DSM-III-R ADHD, ADHD symptoms impeding development, and psychological/educational treatments insufficient effect.
4. No earlier use of stimulant drugs or clonidine, and no psychoactive medications of any kind in the last 6 months.
5. No medical contraindications.
6. No important changes expected for the course of the trial.

Inclusion and exclusion criteria (Table 3.4.2)

(1) Boys as well as girls.

(2) Age 6-15 years old. Rational: subjects needed to be old enough for reading (reaction-time experiments), and they had not to exceed the age range, for which the rating scales could be considered reliable.

(3) Measured IQs greater than 70. Rational: several studies found that stimulant drug response is different in mentally retarded children than in normal intelligent children (Payton et al., 1989; Aman et al., 1991). Before the study we had ourselves the clinical impression, both with respect to clonidine and methylphenidate, that effects and unwanted adverse effects were different in mentally retarded children than in normal intelligent children, although for both drugs we had seen beneficial effects in mentally retarded children. Another argument against the inclusion of mentally retarded children was the finding in several studies, that these children, when using methylphenidate, appear to be at a greater risk for developing side effects (for instance tics, severe social withdrawal) than nonretarded youngsters (Handen et al., 1991). By including mentally retarded ADHD children we would have made our sample unnecessarily heterogeneous making it difficult to draw conclusions which are able to be generalized. A child would not, as yet, be excluded, who had recently obtained an IQ above 70 on an intelligence test, but scored below 70 on the achievement/intelligence test which was used in our study (i.e., the Primary Mental Ability test). As is shown in section 4.6.1, all subjects had PMA-scores above 70, and only 4% scored below 80.

(4) Living in a family home and not an institution. Rational: in institutions, group leaders usually have irregular working-shifts. This makes it difficult to get reliable ratings on the child's behavior during the course of a trial.

(5) Attending (day) schools. Rational: teacher ratings were needed for efficacy measurement in the school situation.

(6) Out-patients of the Department of Child and Adolescent Psychiatry,
Sophia Children's Hospital. Rational: insurance.

(7) A diagnosis of DSM-III-R ADHD (or Pervasive Developmental Disorder, but at the same time meeting the criteria for ADHD), established by at least two of the three experienced clinicians.

(8) In addition to a DSM-III-R diagnosis ADHD, the ADHD symptoms had (according

to the clinical judgment of the project-leader): (a) to impede the child's social/emotional and/or cognitive development, and (b) the existing psychological/educational treatments were not sufficient in relieving the child's problem behaviors and in promoting development.
(9) No earlier use of stimulant drugs or clonidine, and no psychoactive medications of any kind administered within 6 months prior to entering the study. Rational: carry-over effects.
(10) No poor physical health, and free from contraindications to clonidine medication: no hypertension or hypotension, regular pulse, no liver or renal disease. For trial group 3 subjects, in addition, no contraindications to methylphenidate medication: cardiovascular disease, hyperthyroidism. Children with epilepsy were included in trial group 3, if they had had few attacks (and no grand mal) during the last year, a recent EEG showed no alarming epileptic activity, their antiepileptic medication was stable (and did not include benzodiazepines), and their attending neurologist gave permission.
(11) No important changes in school, or home situation (as judged by the project-leader) or in psychological treatment planned or expected for the course of the trial. Rational: no factors unnecessarily interfering with the treatment effect.

3.4.3 Medical precautions

Epilepsy, psychotic symptoms

Gilman et al. (1985) caution that large doses of methylphenidate produce signs of generalized CNS stimulation that may lead to convulsions. The possibility has been suggested that methylphenidate may lower seizure thresholds, and therefore should not be given to children with epilepsy. This phenomenon is rarely if ever seen clinically, however, and it can be avoided by a slight increase in the level of anticonvulsants (Crumrine et al., 1987). Several studies found that methylphenidate may be a safe and effective treatment for children with seizures and concurrent hyperkinesis (Forster & Booker, 1984; Feldman et al., 1989; Greenhill, 1991).

Children with epilepsy were included in trial group 3, if they had had few attacks (and no grand mal) during the last year, a recent EEG showed no alarming epileptic activity, their antiepileptic medication was stable, and their attending neurologist gave permission.

Psychotic symptoms have been reported as side-effects of methylphenidate (Bloom et al., 1988). Nearly all these psychotic reactions have occurred within the therapeutic dose ranges. Tactile and visual hallucinations, paranoid behavior, social withdrawal, and delusional thinking have been reported. We decided to stop medication if a subject of trial 3 might develop psychotic symptoms.

Heart rate, blood pressure, and thyroid function

Blood pressure and pulse rate changes, both up and down, have been observed during

methylphenidate treatment under normal therapeutic regimens (Diener, 1991). Methylphenidate can dramatically elevate blood pressure in children already suffering from hypertension (Greenhill, 1991). Patients with hyperthyroidism are very sensitive to methylphenidate's sympathicomimetic effects (Ciba-Geigy, 1990). Clonidine is an antihypertensive agent.

We excluded children with hypertension or hypotension. Hypertension was defined as a diastolic or systolic sitting blood pressure above the (age-adjusted) 95th percentile, and hypotension as a diastolic or systolic sitting blood pressure below the (age-adjusted) 5th percentile (Report of the Task Force on Blood Pressure Control in Children, 1977). Heart rate and sitting blood pressure were obtained at each visit during the trial. Sudden withdrawal of clonidine gives a rebound hypertension, and an increase of tics (Philipp, 1983; Leckman et al., 1986). Parents were warned against these effects.

Clonidine has a direct effect on the sinus node, and is therefore contraindicated in patients with sick-sinus syndrome (Philipp, 1983). Although this condition is most commonly seen in elderly patients, one must be prepared for this condition in children with a status after surgical correction of congenital heart defects (Behrmann et al., 1987).

When the physical examination was suggestive of hyper- or hypothyroidism, a blood analysis was performed.

Drug metabolism

In patients with renal dysfunction, the half-life of clonidine increases to 18 to 41 hours, and reduction of dosage is necessary (Gilman et al., 1985). In patients with clinical symptoms suggestive of renal dysfunction we therefore performed a blood analysis.

Methylphenidate has been reported to inhibit the metabolism of anticonvulsant drugs (e.g., diphenylhydantoin; Garrettson et al., 1969). Drugs which increase the alkalinity of the urine (e.g., the antiepileptic drug acetazolamide) inhibit the metabolism of methylphenidate. We guarded against using methylphenidate in children with asthma, who used theophylline, because adverse reactions have been reported: feeling agitated, dizzy, or nauseous (Greenhill, 1991).

Growth

Clonidine stimulates growth hormone (GH) release. Evidence from animal studies indicates that clonidine enhances GH secretion by stimulating growth hormone releasing factor neurons within the hypothalamus. The growth response to long-term administration of low dosages clonidine has been investigated in children with non-GH-deficient short stature: Three out of four studies reported an increase of height velocity during treatment (Volta et al., 1991). However, the effect on growth shown by clonidine, was not sufficient to counsel treatment with this drug in short normal children.

Although earlier studies reported a growth-suppressant effect of methylphenidate, later reports have proposed that stimulant use during childhood has no significant impact on adult height and weight (Klein & Mannuzza, 1988). In adolescents, treated with methylphenidate for at least six months, no significant deviation from expected height

and weight velocities was found (Vincent et al., 1990).

We measured standing and sitting height with a wall-mounted Harpenden stadiometer before the start of the medication. Because the duration of the trial (eight weeks) was too short to investigate the effects of clonidine on height velocity, we did not include measurement of height velocity in the study.

We often observed weight gain in ADHD and GTS patients during longterm open treatment with clonidine. Some studies have suggested that this is indicative of water retention. Other studies, however, report that it is unlikely for clonidine to cause substantial fluid retention (Philipp, 1983).

3.4.4 Treatment

Clonidine treatment

A total daily oral clonidine dosage of 4µg/kg was given in this study (divided in a twice-a-day schedule with dosages at breakfast and in the evening), using 25 µg Dixarit^{R} dragees (with matching placebo). Clonidine was gradually introduced during the first week of the study and adjusted to a lower dosage if necessary (in order to diminish adverse effects) before the end of the second week. This dosage was maintained till the end of the 7th week, and tapered off in the eighth week of the study.

Rational for the duration of treatment: Several studies reported on the course of response to clonidine in patients with Tourette's Disorder (GTS). Many GTS patients at the same time are hyperkinetic. Clonidine has been reported to ameliorate hyperactivity in GTS (Cohen et al., 1980; Leckman et al., 1991). Cohen et al. (1980) found the following course of response to clonidine in GTS patients: Within days of the initiation of treatment at 1 µg/kg/day, patients experienced a sense of calm that was characterized by decreased anger or irritability, better management of frustration, a sense of internal "mellowness", and a feeling of being more in control. After about 3 to 4 weeks, on a therapeutic dose of 3 to 4 µg/kg/day, patients recognized progressive therapeutic benefits characterized by decreased compulsive behavior, further improvement in behavioral control, and reduction in phonic and motor symptoms. For some patients, facial tics and other rapid, small movements responded somewhat later than the more complex, compulsive actions. After about three months, patients achieved a plateau of therapeutic benefit. Waxing and waning severity was still present, but on their "worst" days patients were better controlled than they had been "at their best" before the use of clonidine. Five or more months after initiation of clonidine therapy, patients required an increased dosage up to 4 to 6 µg/kg/day to sustain clinical improvement. Later on, the emergence of apparent treatment resistance was observed at a dose considered too high for further augmentation.

Recently, a duration of treatment shorter than three month has been noted as a possible reason that some well-controlled, double-blind clinical trials found no beneficial effect of clonidine in GTS patients (Roos et al., 1987; Leckman et al., 1991). Roos et al. (1987)

criticized a study of Goetz et al. (1987), in which 30 GTS patients aged 8-62 were treated with clonidine in a double-blind crossover trial. The patients' doses were increased over 6 weeks, followed by 6 weeks on a stable dose. Roos et al. (1987) wrote that a drug period of only 6 weeks does not allow a final judgment to be made about the efficacy of clonidine in the treatment of GTS. Goetz responded to Roos et al. that they had misread the article: they had treated for 12 weeks. However, rereading Goetz et al.'s study, we read that "the stable dose of medication was maintained for 6 weeks". Leckman et al. (1991) in their recent double-blind parallel-group clonidine trial of 40 GTS patients aged 7-48 chose a duration of treatment of 12 weeks. They reported that the medication was gradually increased during the first two weeks of the study until the appropriate dosage was obtained. This dosage was maintained during the remaining 10 weeks of the study. Hunt et al. (1985), in their clonidine crossover trial of 10 hyperkinetic children, administered clonidine for 8 weeks. They increased the dose of clonidine by 50 µg every other day until a dose of 4-5 µg/kg/day was achieved. In Hunt et al.'s study (1985) an improvement of rating scores on hyperactivity was found (by parents, teacher, and clinician), which was practically equal after one month of clonidine treatment, compared to the scores after two months of treatment. The principal measure of patient outcome we applied in our study was "respondership". The definition of "respondership" implied "clinically significant improvement" (see section 3.4.5). We aimed at finding pronounced effects, because we considered only pronounced effects relevant with respect to decisions on medication in clinical practice. In our study we investigated the efficacy of clonidine with respect to short term effects on hyperactivity, whereas most studies that were reviewed referred to GTS patients including longterm effects. The evaluation of the effect of clonidine on tic behaviors was not a purpose of our study. In Cohen et al.'s (1980) GTS clonidine study, improvement of behavioral control took place in the first three to four weeks. A "plateau of therapeutic benefit" (with respect to GTS symptoms in general) was reached after about three months. Besides, Leckman et al. (1991), in their GTS clonidine trial found the beneficial effect of clonidine on hyperactivity to be independent of its effects on tic behaviors. However, their findings were not known to us at the moment we planned our study. Based on both the reviewed studies, and our experiences with clonidine in open treatment, we considered six weeks on a stable clonidine dosage long enough for a judgment on the efficacy ("respondership") of clonidine in ADHD patients. In open treatment, after clonidine was introduced during the first week, clinical effects manifested themselves after three to four weeks. When no "pronounced" beneficial clinical effects were manifested after 6 weeks on a stable dose, we have never as yet seen "pronounced" beneficial effects appear after waiting for another month. However, a period of three to four weeks on a stable dose is too short for an effect evaluation, because some patients still have adverse effects (drowsiness) at this time. After five weeks on a stable dose, adverse effects usually have disappeared (if they disappear at all), and after six weeks on a stable dose both parents and teacher have had enough time to reliably evaluate behavioral changes in the child compared to baseline. When we planned the study, we supposed, based on retrospective information, that 14% of patients would still

complain of adverse effects after five weeks on a stable dose. Later on, we augmented our retrospective study, and found a percentage of 21% of the children, still complaining of adverse affects after five weeks of treatment (Gunning et al., 1990). This figure was in accordance with other studies, in which percentages of 10 to 20% were found on a clonidine dosage of 4 µg/kg/day (Leckman et al., 1988).

Rational for dosage: a strong argument for our choice of 4 µg/kg/day was that this was the dosage we used to give in clinical practice for approximately the last 6 years and with which we had favourable experiences. In addition, most clonidine trials used a similar dosage (3-5 µg/kg/day), including an adjustment of dosage to individual needs in order to diminish adverse effects (Cohen et al., 1980; Hunt et al., 1985; and recently Leckman et al., 1991). In open treatment we seldom saw a greater effect on a dosage above 4 µg/kg/day, but repeatedly saw a "clinically significant" effect on a dosage below 4 µg/kg/day (when the dosage had been adjusted in order to diminish adverse effects). However, when dosage had been adjusted to doses below 3 µg/kg/day we seldom still saw beneficial effects.

In our study clonidine was gradually introduced during the first week of the study and adjusted to a lower dosage if necessary before the end of the second week. This dosage was maintained till the end of the 7th week, and tapered off in the eighth week of the study. Other studies (Hunt et al., 1985; Leckman et al., 1991) introduced clonidine more slowly than we did (i.e., in the course of two or even several weeks). For the trial we desired the shortest possible treatment period to make it practicable to treat so many patients over a period of two years. Before the study protocol was written, the author had tested introducing a 4 µg/kg/day clonidine dosage gradually during a week in at least 15 ADHD and GTS patients, and had experienced no problems except for about 10% of patients, who had needed a more gradually course, or did not tolerate a dosage of 4 µg/kg/day at all. In accordance with most studies clonidine was tapered off gradually in the last (i.e., eighth) week of treatment in order to avoid rebound phenomena (tics, hypertensive reaction; Leckman et al., 1986).

Rational for dosage times: In children with GTS, their GTS symptoms usually are worst after school (in the afternoon). Clonidine is mostly given 2- or 3-times-a-day. Clonidine's half-live (approximately 10 hours) is long enough to warrant a twice-a-day schedule. In our clinical experience it is an exception to find a GTS patient, being treated with clonidine and having a worsening of GTS symptoms in the afternoon, to benefit from a change of clonidine dosage from 2- to 3-times-a-day (yet remaining at the same µg/day dosage). Cohen et al. (1980) already observed the development of tolerance (after > 5 months on clonidine). In clinical practice we repeatedly had the impression that children, treated with clonidine, developed tolerance after several months of treatment. When we planned our study, we estimated that the chance of a development of tolerance during a 8 weeks treatment with clonidine was small. However, we planned for our statistical analyses of rating scale scores to check if medication effect was time-dependent. Recently, it has been reported (Leventhal, 1991, personal communication) that children with mental retardation and developmental disorders developed tolerance

to clonidine after approximately 3 months of treatment with clonidine in a dosage of 4 µg/kg/day, divided in a twice-a-day schedule with dosages at breakfast and in the evening. When dosage times were then changed to 8.00 and 12.00 AM tolerance disappeared. This is an interesting observation, worth further investigation.

Methylphenidate treatment

A total daily oral methylphenidate dosage of 0.6 mg/kg was given, divided in a twice-a-day schedule with dosages at breakfast and lunch-time (with the larger dose being given at breakfast). Five milligram capsules were used (and matching placebo). Methylphenidate was gradually introduced during the first week of the study and adjusted to a lower dosage if necessary before the end of the second week. This dosage was maintained untill the end of the 7th week, and tapered off in the eighth week of the study.

Rational for dosage: Review of methylphenidate dosages applied in the treatment of hyperkinetic children showed that a dosage of 0.6 mg/kg/day is often used in clinical trials and recommended for clinical practice (Sleator & Sprague, 1978; Klein, 1987; Schachar et al., 1987; Jacobvitz et al., 1990). Although several studies have documented that factors such as gross body weight play a limited role in determining the behavioral effects of methylphenidate for hyperkinetic children, most trials used dosages standardized on the basis of body weight (Rapport et al., 1989). Because of the short elimination half-time (2.6 hours on 0.6 mg/kg; Shaywitz et al., 1982) most clinicians start methylphenidate on a twice-a-day schedule, with dosages at breakfast and lunch-time. In clinical practice, we often adjust methylphenidate dosages and dosage-times (i.e., higher or lower dosages, 3-times-a-day schedules), but not before the clinical effect has been evaluated. Consequently, in the trial we did not change dosage times, and only adjusted dosage to a lower dose in order to diminish adverse effects if necessary. We gave methylphenidate during meals, because this opposes the appetite diminishing adverse effect of methylphenidate. Gualtieri et al. (1984) found that methylphenidate serum levels do not differ when the drug is ingested in the fasting state or after a full meal.

Rational for a "flexible fixed dosage" both for clonidine and for methylphenidate: The use of standardized (fixed) dosages increases the comparability of research findings, whereas the common clinical practice of titrating dosage to caregiver evaluations has the drawback of making replication difficult (Gadow, 1989). However, individual plasma drug levels of methylphenidate have been reported to vary sixfold from day to day in patients on a fixed dose, and the plasma drug level is usually not correlated with clinical response (Gualtieri et al., 1984). Swanson and Kinsbourne (1979) stated that across the age range of 5 to 15 years, the need for methylphenidate does not seem to increase as the child's body size increases. Taylor et al. (1987) in their methylphenidate crossover trial used a flexible dose regimen (with a maximum of 30 mg daily). In our study, the dose regimen had to be similar for all subjects as a consequence of the study design. The patients in trial groups 1+2 were only given clonidine dragees, but the patients in trial group 3 were given both methylphenidate capsules and clonidine dragees. We chose a

flexible fixed dosage strategy because we saw no disadvantages.

Duration of treatment: In clinical practice the clinical effects of methylphenidate can be evaluated after three to four weeks of treatment. Taylor et al. (1987) in their methylphenidate crossover trial had treatment periods of three weeks with an effect evaluation in the third week. Because it takes more time for clonidine to be evaluated than it takes for methylphenidate (taking into consideration our requirement to make the trial "as blind as possible"), this was another argument for holding the trial treatment periods as short as possible.

Compliance

Compliance was maintained and checked by instructions (both oral and written) to both parents and child and by counting the tablets remaining at the end of treatment. This method proved to be effective (see section 5.2).

Concurrent treatments

"Important changes in school, or home situation (as judged by the project-leader, i.e. the author), or in psychological treatment planned or expected for the course of the trial" were already an exclusion criterion. In addition no additional psychoactive drugs were allowed during the trial, with the exception of for instance promethazine for two days because of an upper respiratory infection.

Thus far, research into the effects of dietary manipulation in hyperkinetic children has given conflicting results (Graham, 1989; Van Elburg & Douwes, 1991; Hunt et al., 1991). At the time of the trial, many parents of hyperkinetic children experimented with additive-free diets. Giving their child medication was a last resource for many parents (and teachers and also other caregivers). Because we had the impression that only a small proportion of hyperkinetic patients improved on a diet (but a small proportion can also be meaningful), whilst on the other hand so many parents tried additive-free diets without any supervision (with respect to the diet, and with respect to the evaluation of a behavioral effect), and because we wanted to reduce the risk of parents starting the diet during the trial treatment period (because of possible interference with the medication effect), the parents of each potential trial subject were asked whether they had ever had the impression of a relation between food and problem behaviors in their child. If, to our judgment, they could give recent examples of problem behaviors developing in contiguity to food ingestion (mostly food-additives and chocolate), then the child was scored as "positive". We proposed parents to try an additive-free test-diet (the "BAS-testdieet") for a period of three weeks. We gave instructions similar to those which were given to parents by the Dutch association for patients with untoward reactions to food-additives (Vereniging BAS; BAS-testdieet September 1989). After three weeks we evaluated the effect, namely the parents' impressions of changes during the food-additive diet. We then listed the child as: (1) "positive" (i.e., the parents' impression was that their child's behavior had improved during the test-period); or (2) the test-diet had been tried, but the parents had no impression of improvement after a three weeks' try;

or (3) the parents never had the impression of a relation between food and problem-behaviors in their child, and did not try the test-diet. In this way we prevented the try-out of additive-free diets during the trial treatment. Although our application of additive-free test-diets was not scientifically based (besides, this was not our aim), we report the methods and results of the diet-tries, because it concerns the subjects participating in the trial.

3.4.5 Measurement of efficacy

Withdrawal of patients (drop-outs)

In the study protocol we formulated: "All protocol violations and major deviations will be recorded. The chance of drop-out during the trial is reduced to a minimum by setting the entry just before randomization. All participating patients, regardless of compliance with protocol, will be included in the analysis of the results (analysis by intention to treat)".

Measurement of efficacy

The principal aim of the study was to compare the effects of clonidine with the effects of placebo. We chose for an analysis by intention to treat (Schouten, 1988): "Only those treatment groups, which came about through aselect assignment, are suitable for a statistical comparison. It is not allowed to change the composition of groups that came about by aselect assignment". Pocock (1983): "All eligible patients, regardless of compliance with protocol should be included in the analysis of results whenever possible. This "pragmatic approach" (opposed to the "explanatory approach" of "analysis of compliers only") is sometimes called "analysis by intention to treat" and is normally preferred since it provides a more valid assessment of treatment efficacy as it relates to actual clinical practice". For our study it was most important to include all the patients in the analyses of efficacy, for whom the clinician considered a try with "hyperactivity medication" meaningful.

We planned two strategies to determine efficacy:

(a) For each trial subject a determination with respect to "respondership"; and

(b) For trial groups as a whole the medication effect (experimental treatment compared to standard treatment) found using a repeated measures ANOVA of rating scale scores.

We decided the project-leader (author) was not to rate outcome measures for the following reasons:

(1) Although the trial was double-blind, the author had more experience concerning effects and adverse effects of the medication than the parents and teacher; as a consequence this might bias his judgment. Moreover, in the case that the author made ratings of outcome measures, we also ran the risk that the mentioned bias might accumulate in the course of the trial. We preferred the rating of outcome measures to be made by the parents and the teacher to a rating by the attending physician, because in

clinical practice, the parents' and teacher's judgment of the drug effect usually is decisive with respect to the continuation of a drug after a medication try.
(2) The author performed a vena-puncture in all subjects: the subjects of trial groups 1 and 2 only in the diagnostic assessment phase, but the subjects of trial group 3 also at the moment of the effect evaluation. In the Sophia Children's Hospital as a matter of principle (and possibly of skill?) the child is vena-punctured by his own doctor. There was no other possibility. As a consequence the contact between subjects and author was often influenced by a fear of a vena-puncture, at least at the time of the effect evaluation. As a consequence efficacy measures depended entirely on the judgment of the parents and the teacher.

Definition of "responder"

The procedure to determine if a subject was a "responder" was planned as follows: After seven weeks of medication the project-leader collected from both the parent(s) and the teacher (independent of one another) a global judgment rating of the extent of change in clinical condition of the subject compared to baseline. In the study protocol it was planned to keep a careful watch to see that the project-leader did not influence the parents' or teacher's evaluation process during the time that the child was in the trial. We realized this watch through regular meetings of the project-leader with a child psychiatrist (FV) who did not meet the trial patients. In these meetings the project-leader had to report what he discussed with the parents and the teacher during the course of the trial. For their rating parents/teacher had to make a choice out of the following categories: the extent of change in clinical condition compared to baseline was:
(a) not "clinically significant"; or
(b) there had been a "clinically significant" improvement; or
(c) there had been a "clinically significant" deterioration.
The procedure included that the project-leader orally explained to the parents/teacher what the trial understood by "clinically significant". The study protocol included this definition:
"The project-leader asks the parents orally (the teacher either by telephone, or by letter, or both): "What has changed in your child's behavioral condition, if you make a comparison between his/her behavior just before the start of the medication, and his/her behavior during the sixth and seventh week of medication?". Whereupon, parents (teacher) accumulate a list of favorable and unfavorable changes, and also of problem behaviors which have not changed. The project-leader also asks the parents (teacher) to include all kinds of possible adverse effects in their opinions. The project-leader explains to the parents (teacher) that he means all changes in condition, irrespective of the possible cause. The project-leader then tells the parents (teacher), that the parents' (teacher's) judgment (at the moment not aware of each others judgment) will be decisive in a decision on (re)initiation for a longer period of the medication that the child has been given (although we are all still blind). Then the project-leader asks the parents (teacher) to give their global judgment, taking into account all aspects (favorable and unfavorable

changes, etc.) they have mentioned. The project-leader tells them (the parents/teacher) that this global judgment must lead them (parents/teacher) to a choice out of the following answer-categories (see above (a), (b), or (c)).
The project-leader explains "clinically significant" to the parents (teacher) as follows: "in the case that you judge "clinically significant improvement", this is defined in that you think the degree of your child's improvement is "pronounced", and so meaningful (although you and I are blind to the code, and we do not know what has caused the changes). After we will have broken the code within a few weeks, you expect a decision to be made about giving this medication for a longer period, assuming that possibly there was real drug inside and you might notice the next weeks that the improvement disappears when tapering off the dosage. Then the project-leader cautions the parents (teacher) that sometimes a child deteriorates after stopping a drug. This does not yet mean that, retrospectively, the drug was effective (stopping a drug means changing the situation; whatever this may mean to the child, the daily support of taking a drug has been stopped). If a child before the start of the medication already displayed a "downward trend", or an "upward trend", the parents (teacher) must answer the question if this trend changed in contiguity with the medication period".

Based on the parents' and teacher's rating of improvement the project-leader at the end of the seventh week, thus still blind to the medication code, rated a composite score:
(a) a clinically significant improvement at home and/or in the school situation;
(b) no clinically significant change; or
(c) a significant deterioration at home and/or in the school situation.

A responder was defined as a subject who was rated a composite score (a). At the same time (at the end of the seventh week) the project-leader rated adverse effects.

During the course of the medication period the project-leader registered for each subject all that was reported by the parents and the teacher with respect to behavior, physical complaints, all kinds of changes or events relevant to the evaluation of effects and safety. The project-leader typewrited these notes, making a "log-book". This log-book consisted of two parts:
(1) the results of the diagnostic assessment phase (child psychiatric diagnosis, no DSM-III-R classification; the results of the medical and neurological examination, including laboratory results; problem behaviors formulated by the parents and the teacher as targets for the trial period; and concurrent treatments) and the decursus during the medication period till the moment of the effect evaluation (at the end of the seventh week);
(2) a report on the period from the moment the child started tapering off his dosage until the moment the code was broken and a decision was made with respect to the next course-of-action. The first part of the log-book served as the information, which formed the base on which an independent rater (FV) rated the effect in the form of the above mentioned "composite score", and the adverse effects.

Rating scale scores

Ratings were obtained from parents and teacher separately. The lists were given to the

parents before the start of the medication, asking them to give a separate envelope with lists and instructions to the teacher. It was prearranged, both orally and written, that parents and teacher would avoid any discussion with each other concerning their impression of the child's behavior during the course of the medication period. The project-leader got the ratings back as soon as they had been filled in: from the parents during the next visit to the clinic, and from the teacher in a closed envelope which was either given to the parents or was sent to the project-leader.

The parents and the teacher got oral as well as written instructions with respect to the scoring of the scales, and how and when to return the lists to the clinic. It was insisted upon that the same person(s) filled in all the ratings (parent/teacher alone, or the parents or two teachers together). The project-leader had to be alarmed in order to find a solution if this was not possible (e.g., a teacher who is ill). Ratings which could not be filled in by the same rater(s) were discarded.

The following ratings were collected during the course of the medication period:

At baseline, and at the end of the 3rd week, the 5th week, and the 7th week the following series of questionnaires were used:

(1) Parent and teacher versions of the Groninger Behavior Observation scale (GOO and GBO respectively);

(2) Parent and teacher scores on a semantic differential instrument measuring target behaviors.

At baseline and at the end of the 7th weeks were used:

(3) The Conners Teacher Rating Scale (CTRS), and

(4) Parent and teacher versions of the abbreviated Groninger Behavior Checklists (GGGS and GGBS respectively).

(5) Finally, there was a GPO rating of the children's behavior during standardized playroom observation (trial group 3 only).

The rating scale scores over the seven weeks of treatment were statistically analyzed using a repeated measures ANOVA (BMDP 5V program).

The explanation of the semantic differential (SD; Osgood; Kerlinger, 1973) which was used: Taylor et al. (1987) used semantic differentials in their methylphenidate crossover trial. Clinicians rated on a scale "What is your overall impression of his behavior at present?" with as poles the pair of adjectives "terrible" and "perfect", and parents as well as teachers scored on a scale "What is your overall impression of your son's behavior at present?" with the poles "terrible" and "perfect". In addition parents rated on a scale, that was worded: "The last time we spoke we decided together that the following were the major problems. Have these problems changed since starting this present medicine? How severe are they now?" (scoring on a scale with the poles "very severe problem", and "no problem"). We decided to use SDs in our study in order to have ratings from parents and teacher with respect to target behaviors for the treatment. The study protocol included the following instruction for the wording and the scoring of the SDs:

"The parents/teacher are asked (and the project-leader helps them) to word maximal

three (but at least one) target problem behavior(s), in terms of observable behavior, which they desire the child to improve on during the trial medication period. They are to choose those problem behaviors, which have a great problem value (are the major problems) in the sense that the parents (teacher respectively) think this problem behavior interferes with the child's development. Therefore we want the child to improve with respect to this behavior in order to get a better trend of development."
The term "problem value" was used as defined by Brinkman (1978). Examples were given of "observable behavior" according to behavior therapy practice: the problem behavior had to be worded as if it only was seen on a videotape (Cladder et al., 1986). Although it was expected that the parents (teacher) would choose target behaviors in the range of ADHD symptoms and related symptomatology (because it was for these problem behaviors that the parents and the author had considered a medication try meaningful), the parents (teacher) were left free in their choice. It was explained that it did not matter if the parents (teacher) chose one, two or three target behaviors, because the statistical analysis scores were averaged. Therefore, the parents (teacher) were advised not to choose target behaviors that they did not consider having a great "problem-value". Parents (teacher) scored each of the target behaviors at the mentioned times (0, 3, 5, and 7 weeks) on a semantic differential for each of the target behaviors: "Before we started the medicine you chose 1-2-3 target problems. How severe are these problems now?"
We used the poles "very much a problem" (left side), and "no problem" (right side of a line of 98 mm).

3.4.6 Measurement of adverse effects

According to Loonen and Zwanikken (1987) we differentiated between "untoward physical effects" and "untoward behavioral effects". We only scored up the physical adverse effects. In their global judgment rating of the extent of change of the subject in the clinical condition compared to baseline the parents (teacher) were asked to include "all kinds of possible adverse effects".

All subjects were evaluated for undesired physical adverse effects. The parents were asked to rate the following adverse effects (scale: no-complaints/just-a-little/very-troublesome -for the child-; after Taylor et al., 1987): drowsiness, insomnia, decreased appetite, nausea, headache, nervousness, motor restlessness, feelings of dizziness, dry mouth, nightmares, apathy, irritability, and "other complaints:...". When child and parents visited the clinic during the trial (at least at 10 days, 4 weeks, and at the end of the 7th week), they were asked about all kinds of physical and behavioral complaints or changes. When appropriate, the child was physically examined. When we heard of adverse effects in the school situation, the teacher was telephoned to inquire about them. For every subject a log-book was written, in which all information on effects and undesired adverse effects was registered (see section 3.4.5). At the end of the seventh

week the project-leader rated the physical adverse effects as reported or observed (still blind to the medication code). The scores were: "acceptable" = physical adverse effects present, however acceptable to the patient (i.e., "not troublesome, just a little, acceptable to the opinion of both parents and teacher and clinician"); or "troublesome" = physical adverse effects present to a degree that they are really troublesome/annoying to the patient (i.e., evident functional impairment).
Afterwards an independent rater (FV) also made a score of adverse effects, using the log-book (i.e., part one, therefore still blind for the medication code). Parents and teachers were instructed to include information on unwanted psychological effects of the medication into their global judgment rating of the extent of change in the subject in clinical condition compared to baseline. In the study protocol an "Adverse events reporting agreement" was signed by both the monitor (BT) and the project-leader.

3.4.7 Informed consent and trial procedure

The study protocol was approved by the Medical Ethical Committee and informed consent was obtained (Appendix 3.4.7).
We planned to investigate all trial 3 subjects in the same following order:
(1) vena-puncture: not before 8.00 and not after 10.00 AM (i.e., within two hours of taking the dosage; several patients came from far away);
(2) playroom observation (duration half an hour; within 2½ hours of taking the dosage); and
(3) reaction-time experiments (within 3½ hours of taking the dosage).
We planned treatment periods so, that evaluation points were not due in a holiday, and did not occur until the teacher had seen the child for at least four days after a holiday.

Indication and procedures for premature termination of the study
In the study protocol we formulated:
(1) "We see no reason to suspect harmful consequences for the participating patients. So there is no reason to set up a monitoring-committee for interim-decisions concerning the continuation of the study";
(2) "Thus far there is no diagnostic method to predict responsiveness on clonidine or methylphenidate in a single patient. So we do not apply a treatment on children in whom we could suspect from the beginning that clonidine would not help";
(3) "There is also no reason to reckon with premature termination from a financial point of view".

3.5 CONCLUSION

This chapter described the methods of the study: the independent variable (DSM-III-R), the dependent variables, and the methods of the medication trial. The next chapter will describe the results of the diagnostic assessment.

Chapter 4

CHAPTER 4 RESULTS OF THE DIAGNOSTIC ASSESSMENT

4.1 Introduction

This chapter describes the results of the diagnostic assessment of the 109 children who participated in the trial. Section 4.2 describes the general characteristics of the children, their families, and the target problem behaviors that were formulated by the parents and the teacher. The independent variables (DSM-III-R classification) are described in section 4.3. The remaining sections report on the dependent variables: the symptom severity scores (section 4.3.2), the medical examination (section 4.4), the behavior rating scales (section 4.5), and the psychological assessment and direct behavioral observation (section 4.6). The chapter concludes with a summary (section 4.7).

4.2 Subjects

From January 1989 to September 1990, 109 subjects entered the study: 93 boys and 16 girls. Table 4.2a shows their main characteristics. The age range was 6-15 years (mean age 8.9, SD 2.0). Of the subjects 59% attended schools for special education. Five subjects entered trial 1, 32 trial 2, and 72 trial 3 (total n=109).

Table 4.2a Sex and age of the subjects entering the study (n=109).

	Trial group 1 n=5	Trial group 2 n=32	Trial group 3 n=72	Trial groups[a] 1+2+3 n=109
sex (M/F)	3 /2	28/4	62/10	93/16
age: mean (SD)	8.2 (1.3)	9.4 (2.2)	8.8 (1.9)	8.9 (2.0)
special education	40.0%	50.0%	63.9%	58.7%

[a] Definition of trial groups: 1 = ADHD + Pervasive Developmental Disorder; 2 = ADHD + Tic Disorder; 3 = ADHD, no PDD, no Tic Disorder.

All subjects had been referred by physicians. Table 4.2b shows the specialisms of the physicians who referred the subjects. Fourty percent of the subjects were referred by a school-doctor. Five of these subjects were referred as a result of a collaborative research project of the Sophia Children's Hospital and the Pedological Institute Rotterdam (see Appendix 4.2).

Table 4.2b Distribution of specialities of the physicians who referred the subjects.

	N	%
school-doctor	43	39.5
general practitioner	24	22.0
child psychiatrist	20	18.4
pediatrician	14	12.8
neurologist	8	7.3
	109	100.0

The families of the subjects

Ninety-four percent of the subjects was Caucasian. Ninetytwo percent (n=100) of the children lived with both a "father" and a "mother", and eight percent (n=9) lived with a single parent. This was always the mother. Of the children with two "parents", 89 lived with both biological parents, eight lived with both a biological parent and a stepparent, and three lived with adoptive or foster parents. Twelve percent of the subjects lived in a family with more than three children.

The socioeconomic status (SES) of the parents was scored on a six-step occupation scale (Van Westerlaak et al., 1975). If both parents worked, the higher-status occupation was used to score SES. Table 4.2c shows the percent of each occupational level for the parents of the subjects. Fourtyone percent of the parents came from lower SES (classes 1+2), and in 7.3% of the families the parent(s) was (were) disabled or unemployed. Table 4.2d shows the educational level of the parents of the subjects. For each parent we scored the highest level of education, which had been finished. If a child lived with both parents, the higher level of the two was used. Fourtyfour percent finished education after primary school or with a certificate of lower vocational education.

Table 4.2e gives the distribution of urbanization (CBS, 1989). Fourtythree percent of the children lived in towns with at least 50,000 inhabitants.

Table 4.2c Occupational level of parents of subjects.

1.	Unskilled employees	8	(7.3%)
2.	Skilled manual employees	37	(33.9%)
3.	Clerical, technicians, minor professionals	26	(23.9%)
4.	Owners of small businesses	7	(6.4%)
5.	Supervisory, lesser professionals	10	(9.2%)
6.	Executives, major professionals, owners of large businesses.	13	(11.9%)
	No profession (disabled, unemployed)	8	(7.3%)
		109	(100%)

Table 4.2d Educational level of parents of subjects.

1. Special education	0	
2. Primary school	9	(8.3%)
3. Lower vocational education	39	(35.8%)
4. Intermediate vocational education or MAVO	28	(25.7%)
5 HAVO/VWO	18	(16.5%)
6. Higher education	15	(13.8%)
	109	(100%)

Table 4.2e Percentage of urbanization for the subjects.

1.Rural: more than 20% of the population has agricultural profession	8	(7.3%)
2. Semi-rural: less than 20% of the population has agricultural profession, fewer than 30,000 inhabitants	5	(4.6%)
3.Suburban: less than 20% of the population has agricultural, more than 30% commuters	37	(33.9%)
4. Small towns: 2,000 to 50,000 inhabitants	12	(11.0%)
5.Urban: 50,000 to over 100,000 inhabitants	47	(43.1%)
	109	(100%)

Prior treatment

Table 4.2f shows the type of treatment for problem behaviors, which had been given to the subjects in the year, preceding their participation in the study. Parent guidance or home training had been given to 45% of the subjects. Five percent of the children had been given psychotherapy and six percent were still in treatment at a day-center. In the category "prior treatment" we also want to include the placement of a child at a school for special education, because this often is not only for learning problems but also because of problem behaviors. Fifty-nine percent of the children were at a school for special education.

Table 4.2f Percentages of subjects who received treatment for problem behaviors in the year preceding their participation in the trial.

Parent guidance or hometraining	45.0%
Individual or group psychotherapy	4.6%
Treatment in a day-center (after school-time)	6.4%

Psychiatric disturbance in the family

Based on the information obtained with the Malaise Inventory, we classified the psychiatric symptoms of the "parents", with whom the child lived. "Parents" were either biological or stepparents. The information for the Malaise Inventory was obtained in

interviews with the mother of the child (52%), the father (6%), or both parents (42%). We scored symptom areas which gave disability, according to the judgment of the interviewer. The results are shown in table 4.2g. When a parent had more than one problem area, we only scored the one which was most disabling.

Table 4.2g Psychiatric symptoms of the parents as reported in the Malaise Inventory.

	Fathers n=100	Mothers n=109
Anxiety problems, depression or somatoform disturbances	4%	27%
Tourette's Disorder	2%	1%
Alcohol dependence or abuse, antisocial or borderline personality disorder	14%	4%
ADHD symptomatology		3%
Total percentage:	20%	35%

It was found that 20% of the fathers, and 35% of the mothers had disabling psychiatric symptoms. Alcohol abuse was most often reported for fathers and anxiety problems were most often reported for mothers.

We assessed the existence of childhood hyperactivity for first degree relatives of our subjects. The parents were asked a series of questions about the presence of marked overactivity, inattentiveness and impulsivity in their own history. Childhood hyperactivity was deemed to have existed if parents recalled having serious problems related to at least one of these symptoms. Whenever possible, we made a judgment for both biological parents. We included judgments of childhood hyperactivity based on information from the present parent concerning the absent spouse. In a similar way a judgment was made for siblings of our subjects, and for other family members. We also enquired after tics, particularly during childhood. We classified the results as follows: (1) A first degree family member with childhood hyperactivity; (2) A positive family history with respect to tics; (3) childhood hyperactivity in a family member > 1st degree, and no childhood hyperactivity in a 1st degree family member. We could obtain information on 106 subjects. The children in adoption or foster care had to be excluded.

It was found that 39% of the subjects had a first degree relative with childhood hyperactivity. A family history of tics was found in 11% (n=12). Of the latter subjects, 10 had Tic Disorder. A history of childhood hyperactivity only in family members > 1st degree was found in 18%.

Problems parents and problems teacher

Both the parents and the teacher formulated target problem behaviors with respect to the subjects. After completing the trial we grouped these target behaviors into the following categories:

(1) "Hyperactive": These were problem behaviors within the range of problem behaviors, described in the DSM-III-R category ADHD.
(2) "Oppositional": These were problem behaviors within the range of problem behaviors, described in the DSM-III-R categories Oppositional Defiant Disorder or Conduct Disorder.
(3) "Tics".
(4) "Anxiety".
(5) "Handwriting".
(6) "Difficulty falling asleep".

Three of the teachers (n=3/109) did not formulate any target behaviors because they felt that the child showed no problem behaviors in the school situation. Most parents and teachers formulated three target behaviors for a child.

For 98% of the subjects, "Hyperactive" target behaviors were formulated by either the parents or the teacher. The category "Hyperactive" included behaviors such as: overactive, difficulty remaining seated, attention problems and interruptions/"doesn't realise he's going too far" (not due to oppositional behavior).

"Oppositional" target behaviors were formulated for 69% of the subjects, either for the home or for the school situation. "Oppositional" included behaviors such as: teasing, irritability, arguing, hitting/fighting, "does not take "NO", and stealing.

"Tics" were formulated as target problems for 27% of the children with Tic Disorders.

Seventeen percent of the children had target behaviors in the category "Anxiety". This category included anxiety, and, for two subjects, depressed mood.

The category "handwriting" included fine manipulative abilities, particularly handwriting, and sometimes gross motor achievement. Six percent of the subjects had target problems in this area.

"Difficulty falling asleep" also included difficulties in getting a child to his bed. Parents chose problems in this area as a target in treatment for 11% of the subjects. Bedwetting was formulated as a target for two children, encopresis for one child, and stuttering also for one child.

Parents's impressions with respect to the relation food - problem behaviors in their child

The parents of each subject were asked whether they had ever had the impression of a relation between food and problem behaviors in their child. When parents wanted to try an additive-free test-diet, they were supervised with respect to the diet and the evaluation of the behavioral effect. All diet-tries were before the trial treatment period. No children were withdrawn from the trial after having tried an additive-free diet. When a child improved on diet, the diet was continued during the trial treatment period. The parents' impressions were as follows (Gunning, 1991):
(1) For 20 of the 109 subjects parents could give recent examples of problem behaviors developing in contiguity to food ingestion, or noticed a meaningful improvement of problem behaviors during an additive-free test diet (18.3%; 4 in trial groups 1+2, and 16

in trial group 3) .
(2) For 36 children, parents did not have the impression of a meaningful (however little) improvement after a three weeks' try (33.0%; 10 in trial groups 1+2, and 26 in trial group 3).
(3) For 53 children, parents had never had the impression of a relation between food and problem-behaviors in their child, and did not try the test-diet (48.6%; 23 in trial groups 1+2, and 30 in trial group 3).

4.3 Results of the psychiatric assessment

4.3.1 DSM-III-R classification

All 109 children were able to complete their interviews, although for five children two appointments were necessary because they were not able to cooperate for longer than half an hour. Parent interviews were also completed for all the patients. Most parent interviews were completed with the mother (52%) or both parents jointly (42%), but sometimes with the father (6%). Subsequently a summarizing report was made. Appendix 4.3.1a shows an example of a descriptive diagnosis as reported in the summarizing report.

Appendix 4.3.1b shows the project-leader's scoring on the ADHD Rating Scale for each subject. All 109 subjects obtained an item count of $\geq$ 8-out-of-14 of items scoring ≥ 2. When applying the recently published criteria for the ADHD Rating Scale (Barkley, 1990), we found that 28 subjects, all boys (25.7%), did not meet the new criteria (see Appendix 4.3.1b).

A diagnostic case conference was held three times during the course of the trial. The first conference was held when 40 subjects had entered the study. It was considered important to recapitulate the DSM-III-R classification instructions:
(1) Problem behaviors in a patient with Tourette's Disorder had to be classified in addition to a diagnosis Tourette's Disorder, when symptomatology met criteria (e.g., Oppositional Defiant Disorder, Overanxious Disorder); (2) In children with PDD NOS a diagnosis of ADHD is preempted; (3) A diagnosis of Conduct Disorder preempts a diagnosis of Oppositional Defiant Disorder.
Further, raters perceived that even when they had "all" the necessary information at their disposal, it was often difficult to make a choice between Conduct Disorder and Oppositional Defiant Disorder. Six ratings, for which the project-leader considered that the rater had misunderstood the DSM-III-R instructions, were given afresh to the same rater. In no other ratings have any changes been wrought. A consensus procedure was necessary for cases, for which no two raters agreed on the classification (see Appendix 4.3.1a for details). It appeared that raters had experienced no problems with the classification Pervasive Developmental Disorder NOS in the few children for whom this

diagnosis had been considered.

Table 4.3.1a shows the DSM-III-R classifications on which two of the three raters agreed or which were agreed on as a result of a diagnostic case conference for each trial group. The number exceeds 109, because more than one classification was possible.

Table 4.3.1a DSM-III-R classifications in each trial group
(total number of patients: 109; trial group 1 n=5, trial group 2 n=32. and trial group 3 n=72).

	DSM-III-R **classifications**	Trial **group 1**	Trial **group 2**	Trial **group 3**
* ADHD	(n=104):	n.a.	32	72
* PDD NOS[a]	(n=5):	5	n.a.	n.a.
* Tourette's Disorder	(n=21):	1	20	n.a.
* CMTD	(n=7):	0	7	n.a.
* Transient Tic Disorder	(n=5):	0	5	n.a.
* Conduct Disorder	(n=10):	0	2	8
* ODD[c]	(n=33):	0	9	24
* Overanxious Disorder	(n=2):	0	1	1
* Dysthymia	(n=3):	0	1	2
* Depressive Disorder NOS	(n=2):	0	0	2

[a] PDD NOS: Pervasive Developmental Disorder Not Otherwise Specified; [b] CMTD: Chronic Motor Tic Disorder; [c] ODD: Oppositional Defiant Disorder. n.a. = not applicable.

All subjects met the DSM-III-R criteria for ADHD. In addition the following DSM-III-R diagnoses were made:

(1) Five children were classified Pervasive Developmental Disorder NOS;

(2) Thirty-three children had Tic Disorder. This group comprised 21 children with Tourette's Disorder, seven children with Chronic Motor Tic Disorder and five children with Transient Tic Disorder.

(3) Ten children had Conduct Disorder and 33 Oppositional Defiant Disorder.

(4) Two subjects had Overanxious Disorder, three Dysthymia, and two Depressive Disorder NOS.

DSM-III-R Interrater reliability

We determined the degree of correspondence between raters by computing kappa coefficients of agreement (kappa) and interrater correlation coefficients (Φ). Kappa is a measure of agreement with desirable properties (Fleiss, 1981): If there is complete agreement, then kappa = +1; if observed agreement is greater than or equal to chance agreement, then kappa $\geq$ 0, and if observed agreement is less than or equal to chance

agreement, then kappa ≤ 0. Interrater correlation coefficient Φ is another widely used measure of interrater reliability. Φ is defined as: $\Phi = \sqrt{(X^2/N)}$. Kappa is identical to Φ if $k_1/k_2 = r_1/r_2$ (k_1 and k_2 are sums of columns, r_1 and r_2 are sums of rows).

We calculated kappa's and phi's for each pair of raters, and kappa's between three raters. Because ratings were at random distributed to two of the three child psychiatrists, "rater 1" and "rater 2" only represent the first and the second child psychiatrist, by whom the subject was rated. Because we were interested in the correspondence between raters on clusters of disorders, we first combined the following diagnoses for this computation:
(a) Tourette's Disorder, Chronic Motor Tic Disorder, and Transient Tic Disorder into a cluster "Tic Disorders";
(b) Conduct Disorder and Oppositional Defiant Disorder into a cluster "Defiance"; and
(c) Overanxious Disorder, Dysthymia, and Depressive Disorder NOS into a cluster "Emotional Disorders".

Table 4.3.1b shows kappa coefficients of agreement, and interrater correlation coefficients (phi) for each pair of raters, and kappa's between three raters, for DSM-III-R classifications. Because kappa's (and phi's) for the diagnoses ADHD, Pervasive Developmental Disorder, and Tic Disorders were "1", these diagnoses have been left out in table 4.3.1b. Kappa's were moderate for "Defiance" and weak for "Emotional Disorders". We will return to this subject in the discussion (section 7.2).

Table 4.3.1b Kappa coefficients of agreement, and interrater correlation coefficients (phi) for each pair of raters, and kappa's between three raters, for DSM-III-R clusters "Defiance" and "Emotional Disorder".

		author versus rater 1	author versus rater 2	rater 1 versus rater 2	author vs rater 1 vs rater 2
Defiance[a]	kappa:	0.68	0.62	0.67	0.66
	phi:	0.68	0.63	0.67	
Emot.Dis.[b]	kappa:	0.11	0.56	0.07	0.26
	phi:	0.11	0.60	0.07	

[a] Defiance = Conduct Disorder and Oppositional Defiant Disorder.
[b] Emotional Disorder = Overanxious Disorder, Dysthymia, and Depressive Disorder NOS.

Age of onset of ADHD symptomatology

A history of the problem behaviors, and a developmental history were obtained from the parents. Based on this information, it was assessed at what age the child started to have ADHD problem behaviors. It was found that the onset was during the first year of life in 18% of the subjects, between age 1 and age 3 in 48%, and after age 3 but before the age of seven in 34% of the subjects.

Enuresis, encopresis and stuttering

Twenty-four subjects (22.0%) fulfilled the DSM-III-R criteria for Functional Enuresis, and seven (6.4%) met the criteria for Functional encopresis. Nine (8.3%) subjects met the criteria for Stuttering. Of these subjects three had Tic Disorder.

4.3.1 Symptom severity scores

For each subject a global clinical judgment was made by rating the severity of symptoms on each of the following three dimensions: "hyperactivity" (H-score), "conduct disorder" (CD-score) and "emotional disorder" (E-score). For each of these dimensions a 4 point rating scale was used (0="absent", 1="mild", 2="moderate", or 3="severe").

Table 4.3.1a shows the sum scores of the symptom severity rating for the three trial groups. For individual subjects the results are shown in Appendix 4.3.1b. Table 4.3.1b shows the proportion of subjects with symptom severity scores ≥ 2. Table 4.3.1c shows the Pearson correlations between symptom severity scores for the trial groups 2 and 3.

We compared the symptom severity sum scores in trial groups 2 and 3, using Student's t-test (two-sided). There were no significant differences (table 4.3.1a). We compared the proportion of subjects in trial groups 2 and 3, scoring ≥ 2 on the dimensions H, CD, and E respectively, using a Fisher's exact test (two-sided). There were no significant differences (Table 4.3.1b). Table 4.3.1b shows that only 8% of the subjects had both CD- and E-scores equal to 0. We might consider this group of subjects as the "pure hyperactives". Next, it is interesting to note, that of the subjects with CD-score ≥ 2 (n=45), only 2 were judged mildly "hyperactive" (H-score = 1). Thus, nearly all subjects who scored moderate to severe on "conduct disorder", also scored moderate to severe on "hyperactivity". Finally, it was shown that all subjects with both CD- and E-scores ≥ 2, also had H-scores ≥ 2. Table 4.3.1c shows that both for trial group 2 and trial group 3 significant positive correlations were found between "hyperactivity" and "conduct disorder" symptom severity scores (r = 0.32). For trial 3, but not trial 2, a significant negative correlation was found between "conduct disorder" and "emotional disorder" symptom severity scores (r = -0.25).

Table 4.3.1a Symptom severity sum scores for the three trial groups.

	Trial group 1 (n=5)	Trial group 2 (n=32)	test[a] p-value	Trial group 3 (n=72)	Trial groups 1+2+3 (n=109)
H-score (mean±SD)	2.4±0.5	2.2±0.7	0.062 **NS**	2.5±0.7	2.4±0.7
CD-score (mean±SD)	1.0±0.9	1.3±1.0	0.058 **NS**	1.4±1.0	1.2±1.0
E-score (mean±SD)	2.0±1.1	1.3±1.0	0.123 **NS**	0.9±0.9	1.1±1.0

[a] t-test (two-sided)

Table 4.3.1b Proportion of subjects with symptom severity scores ≥ 2.[a]

	Trial group 1 (n=5)	Trial group 2 (n=32)	test[b] p-value	Trial group 3 (n=72)	Trial groups 1+2+3 (n=109)
H ≥ 1, CD=0, E=0	1	3		5	9 (8%)
CD = 0	2	12 (38%)		17 (24%)	31 (28%)
E = 0	1	9 (28%)		29 (40%)	39 (36%)
H ≥ 2	5	27 (84%)	0.576 **NS**	65 (90%)	97 (89%)
CD ≥ 2	2	10 (31%)	0.237 **NS**	33 (46%)	45 (41%)
CD ≥ 2, H = 1	0	1		1	2
CD≥ 2, H ≥ 2	2	9 (28%)		32 (44%)	43 (39%)
E ≥ 2	4	13 (41%)	0.434 **NS**	22 (31%)	39[c](36%)
E ≥ 2, CD ≥ 2	2	2		6	10[d] (9%)

[a] Scores: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.
H = Hyperactivity score, CD = conduct disorder, E = emotional disorder.
H-scores were always ≥1.
[b] Fisher's exact test (two-sided).
[c] Of the subjects with E-score ≥ 2 only 3 had a H-score = 1.
[d] Of the subjects with both E- and CD-score ≥ 2, all had H-score ≥ 2.

Table 4.3.1c Pearson correlations among symptom severity scores
(H: "hyperactivity", CD: "conduct disorder", E: "emotional disorder").

	Trial 2 (n=32)		Trial 3 (n=72)		Trial 1+2+3 (n=109)	
	CD-scores r/p-value	E-scores r/p-value	CD-scores r/p-value	E-scores r/p-value	CD-scores r/p-value	E-scores r/pvalue
H-scores	.32/.037*	.07/.354	.32/.003**	.11/.177	.33/.000**	.05/.302
E-scores	-.17/.179		-.25/.015*		-.21/.013*	

* $p < .05$, ** $p < .01$

4.4 The Medical examination

4.4.1 Physical examination

The physical examination was carried out by the project-leader with a parent present. On the basis of the physical examination four children were referred to an oculist because of a weak visual acuity, two girls were referred to the child endocrinologist because of a premature pubarche, and one boy was referred to the hematologist because of recurrent bruises (not due to child abuse).

For the rest the following somatic disorders were found in the subjects:
(1) Epilepsy: One girl (No. 3, trial group 1) had experienced a tonic-clonic seizure once in her live (half a year before the trial period). She was examined with a magnetic resonance scan, which revealed an arachnoidal cyst in the left temporal region. Another

girl (No. 7, trial group 3) had sporadic generalized tonic clonic seizures and used carbamazepine. One boy (No. 44, trial group 2) had complex partial seizures and also used carbamazepine.
(2) Heart diseases: One boy (No. 20, trial group 3) had a small ventricular septal defect. Another boy (No. 50, trial group 2) had a status after a Senning operation because of a congenital transposition of the great arteries. A third boy (No. 105, trial group 2) had a status after a patent ductus arteriosus.
(3) CARA: Eight children had CARA. Of these four were on medication: Beclometason, salbutamol, cetirizine and/or cromoglicine acid. Medication included no (psycho-active) antihistaminica.
(4) Miscellaneous: A boy (No. 32, trial group 3) had congenital hypothyroidism and used thyroxine. A boy (No. 39, trial group 3) had a status after marsupialization of a traumatic pancreatic cyst. A girl (No. 38, trial group 3) had a brother and other family members with the Syndrome of Aarskog. A girl (No. 102, trial group 3) had a pubertas praecox caused by ovarian cysts. One boy (No. 27, trial group 3) had an atresia of the right ear, and one girl (No. 58, trial group 3) was deaf on one side.

4.4.2 Minor physical anomalies

For three children (No. 3, 16, and 65) the weight score on the list of Waldrop and Halverson (1971) was 5 or more. For these children we consulted the clinical geneticist in order to rule out a specific malformation syndrome. However, no specific malformation syndrome was detected. For another boy we also consulted the geneticist. He had a Waldrop-score of only 0, but showed symptoms (pigeon-breast, tall and slender, hyperextension of joints) suggestive of Marfan syndrome.

A head circumference above the 98th percentile was found in 12 subjects (11.0%).

4.4.3 Developmental neurological examination

The subjects were neurologically examined using the developmental neurological examination according to Touwen (1979). Figure 4.4.3 shows the distribution of deviant neurological clusters for the subjects. The clusters "coordination and balance", "fine manipulative ability", and "miscellaneous" were most frequently found deviant. Diadochokinesis, tandem gait, and standing on one leg were the tests which were most frequently deviant in the cluster "coordination and balance". Of the tests in cluster "fine manipulative ability", the finger-opposition and the circle test were most frequently deviant. Scores in cluster "rarely occurring miscellaneous dysfunctions" were mostly due to an excessive amount of associative movements for age during diadochokinesis, and during walking on toes or on heels. One boy (No. 66) was found to have a one-sided rectus paralysis (VIth nerve).

Subjects could be classified as:

1. Minor Neurological Dysfunction: 33.9% (n=27)
   (MND-1 n=29, and MND-2 n=8).
2. Neurologically normal: 64.2% (n=70).
3. Neurologically abnormal: 1.8% (n=2).

The two neurologically abnormal subjects were a boy (No. 9) with a right-sided hemiplegia and a mild dysphasia, and a boy (No. 57) with a right-sided hemiplegia and a congenital nystagmus.

Because of dysfunctions found during the neurological examination, fourteen subjects were referred to an occupational or physical therapist, and two children were referred to an orthopaedic surgeon (because of genua vara, and backache due to a M.Scheuermann, respectively).

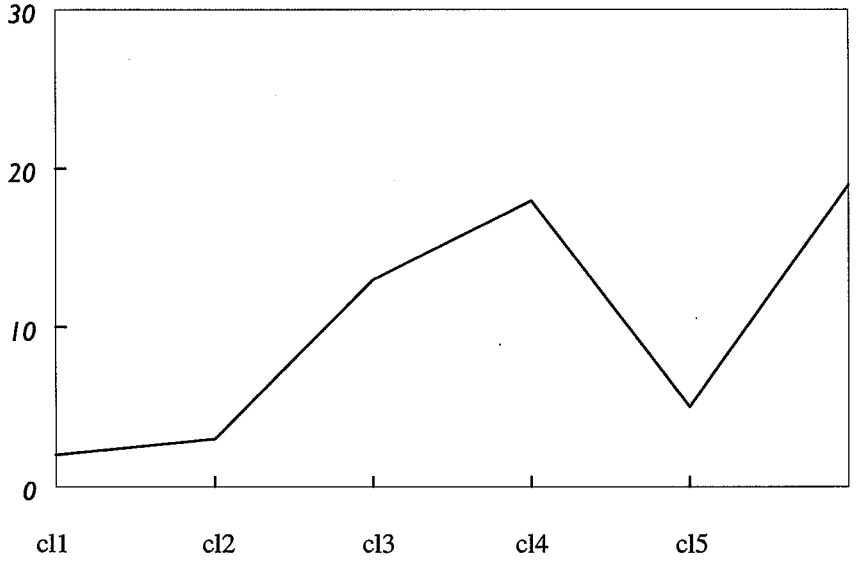

Figure 4.4.3 Distribution of deviant neurological clusters in subjects.
Y-axis: percentage of children with deviant cluster;
X-axis: cluster.

cl 1: posture / muscle tone
cl 2: reflexes
cl 3: coordination and balance
cl 4: fine manipulative ability
cl 5: choreiform dyskinesia
cl 6: miscellaneous

4.5 Behavior rating scales

4.5.1 CBCL and TRF

Table 4.5.1a shows the proportion of subjects, who had CBCL/TRF total problem scores in the clinical range (i.e. above the 90th percentile for nonreferred US boys/girls, T-score > 63; Achenbach & Edelbrock, 1983, 1986). The percentage of children with scores in the clinical range was higher for parent than for teacher reported total problem scores (89% and 73% respectively). Sixty-seven percent had both CBCL and TRF total problem scores in the clinical range, and only 5% had neither CBCL nor TRF total problem scores in the clinical range. We compared the proportions of children with total problem scores in the clinical range between trial groups 2 and 3, using Fisher's exact test (two-sided). There were no significant differences (table 4.5.1a).

Table 4.5.1a Proportions of subjects who had CBCL/TRF total problem scores (TPS) in the clinical range (i.e. above the 90th percentile for nonreferred US boys/girls[a], T-score > 63).

	Trial group 1 n/N	Trial group 2 n/N (%)	Stat.compar. trial groups 2 versus 3 (Fisher's[b])	Trial group 3 n/N (%)	Trial groups 1+2+3 n/N (%)
CBCL TPS in the clinical range	5/5	27/32 (84%)	←NS→	65/72 (90%)	97/109 (89%)
TRF TPS in the clinical range	5/5	27/32 (84%)	←NS→	47/72 (65%)	79/109 (73%)
Both CBCL and TRF TPS cl.range	5/5	24/32 (75%)	←NS→	44/72 (61%)	73/109 (67%)
CBCL + TRF TPS < 90th perc.	0/5	1/32		4/72	5/109 (5%)

[a] taken from norms given by Achenbach and Edelbrock (1983, 1986).
[b] statistical comparison trial groups 2 and 3 (p-value Fisher's exact test, two-sided).

Appendices 4.5.1a-4.5.1b show the mean CBCL/TRF total problem T-scores for subjects and for Achenbach and Edelbrock's (1983, 1986) normative samples of referred clinically and nonreferred USA boys/girls. The subjects in all trial and age subgroups had mean total problem T-scores on both CBCL and TRF which were much higher than in nonreferred samples, and slightly higher than in samples of referred children. For mean CBCL/TRF Internalizing/Externalizing and factor T-scores we found similar results (appendices 4.5.1c-4.5.1f).

We found that a high percentage (65%) of our boys aged 6-11 had CBCL Hyperactive factor T-scores in the clinical range. However, only 21% of the boys aged 6-11 had either

TRF Inattentive or Nervous-Overactive factor T-scores in the clinical range (appendix 4.5.1g).

Table 4.5.1b shows the distribution of CBCL profile types for the subjects aged 6-11 and for Achenbach and Edelbrock's (1983) sample of 6-11-year-old clinically referred boys/girls. In order to be able to compare our subjects with Achenbach and Edelbrock's (1983) data, a subject was classified to a profile type on the basis of his/her highest intraclass correlation coefficient (ICC) > .00. We report data on subjects aged 6-11 (n=97). Two children had to be excluded because their parents omitted more than 8 items on the CBCL. For children with (raw) total problem scores ≤ 25 or ≥ 100, no ICC was computed. Children whose profiles did not correlate positively with any type (ICC ≤ .00) are indicated in the table as "unclassified". Data show that as expected the Hyperactive profile type was most frequently found (40% of the boys, and 27% of the girls), which is much more frequent than in Achenbach et al.'s (1983) sample. Next, the Depressed-Social Withdrawal-Aggressive profile type is rather frequent in boys, and the Aggressive-Cruel profile type in girls. When interpreting these data we must bear in mind that the number of girls was very small (n=10).

Table 4.5.1b CBCL Profiles for subjects and USA referred boys/girls[a] aged 6-11.

	Trial group 1 n=5	Trial group 2 n=26	Trial group 3 n=64	Trial gr.1+2+3 n=95[b]	USA norm[a]
CBCL profile type:					
Boys:	n	n	n	n (%)	(%)
Schizoid-Social Withdrawal		1	3	4 (5.0%)	4.2%
Depressed-SocWithdr-Aggr.	1	4	7	12 (15.0%)	7.6%
Schizoid		2	1	3 (3.8%)	13.9%
Somatic Complaints		2	1	3 (3.8%)	16.1%
Hyperactive	2	8	22	32 (40.0%)	14.1%
Delinquent		1	9	10 (12.5%)	22.4%
Unclassified		1	5	6 (7.5%)	6.8%
Total score ≤ 25 / ≥ 100		4	6	10 (12.5%)	14.9%
				80 (100%)	100%
Girls:	n	n	n	n (%)	(%)
Depressed-Social Withdrawal			2	2 (13.3%)	12.9%
Somatic Complaints			1	1 (6.7%)	14.0%
Schizoid-Obsessive				0 (0%)	5.1%
Sex Problems			2	2 (13.3%)	10.1%
Hyperactive	2	1	1	4 (26.7%)	10.6%
Delinquent		1		1 (6.7%)	12.9%
Aggressive-Cruel		1	2	3 (20.0%)	15.4%
Unclassified				0 (0%)	2.7%
Total score ≤ 25 / ≥ 100			2	2 (13.3%)	16.3%
				15 (100%)	100%

[a] taken from norms given by Achenbach and Edelbrock (1983): 1050 boys, 435 girls.

[b] of the 109 subjects 12 were > 11 yrs old; in addition for 2 boys ICCs were not computed because parent omitted more than 8 items.

We compared subjects who attended normal schools (n=45) with subjects attending schools for special education (n=64) on CBCL and TRF total problem, Internalizing and Externalizing scores, using a Mann-Whitney U test (two-sided). It was found that subjects attending special education had significantly higher CBCL total problem and externalizing scores than controls. TRF scores showed no significant difference between the two groups (table 4.5.1c).

Table 4.5.1c CBCL/TRF total problem, Internalizing, and Externalizing T-scores for two subgroups of subjects: (1) attending regular schools; and (2) attending special education.

	Regular school n=45	Special education n=64	Test[a] p-value
CBCL:			
Total problems	71.20 (6.37)	73.98 (8.73)	0.028 *
Internalizing	66.98 (7.51)	68.83 (8.57)	0.139
Externalizing	72.16 (5.76)	74.95 (7.61)	0.006 **
TRF:			
Total problems	66.38 (5.63)	66.97 (6.34)	0.468
Internalizing	63.22 (5.88)	61.94 (6.98)	0.449
Externalizing	66.09 (5.94)	67.25 (6.91)	0.415

[a] Mann-Whitney U test (two-sided); * $p < .05$, ** $p < .01$

4.5.2 The Groningen Behavior Observation scales (GOO/GBO) and Conners Teacher Rating Scale (CTRS)

Barkley (1990) cautioned for retest effects using the CTRS with scores being significantly lower at the second administration. Therefore, we administered both the CTRS and GOO/GBO before the child's first visit to the clinic. A second administration (3-10 weeks later) was used as a baseline rating for pre-post treatment effects. Table 4.5.2a shows mean scores of these "assessment" and "baseline" measurements. We compared these measures, using Mann-Whitney U test (two-sided), and found no significant decline. Because "baseline" measures are more relevant for the trial than "assessment" measures, we shall report the data of the "baseline" administration. The CBCL and TRF data originate from the assessment administration: Over 1-week intervals, Achenbach and Edelbrock (1983, 1986) found declines in problem behavior scores which were small for most CBCL/TRF scales. In our study it was considered

appropriate to compare "assessment" CBCL/TRF ratings with "baseline" GOO/GBO/CTRS ratings.

Table 4.5.2a Mean GOO/GBO/CTRS scores of subjects at "assessment" and at "baseline" measurement.

	"Assessment" mean (SD) n=109	"Baseline" mean (SD) n=109	Mann-Whitney U test
GOO	45.61 (7.59)	45.27 (7.64)	NS
GBO	43.69 (8.81)	43.07 (8.82)	NS
CTRS hact. factor	14.83 (3.29)	14.85 (3.21)	NS
CTRS sum score	79.46 (13.64)	82.11 (13.00)	NS

Table 4.5.2b shows the proportions of subjects who had GOO/GBO/CTRS scores above the 90th percentile of normative samples. We confined ourselves to the group of children aged 6-12 (94% of all subjects), because the normative sample had this age range. More subjects scored above the 90th percentile on the parent reported GOO than on the teacher reported GBO (70% and 43% respectively). The percentage of children scoring above the 90th percentile on both GOO and GBO (the group which might be considered pervasively hyperactive) was 33%. A large proportion of the children (24%) had scores $\leq$ the 90th percentile on both GOO and GBO. Although selected for their hyperactivity, CTRS findings showed that subjects had similar percentages of scores above the 90th percentile on factor 1 (acting-out) and factor 4 (anxiety-withdrawal) as on factor 3 (hyperactivity) (37%, 32%, and 30% respectively). We compared the proportions of children with scores above the 90th percentile between trial groups 2 and 3, using Fisher's exact test (two-sided): trial group 3 had significantly more children with scores above the 90th percentile on both GOO and GBO than trial group trial 2 ($p = 0.036$). For GOO, GBO and CTRS we found no other significant differences between trial groups 2 and 3 (table 4.5.2b).

Table 4.5.2b Proportions of subjects aged 6-12, who had scores on the GOO/GBO/CTRS above the 90th percentile for normative samples[a].

	Trial 1 n/N	Trial 2 n/N (%)	Statist.comp. trial 2 vs 3 (Fisher's[b])	Trial 3 n/N (%)	Trial 1+2+3 n/N (%)
GOO score >P90	3/5	18/29 (62.1%)	←NS →	47/68 (69.1%)	71/102 (69.6%)
GBO score >P90	1/5	9/29 (31.0%)	←NS →	34/68 (50.0%)	44/102 (43.1%)
Both GOO and GBO score >P90	1/5	5/29 (17.2%)	←* →	28/68 (41.2%)	34/102 (33.3%)
Neither GBO nor GOO score >P90	2/5	7/29 (24.1%)	←NS →	15/68 (22.1%)	24/102 (23.5%)
CTRS Acting-out factor >P90	2/5	9/29 (31.0%)	←NS →	27/68 (39.7%)	38/102 (37.3%)
CTRS Hyperact. factor >P90	1/5	8/29 (27.6%)	←NS →	22/68 (32.4%)	31/102 (30.4%)
CTRS Anxiety-Withdr.f.>P90	4/5	12/29 (41.4%)	←NS →	17/68 (25.0%)	33/102 (32.4%)
CTRS full-scale >P90	3/5	15/29 (51.7%)	←NS →	37/68 (54.4%)	55/102 (53.9%)

[a] taken from norms given by: GOO (age 7-10 yrs; Boorsma, 1990); GBO (age 6-13 yrs; Vaessen, 1990); CTRS (age 6-13 yrs; Blöte & Curfs, 1986).
[b] statistical comparison trial groups 2 and 3 (p-value Fisher's exact test, two-sided): * = $p < 0.05$.

4.6 Psychological assessment and direct behavioral observation

4.6.1 Primary Mental Ability test (PMA)

PMA test results were obtained from the subjects aged 6-12 (n=105). Subjects had a mean PMA-score of 100.4 (SD 11.7). Four children (4%) had a PMA-score < 80. Eighty-six children (82%) had a PMA-score in the normal range (≥ 90).

The children with a PMA-score in the normal range were classified as follows:
(1) a specific low score on language: n=26 (30%);
(2) a specific low score on arithmetic: n=7 (8%);

(3) both arithmetic and language dysfunctions: n=17 (20%);
(4) no learning problems: n=36 (42%).

Consequently, 33 of the 86 subjects with a PMA-score in the normal range fitted our definition of LD. More children from trial groups 1 and 3 fitted our definition of LD than from trial group 2 (see table 4.6.1a).

Table 4.6.1b shows the mean PMA-scores for the subjects in the different trialgroup/drug conditions. Using the Mann-Whitney U test for two groups (two-sided), and the Kruskal-Wallis 1-way ANOVA for three groups, we compared PMA-scores in the different trialgroup/drug conditions and found no significant differences.

Table 4.6.1a Primary Mental Ability test results of the subjects.

	Trial group 1 n=5	Trial group 2 n=32	Trial group 3 n=72	Trial groups[a] 1+2+3 n=109
PMA: mean (SD)[b]	101.6 (17.2)	100.3 (13.1)	100.3 (10.8)	100.4 (11.7)
PMA-score: range	72-113	80-124	75-125	72-125
% LD[c]	50.0	22.7	43.3	38.4

[a] Definition of trial groups: 1 = ADHD + Pervasive Developmental Disorder; 2 = ADHD + Tic Disorder; 3 = ADHD, no PDD, no Tic Disorder.
[b] PMA = Primary Mental Ability test score.
[c] % LD = percent of subjects with a PMA-score > 90, who had specific low scores on language or arithmetic.

Table 4.6.1b PMA-scores for subjects in the different trialgroup/drug conditions.

	Trial group 1 mean (SD)	Trial group 2 mean (SD)	Trial group 3 mean (SD)
all subjects	101.6 (17.2)	100.3 (13.1)	100.3 (10.8)
clonidine		101.7 (13.6)	101.3 (12.4)
placebo		98.9 (12.8)	101.3 (8.4)
methylphenidate			98.2 (11.4)
p-value		0.925[a]	0.357[b]

[a] Mann-Whitney U test (two-sided); comparison subjects trial group 2 versus trial group 3: p = 0.930.
[b] Kruskal-Wallis 1-way ANOVA.

4.6.2 WISC-R Freedom from Distractibility Factor (FDF)

Table 4.6.2 shows the mean FDF-scores for the subjects in the different trial/drug conditions. Using the Mann-Whitney U test (two-sided), and the Kruskal-Wallis 1-way ANOVA, we compared FDF-scores in the different trial/drug conditions and found no significant differences.

The FDF-scores of all trial subjects were compared with those of 18 nonhyperactive controls (mean FDF-score 107.3 ± 16.1) using Student's t-test. Controls scored significantly higher than trial subjects on FDF-score ($t=4.42$, $df=125$, $p < 0.001$).

Table 4.6.2 FDF-scores for subjects in the different trialgroup/drug conditions.

	Trial group 1 mean (SD)	Trial group 2 mean (SD)	Trial group 3 mean (SD)
all subjects	88.2 (14.2)	93.2 (14.6)	89.8 (14.5)
clonidine		92.7 (17.1)	89.0 (12.7)
placebo		93.7 (12.2)	93.8 (16.2)
methylphenidate			86.6 (14.1)
p-value		0.748[a]	0.292[b]

[a] Mann-Whitney U test (two-sided); comparison subjects trial group 2 versus trial group 3, $p = 0.279$.
[b] Kruskal-Wallis 1-way ANOVA.

4.6.3 GPO rating of behavior during psychological testing and playroom observation

Table 4.6.3a shows the Pearson correlations between the GPO ratings made by the test leader ("GPO-Irma") and the GPO ratings independently scored from videotape by a research-assistant ("GPO-other") during PPCT, FDF, playroom t_0 (before treatment), and playroom t_7 (in the 7th week of treatment). GPO-Irma and GPO-other appeared to be highly correlated (r's between 0.78 and 0.90). The high correlation coefficients that were found, however, did not prevent that GPO-Irma and GPO-other sometimes differed considerably for the higher score range. This is shown in figures 4.6.3a-4.6.3d: in the higher GPO score range the "other" research-assistants tended to score higher than "Irma". For subsequent analyses we will use "Irma" GPO ratings, because we may expect that intra-rater reliability is better for "Irma" ratings than for "other".

Table 4.6.3a Pearson correlations between the GPO-ratings made by the test leader ("GPO Irma"), and the GPO-ratings independently scored from videotape by a research-assistant ("GPO other") during PPCT, FDF, playroom t_0 (before treatment), and playroom t_7 (in the 7th week of treatment).

	GPO-PPCT other	GPO-FDF other	GPO-play t_0 other	GPO-play t_7 other
GPO-PPCT Irma	0.90 **			
GPO-FDF Irma		0.84 **		
GPO-Playroom t_0 Irma			0.80 **	
GPO-Playroom t_7 Irma				0.78 **

** $p < .01$

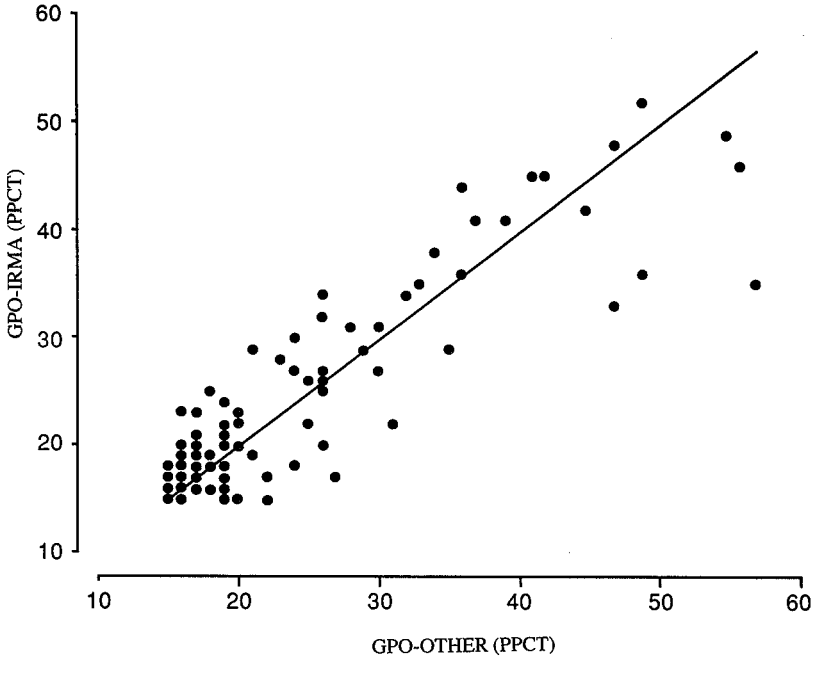

Figure 4.6.3aGPO-PPCT ratings made by the test leader (GPO-Irma) and GPO-PPCT ratings made by a research-assistant (GPO-other) for all trial subjects.

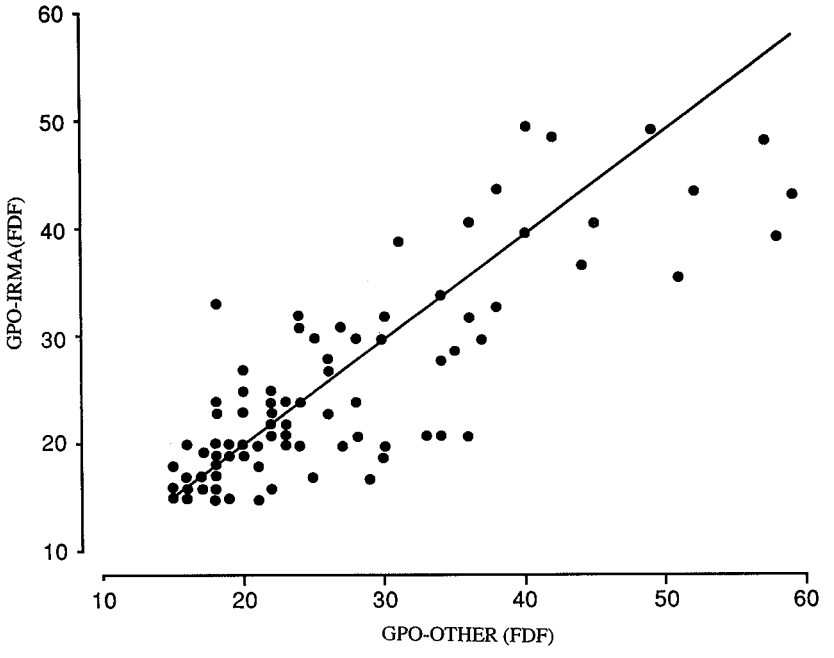

Figure 4.6.3bGPO-FDF ratings made by the test leader (GPO-Irma) and GPO-FDF ratings made by a research-assistant (GPO-other) for all trial subjects.

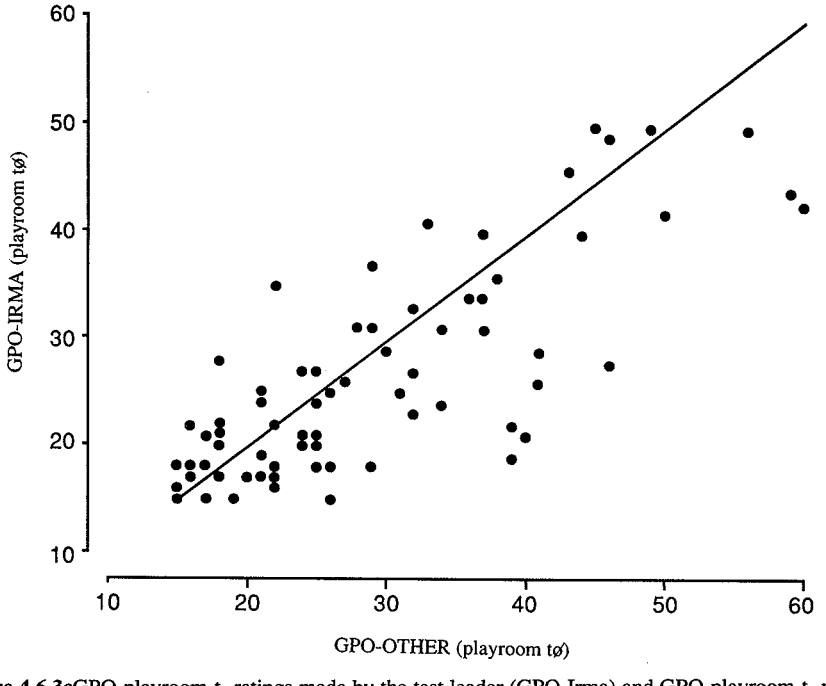

Figure 4.6.3cGPO-playroom-t_0 ratings made by the test leader (GPO-Irma) and GPO-playroom-t_0 ratings made by a research-assistant (GPO-other) for the children of trial group 3.

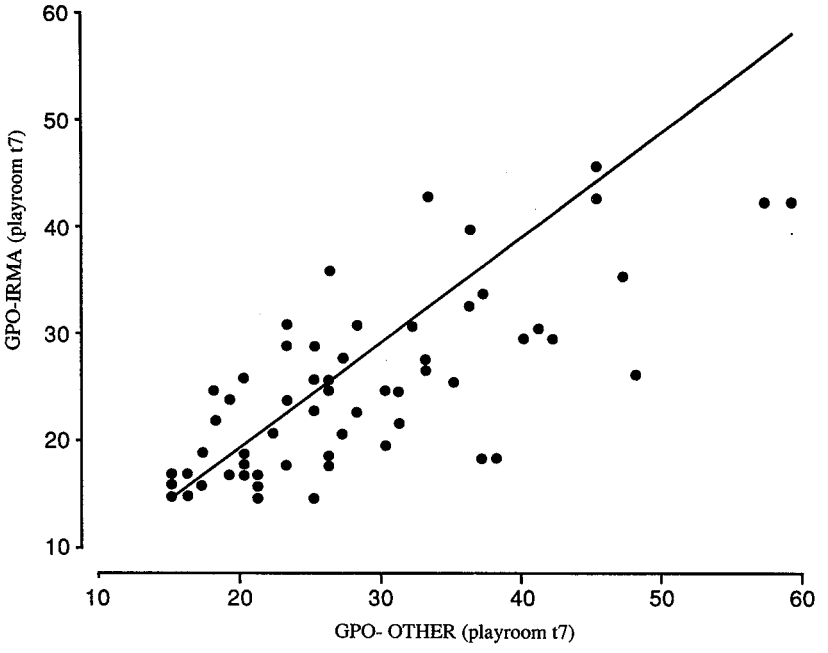

Figure 4.6.3dGPO-playroom-t_7 ratings made by the test leader (GPO-Irma) and GPO-playroom-t_7 ratings made by a research-assistant (GPO-other) for the children of trial group 3.

We computed Pearson correlation coefficients between "Irma" GPO-PPCT, "Irma" GPO-FDF, GOO scores, and GBO scores (see table 4.6.3b). Correlations between GOO and GBO (r=.05), between GPO-PPCT and GOO/GBO (r=-.04 and r=.09 respectively), and between GPO-FDF and GOO/GBO (r=-.04 and r=.13 respectively) were low. GPO-PPCT and GPO-FDF showed a high correlation (r=0.85, p=0.000).

Table 4.6.3b Pearson correlation coefficients between GOO score, GBO score, "Irma" GPO-PPCT, and "Irma" GPO-FDF, for subjects (n=109).

	GOO	GBO	GPO-PPCT Irma
GBO-score	.05 NS		
Irma GPO-PPCT	-.04 NS	.09 NS	
Irma GPO-FDF	-.04 NS	.13 NS	.85 **

** $p < .01$

4.6.4 Bourdon-Wiersma paper-and-pencil test (PPCT)

Table 4.6.4a shows mean cancellation time, within-subject variability in cancellation time, and error percentage in the different trial groups. We compared the three trial groups with respect to performance on PPCT, using a Kruskal Wallis 1-way ANOVA, and found no significant differences (p-values: mean cancellation time 0.355, within-subject variability in cancellation time 0.769, and error percentage 0.087).

Table 4.6.4a Bourdon-Wiersma PPCT results of the subjects.

	Trial group 1 n=5 mean (SD)	Trial group 2 n=32 mean (SD)	Trial group 3 n=72 mean (SD)	Trial groups[a] 1+2+3 n=109 mean (SD)
PPCT:				
CT[b]: mean (SD)	19.1 (1.8)	21.3 (6.4)	22.0 (6.0)	21.7 (6.0)
Variab[b]: mean (SD)	4.9 (2.1)	4.7 (2.8)	5.1 (3.7)	5.0 (3.4)
% Error: mean (SD)	10.6 (5.8)	6.7 (5.4)	5.8 (5.4)	6.3 (5.5)

[a] Definition of trial groups: 1 = ADHD + Pervasive Developmental Disorder; 2 = ADHD + Tic Disorder; 3 = ADHD, no PDD, no Tic Disorder.
[b] Bourdon-Wiersma PPCT: CT = cancellation time; Variab = within-subject variability in cancellation time; % Error = error percentage.

PPCT performance: A comparison with controls

Eighteen children from regular schools were selected as controls (13 boys and 5 girls, aged 7-11). The controls had GOO scores below the 50th percentile, indicating low hyperactivity levels in the home situation. Reaction-time-experiments as well as FDF and PPCT tests were performed with the controls using the same procedures as for subjects.

Table 4.6.4b shows age, mean FDF-score and performances on PPCT of the controls (n=18), and of the subjects (n=109). Although the age range was slightly different for controls and subjects (7-11 and 6-15 years, respectively), the two groups did not significantly differ with respect to age, when we compared the two samples, using a Student's t-test (two-sided) with an adjustment of the number of degrees of freedom because the variances were heterogeneous (t=0.69, df=37, p=0.493). As was already reported in section 4.6.2, the controls had a significantly higher FDF-score than subjects.

When the performance on PPCT was compared between controls and subjects, using a Student's t-test (two-sided), we found that variability of cancellation time was significantly greater in subjects than in controls (t=-3.41, df=61, p=0.001). We found no significant difference with respect to mean cancellation time (t=-1.80, df=125, p=0.074),

and with respect to error percentage (t=-.92, df=125, p=0.359).

Table 4.6.4b Age, FDF-score, and performance on PPCT of controls and subjects.

	controls mean±SD (n=18)	trial mean±SD (n=109)	t-test p-value
age (mean±SD)	8.7±1.2	8.9±2.0	NS
age range (yrs)	7-11	6-15[a]	
FDF-score	107.3±16.5	90.7±14.5	0.000 **
PPCT:			
mean cancellation time (sec.)	18.98±4.74	21.65±6.03	NS
variability cancell.time	3.44±1.39	4.99±3.40	0.001 **
error percentage	5.15±4.09	6.05±5.05	NS

[a] the trial group included 12 subjects older than 11 yrs, and 4 subjects aged 6 (together n=16, 14.7%).
** $p < 0.01$

Subsequently we compared PPCT performance between the controls and the subjects, using a multiple regression analysis. First, we checked the homogeneity of variances between controls and subjects. After logarithmic transformation we found homogeneity for mean cancellation time and error percentage. Because no homogeneity was found for variability of cancellation time, a multiple regression analysis was not performed for this measure. We performed a multiple regression analysis on mean cancellation time and error percentage (after logarithmic transformation) and found, when controlling for sex, age and FDF-score, no significant difference between controls and subjects for mean cancellation time (p=0.065) and error percentage (p=0.831; see table 4.6.4c).

We conclude that a significant difference was found between controls and subjects with respect to variability of cancellation time.

Table 4.6.4c Comparison between controls and subjects using a multiple regression analysis with mean cancellation time and error percentage as dependent variables and controlling for sex, age, and FDF-score.

	B	SE B	p-value
Mean cancellation time			
Sex (1=M, 2=F)	.01	.05	0.764
Age	- .10	$9.53*10^{-3}$	0.000 **
FDF-score	$-3.07*10^{-3}$	$1.22*10^{-3}$	0.013 *
Group (1=controls, 2=trial)	- .10	.05	0.065
Constant	4.27	.16	
R square = .48			
Error percentage			
Sex (1=M, 2=F)	- .11	.15	0.477
Age	- .08	.03	0.018 *
FDF-score	$-9.83*10^{-3}$	$4.07*10^{-3}$	0.017 *
Group (1=controls, 2=trial)	.04	.18	0.831
Constant	3.39	.55	
R square = .07			

* $p < .05$, ** $p < .01$

Relation between PPCT performance and GPO-PPCT ratings

We found significant positive correlations between GPO-scores during PPCT (GPO-PPCT) and PPCT performance (see table 4.6.4d). The lower GPO-PPCT score a child had, the better his performance (i.e., a faster mean cancellation time, a lower variability and a lower error percentage). It was found that GPO-PPCT showed neither a significant correlation with GOO-score (r=-0.04, p=0.336), nor with GBO-score (r=0.09, p=0.166). No significant correlations were found between GOO and GBO on the one hand, and PPCT performance on the other (see table 4.6.4d). GOO and GBO showed no significant correlation with each other (r=0.05, p=0.301). This means that hyperactivity was not pervasive in our subjects, when pervasiveness was defined in terms of high scores on both parent and teacher ratings.

Table 4.6.4d Pearson correlations between PPCT performance and behavioral ratings.

	GOO-score r (p-value)	GBO-score r (p-value)	GPO-PPCT r (p-value)
PPCT:			
mean cancellation time	.05 (0.301)	.02 (0.423)	.42 (0.000) **
variability cancell.time	-.01 (0.468)	.03 (0.369)	.64 (0.000) **
error percentage	.12 (0.109)	.08 (0.205)	.36 (0.000) **

** $p < .01$

Table 4.6.4e Pearson correlations between PPCT performance and sex, age, and FDF-score.

	sex (p-value) (n=109)	age r (p-value) (n=109)	FDF-score r (p-value) (n=109)	PMA-score r (p-value) (n=105)
PPCT:				
mean cancell.time	(0.291)	-.61 (0.000)**	-.01 (0.443)	-.34 (0.000)**
variab.canc.time	(0.210)	-.52 (0.000)**	-.12 (0.107)	-.39 (0.000)**
error percentage	(0.399)	-.23 (0.009)**	-.18 (0.031)*	-.25 (0.005)**

* $p < .05$, ** $p < .01$

In order to explain the positive correlation between GPO-PPCT and PPCT performance, we computed correlations of PPCT performance on the one hand, and sex, age, FDF-score, and PMA-score on the other (see table 4.6.4e). We found a significant negative correlation between age and PPCT performance: The younger the child the worse was PPCT performance. Significant negative correlations were found between PMA-score and PPCT performance. Age showed a significant negative correlation with GPO-PPCT (r=-.43, p=0.000). PMA-score showed a significant negative correlation with GPO-PPCT (r=-.40, p=0.000). PMA-score showed a moderately high correlation with FDF-score (r=.50, p=0.000). Sex showed a marginally significant positive correlation with GPO-PPCT (p=0.032): Girls obtained higher GPO-scores than boys.

Subsequently we investigated the relation between PPCT performance and GPO-PPCT, using a linear regression analysis, after log transformation of mean cancellation time, variability of cancellation time, and error percentage, and controlling for sex, age and PMA-score (see table 4.6.4f). We found no significant effect for mean cancellation time (p=0.331). A significant effect for variability of cancellation time (p=0.000) was found and for error percentage (p=0.042). FDF-score had no significant additional effect.

Table 4.6.4f Relation between PPCT performance (dependent variable) and GPO-PPCT, using a linear regression analysis and controlling for sex, age and PMA-score.

	B	SE B	p-value
Mean cancellation time:			
GPO-PPCT	$2.27*10^{-3}$	$2.33*10^{-3}$	0.331
Age	- .08	.01	0.000 **
PMA-score	$-4.82*10^{-3}$	$1.75*10^{-3}$	0.072
Sex	- .03	.05	0.558
Constant	4.19	.25	
Adjusted R square = .40			
Variability of canc.time:			
GPO-PPCT	.02	$4.71*10^{-3}$	0.000 **
Age	- .11	.02	0.000 **
PMA-score	$-9.24*10^{-3}$	$3.55*10^{-3}$	0.011 *
Sex	- .02	.10	0.826
Constant	2.80	.51	
Adjusted R square = .51			
Error percentage:			
GPO-PPCT	.02	.01	0.042 *
Sex	- .22	.22	0.324
PMA-score	$-7.69*10^{-3}$	$7.66*10^{-3}$	0.318
Age	- .03	.05	0.530
Constant	2.36	1.09	
Adjusted R square = .06			

* $p < .05$, ** $p < .01$

In order to estimate the relative contribution of the independent variables sex, age, and PMA-score to the effect of GPO-PPCT on PPCT performance, we applied a procedure of backward elimination of sex, age, and PMA-score. In table 4.6.4f we have reported the variables sex, age and PMA-score in order of elimination (the first variable that was eliminated at the bottom). With respect to mean cancellation time, sex was omited first, leaving behind both age (p=0.000), and PMA-score (p=0.008). The adjusted R square increased from .40 to .41. Thus, elimination of age resulted in the effect of PMA-score becoming significant. With respect to variability of mean cancellation time, sex was also omitted first, leaving behind age (p=0.000) and PMA-score (0.011). The adjusted R square increased from .51 to .52. With respect to error percentage, age was omitted first, then PMA-score, and finally sex, leaving behind GPO-PPCT (p=0.004). The adjusted

R square increased from .06 to .07.

We conclude that the positive correlation between GPO-PPCT and mean cancellation time is primarily due to age and PMA-score: The younger and the less intelligent the child, the worse was his mean cancellation time and the higher his GPO-PPCT score. For variability of cancellation time, and for error percentage, we found that the higher the child's GPO-PPCT score, the worse his performance. With respect to the relation between variability of cancellation time and GPO-PPCT, we found a significant contribution of both age and PMA-score (the younger and less intelligent the child, the more variable his cancellation time).

Relation between PPCT performance and aggressiveness / hyperactivity ratings

Halperin et al. (1988) demonstrated that Continuous Performance Test (CPT) error subtypes form distinct measures of inattention, impulsivity, and dyscontrol. Halperin et al. (1990) performed CPTs on non-referred school children, who had been divided into four groups based upon the IOWA Conners Teacher's Questionnaire: pure hyperactive, pure aggressive, mixed hyperactive/aggressive, and normal controls. CPT results indicated that the pure hyperactive group was more inattentive than the other groups, and the mixed hyperactive/aggressive group was the most impulsive.

In order to investigate the relation between parent / teacher reported hyperactivity and aggressiveness on the one hand, and PPCT performance on the other, we performed a multivariate linear regression analysis with PPCT performance (after log transformation) as the dependent variable, and hyperactivity and aggressiveness as the independent variables. We confined our analysis to the subjects aged 6-11 (n=97). Hyperactivity was represented by CBCL Hyperactive, TRF Inattentive, and TRF Nervous-Overactive scores. Aggressiveness was represented by CBCL and TRF Aggressive factor scores. In order to estimate the relative contribution of hyperactivity and aggressiveness to PPCT performance, we applied a procedure of backward elimination of hyperactivity and aggressiveness. No significant effects were found of CBCL Hyperactive and CBCL Aggressive factor scores on PPCT performance even after backward elimination. TRF factor scores also had no significant effects on PPCT performance. However, after elimination we found significant effects of TRF Nervous-Overactive factor scores on both PPCT mean cancellation time, and variability of cancellation time. These results are shown in table 4.6.4g.

We conclude that there is a relation between teacher reported hyperactivity (TRF Nervous-Overactive factor score) and PPCT mean cancellation time and variability of cancellation time.

Table 4.6.4g Multivariate linear regression analysis, investigating the relation between teacher (TRF) reported hyperactivity and aggressiveness on the one hand, and PPCT performance on the other in subjects aged 6-11 (n=97).[a]

Mean cancellation time:		
Nervous-Overactive	p=0.083	→ [b] p=0.040 *
Aggressive	p=0.076	
Inattentive	p=0.286	
Adjusted R square = .05		→ [b] .03
Variability of canc.time:		
Nervous-Overactive	p=0.141	→ [b] p=0.039 *
Aggressive	p=0.053	
Inattentive	p=0.476	
Adjusted R square = .03		→ [b] .04
Error percentage:		
Nervous-Overactive	p=0.358	
Inattentive	p=0.794	
Aggressive	p=0.833	
Adjusted R square = .02		

[a] PPCT performance is the dependent variable. The independent variables have been placed in order of elimination in a backward elimination procedure (the first variable that was omitted at the bottom).
[b] result after backward elimination of independent variables.
* $p < .05$.

Classification of pervasiveness

We classified subjects in their degree of pervasiveness on the basis of hyperactivity ratings in four situations. We used the following scales and cutoff points:
(1) Hyperactivity in the home situation: GOO. Cutoff: the 90th percentile score found for Boorsma's (1990) normative sample;
(2) Hyperactivity in the school situation: GBO. Cutoff: the 90th percentile score found for Vaessen's (1990) normative sample;
(3) Behavior during PPCT: GPO ("GPO-PPCT"). Cutoff: the 50th percentile score found for the subjects. This appeared to be a GPO-score of 19.
(4) Behavior during FDF: GPO ("GPO-FDF"). Cutoff: the 50th percentile score found for the subjects. This appeared to be a GPO-score of 20.

Subjects were classified as follows:
(a) Extremely pervasive hyperactives: these were subjects scoring above cutoffs on all four measures (GOO, GBO, GPO-PPCT, and GPO-FDF). 19 subjects fulfilled this norm (17.4%);
(b) Moderately pervasive hyperactives: these were subjects scoring above cutoffs on three of the four measures. 27 subjects fulfilled this norm (24.8%);
(c) Mildly pervasive or situationally hyperactives: these were subjects scoring above cutoffs on less than three of the four measures. 63 subjects fulfilled this norm (57.8%).

Table 4.6.4h shows performance on PPCT, and FDF-score, for extremely, moderately, and mildly pervasive or situationally hyperactives. We compared these three groups with respect to performance on PPCT and FDF-score, using a Kruskal Wallis 1-way ANOVA and found significant differences for mean cancellation time (p=0.000), variability of cancellation time (p=0.000), and error percentage (p=0.002). For variability of cancellation time and for error percentage we found that the more pervasively hyperactive the child was, the worse the PPCT performance. For FDF-score we found no significant differences (p=0.449).

Table 4.6.4h Performance on PPCT, and FDF-score, for extremely, moderately, and mildly pervasive or situationally hyperactives.

	Extremely pervasive hyperactives mean ± SD (n=19)	Moderately pervasive hyperactives mean ± SD (n=27)	Mildly perv. or situat. hyperactives mean ± SD (n=63)
mean cancellation time (sec.)	23.78±4.86	24.00±5.84	20.00±6.03
variability cancell.time	7.03±2.84	5.96±3.02	3.96±3.35
error percentage	9.38±6.44	7.26±5.61	4.52±3.57
FDF-score	91.3±13.0	88.30±19.1	91.6±12.7

PPCT performance: Comparison between extremely, moderately, mildly pervasive hyperactives and controls

We compared PPCT performance between the extremely, the moderately, the mildly pervasive hyperactives and the controls using a Student-Newman-Keuls Procedure, and a multiple regression analysis. First, we checked the homogeneity of variances between the four groups. We found homogeneity for PPCT performance measures (for variability of cancellation time, and error percentage, after logarithmic transformation). In order to compare the differences between the extremely, moderately, mildly pervasive hyperactives and the controls, we compared pairs of groups at a 5% level, using a Student-Newman-Keuls Procedure (after logarithmic transformation of variability of cancellation time and error percentage). Both for mean cancellation time and for variability of cancellation time we found significant differences between the controls and the mildly pervasive hyperactive children on the one hand, and the extremely and moderately pervasive hyperactives on the other: performance was worse in the extremely and moderately pervasive hyperactives. For error percentage we found significant differences between the controls and the mildly pervasive hyperactives on the one hand, and the extremely pervasive hyperactives on the other: the extremely pervasive hyperactives made more errors.

In order to explain the significant differences that were found using the Student-Newman-Keuls Procedure, we performed a multiple regression analysis taking the PPCT performance measures as the dependent variables (variability of cancellation time and error percentage after logarithmic transformation), controlling for sex, age and FDF-score (see table 4.6.4i). We found that for mean cancellation time and for error percentage the controls did not differ significantly with each of the four groups. However, we found a significant difference between the extremely pervasive hyperactives and the controls for variability of cancellation time (p=0.004). In order to estimate the relative contribution of the independent variables sex, age, and FDF-score to the effect of the four groups on PPCT performance, we applied a procedure of backward elimination of sex, age, and FDF-score. In table 4.6.4i we report the variables sex, age and FDF-score in order of elimination (the first variable that was eliminated being at the bottom). With respect to mean cancellation time, sex was omitted first, leaving behind both age (p=0.000), and FDF-score (p=0.019). The adjusted R square remains .40. With respect to variability of mean cancellation time, sex was also omitted first, leaving behind age (p=0.000) and FDF-score (0.001). The adjusted R square dropped from .48 to .47. With respect to error percentage, sex was omitted first, then age, and leaving behind FDF-score (p=0.094). The adjusted R square increased from .09 to .10.

We conclude that the difference that was found for mean cancellation time between the controls and the mildly pervasive hyperactives on the one hand, and the moderately and extremely pervasive hyperactives on the other, is caused by age and FDF-score: the younger the child and the lower his FDF-score, the worse was his mean cancellation time and the more pervasive his hyperactivity. However, after controlling for sex, age and FDF-score there remains a significant difference between the extremely pervasive hyperactives and the controls for variability of cancellation time. With respect to the relation between the four groups and variability of cancellation time, we found a significant contribution of both age and FDF-score (the younger the child and the lower his FDF-score, the more variable was his cancellation time).

Table 4.6.4i Relation between extremely, moderately, mildly pervasive hyperactives and controls with respect to PPCT performance, using a multiple regression analysis, taking the PPCT performance measures as the dependent variables and controlling for sex, age and FDF-score.[a]

	B	SE B	p-value	
Mean cancellation time				
Extremely perv.hyperact.	1.84	1.64	0.265	}
Moderately perv.hyperact.	2.64	1.53	0.088	}[b] 0.391
Mildly perv.hyperact.	1.81	1.31	0.170	}
Sex	.27	1.12	0.811	
Age	-2.02	.25	0.000**	
FDF-score	- .07	.03	0.020*	
Constant	43.76	4.86		
Adjusted R square = .40				
Variab. of cancell.time				
Extremely perv.hyperact.	.43	.15	0.004**	}
Moderately perv.hyperact.	.26	.14	0.059	}[b] 0.007**
Mildly perv.hyperact.	.06	.12	0.608	}
Age	- .17	.02	0.000**	
FDF-score	$-9.39*10^{-3}$	$2.67*10^{-3}$	0.001**	
Sex	.16	.10	0.121	
Constant	3.45	.43		
Adjusted R square = .48				
Error percentage				
Extremely perv.hyperact.	.34	.22	0.132	}
Moderately perv.hyperact.	.09	.21	0.660	}[b] 0.038*
Mildly perv.hyperact.	- .16	.18	0.361	}
FDF-score	$-7.77*10^{-3}$	$4.06*10^{-3}$	0.058	
Age	- .03	.03	0.317	
Sex	- .10	.15	0.496	
Constant	2.88	.66		
Adjusted R square = .09				

The independent variables sex, age and FDF-score have been placed in order of elimination in a backward elimination procedure (the first variable that was eliminated at the bottom).
[b] overall p-value for the four groups.
* $p < .05$; ** $p < .01$.

Evidence for a sustained attention deficit?

A sustained attention effect is defined as a decrease in task efficiency with task duration. Similar to the manner in which Van der Meere et al. (1991) analyzed their PPCT-data, we calculated PPCT performance for blocks 1 (PPCT lines 1-8), 2 (lines 9-

16), and 3 (lines 17-24; see table 4.6.4j). We tested to see if PPCT performance showed a linear trend with task duration, and checked if this linear trend differed between the extremely, the moderately, the mildly pervasive hyperactives and the controls.

In order to investigate if there was a linear trend of PPCT performance with task duration we performed a repeated measures ANOVA with three polynomial contrasts (i.e., constant, linear, and quadratic). We found a linear trend for mean cancellation time (p=0.000), and non-linear trends for variability of cancellation time (p=0.532) and error percentage (p=0.526).

Subsequently we checked if the linear trend that was found for the mean cancellation time, differed between the controls and the groups of extremely, moderately and mildly pervasive hyperactive children by calculating the two differences (block 2 - block 1: first period, and block 3 - block 2: second period), and comparing them, using a repeated measures ANOVA. We found no differences: $F(6,240) = 1.31$, $p=0.253$; with for the first period: $F(3,122) = 0.13$, $p=0.942$; and for the second period: $F(3,122) = 2.57$, $p=0.057$. The mean cancellation time shows a degree of linear increase which is significant in the first period ($F(1,122) = 6.33$, $p=0.013$), but not significant in the second period ($F(1,122) = 3.06$, $p=0.083$). When we tested this degree of linear increase bivariate (over both periods), we found a significant degree of increase for mean cancellation time ($F(2,121) = 7.48$, $p=0.001$). Table 4.6.4j shows that mean cancellation time, for controls and the other three groups together, was 20.52 for block 1, 21.36 for block 2, and 21.90 for block 3.

We conclude that the degree of linear increase of mean cancellation time was significant in the first period. However, we found no differential significant effect. Therefore we conclude that there was no sustained attention effect in our subjects.

Table 4.6.4j PPCT performance for blocks 1 (PPCT lines 1-8), 2 (lines 9-16), and 3 (lines 17-24), for extremely, moderately, mildly pervasive hyperactives and controls.

	Block 1	Block 2	Block 3
Mean cancellation time			
patients + controls	20.52±5.83	21.36±6.93	21.90±5.60
patients (n=109)	20.85±5.95	21.69±7.15	22.37±5.59
controls	18.51±4.73	19.33±5.09	19.08±4.93
Mildly perv. (n=63)	19.01±5.27	19.92±7.56	20.68±5.02
Moderat.perv.(n=27)	23.35±6.28	23.99±6.07	25.04±5.96
Extrem.perv. (n=19)	23.42±5.62	24.30±5.55	24.11±5.07
Variab. of cancell.time			
patients (n=109)	4.15±2.51	4.49±4.02	4.30±2.90
controls	3.06±1.95	2.72±1.73	2.68±1.26
Mildly perv. (n=63)	3.11±1.82	3.50±3.73	3.25±2.44
Moderat.perv.(n=27)	5.22±2.19	5.74±4.43	5.36±2.81
Extrem.perv. (n=19)	6.06±3.19	5.99±3.51	6.24±3.01

Error percentage			
patients (n=109)	6.67±5.95	5.28±4.96	7.22±11.05
controls	5.10±4.48	5.79±6.31	5.12±4.64
Mildly perv. (n=63)	4.95±4.48	4.19±4.06	6.16±12.85
Moderat.perv.(n=27)	7.86±6.34	6.84±5.89	7.02±6.54
Extrem.perv. (n=19)	10.67±7.47	6.65±5.57	11.01±9.09

4.7 Summary

This chapter presented the results of the diagnostic assessment. A total of 109 children entered the trial (93 boys and 16 girls). All had been given prior assistance for behavioral problems.

On the basis of their DSM-III-R classification, they were assigned to one of three trial groups: (1) ADHD + Pervasive Developmental Disorder (PDD) (n=5); (2) ADHD + Tic Disorder (TD), and no PDD (n=32); or (3) ADHD, and no PDD or TD (n=72). Thirty-nine percent of the children were given a classification Oppositional-defiant Disorder or Conduct Disorder in addition to ADHD, and 6% had an emotional disorder besides ADHD.

On the basis of the developmental neurological examination, 34% of the children were classified as Minor Neurological Dysfunction and 2% as neurologically abnormal.

From behavioral rating scale scores it appeared that 33% of the children was pervasively hyperactive (i.e., hyperactive both at school and at home).

Using the Primary Mental Ability test, 31% of the children were diagnosed as learning-disabled.

All children were classified according to the degree of pervasiveness of their hyperactivity using parent/teacher behavioral rating scores and behavior observation scores during psychological testing as criteria for pervasiveness. The results from the paper-and-pencil cancellation test (PPCT) were then compared with those of normal controls. We found that the pervasively hyperactive children had a more variable PPCT cancellation time than normal controls, and that this variability of cancellation time was moderately high correlated with the child's behavior during PPCT testing. Moreover, mean cancellation time decreased with task duration, but this effect did not appear specifically in the ADHD children.

The results of the diagnostic assessment will be discussed in Chapter 7. The next chapter (Chapter 5) will present the results of the medication trial.

Chapter 5

CHAPTER 5 RESULTS OF THE MEDICATION TRIAL

5.1 Introduction

Chapter 4 presented the results of the diagnostic assessment. This chapter deals with the results of the medication trial.

The principal aim of the study was to compare the effects of clonidine with the effects of placebo. In section 5.2 we first report on withdrawals, protocol violations, comedication and dosage adjustments. Then we report on drug effects (section 5.3). We used three strategies to determine drug effects: (1) a rating of responder status (section 5.3.1); (2) a statistical analysis of behavior rating scale scores during treatment (section 5.3.2); and (3) a statistical analysis of behavior rating scale scores of behavior during playroom sessions (section 5.3.3).

Section 5.4 reports on clinical impressions during the treatment period, section 5.5 reports on adverse effects, and section 5.6 on predictors of drug responsiveness. The chapter concludes with a summary. The results of the medication trial will be discussed in Chapter 7.

5.2 Withdrawals, protocol violations, comedication and dosage adjustments

Withdrawals

A total of 108 subjects successfully completed the 8-week clinical trial. One patient (subject No. 59, trial group 3) dropped out at the end of his fifth week on medication because of deterioration (as appeared, afterwards, on placebo). This subject was included in the analysis of the results (analysis by intention to treat).

Protocol violations

Compliance control was maintained by instructions to both parents and child and by counting the tablets remaining at the end of treatment. There was only one patient whose compliance was poor. This patient (subject No.76, treatment group 3) had taken about 80% of the dosage because of undesired adverse effects. This protocol violation was noticed at the end of the sixth week of treatment. We let the patient complete his treatment on an 80% dosage. Afterwards we found that the medication had been methylphenidate. This child was included in the analysis of the results (analysis by intention to treat).

Comedication

Children who already used medication before entering the study continued to use their medication during the trial treatment period. These were 3 children who used carbamaze-

pine, 4 children who used nonpsychoactive medication for their CARA, and one child who used thyroxine for his hypothyroidism. Two children started the use of medication during their trial treatment: One boy (No. 35) used acetylsalicylic acid during the first week of the trial because of fever, and one boy (No. 50) used a homeopathic drug (flower drops) during the 2nd and 3rd week of the trial because of difficulty falling asleep.

Dosage adjustments

Dosage adjustments were "standard" or more. "Standard" was defined as an adjustment of 4 → 3.25 µg/kg/day for clonidine, and 0.6 → 0.4 mg/kg/day for methylphenidate. A dosage adjustment for the subjects of trial group 3 included an adjustment of both the clonidine and methylphenidate dosages, each to a similar degree. Dosage adjustments have been applied because of annoying adverse effects (e.g., drowsiness, nausea, decreased appetite, difficulty falling asleep, headache).

Before the end of the 2nd trial week standard dosage adjustments were applied in 6 subjects. All of these were subjects of trial 3: No. 15 (clonidine), No. 58 and 74 (placebo), and No. 43, 60, and 76 (methylphenidate). For one subject dosage was adjusted from 4 to 2 µg/kg/day before the end of the second trial week (No. 47, trial 2, clonidine).

After the end of the second trial week, but before the end of the fourth week, standard dosage adjustments were applied in: No. 105 (trial 2, placebo), No. 106 (trial 3, clonidine), No. 97 (trial 3, placebo), and No. 14 (trial 3, methylphenidate). For three subjects a dosage adjustment of "more than standard" was applied after the end of the second week (but before the end of the fourth week): No. 88 (trial 2, clonidine 4 → 2.7 µg/kg/day), No. 59 and No. 91 (both subjects were from trial 3: placebo; dosage adjustment clonidine 4 → 2.4 µg/kg/day and methylphenidate 0.6 → 0.3 mg/kg/day).

5.3 Efficacy

5.3.1 Responders

A responder was defined as a subject who had shown a clinically significant improvement at home and/or in the school situation during the treatment. Two child psychiatrists rated each child with respect to the responder criterion (see section 3.4.5). Before a consensus procedure, a kappa coefficient of agreement was computed between these two raters (FV, BG; kappa: 0.97). Table 5.3.1 shows the percentages of responders in the three trial groups. We found significantly more responders in the clonidine group, as well as in the methylphenidate group, as compared with placebo, for trial group 3 only (X^2 test, p=0.013, both for clonidine and for methylphenidate versus placebo). For trial groups 1 and 2 we found no significant effect of clonidine versus placebo with respect to the number of responders (trial group 2 Fisher's exact test, two-tailed: p=1).

Table 5.3.1 Percentages of responders in the three trial groups.

Trial groups:	**Responders (%):**	
Trial 1 (n=5):		
Clonidine (n=2)	0%	
Placebo (n=3)	0%	
Trial 2 (n=32):		
Clonidine (n=16)	25%	
		NS[a]
Placebo (n=16)	31%	
Trial 3 (n=72):		
Clonidine (n=24)	50%	
		p=0.013 *[b]
Placebo (n=24)	13%	
		p=0.013 *[b]
Methylphenidate (n=24)	50%	

[a] Fisher's exact test (two-tailed).
[b] Chi-square test; * $p < 0.05$.

5.3.2 Rating scale scores

Appendix 5.3.2a shows the mean rating scale scores of the subjects during treatment for the different trial group/drug combinations. These trial group/drug combinations constitute the "branches" of the trial. We compared the course of rating scale scores between these branches. We formulated the null-hypothesis as no significant difference between two trial branches. Table 5.3.2a shows the trial groups and the drug comparisons which were used in the efficacy analysis of the rating scale scores. We did not perform a comparison for the subjects of trial group 1 subjects (clonidine versus placebo), because the number of subjects (n=5) was too small.

In order to rule out the possibility of heterogeneity of the covariance matrix in the repeated measurements of the variables between the trial groups 1+2 and trial group 3, a homogeneity test was performed, using Box's M. It was found that homogeneity could be rejected for GOO, GBO, CTRS factors, GGGS factors, GGBS factors, and for problems parents. However, we could not reject homogeneity for problems teacher (p=0.001). As a consequence we analyzed separately the trials 1+2 and 3 for the variable "problems teacher".

Table 5.3.2a The trial groups and drug comparisons which were used in the efficacy analysis of the rating scale scores.

trial groups 1+2+3	trial group 2	trial-group 3
clonidine (n=42) versus placebo (n=43)	clonidine (n=16) versus placebo (n=16)	clonidine (n=24) vs placebo (n=24) vs methylphenidate (n=24)

The course of the rating scale scores of the subjects during the 7 weeks of treatment was compared using the analysis of variance for repeated measurements with the BMDP 5V program, which can include cases with missing values. This program uses the Wald chi-square for testing significance of the effects (Schluchter, 1988). In this analysis there were three repeated measurements of the dependent variable (t_3, t_5, and t_7), apart from the baseline measurement (t_0) which was included as a covariate. For the CTRS, GGGS and GGBS there was only one repeated measurement. The relevant effect is given by the coefficient belonging to the grouping factor (medication effect Γ).

First we tested if the regression effect and the intercept were time dependent (time-by-baseline interaction, model 1, appendix 5.3.2b). If regression effect and intercept were not time dependent we tested if the medication effect was time dependent (time-by-treatment group interaction, model 2). If the medication effect was not time dependent, we could assume an average medication effect and model 1 would be applicable.

We defined the medication effect (Γ) as the deviation of clonidine from placebo (respectively methylphenidate from placebo, respectively clonidine from methylphenidate). For CTRS, GGGS and GGBS the intercept (α) and regression effect (β) are not time dependent as a consequence of only one measurement apart from the baseline. Appendix 5.3.2b shows the estimated medication effect, its S.E., and the p-value of the medication effect for the comparisons that were made.

Trial groups 1+2+3, clonidine vs placebo: When we pooled treatment groups 1, 2, and 3, we found a significant medication effect of clonidine compared to placebo for the variables GBO (p=.001), CTRS Acting-out factor (p=.003), CTRS Hyperactivity factor (p=.001), CTRS sum score (p=.002), GGGS factor Hyperactive (p=.001), GGBS factor Taskorientation Good (p=.004), and GGBS factor Taskorientation Weak (p=.020).

We examined which treatment groups were responsible for these effects by comparing the drug effects in the trial groups 2 and 3 (see appendix 5.3.2b):

The effect of clonidine on hyperactivity at home: With respect to the effect of clonidine versus placebo on hyperactivity in the home situation (GOO score), it was found that the effect was stronger in trial group 3 (Γ=-2.10) than in trial group 2 (Γ=0.51). However, the effects were not significant in either of the two treatment groups.

Likewise, the effect on GGGS factor Hyperactive was stronger in trial group 3 (Γ=-2.20) than in trial group 2 (Γ=-1.14). The effect on GGGS factor Hyperactive

reached significance in the pooled analysis (trial groups 1 + 2 + 3; p=.001), and in trial group 3 (p=.003).

We conclude that clonidine (compared to placebo) had a significant effect on hyperactivity in ADHD patients without either Pervasive Developmental Disorder or Tic Disorder at home.

The effect of clonidine on hyperactivity at school: With respect to the effect of clonidine versus placebo on hyperactivity in the school situation, it was found that the effect on GBO (hyperactivity school situation) was stronger in trial group 3 (Γ=-4.57) than in trial group 2 (Γ= -2.93), and only reached significance in trial group 3 (p=.004) and in the pooled analysis (p=.001).

On the other hand, the effect on CTRS Hyperactivity factor was stronger in trial group 2 (Γ=-2.06) than in trial group 3 (Γ=-1.44), and reached significance in trial group 2 (p=.022) and in the pooled analysis (p=.001).

Trial group 2 subjects obtained significantly higher scores on the items, constituting the GGBS factor Extravert (p=.024). They showed an increase in the behaviors constituting this factor: "expresses himself/herself spontaneously to other children in the class", "one sees him/her in the company of classmates", "what he/she proposes, is usually accepted by classmates", "he/she will stick up for a person, who is wrongly accused", and "speaks in a cheerful tone".

Trial group 3 subjects obtained a significantly better (higher) score on GGBS factor Taskorientation Good (p=.003). This factor includes the following items: "carries on with his/her schoolwork, even when not watched", "immediately clears things away when he/she has to start a new task", and "quietly goes on with his/her work, even when disturbed".

We conclude that clonidine (compared to placebo) had a significant effect on hyperactivity in the school situation in ADHD patients with Tic Disorder as well as in ADHD patients without either Pervasive Developmental Disorder or Tic Disorder.

The effect of clonidine on "Acting-out" and "Anxiety-Withdrawal" at school: With respect to the effect of clonidine versus placebo on CTRS Acting-out factor, it was found that the effect was stronger in trial group 3 (Γ=-4.26) than in trial group 2 (Γ= -2.56), and only reached significance in trial group 3 (p=.004), and in the pooled analysis (p=.003). The effect on CTRS Anxiety-Withdrawal factor was as little in trial group 2 (Γ= 0.53), as it was in trial group 3 (Γ= 0.42), and did not reach significance in either of the trial groups or in the pooled analysis.

Is the clonidine effect time dependent? The effect of clonidine (compared to placebo) was not time dependent except for the "problems parents" variable in trial group 3: the medication effect was significant after three weeks of treatment (p=.039), but was not more significant after five, and after seven weeks of treatment (see appendix 5.3.2b).

The effect of methylphenidate: With respect to the effect of methylphenidate versus placebo, it was found that methylphenidate had a significant effect on hyperactivity in the home situation (GGGS factor hyperactive; p=.049) as well as in the school situation (GBO: p=.028; CTRS hyperactivity factor: p=..006).

Methylphenidate gave a significant improvement in both the "problems parents" score (p=.012) and the "problems teacher" score (p=.009).

Children obtained a significantly better (higher) score on GGGS factor Social Positive (p=.036), a significantly better (higher) score on GGBS factor Taskorientation Good (p=.003), and a significantly better (lower) score on GGBS factor Taskorientation Weak (p=.013).

The GGGS factor Social Positive is made up of the items: "tries to perform an allotted task as well as possible", "comes in immediately when called", "usually sits calmly at the table", and "can easily give up something to another child".

The GGBS factor Taskorientation Weak includes: "works precipitately, without thinking first", "sits fidgeting on his/her chair", "talks as soon as a chance occurs", "looks up from his/her work as soon as something draws his/her attention inside or outside the classroom", and "his/her pace of work varies much".

The effect of methylphenidate never was time dependent. Methylphenidate also had a significant effect on CTRS Acting-Out factor, but not on CTRS Anxiety-Withdrawal factor.

We conclude that methylphenidate (compared to placebo) had a significant effect on hyperactivity in ADHD patients without either Pervasive Developmental Disorder or Tic Disorder in both the school situation and the home situation.

The effects of clonidine compared to methylphenidate: With respect to the effects of clonidine compared to methylphenidate, we found that after 7 weeks of treatment the GOO score was higher (worse) in subjects treated with clonidine than in subjects treated with methylphenidate (Γ=0.32), but the difference was not significant (see appendix 5.3.2b).

Although we also found no significant difference in effect on the GBO score, the methylphenidate effect with regards to "problems teacher" was significantly better compared to clonidine (Γ=-8.00; p=.032). For CTRS Acting-Out and Anxiety-Withdrawal factors we found no significant difference in effect between methylphenidate and clonidine.

We conclude that there was no significant difference in effect between clonidine and methylphenidate on hyperactivity in ADHD patients without either Pervasive Developmental Disorder or Tic Disorder. However, the improvement of target problem behaviors as observed by the teachers, was significantly greater in the methylphenidate group compared with the clonidine group.

5.3.3 GPO rating of behavior during playroom observation

GPO ratings of the children's behavior during standardized playroom sessions (GPO-play) were obtained for the subjects of trial group 3. To investigate the medication effect on the course of the GPO-play scores we performed a linear regression analysis taking the baseline measurement as a covariate. It was found that both clonidine and methyl-

phenidate gave a significant effect on GPO-play when compared with placebo (p=.017 and p=.007 respectively). When the effect of clonidine was compared with the effect of methylphenidate no significant effect on GPO-play was found (p=.875; see table 5.3.3).

Table 5.3.3 Linear regression analysis of medication effects on the course of GPO-play scores with GPO-play baseline measurement as covariate.

	Effect B	S.E.	R Square
clonidine/placebo:	4.07	1.64	0.69
placebo/methylphenidate:	-5.37	1.89	0.56
clonidine/methylphenidate:	-0.29	1.84	0.45

5.4 Clinical impressions during the treatment period

Placebo was a very effective treatment in some patients (see table 5.3.1), while in other patients the ADHD symptoms deteriorated during placebo treatment. Parents of patients who improved during placebo, could hardly believe that their child had been treated with placebo. They noticed a clinically significant improvement after the start of the treatment. Most of the time they reported a clinically significant deterioration during tapering off. Other patients deteriorated during placebo treatment. It seemed that these children hoped that the treatment would help them to curb their ADHD symptoms, but that these children lost courage as soon as they noticed that the treatment did not benefit them.

Although there were subjects in whom it seemed obvious that they were on clonidine or placebo, or methylphenidate, the blinding very often made guesses unreliable. Repeatedly parents who thought for certain, based on the effects and adverse effects which they noticed, that their child had received either clonidine, or methylphenidate, or placebo, appeared to be wrong as soon as the medication code had been broken. In trial groups 1 and 2 the blinding seemed to be as good as in trial group 3. Even the project-leader, guessing for himself which medication a child might have had, guessed wrong many times.

Deterioration

Table 5.4 shows the subjects (n=18/109, 17%), who at the end of the 7th week of treatment were rated by either the parents or the teacher as showing a clinically significant deterioration compared to baseline. The definition of a "clinically significant deterioration" was given in section 3.4.5. A clinically significant deterioration was observed in 7% (n=7/42) of the patients treated with clonidine, in 21% (n=9/43) of the

patients treated with placebo (n=9/43, 21%), and in 25% (n=6/24) of the patients treated with methylphenidate. Details of all these subjects follow after the table 5.4.

Table 5.4 Subjects, who at the end of the 7th week of treatment were rated by either the parents or the teacher as showing a clinically significant deterioration compared to baseline.

	Trial 1 (n=5)	Trial 2 (n=32)	Trial 3 (n=72)
Clonidine (n=42):		1	2
Placebo (n=43):	1	2	6
Methylphenidate (n=24):	n.a.	n.a.	6

Deterioration during treatment with clonidine

During treatment with clonidine a clinically significant deterioration was observed in three children (table 5.4). Subject No. 8 was an intelligent, 7-year old boy with Tourette's Syndrome and ADHD, who became more restless and nervous during treatment with clonidine. These symptoms developed simultaneously with a new "wave" of rather annoying tics and restlessness, and have possibly been caused by this new Tourette wave. Subject No. 87 was a 9-year old boy with borderline intellectual functioning and DSM-III-R classification ADHD, who became more restless and cross during treatment with clonidine. Subject No. 106 was an intelligent, 9-year old boy with a DSM-III-R classification of both ADHD and Conduct Disorder, who remained listless and became more cross than ever before during treatment with clonidine, even after standard dosage adjustment.

During treatment with clonidine no clinically alarming behavioral or physical adverse effects were reported by either the parents or the teachers.

Deterioration during treatment with placebo

Of the nine children, who deteriorated during treatment with placebo (see table 5.4), the detioration was clinically alarming in five (Nos. 25, 58, 59, 68, and 91), and was "clinically significant", but not really alarming in four (Nos. 3, 29, 95, and 97).

Subject No. 3 was a 10-year old, severe hyperkinetic girl with a Pervasive Developmental Disorder and borderline intellectual functioning, whose behavior problems already showed a deteriorating course before treatment was started. In the school situation, this process quickened during treatment with clonidine. This girl showed no physical adverse effects during treatment. Subject No. 58 was a normal intelligent, 7-year old girl with hyperkinesis, severe oppositional behavior, and depressive symptoms, whose behavior problems showed a course similar to that in subject No. 3. Subject No. 95 was a case similar to No. 58, both diagnostically and with respect to the course of treatment.

Subject No. 25 was a 8-year old boy with ADHD and chronic motor tics, who showed signs of weariness during treatment with placebo, and became more irritable and more physically aggressive than ever before.

Subject No. 29 was an 8-year old hyperkinetic girl with borderline intellectual functioning, who moved house in her 4th week of treatment. The council suddenly assigned a house to her family. The removal apparently worked enervating for this girl. She became irritable and drew back into herself.

Subject No. 59 was a 7-year old boy with a severe hyperkinesis, who became more irritable, verbally aggressive, and overactive during treatment. No physical adverse effects were reported. We adjusted the dosage, but the process of deterioration continued both at home and at school, and we had to stop medication after five weeks of treatment. The boy's mother reported that her son was quiet again as soon as the medication was stopped. However, his behavior problems then returned, and we had to try other medication. Subject No. 68 was an 8-year old boy with ADHD, stuttering and some oppositional behavior, who, only at school, became more aggressive and stuttered more during treatment. Subject No. 97 was an 8-year old severe hyperkinetic and oppositional boy, whose restlessness deteriorated in the school situation during the last weeks of treatment.

Subject No. 91 was an 8-year old hyperkinetic boy with severe oppositional behavior, who had a history of being sensitive to blue food-additives (especially E 131). This reaction had not been examined in a double-blind, placebo-controlled oral challange test, but had been observed each time when the boy ate blue food-additives. Both the verum and placebo clonidine dragees contained a blue food-additive (E 132), which potentially is able to release histamine in sensitive subjects. The colorless "methylphenidate" placebo capsules contained lactose. This boy did not have a history of lactose intolerance. During treatment with placebo (trial group 3), the boy immediately developed the same symptoms as he had shown before as a reaction to blue food-additives. He became more restless, irritable and aggressive, both at home and at school. He had a decreased appetite, was sweaty, and, during the second week, had diarrhoea, without other signs of a viral or bacterial infection. After two weeks of treatment we reduced the dosage by 40%. Thereafter the restlessness and irritability improved temporarily. Both the excessive restlessness and the irritability/aggressiveness returned, however, and lasted till the end of the medication period. When the medication was stopped after the eight week of treatment, the restlessness and the irritability improved considerably. Our observations have been confined to clinical impressions. Because we did not employ a double-blind, placebo-controlled oral challange test with blue food-additives, it is not possible to draw well-founded conclusions with respect to the role of food-additives in this case history.

Deterioration during treatment with methylphenidate

Of the six children, who deteriorated during treatment with methylphenidate (see table 5.4), the detioration was clinically rather alarming in four (Nos. 5, 14, 19, and 76). In two other children the adverse behavioral and physical effects were at least annoying (Nos.

13 and 101).

Most frequently we observed an increase of oppositional behavior. These children commonly had been classified as Oppositional Defiant Disorder or Conduct Disorder, but an increase of oppositional behavior was also observed in a boy, who had never shown such behavior problems before. Subject No. 5 was an intelligent 7-years old boy, with both ADHD and a severe Oppositional Defiant Disorder. This patient became more aggressive and more cross during methylphenidate. Even more alarming was that he became reckless of danger, and even a little suicidal. He had shown these symptoms before, but during methylphenidate he was less approachable than ever. Subject No. 13 was a normal intelligent, 9-year old boy, who also had both ADHD and a severe Oppositional Defiant Disorder. This boy became more cross and oppositional during methylphenidate, and less approachable. Subject No. 19 was a normal intelligent, 10-years old boy with both ADHD and a Conduct Disorder, who became very cross and showed very dangerous and aggressive behavior during methylphenidate. He sat fire to a tin with thinner, and jumped from his window at the first floor because he was cross. Subject No. 101 was an 8-year old, normal intelligent boy with DSM-III-R classification ADHD, who had never shown considerable oppositional behavior, but who became cross and very oppositional during methylphenidate.

Subject No. 14 was a 8-years old boy with a borderline intellectual functioning and a quick temper (DSM-III-R classification ADHD). In the first week of treatment this boy became more cross and short-tempered than he already was, and in the following weeks he started stealing money to buy sweets; he tore his teddy bears to pieces, and set fire three times in one week, even calling the fire-brigade. Dosage was adjusted, whereupon these behavioral adverse effects lessened a little.

Subject No. 76 was a normal intelligent, 15-years old boy with deviant behavior, hyperkinesis, and a depressed mood. His DSM-III-R classification was Conduct Disorder and ADHD. During the first week of treatment this boy developed annoying complaints of decreased appetite, difficulty falling asleep, and headaches. After ten days of treatment we decreased both his "clonidine" and his "methylphenidate" dosage by 25%. After three weeks of treatment there were no longer any adverse effects. By that time, however, he had already lost ten pounds in weight. His condition seemed to remain stable and acceptable during the following weeks. However, after six weeks of treatment he told his mother that he regularly skipped his medication, because, since he started the medication, he had fits of apathy and depression. After he had once again been teased by classmates he had even seriously contemplated committing suicide. He saw his life as a complete failure. We assessed that besides the medication effect, the teasing at school and the serious critique the boy's teacher uttered to him concerning his parents, played an important role in causing depressed moods. We provided a supportive contact during the rest of the double-blind medication period. When the medication was tapered off in the 8th week, the patient's complaints of apathy disappeared completely. After nine weeks of treatment we broke the code and found out that this patient had been treated with methylphenidate.

Tics during the trial

Based on both the reports from parents/teacher and on clinical observations, children with Tic Disorders (n=33) could be classified as:

(1) Having tics at the start of the trial period: 70% (23/33). Of these children tics remained unchanged in 16 children (11 op clonidine, and five on placebo), got worse in two patients (on clonidine), and improved in five (one on clonidine, four on placebo).

(2) Having no tics at the start of the trial period: 30% (n=10/33). None of these children developed tics during the trial (two were on clonidine, and eight were on placebo).

Therefore, the percentage of children whose tics showed improvement after seven weeks of treatment was 7% (n=1) in the clonidine group and 44% (n=4) in the placebo group.

5.5. Advere effects

Adverse effects during the course of the trial

Adverse effects during treatment with clonidine: For the subjects who received clonidine the following adverse effects were recorded after ten days of treatment:

(1) Drowsiness: 64% (n=27/42). Drowsiness was seen in the form of an increased need for short naps, especially when the child had no activities to do. Children who showed drowsiness were described by their parents as "weary" (in Dutch: "mat, moe, lusteloos"). During the first weeks drowsiness was commonly accompanied by mild to moderate complaints of nausea, decreased appetite, and headache. Drowsiness was most marked during the first hour after dosage, especially in the evening. One child experienced drowsiness when he cycled to school. He even sat nodding off on his bicycle. This observation indicates that drowsiness during clonidine treatment is not only seen when the child has no activities to do, and that participation in the traffic is potentially dangerous as long as the child shows any drowsiness.

(2) Frequent nightly awakenings: 10% (n=4/42). These were sometimes accompanied by nightmares.

(3) Dry mouth: 5% (n=2/42).

Adverse effects during treatment with placebo: For those subjects who received placebo the following was recorded after ten days of treatment:

(1) Drowsiness: 35% (n=15/43). Drowsiness was seen in the same form as was reported for patients on clonidine or methylphenidate.

(2) Bedwetting: 5% (n=2/43). This was observed in children who were "never" "wet" anymore.

(3) Dry mouth: 5% (n=2/43).

(4) Frequent nightly awakenings: 2% (n=1/43).

Adverse effects during treatment with methylphenidate: For the subjects who were administered methylphenidate (trial group 3), the following adverse effects were recorded after ten days of treatment:

(1) Clammy, sick, weary, dark rings under the eyes, enlarged pupils, headache, decreased appetite: 54% (n=13/24). These complaints were most annoying during the first hour after dosage.
(2) Difficulty falling asleep: 29% (n=7/24). Of these children most were reported to sleep deeper during the night. Some children, however, had frequent nightly awakenings.
(3) Bedwetting: 13% (n=3/24) (in children who were "never" "wet" anymore).
(4) Tics: One boy had a mild head-shake-tic during the first and second week of treatment. Another boy had a sniffing-tic that started during the first week, and stopped after three weeks of treatment. These children had never had tics before and had a negative family history with respect to tics.

Rating of adverse effects at seven weeks

Table 5.5a shows the percentages of subjects rated as having physical adverse effects at seven weeks. Ratings are given after consensus procedure. Before consensus a kappa coefficient of agreement was computed (FV, BG; kappa 0.86). Table 5.5b shows the physical adverse effects as they were scored at seven weeks.

Table 5.5a Percentages of subjects rated as having physical adverse effects after 7 weeks of treatment.

	percent adverse effects	percent annoying
Clonidine (n=42):	52%	5%
Placebo (n=43):	37%	7%
Methylphenidate (n=24):	58%	21%

Table 5.5b Physical adverse effects as scored after 7 weeks of treatment.

Clonidine:
(1) drowsiness 38% (12% only for an hour after dosage),
(2) decreased appetite 10%,
(3) dry mouth 5%,
(4) cutaneous eruption 2%.

Placebo:
(1) drowsiness 21% (5% only for an hour after dosage),
(2) dry mouth 7%,
(3) pale/clammy 5%,
(4) decreased appetite 5%,
(5) difficulty falling asleep 2%, and
(6) bedwetting 2%.

Methylphenidate:
(1) difficulty falling asleep 21%,
(2) decreased appetite 13%,
(3) drowsiness 8%,
(4) headache 8%,
(5) bedwetting 8%,
(6) enlarged pupils 8%.

Blood pressure changes

Table 5.5c shows mean systolic and diastolic blood pressures sitting (in mmHg) at baseline and after 10 days of medication for the trial/drug combinations.

The reduction in both systolic and diastolic blood pressure was larger in the clonidine condition than in the placebo and methylphenidate condition. In comparison with placebo the reduction in blood pressure during treatment with clonidine reached statistical significance for the trial group 3 subjects (p=.043 for systolic, and p=.011 for diastolic blood pressure), but not for trial group 2 subjects (statistical test: Mann-Whitney U test, two-sided, table 5.5c).

Methylphenidate gave no significant change in systolic or distolic blood pressure, as compared with placebo.

Table 5.5c Mean systolic and diastolic sitting blood pressures (in mmHg) at baseline and after 10 days of medication, and change in blood pressure for trial/drug combinations.

	At baseline mean ± SD	**After 10 days of medication** mean ± SD	**Change in blood pressure** mean ± SD
Trial 2 (n=32):			
Systolic			
clonidine	108.3±7.5	98.8±9.0	-11.0±8.7
	NS[a]	NS[a]	NS[a]
placebo	110.0±7.5	102.1±6.7	- 7.9±8.9
Diastolic			
clonidine	73.7±5.8	67.5±8.2	- 7.0±8.2
	NS[a]	NS[a]	NS[a]
placebo	72.2±6.3	70.4±5.4	- 1.4±8.9
Trial 3 (n=72):			
Systolic			
clonidine	110.6±8.4	99.1±6.9	-12.2± 9.1
	NS[a]	NS[a]	p=.043*[a]
placebo	110.8±7.0	105.0±9.7	- 5.4±10.8
	NS[a]	NS[a]	NS[a]
methylphen.	111.3±7.7	103.9±9.5	- 7.5±10.8
	NS[b]	NS[b]	NS[b]
Diastolic			
clonidine	73.3±5.8	63.3±7.2	-10.0±8.0
	NS[a]	p=.020*[a]	p=.011*[a]
placebo	73.1±6.0	68.5±9.6	- 4.3±8.8
	NS[a]	NS[a]	NS[a]
methylphen.	72.5±5.3	69.5±5.3	- 3.2±8.0
	NS[b]	p=.010*[b]	p=.012*[b]

[a] Mann-Whitney U test (two groups; two-sided).
[b] Kruskal-Wallis 1-way ANOVA (three groups).
* $p < .05$.

5.6 *Predictors of drug responsiveness*

The relation between hyperactivity ratings and drug responder status

We investigated the relation between GOO, GBO, GPO-PPCT, GPO-FDF, and GPO-play scores (GPOs as scored by "Irma") on the one hand, and drug responder status on the other in each of the trial-group/drug conditions. For drug responder status we used the "responder" rating as defined in section 3.4.5. Before we could test this relation, we had to check the possible confounding effects of sex and age. Due to randomization, sex was equally distributed. We assessed, however, if the sex distribution differed between "responders" and "non-responders" in each of the trial-group/drug combinations and found no differences. Next we tested if the age distribution differed between responders and non-responders in each of the trial-group/drug combinations, using the Mann-Whitney U test, and found no significant differences except in the trial-group-3/ clonidine condition (p=0.008). For the trial-group-3 /clonidine condition we then investigated the relation between GOO, GBO, GPO-PPCT, GPO-FDF, and GPO-play on the one hand, and drug responder status on the other, using a linear regression analysis, controlling for age, and found no significant relation (see table 5.6a).

Table 5.6a Relation between GOO, GBO, GPO-PPCT, GPO-FDF, and GPO-play scores on the one hand, and drug responder status on the other in each of the trial-drug-conditions, using the Mann-Whitney U test (two-sided).

Trial	Drug	GOO	GBO	GPOBW	GPOKF	GPOSP
all	all	.821 NS n=109	.656 NS n=109	.653 NS n=109	.857 NS n=109	.005** [ab] n=72
all	clon	.756 NS	.568 NS	.523 NS	.342 NS	.156 NS
all	plac	.159 NS	.755 NS	.766 NS	.790 NS	.080 NS
2	clon	.855 NS	.951 NS	.010 [c]	.018 [c]	n.a.
2	plac	.607 NS	.088 NS	.087 NS	.153 NS	n.a.
3[d]	clon	.258 NS	.585 NS	.073 NS	.243 NS	.897 NS
3	plac	.149 NS	.255 NS	.336 NS	.097 NS	.090 NS
3	mph	.418 NS	.525 NS	.706 NS	.352 NS	.183 NS

[a] nonresponders scoring significantly ($p<0.05$) higher than responders.
[b] GPO-play in trial group 3 only.
[c] responders scoring significantly ($p<0.05$) higher than nonresponders.
[d] For this trial group/drug condition a linear regression analysis was used, controlling for age.
* $p < .05$; ** $p < .01$.

We concluded, that there were no confounding effects of sex and age in the other trial-drug-conditions, and used the Mann-Whitney U test to investigate the relation between GOO, GBO, GPO-PPCT, GPO-FDF, and GPO-play on the one hand, and drug responder status on the other in each of the trial-drug-conditions (see table 5.6a).

It was found that GOO, GBO, and GPO-play scores had no predictive value as to drug responder status. GPO-PPCT and GPO-FDF scores were significantly higher in responders than in nonresponders in the trial-group-2/clonidine condition. However, we may expect that subjects with higher GPO-scores already have a greater chance to become responders, due to a regression to the mean effect. Therefore, we conclude that we did not find any evident relationship between GOO, GBO and GPO scores on the one hand, and drug responder status on the other.

Potential predictors of drug responsiveness

We confined ourselves to test the relation between patient characteristics and respondership only for measures that have been reported in the literature as possible predictive factors, and which do not necessarily show a high correlation with hyperactivity ratings. For this purpose we selected the DSM-III-R categories Conduct Disorder and Oppositional Defiant Disorder, the DSM-III-R categories for emotional disorder, and neurodevelopmental status.

Table 5.6.b shows the number of subjects with the abovementioned diagnoses in each of the trial-group/drug conditions. It is evident, that the number of subjects in each of the three diagnostic categories is too small to use these categories as potential predictors of drug responsiveness.

Table 5.6b Number of subjects in each of the trial-group/drug conditions with diagnoses Conduct or Oppositional Defiant Disorder, Emotional Disorder, or Minor Neurological Dysfunction.

	Clonidine:		**Placebo:**		**Methylphenidate:**	
	Responders	Nonresponders	Responders	Nonresponders	Responders	Nonresponders
Trial 2:						
CD/ODD	0	4	2	5		
Emot.dis.	1	1				
MND 1/2	1	5	1	4		
Trial 3:						
CD/ODD	5	6	2	9	4	7
Emot.dis.	1	1		2	1	
MND 1/2	5	5	2	6	1	5

5.7 Summary

This chapter presented the results of the medication trial. All children but one completed treatment. The statistical analyses of the results were performed according to the "intention to treat" principle. Each child was treated with medication for 8 weeks.

The parents' and teacher's judgments were used to determine whether a child had shown a "clinically significant improvement" during the treatment period. Those who had improved were the "responders". In the trial groups 1 and 2, the difference between the clonidine-treated, and the placebo-treated children, was nonsignificant with respect to responder status. In trial group 3, the percentage of responders in the clonidine-treated group was as high as in the methylphenidate-treated group (50%), and significantly higher than in the placebo treated group (13%). A statistical analysis of the behavioral ratings during treatment showed similar results. Slight nuances could be observed: (1) in trial group 2, clonidine had a significant effect on hyperactivity in the school situation compared with placebo; (2) methylphenidate, not clonidine, improved both the parents' and teacher's target problem behaviors.

After 7 weeks of treatment high numbers of children showed adverse effects: 52% in the clonidine group, 37% in the placebo group, and 58% in the methylphenidate group. In the latter group, the percentage of annoying adverse effects was much higher than in the clonidine and placebo groups (21%, 5%, and 7% respectively).

We did not find child characteristics predictive of a favorable drug response.

The results of the medication trial will be discussed in Chapter 7. First, Chapter 6 will present now a review of the literature on biochemical studies of hyperkinesis, followed by the results of the biochemical study.

Chapter 6

CHAPTER 6 PLASMA AND URINARY MHPG LEVELS IN HYPERKINETIC CHILDREN, BEFORE AND AFTER TREATMENT WITH CLONIDINE AND METHYLPHENIDATE

6.1 Biochemical studies of hyperkinesis

Hypotheses concerning the neurochemical basis of hyperkinesis are derived from three sources (Gualtieri, 1991):
(1) The known neurochemical effects of drugs that are effective in treating hyperkinesis;
(2) Neurochemical lesions in laboratory animals whose behaviors mimic hyperkinetic symptoms; and
(3) Measures of neurotransmitter metabolites in the urine, blood, and cerebrospinal fluid of hyperkinetic patients.

Before dealing with the biochemical studies of hyperkinesis, we will briefly review the biochemistry of the catecholamines (Cooper et al., 1986): Tyrosine is the amino acid precursor of the catecholamines dopamine (DA) and norepinephrine (NE). Tyrosine is hydroxylated to dihydroxyphenylalanine (DOPA), which in turn is decarboxylated to dopamine. NE is synthesized from DA, and NE is subsequently converted to epinephrine. Catabolism of the catecholamines is regulated by two enzymes, monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). DA is converted to homovanillic acid (HVA), and NE to vanillylmandelic acid (VMA), the predominant product in the periphery, and 3-methoxy-4-hydroxyphenylglycol (MHPG), the predominant product in the brain. The indoleamine, serotonin (5-hydroxytryptamine, 5-HT), is derived from the amino acid tryptophan. Tryptophan is converted to 5-hydroxytryptophan (5-HTP), which is decarboxylated to 5-HT. Degradation by MAO produces the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA).

The dopaminergic system and hyperkinesis

First, studies affirming the possible relationship between DA and hyperkinesis will be reviewed. Then, the observations that question this relationship.

A hypothesis of dopamine deficiency in the pathophysiology of hyperkinesis was first suggested as a result of the analogy between the symptoms of children suffering from hyperkinesis and children who suffered from the pandemic of Von Economo's encephalitis at the beginning of this century. As a result of this viral infection, children exhibited attentional and motor symptoms, whilst adults developed Parkinson's disease. Since Parkinson's disease is related to dopamine deficiency it suggests that the behavioral disorder observed in hyperkinetic children might also result from a dysfunction of the dopaminergic system (Wender, 1971).

Determination of amine and metabolite levels in the cerebrospinal fluid (CSF) offered

the possibility to assess the function of the dopaminergic system. Basal CSF levels of HVA did not differ in hyperkinetic children when compared with controls (Shetty & Chase, 1976). However, following treatment with d-amphetamine, a significant reduction in HVA levels was found in hyperkinetic children. This reduction correlated with the beneficial effect of the drug. HVA levels in CSF following probenecid loading were found to be significantly lower in children with hyperkinesis as compared with a control group of children with other neurological disorders (Shaywitz et al., 1977).

The dopamine deficiency theory of hyperkinesis was further supported by the finding of Shaywitz et al. (1976), that DA depletion in baby rats following administration of 6-hydroxydopamine produced a transient state of hyperactivity and impaired learning, that was ameliorated by stimulants. Later, Shaywitz et al. (1984) found clinical evidence for action of methylphenidate on dopamine pathways: Methylphenidate gave an elevation in serum growth hormone and a reduction in serum prolactin concentrations. Dopamine plays a role in regulating breadth of attention and processes of cognitive selection (Hunt et al., 1991b). Medications that deplete dopamine (reserpine) or block dopamine receptors (haloperidol) can blunt attention. Dopamine agonists (stimulants) narrow the attentional field, enhance the focus on and the salience of a stimulus, and diminish the power of distractions.

One line of evidence that strongly supports a focus on dopaminergic functioning is recent work on cerebral blood flow. In single photon emission computerized tomography (SPECT) imaging studies using ^{133}Xe to measure regional cerebral blood flow, hypoperfusion was observed in striatal regions in hyperkinetic children as compared to normal controls (Lou et al., 1989). The hypoperfusion is presumed to reflect reduced metabolism and neuronal activity in the striatum. The striatum is part of the dopaminergic system. The low perfusion was partially reversed after administration of methylphenidate. This finding suggests decreased dopamine functioning in hyperkinesis.

The following observations question the relationship between DA and hyperkinesis. Weizman et al. (1990) state that two findings are not in accordance with the dopaminergic hypothesis: (1) Levoamphetamine, which is relatively devoid of dopamine agonistic activity, was reported to be efficient in the treatment of hyperkinesis; and (2) antipsychotics (dopamine antagonists) do not aggravate the disorder, nor do they interfere with the beneficial effect obtained by methylphenidate administration. In fact, antipsychotics do decrease hyperkinetic symptoms. This may be caused by the fact, that the α–adrenergic blocking activity of antipsychotics is more prominent relative to dopaminergic action with the low doses used in hyperkinesis (Zametkin & Rapoport, 1987a). Furthermore, the assumption that dopamine depletion is a prerequisite for the beneficial effect of stimulants is not in accordance with the finding that stimulants improve attention and reduce motor activity in normal children (Rapoport et al., 1978a), as well as in children with pure reading disability without attention deficit (Klein & Klein, 1978). Moreover, dopamine agonists such as piribidel, amantadine and L-dopa have not proved sufficient in the treatment of ADHD (Zametkin & Rapoport, 1987a).

The noradrenergic system and hyperkinesis, MHPG

There is a barrier with regards to the movement of NE out of the CNS. The CNS contributes about 20-30% of all NE metabolites in the body (Kopin et al., 1984). These metabolites first enter the circulation (plasma) and then the urine. Central NE enters the circulation predominantly converted to free MHPG (Karoum et al., 1977). Peripherally released NE partly (50%) enters the circulation as free MHPG and partly (50%) in the form of other metabolites of which VMA is most important (Kopin et al., 1984). Since plasma free MHPG, after entering the circulation, is further metabolized to VMA to the extent of about 50%, only about one half of central MHPG released into the circulation appears in the urine as MHPG. Thus, the CNS contributes only about 20% of total urinary MHPG (Kopin et al., 1984). The same holds true of free plasma MHPG (Filser et al., 1986). Total urinary MHPG consists of about 10% free MHPG, 30% MHPG sulfate and 60% MHPG glucuronide (Peyrin & Pequignot, 1983; Filser et al., 1988). The percentage representation of central MHPG is much higher in the urinary MHPG sulfate fraction than in the free and glucuronide fractions of urinary MHPG (Peyrin & Pequignot, 1983; Filser et al., 1988).

Although only a small part of urinary and plasma MHPG is of central origin, several studies found significant correlations among brain, CSF, plasma and urinary concentrations of MHPG (see Maas & Leckman, 1983, for a review). Maas and Leckman (1983) suggested that the central and the peripheral noradrenergic systems might be connected by an interactive linkage. The NE neuronal cell bodies in the locus coeruleus (LC), and their projections, account for a large fraction of total brain NE. Caudal projections from the LC are probably of importance for the regulation of heart rate and blood pressure, functions that are controlled, in part, by the sympathetic nervous system. The increase in plasma MHPG after stimulation of the LC is significantly reduced after ganglionic blocking. Both urinary and plasma MHPG concentrations were found to be significantly correlated with blood pressure.

In the case that the central and the peripheral noradrenergic systems are connected by an interactive linkage, the relative contributions of the central and peripheral noradrenergic systems to urinary or plasma MHPG become less important (Filser et al., 1986). Moreover, even if MHPG findings in hyperkinetic children cannot directly be correlated with the activity of central noradrenergic neurons, their empirical value remains.

The finding that for some drugs (d-amphetamine, methylphenidate, desipramine) the beneficial effect correlated with changes in plasma and urinary MHPG has been considered as a strong argument for a noradrenergic hypothesis in hyperkinesis (Zametkin & Rapoport, 1987b). However, for other drugs no correlation has been found between MHPG change and clinical effect.

A relation between a reduction in MHPG excretion and a beneficial clinical response was found during treatment with d-amphetamine (Shekim et al., 1979; Brown et al., 1981; Elia et al., 1990), methylphenidate (Yu-cun & Yu-feng, 1984; Serfontein et al., 1988) and desipramine (Donnelly et al., 1986). In Shekim et al.'s (1979) study, pretreatment MHPG excretion did not predict the clinical response to d-amphetamine. Zametkin et al. (1985b) found no plasma MHPG change after treatment with d-

amphetamine. However, Elia et al. (1990) found a significant reduction in both plasma and urinary MHPG after treatment with d-amphetamine, but not after treatment with methylphenidate. In Serfontein's (1988) study, a higher pretreatment MHPG excretion predicted a benificial response to methylphenidate. A fourth study in which hyperkinetic children were treated with methylphenidate found no relation between MHPG change and clinical drug response (Zametkin et al., 1985a).

No relation between MHPG change and clinical drug response was found in other studies. Pemoline (Zametkin et al., 1986), which is efficient in the treatment of hyperactivity, had no significant effect on urinary MHPG excretion. Some drugs cause a large decrease in urinary and plasma MHPG (fenfluramine), but have no behavioral effect in hyperkinesis (Zametkin & Rapoport, 1987a).

The following finding showed that the beneficial effect of psychostimulants on attention is mediated by the dopaminergic system rather than by the noradrenergic system. According to the dopaminergic hypothesis, the d- and l-isomers of amphetamine differ in their effect on dopaminergic function, while they are identical in their effect on the noradrenergic function. Both isomers are effective in the treatment of ADHD but the d-isomer, which possesses dopaminergic agonist activity, is more active in attention improvement (Arnold et al., 1976). The finding that MAO inhibitors have a beneficial effect in hyperkinesis (Zametkin & Rapoport, 1987a) suggested that noradrenergic mechanisms are involved because the common mechanism of action of the MAO inhibitor is an activation of noradrenergic metabolism (Weizman et al., 1990).

The finding of elevated noragrenergic metabolites in the CSF of a child with Tourette's Disorder (GTS), led Cohen et al. (1979) to a test with clonidine in GTS. Thereupon, Cohen et al.'s (1980) observation that in Tourette patients not only tics but also ADHD and obsessive-compulsive behaviors appeared responsive to treatment with clonidine led to Hunt et al.'s (1985) trial of clonidine in hyperkinesis.

Table 6.1 Urine comparisons of ADHD children and normal controls.

Investigators	ADHD (N)	Control (N)	Findings
Shekim, 1977	7	12	decreased MHPG in ADHD.
Shekim, 1979	15	13	decreased MHPG in ADHD.
Shekim, 1983	9	9	decreased MHPG in ADHD.
Yu-cun, 1984	73	51	decreased MHPG in ADHD.
Serfontein,1988	52	57	decreased MHPG in ADHD.
Khan, 1981	10	10	increased MHPG in ADHD.
Wender, 1971	9	6	no difference in ADHD.
Rapoport, 1978	13	14	no difference in ADHD.

Studies of urinary MHPG excretion in hyperkinetic children produced contradictory findings (see Table 6.1). Three laboratories reported that these children excreted less MHPG than normal subjects (Shekim et al., 1977, 1979, 1983; Yu-cun & Yu-feng, 1984; Serfontein et al., 1988). No differences were found in two other independent studies (Rapoport et al., 1978a; Wender et al., 1971). Khan and Dekirmenjian (1981) reported levels of MHPG excretion in hyperkinetic children that were nearly identical to those reported by Shekim (830 and 666-806 µg/24hrs, respectively). However, Khan and Dekirmenjian (1981) found unexplainably low urinary MHPG levels in their control group in comparison with Shekim (649 and 872-1078 µg/24hrs). With respect to the selection of the control group Khan and Dekirmenjian's study can be criticized, because criteria for the selection of the control group were: "The control group comprised of 10 boys aged 6-11 who were selected from a middle class neighborhood on the basis of their age and their willingness to participate in the study. All of these children were known to one of us and were not hyperactive".

A possible source of artifact in urinary MHPG studies may be prolonged depression of MHPG after medication has been discontinued. As the standard "washout" period for most of the studies was only 2 weeks the reported differences between ADHD children and normal subjects might reflect prior drug use (Zametkin et al., 1985b, 1987b).

The serotonergic system and hyperkinesis

A serotonergic hypothesis has been developed from preclinical reports of increased aggression and activity in serotonin depleted animals and inconsistent findings of altered platelet or blood 5-HT in hyperkinetic subjects. As drugs such as the tricyclic antidepressants or monoamine oxidase inhibitors affect serotonin metabolism, their efficacy could also be inferred to support the 5-HT hypothesis. Treatment trials with L-tryptophan and with fenfluramine in hyperkinetic boys gave contradictory results (Zametkin & Rapoport, 1987a). The possible involvement of serotonin in hyperkinesis is supported by the beneficial effect of clomipramine (a tricyclic antidepressant) and clorgyline (a MAO inhibitor) in hyperkinesis (Weizman et al., 1990). Methylphenidate and amphetamine also possess serotonergic agonist activity (Sloviter et al., 1978).

However, the finding that hyperkinetic children do not differ from normal controls in CSF urinary 5-HIAA concentration (Wender et al., 1971; Shaywitz et al., 1977) does not support the serotonergic hypothesis. Moreover, high-affinity [^{3}H]imipramine binding to platelets, which labels the serotonin uptake site, did not discriminate between hyperkinetic children and controls (Weizman et al., 1990). Furthermore, methylphenidate treatment in hyperactive children does not alter platelet serotonin levels, urinary 5-HIAA, and imipramine binding (Weizman et al., 1990).

To summarize, it seems that most findings argue against an obvious or major role of serotonin in hyperkinesis as well as in the mode of action of methylphenidate in hyperkinesis.

6.2 Neurotransmitters and hyperkinesis: Conclusion and aims

It is likely that multiple neurotransmitter systems are involved in the cognitive and behavioral functioning of hyperkinetic children, and in the realization of medication effects (e.g., clonidine, methylphenidate). Clonidine acts specifically on the noradrenergic system but has indirect effects on the dopaminergic system. Methylphenidate increases the release of DA, NE, and 5-HT (Hunt et al., 1991a). The noradrenergic system plays an important role in the understanding of neurochemical mechanisms involved in hyperkinesis. In addition, the noradrenergic system seems to be the right area to investigate the differential effects of clonidine and methylphenidate on neurochemical mechanisms. Although we are also interested in the actions of clonidine and methylphenidate on the dopaminergic system, we decided, taking into account the high costs of a neurochemical investigation, to confine our study to the major central metabolite of the noradrenergic system, MHPG.

The aims of the neurochemical study were:
(1) to compare plasma and urinary MHPG levels of hyperkinetic patients with MHPG levels in normal controls; and
(2) to investigate the differential effects of clonidine and methylphenidate on plasma and urinary MHPG levels in hyperkinetic children.

6.3 Methods

Subjects

The study group consisted of the subjects of trial group 3 (n=72; see chapter 3). All these patients were drug-naive with respect to both clonidine and methylphenidate and had not used any psychoactive medications within 6 months prior to entering the study.

The control group for urinary MHPG consisted of 54 normal children aged 6-12, who were pupils of an urban primary school and scored below the clinical range on both the total problem score, and the Hyperactive factor score of the CBCL.

For a comparison with the children of the study group control plasmas were selected, matched for sex and age (n=27, age 7-12). Controls were children from an urban epidemiological sample (De Man, 1991), who scored below the clinical range on both the total problem score, and the Hyperactive factor score of the CBCL.

Procedure

The urine and plasma sampling procedures were the same for control and study groups. Samples were analyzed within 6 months after collection.

Twenty-four hour urines and plasma samples were collected from each child in the study group both before the start of the medication trial and in the 7th week of treatment. Blood samples were obtained during the week following the weekend of the urine

collection.

The 24-hr urine was collected during the weekends by the parents at home. Sodium metabisulphite, 0.5 g, was added to each urine sample as a preservative for MHPG and the samples were refrigerated immediately after the child urinated. The samples were kept frozen until analysis.

Blood (venous, 10 ml) was collected between 8:00 and 10:00 A.M. in siliconized glass tubes containing 0.15% EDTA. The blood was immediately centrifuged for 20 min at 2650 g, and the plasma separated. Twenty µl 2% sodium metabisulphite was added to 2 ml of plasma and the sample was frozen at -80°C until analysis.

Subjects were not placed on a diet before urine collection and plasma sampling. Baker et al. (1988) found that the dietary intake of tyrosine and tyramine was not related to MHPG plasma levels in normal adults.

Total urinary MHPG: Biochemical methods

How complete the urine collection was, was controlled by measuring urinary volume and creatinine levels. Urine specimens of low volume and/or low creatinine were discarded. Both in the control group and in the study group only the urines were retained of children with volumes of more than 250 ml/24hrs, and a creatinine excretion above the lower 5% limit for boys and girls (i.e., 44 and 97 µmol/kg/day, respectively). In the control group, 54 urine samples were retained. In the study group, 65 pretreatment samples were retained (7 urines were discarded, or were missing), and 59 samples that had been collected in the 7th week of treatment (13 urine samples were discarded, or missing, of which ten in the placebo group).

In the urine samples of the control group, total urinary MHPG levels were determined using the procedure described by Moleman and Borstrok (1982).

In the urine samples of the study group, total urinary MHPG levels were determined, using a slight modification of the procedure described by Moleman and Borstrok (1982). The modification consisted of: (1) no precipitation with $BaCl_2$ before enzymatic hydrolysis; (2) no extraction in acetic acid; the extract is directly evaporated to dryness and dissolved in HPLC-eluens; and (3) no electrochemical detection but native fluorescence. Although we may suppose that the difference in biochemical method between control and study samples is negligible small, we could not check this.

Twenty-four hour urinary MHPG levels were corrected for body weight by expressing 24-hr urinary MHPG as a ratio to 24-hr creatinine excretion (µmol MHPG / mmol creatinine).

Plasma free MHPG: Biochemical methods

MHPG was extracted within 6 months using a slight modification of the procedure described by Moleman and Bortsrok (1982). In short, 0.5 ml plasma, 20µl internal standard (2 µg iso-MHPG/ml), and 3 ml ethyl acetate were added to a seraclear tube containing 0.75 g NaCl and 0.1 g florisil. The tube was shaken for 20 min and centrifuged for 10 min at 2750 g. Two ml of the organic layer was evaporated to dryness at 40°C under

vacuum in a Buchler Vortex Evaporator, and the residue was dissolved in 0.5 ml of the mobile phase.

Chromatographic conditions: The mobile phase consisted of 50 mM sodium phosphate and 0.67 mM disodium EDTA containing 1% isopropanol, pH 2.7. Ten µl or 20 µl samples were injected onto a reversed phase column (ODS-Hypersil, 5 µm particle size, 200 x 2.1 mm, Hewlett Packard), which was protected by a guard column (20 x 2.1 mm) of the same material. The flow rate was set at 0.25 ml/min and the column temperature was 28°C. The detection system consisted of a Model 5100A Coulochem detector equipped with a 5021 conditioning cell and a 5011 high sensitivity cell (ESA, Bedford, MA, USA). The potentials for the conditioning cell and detectors 1 and 2 were +0.45, -0.05, and -0.43 V, respectively. The gain was 15 x 100. The detector was linked to a HP 3396A integrator (Hewlett Packard) and quantification was done by measuring peak heights. The limit of detection at a signal to noise ratio of 2 was 10 fmol (approx. 2 pg) MHPG per injection. The retention times of MHPG and iso-MHPG were 7.6 and 12.8 min. respectively. The intra- and inter-essay coefficients of variation of duplicate analysis of plasma samples were 2.6% (n=8) and 4.9% (n=18), respectively. The recovery of iso-MHPG added to the plasma samples was 79 ± 4% (n=14).

6.4 Results

Table 6.4a MHPG excretion per 24 hours (mean ± SD) in patients and controls.

	MHPG t_0 µmol/24h	MHPG t_7 µmol/24h	MHPG/creat[a] t_0	MHPG/creat[a] t_7
All patients:	4.57±1.69	4.87±2.40	1.32±0.55	1.36±0.53
N=72	N=65	N=59	N=68	N=62
Clonidine:	4.82±1.50	4.93±1.97	1.36±0.54	1.27±0.36
N=24	N=22	N=22	N=23	N=23
Placebo:	4.22±1.60	4.71±2.14	1.27±0.47	1.29±0.50
N=24	N=20	N=14	N=21	N=15
Methylphenidate:	4.64±1.89	4.92±2.87	1.31±0.61	1.49±0.65
N=24	N=23	N=23	N=24	N=24
Controls[b]:				
M (n=29)	5.61±1.45		1.10±0.21	
F (n=25)	6.00±1.73		1.11±0.22	

[a] µmol MHPG / mmol creatinine.
[b] Age range controls: 6-12. When comparing with subjects we controlled for age and sex.

Table 6.4b Plasma MHPG (mean ± SD) in patients (aged 6-15) and controls, matched for sex and age.

	MHPG t_0 ng/ml	MHPG t_7 ng/ml
All patients: N=72	3.55±0.90 N=68	3.39±0.71 N=69
Clonidine: N=24	3.50±0.85 N=24	3.12±0.70 N=23
Placebo: N=24	3.65±0.79 N=21	3.72±0.73 N=22
Methylphenidate: N=24	3.51±1.00 N=23	3.35±0.54 N=24
Controls[a]: N=27	3.97±0.55 N=27	

[a] Control plasmas were selected matched for sex and age for a comparison with subjects (n=27, 23M and 4F , age 7-12).

Urine samples

(1). Do ADHD children excrete less, equal or more MHPG than controls?

Because our control urines were for the age range 6-12 years, we made a comparison with subjects aged 6-12 (discarding three urines of subjects older than 12). We performed a multiple regression analysis taking the MHPG excretion as the dependent variable after logarithmic transformation and controlling for age and sex. We found that the MHPG/ 24hrs excretion in the ADHD patients was significantly lower than the MHPG excretion in control children. For MHPG/creatinine ratios we found no significant difference between patients and controls (see Table 6.4c). The logarithmic transformation was applied in order to make the variance of the error term homogeneous. Patients had an 18% lower MHPG/24hrs excretion: $100\ (1 - e^{B}) = 100\ (1 - e^{-0.20}) = 18\%$.

In short: ADHD children excreted significantly less MHPG/24hrs than controls.

Table 6.4c Comparison of MHPG excretion between control children (N=54) and ADHD patients (N=65), using multiple regression analysis, controlling for age and sex.

	B	SE B	p-value
MHPG/24hrs:			
Group (1=controls,2=patients)	-0.20	.06	.001 **
Age (in years)	.09	.02	.000 **
Sex (1=boy, 2=girl)	.05	.06	.428
Constant	1.03	.21	
R Square = .35			
MHPG/creatinine:			
Group (1=controls,2=patients)	.10	.06	.093 NS
Age (in years)	- .03	.02	.121
Sex (1=boy, 2=girl)	- .004	.07	.951
Constant	.22	.22	
R Square = .06			

* $p < .05$; ** $p < .01$.

(2). We tested if subgroups could be detected in the distribution of baseline values of MHPG excretion. We found no signs of a bimodal distribution.

(3). Does a relationship exist between (clinical) respondership and pretreatment urinary MHPG excretion?

Using the Mann-Whitney U test (two-sided), we compared baseline MHPG excretion of clinical responders with baseline MHPG excretion of nonresponders. We found no significant difference (MHPG/24hrs $p = .08$; MHPG/creatinine $p = .35$). Using a logistic regression model, we investigated the relationship between respondership and MHPG excretion, controlling for drug condition. We found no significant effect of MHPG excretion on respondership (see table 6.4d).

In short: Baseline MHPG excretion did not predict clinical respondership to clonidine or methylphenidate.

Table 6.4d Relationship between clinical respondership and MHPG excretion, controlling for drug condition (logistic regression).

	B	SE	p-value
Drug (1=clonidine, 0=placebo)	1.57	.77	.042 *
Drug (1=methylph., 0=placebo)	1.70	.76	.026 *
baseline MHPG/24hrs	.37	.21	.077 NS
baseline MHPG/creatinine	- .82	.64	.198 NS
Constant	-2.44	1.00	

* $p < .05$.

(4). What is the effect of methylphenidate and of clonidine on urinary MHPG excretion?

We compared the effects of medication on the change (δ) of MHPG/24hr and MHPG/creatinine under the three medication conditions, using a Kruskal Wallis 1-way ANOVA, and found no significant differences in effects: δMHPG/24hrs: $p = .58$ (ns); δMHPG/creat: $p = .17$ (ns).

Using multiple regression analysis, taking MHPG excretion after treatment as the dependent variable, and controlling for baseline MHPG excretion, we also did not find significant differences in effects between medication conditions (see table 6.4e). The multiple regression analysis also shows that the correlation between baseline and after treatment MHPG/creatinine levels is lower (B=.26) than the correlation between the baseline and after treatment MHPG/24hrs (B=.86). This could be interpreted as that MHPG/creatinine levels are less stable than MHPG/24hrs levels.

In short: We found no significant effects of medication on MHPG excretion, comparing the three treatment groups (clonidine, placebo, methylphenidate).

Table 6.4e Comparison of the effects of medication on changes in MHPG excretion, using multiple regression analysis, taking MHPG excretion after treatment as the dependent variable, and controlling for baseline MHPG excretion.

	B	SE B	p-value
MHPG/24hrs after treatment:			
Drug (1=clonidine, 0=placebo)	- .33	.77	.675 NS
Drug (1=methylph., 0=placebo)	- .59	.79	.461 NS
Baseline MHPG/24hrs	.86	.15	.000 **
Constant	1.31	.90	
R Square = .40			
MHPG/creat. after treatment:			
Drug (1=clonidine, 0=placebo)	.09	.19	.643 NS
Drug (1=methylph., 0=placebo)	- .13	.19	.505 NS
Baseline MHPG/creatinine	.26	.12	.036 *
Constant	1.06	.21	
R Square = .11*			

$p < .05$; ** $p < .01$.

(5). Is this effect different in (clinical) responders than in nonresponders?

We compared the change (δ) in MHPG excretion between clinical responders and nonresponders in each of the three treatment groups (clonidine, placebo, methylphenidate), using the Mann-Whitney U test (two-sided), and found no significant effects (see table 6.4f).

Table 6.4f Comparison of effects of medication on MHPG excretion in clinical responders and nonresponders (Mann-Whitney U test, two-sided).

	clonidine δ(SD)	placebo δ(SD)	methylphenidate δ(SD)
δMHPG/24hrs			
responders:	.32 (2.24)	missing	.55 (2.87)
nonrespond:	-.23 (1.48)	missing	.05 (1.18)
p-value:	.49 NS		.64 NS
δ MHPG/creat.			
responders:	.13 (.43)	.60 (.00)	.09 (1.0)
nonrespond:	-.23 (.63)	.10 (.46)	.27 (.69)
p-value:	.18 NS	.31 NS	1.0 NS

Plasma

(1). Do ADHD children have lower, equal or higher levels of plasma MHPG than normal subjects?

Using multiple regression analysis, taking plasma MHPG as the dependent variable, we found, when controlling for age and sex, that the plasma MHPG in the ADHD patients was significantly lower than the plasma MHPG in control children (see table 6.4g).

In short: Patients had a significantly lower plasma MHPG than controls.

Table 6.4g Comparison of plasma MHPG between ADHD patients (N=68) and control children (N=27), using multiple regression analysis and controlling for age and sex.

	B	SE B	p-value
Plasma MHPG:			
Group (1=controls,2=patients)	- .41	.19	.032 *
Age (in years)	- .04	.05	.464
Sex (1=boy, 2=girl)	- .19	.24	.438
Constant	4.89	.61	
R Square = .06			

* $p < .05$.

(2). We tested if subgroups could be detected in the distribution of baseline plasma MHPG values. We found no signs of a bimodal distribution.

(3). Does a relationship exist between (clinical) respondership and pretreatment plasma MHPG levels?

Using the Mann-Whitney U test (two-sided), we compared baseline plasma MHPG of clinical responders with baseline plasma MHPG of nonresponders. We found no significant difference ($p = .24$). Using a logistic regression model, we investigated the relationship between respondership and plasma MHPG, controlling for drug condition. We found no significant effect of plasma MHPG on respondership (see table 6.4h).

In short: Baseline plasma MHPG did not predict clinical respondership to clonidine or methylphenidate.

Table 6.4h Relationship between clinical respondership and plasma MHPG, controlling for drug condition (logistic regression).

	B	SE	p-value
Drug (1=clonidine, 0=placebo)	1.79	.75	.017 *
Drug (1=methylph., 0=placebo)	1.87	.75	.013 *
baseline plasma MHPG	- .04	.29	.892 NS
Constant	-1.65	1.23	

* $p < .05$.

(4). What is the effect of methylphenidate and of clonidine on plasma MHPG levels?

We compared the effects of medication on the change (δ) of plasma MHPG under the three medication conditions, using a Kruskal Wallis 1-way ANOVA, and found no significant differences in effects: δplasma MHPG: $p = .08$ (ns).

Thereupon, we performed a multiple regression analysis, taking plasma MHPG after treatment as the dependent variable, and controlling for baseline plasma MHPG. We found significant effects on the change of plasma MHPG both in the clonidine and in the methylphenidate condition, in comparison with the effects in the placebo condition (see table 6.4i). The multiple regression analysis also showed a good correlation between baseline and after treatment plasma MHPG levels (B=.58).

In short: We found significant medication effects of both clonidine and methylphenidate on plasma MHPG, when compared with placebo. The decline in plasma MHPG, that was found, was greater in the methylphenidate condition (B=-.48) than in the clonidine condition (B=-.29).

Table 6.4i Comparison of the effects of medication on changes in plasma MHPG, using multiple regression analysis, taking plasma MHPG after treatment as the dependent variable, and controlling for baseline plasma MHPG.

	B	SE B	p-value
Plasma MHPG after treatment:			
Drug (1=clonidine, 0=placebo)	- .29	.14	.039 *
Drug (1=methylph., 0=placebo)	- .48	.14	.001 *
Baseline plasma MHPG	.58	.06	.000 **
Constant	1.59	.25	
R Square = .63			

* $p < .05$; ** $p < .01$.

(5). Is this effect different in (clinical) responders than in nonresponders?

We compared the change (δ) in plasma MHPG between clinical responders and nonresponders in each of the three treatment groups (clonidine, placebo, methylphenidate), using the Mann-Whitney U test (two-sided), and found no significant effects (see table 6.4j).

Table 6.4j Comparison of effects of medication on plasma MHPG in clinical responders and nonresponders (Mann-Whitney U test, two-sided).

	clonidine δ(SD)	placebo δ(SD)	methylphenidate δ(SD)
δplasma MHPG			
responders:	-.37 (.46)	.03 (.49)	-.04 (.69)
nonrespond:	-.28 (.57)	.09 (.50)	-.30 (.74)
p-value:	.69 NS	.83 NS	.35 NS

Urine and plasma

(1). Correlation between urine and plasma MHPG levels (pretreatment).

We found no significant correlations between pretreatment urine and plasma levels. We found a significant correlation between MHPG/24hrs and MHPG/creatinine levels (r=.57, p=.000).

(2). The association between MHPG levels in plasma and 24hrs urine and a positive family history of hyperactivity (according to clinical judgement).

1st degree relative hyperactive:	46% (N=33)
>1st degree relative hyperactive:	13% (N=9)
no relatives hyperactive:	38% (N=27)
adoptive children:	4% (N=3)
total:	100% (N=72)

Using the Mann-Whitney U test (two-sided), we compared baseline MHPG levels in plasma and 24hrs urine of subjects with a positive family history of hyperactivity with baseline MHPG levels of subjects without a positive family history. We performed two comparisons:
(1) We compared the subjects with a 1st degree hyperactive relative with the other subjects;
(2) We combined subjects with 1st or >1st degree hyperactive relatives and compared these subjects with the other subjects (the adoptive children were excluded). Table 6.4k shows the results. We found no significant differences.

Table 6.4k Comparison of MHPG levels in plasma and 24hrs urine between subjects with and subjects without a positive family history of hyperactivity, using the Mann-Whitney U test (two-sided).

	MHPG plasma mean/SD	MHPG/24hrs mean/SD	MHPG/creat. mean/SD
1st degree			
positive	3.48±0.61	4.39±1.66	1.35±0.56
negative	3.56±1.09	4.63±1.87	1.35±0.56
p-value:	0.51 NS	0.42 NS	0.91 NS
1st & >1st degree			
positive	3.45±0.67	4.47±1.76	1.36±0.65
negative	3.64±1.16	4.59±1.81	1.33±0.38
p-value:	0.83 NS	0.52 NS	0.65 NS

6.5 Summary

The noradrenergic system plays an important role in the understanding of neuro-chemical mechanisms involved in hyperkinesis. Free plasma MHPG and total urinary MHPG were chosen as probes for central noradrenergic events in our study. Both

clonidine and methylphenidate act on the noradrenergic system.

The aims of the biochemical study were:
(1) to compare the ADHD children with normal controls with respect to free plasma MHPG and 24-hrs total urinary MHPG; and (2) to compare the differential effects of clonidine and methylphenidate on MHPG.

Only the children of trial group 3 were investigated with respect to MHPG. This group had significantly lower levels of MHPG than the controls, both in 24-hrs urine and in plasma. They also had a significant decrease in plasma MHPG following both clonidine and methylphenidate treatment, compared with placebo. Possible explanations for these findings will be presented in the discussion of the entire study (Chapter 7).

Chapter 7

CHAPTER 7 DISCUSSION AND RECOMMENDATIONS

7.1 Introduction

This study was set up to compare the efficacy and safety of clonidine with those of placebo and the "first-line" drug methylphenidate in relation to short-term effects on hyperactivity in children with DSM-III-R classification ADHD.

In this chapter we shall successively evaluate the results of our study: the psychiatric and medical assessment (section 7.2), the psychological test results (section 7.3), the clinical effects and adverse effects of clonidine and methylphenidate (section 7.4) and the results of the neurochemical study (section 7.5). The chapter concludes with recommendations for the use of clonidine and methylphenidate in hyperkinesis (section 7.6).

7.2 The psychiatric and medical assessment

The reliability of the DSM-III-R diagnosis ADHD in this study

The principal criterion for inclusion of a child in the study was a diagnosis of DSM-III-R ADHD. We will discuss two problems with respect to the reliability of the diagnosis ADHD in this study: (1) there was hardly any control for the project-leader's interpretation bias; and (2) since the study was designed to treat children fulfilling the DSM-III-R criteria for ADHD, it was hardly surprising to find a 100% interrater reliability with respect to the diagnosis of ADHD.

The project-leader provided the DSM-III-R raters with all the information from the diagnostic assessment: the Child Assessment Schedule, the Graham/Rutter parent interview, the parent and teacher reported rating scale scores and the diagnostic summarizing report. In addition, the raters had access to videotapes of the child's behavior during psychological testing and during standardized playroom observation.

The diagnostic criteria for ADHD include an item list of 14 symptoms of which at least eight must be present for a diagnosis of ADHD. A symptom is considered present if the behavior is developmentally inappropriate for the child's mental age. A problem in the assessment of ADHD is that whereas clinicians usually prefer to rely on their own impressions of the child's behavior in their office, the clinic situation is not the most appropriate one to judge ADHD symptoms. Signs of ADHD may be minimal in such a setting which is novel and includes a one-to-one situation (APA, 1987).

The DSM-III-R category ADHD includes both situationally and pervasively hyperactive children. Situationally hyperactive children show their symptoms primarily at home or at school. Pervasively hyperactive children show their symptoms in both situations. Therefore, both the project-leader and the two independent raters were faced

with the difficult task to assess whether at least eight of 14 ADHD symptoms were present at home and/or at school. Although the project-leader reported the parents' and teacher's statements on problem behaviors as accurately as possible, the raters were given no opportunity to assess the parents' and teacher's information themselves and therefore there was no control for the project-leader's interpretation bias.

When we planned the study we considered making the inclusion criterion more specific by including a parent or teacher reported hyperactivity rating scale score above the 90th percentile in addition to a DSM-III-R diagnosis of ADHD. We decided not to include rating scale scores as an additional inclusion criterion because we required the study children to be representative of those ADHD patients we use to subscribe medication in child psychiatric practice. In child psychiatric practice we only subscribe medication to children with a DSM-III-R diagnosis ADHD whose ADHD symptoms impede their development and for whom existing treatments have proved to be insufficient. In the study we applied these three inclusion criteria (i.e., ADHD, impeding development, existing treatment insufficient). Of these criteria we only checked the first for interrater agreement. The hyperactivity rating scale scores were included in the clinical assessment as information about the child's hyperactivity at home and at school. We found that 70% of the children had parent reported hyperactivity ratings (GOO) above the 90th percentile and 43% had teacher reported hyperactivity ratings (GBO) scores above the 90th percentile.

Although our procedure for diagnosing ADHD was intended as only a sort of check on the project-leader's child psychiatric diagnosis, this procedure could be criticized in that it may not have been specific enough and that assessment bias has not been sufficiently controlled for. Therefore, we recommend for future studies:
(1) to make separate and independent DSM-III-R ADHD ratings for the home, school and clinic situation and to integrate these data afterwards into a composite ADHD rating; and (2) to let an independent research team decide on the presence of ADHD, and therefore the entry of a subject to a study.

The second issue we want to discuss in this section is that we found a 100% interrater reliability with respect to the diagnosis of ADHD (kappa = 1). Firstly, this is hardly surprising since raters implicitly knew that the project-leader had already diagnosed ADHD. Secondly, the coefficient kappa depends on the prevalence of a disease in the sample (Schouten, 1985): the higher the prevalence is, the better the coefficient kappa. Kappas have little value if nearly all individuals are assigned to the same category. Thirdly, the degree of agreement among raters provides no more than an upper limit on the degree of accuracy present in the ratings. When a high degree of agreement is found among raters, there is a possibility, but by no means a guarantee, that the ratings reflect the dimension they are purported to reflect (Fleiss, 1981). Therefore, we conclude that the "perfect" interrater reliability that we found with respect to ADHD in our study, does not necessarily indicate that the assessment procedure was reliable.

Reliability of related psychiatric disorders

We used the DSM-III-R classification by three independent raters as a sort of check on the project-leader's child psychiatric diagnosis. This check was important for the assignment of subjects to the three trial groups. In order to improve the interrater reliability, we provided the raters with written DSM-III-R classification instructions. The raters reached a 100% agreement with respect to the DSM-III-R classifications Pervasive Developmental Disorder NOS (PDD NOS) and Tic Disorder. For "defiance" the kappa coefficient of agreement was moderate (0.66). For "emotional disorder" we found a kappa of only 0.26.

With respect to the DSM-III-R category Pervasive Developmental Disorder NOS (PDD NOS) we found a "perfect" interrater reliability. The reason for this may be, that we had been highly specific in our definition of PDD NOS. If a disease has been highly specifically defined, this increases the chance that a high degree of interrater agreement will be found.

With respect to the diagnosis of Tic Disorder we want to comment the following. The summarizing report contained precise descriptions of the symptoms on which the project-leader had based his diagnosis of tics. It is not surprising that the raters followed the project-leader's judgment as to what were "tics", since they could not observe the child themselves or assess what was communicated with regards tic-like phenomena.

With respect to the category "defiance", the raters have much more freedom to make their own judgment. The reason for this was due especially to the way in which DSM-III-R formulates rating instructions for Oppositional Defiant Disorder: "Note: Consider a criterion met only if the behavior is considerably more frequent than that of most people of the same mental age". In fact, DSM-III-R mentions a similar clause for ADHD. However, raters in our study had little freedom in classifying ADHD for reasons explained above. The kappas found for interrater reliability on Defiance can be considered as representing moderate agreement beyond chance, having taken into consideration the rather high prevalence of Defiance in our sample (Fleiss, 1981; Schouten, 1985).

We found rather low kappas for "emotional disorder". This is possibly for the following reasons: (1) raters are possibly less aware of the occurrence of emotional disorders in a population of children with ADHD; (2) the information that the project-leader collected on emotional problems was possibly not good enough for a DSM-III-R classification; and (3) what Schouten (1985) found out concerning the lower kappa according as the prevalence of a disease in a population of individuals is lower applies here. Nevertheless, the interrater reliability for emotional disorders remains very low in our study. This aspect deserves further investigation in future studies.

Overlap of ADHD with other child psychiatric disorders

Thirty-nine percent of the subjects got a DSM-III-R diagnosis of either Oppositional Defiant Disorder or Conduct Disorder, and 6% got a diagnosis of Overanxious Disorder, Dysthymia, or Depressive Disorder NOS. It is difficult to compare our figures with

earlier findings because earlier studies used the DSM-III or ICD-9, or made other clusters of disorders (see section 2.6). Our data corroborate earlier findings in that there is a considerable overlap between ADHD and both defiance and emotional disorders (Anderson et al., 1987; Szatmari et al., 1989a). In addition, both our data on "problems parents/teacher" and our symptom severity scores, show this overlap.

Twenty-two percent of the subjects fulfilled the DSM-III-R criteria for Functional Enuresis, and 6% fulfilled the criteria for Functional Encopresis. The percentage of enuresis in our subjects is much higher than the prevalence of enuresis which Verhulst (1985) found for boys in a general population sample (between 1 and 16% in the age range 6-15 years). Thus far, study results have been conflicting with respect to whether enuresis and encopresis are more likely to occur in ADHD children than in normal children (Barkley, 1990).

In a controlled study, Comings (1990) found that stuttering was more common in patients with Tourette's Disorder than in controls. Stuttering was not more common in ADHD patients than in controls. Eight percent of the subjects fulfilled the criteria for Stuttering in our study. Three of these subjects had Tic Disorder.

Parental psychopathology

The data on parental psychopathology in our study have primarily been used to assess the parents' strengths and weaknesses. This information was important when drafting treatment plans for the hyperkinetic children. A high prevalence of several psychiatric disorders has been reported in parents of hyperkinetic children: Hyperkinesis, conduct problems and antisocial behavior, alcoholism, hysteria or affective disorder, and learning disabilities (Cantwell, 1972; Biederman et al., 1986; Schachar & Wachsmuth, 1990). We found a high prevalence (27%) of anxiety problems, depression, and somatoform disturbances in the mothers of our subjects. Our clinical impression was, that these complaints were at least partly due to the stress that these mothers experienced in their role as caregivers of a hyperkinetic child.

We used the "Malaise Inventory" to assess parental psychiatric symptoms that had occurred during the last two years. The Malaise Inventory has been reported to differentiate well between parents with and without psychiatric disorder (Rutter et al., 1970). However, studies that investigated the prevalence of parental psychopathology: (1) used assessment instruments which are capable of generating DSM-III-(R) diagnoses (e.g., the Diagnostic Interview Schedule); (2) assessed both lifetime and current diagnoses; (3) used assessment procedures in which the interviewer was blind to the child's diagnosis; and (4) did not elicit information from a parent about the absent parent (Schachar & Wachsmuth, 1990). Therefore, our data are not suited for a comparison with prevalence data from earlier studies on parental psychopathology in hyperkinetic children.

The use of a medical examination of hyperkinetic children

In our study, the medical examination included a limited general pediatric examina-

tion, an assessment of minor physical anomalies, and a developmental neurological examination. We primarily used the medical examination to detect conditions which have been reported to be associated with hyperkinetic symptoms (e.g., hearing deficits, Marfan syndrome), and conditions which form a contraindication for treatment with either clonidine or methylphenidate (e.g., hypertension). In our opinion, hyperkinetic children must be examined for these two possibilities, before medication is introduced. If a child psychiatrist performs a medical examination him/herself, this examination must be thorough enough to be able to conclude if a further examination by a pediatrician or a child neurologist is indicated.

Based on our developmental neurological examination, we could classify 34% of the subjects as having Minor Neurological Dysfunction (MND-1 or MND-2), and 2% of the subjects as neurologically abnormal. Children with MND have been found to be more vulnerable with regard to behavioral development and school achievement than neurologically normal children (Hadders-Algra et al., 1986). Touwen (1991) found a prevalence of 20% MND in normal schools, whereas the prevalence was 70% in special schools and 70% in children who received residential treatment for learning and behavioral problems. The prognosis was not worse for children with MND as compared with children without MND in a group of children in residential treatment. A diagnosis of MND has no specific relation to hyperkinesis (Vitiello et al., 1989).

We conclude that when a child psychiatrist performs a developmental neurological examination in a hyperkinetic child, this is to judge if a further neurological examination is indicated and to assess whether possible further treatment by an occupational or physical therapist is required, or that the child may be in need of some assistance with fine motor tasks or physical education in school.

7.3 Psychological test results

Learning disabilities

Based on their Primary Mental Ability test performance, 38% of our subjects were diagnosed as learning disabled (LD). Fifty-nine percent of the subjects attended schools for special education. Attendance at a special school was mostly because of learning and/or behavioral problems. We defined LD as a language or arithmetic dysfunction while having normal intelligence. Barkley (1990) diagnosed LD when a child had specific low achievement scores and a discrepancy between IQ and achievement. In a sample of 42 ADHD children Barkley (1990) found that between 19% and 26% of the children had at least one type of LD, either in arithmetic, reading, or spelling. In a normal sample between 0% and 3% of the children were diagnosed LD. The higher percentage of ADHD children diagnosed as LD that was found in our study is probably due to the difference in definition of LD. Although we cannot compare our data with percentages of LD in normal children, our findings seem to corroborate those of earlier studies showing a high prevalence of LD in ADHD children (Lambert & Sandoval, 1980; Anderson et al., 1987;

August & Garfinkel, 1989; Barkley, 1990).

GPO rating of behavior during testing and playroom observation

With respect to the GPO ratings we first will evaluate interrater reliability and then will discuss why we used these ratings to subdivide our children in groups differing in pervasiveness of their hyperactivity.

The GPO is a rating scale used as a direct observation measure of hyperactivity. Because our raters knew that the subjects were hyperactive, we used the GPO as a general behavioral measure. We found high interrater agreements both for GPO ratings of behavior during psychological testing and for GPO ratings of behavior during standardized playroom sessions (r ranged between 0.78 and 0.90, three of the four raters had r's $\geq$ 0.80).

In Van Hoeken's (1990) study, six raters independently evaluated 40 children during psychological testing (PPCT and Motor Impairment Test) using the GPO. Their sample included both hyperactive and normal control children, and the raters were blind to the group classification of the subjects. Correlations between pairs of raters were found ranging from .63 to .91. Only 3 of the 15 pairs obtained correlations $\geq$ .80 and this level was only reached for those pairs of raters that had practiced together. A minimum interrater agreement of .80 is generally considered necessary for research purposes. Although it is likely that the use of a glossary and a standard videotape have improved GPO interrater agreement in our study, we cannot compare our results with those of Van Hoeken (1990), because our raters were not blind to the group classification of the subjects. It is likely that the raters' knowledge of the subjects meeting ADHD requirements has influenced their GPO rating. We had foreseen this problem, but could not organize that normal controls were tested at the same place as the ADHD patients (the controls were tested in Groningen, the patients in Rotterdam). This was only a minor disadvantage for our study because the main purpose was to measure drug effects.

We used GPO ratings to subdivide our children in groups differing in pervasiveness of their hyperactivity. Van der Meere et al. (1991) investigated a group of children who were pervasively hyperactive, according to parent and teacher ratings. They obtained GPO ratings of the children's behavior during three tests (i.e., PPCT, WISC-R, and test of motor impairment), and found a high within-task interrater reliability, and a low between-task interrater reliability for the GPO-ratings. It was concluded that the subjects differed in their degree of pervasiveness in the three test conditions. Although the high between-task correlation for GPO-PPCT and GPO-FDF, that we found in our study, indicated a lesser degree of independence than was found between the GPO-ratings in Van der Meere et al.'s (1991) study, we decided to use GOO, GBO, GPO-PPCT, and GPO-FDF as filters to subdivide our sample into groups of children differing in pervasiveness of their hyperactivity. We used this subdivision for an analysis of the performance on PPCT. These results will be discussed now.

Performance on the paper-and-pencil cancellation task (PPCT)

Using a self-paced attention task (PPCT) we found that the group of extremely pervasive hyperactive subjects had a more variable cancellation time than controls when applying multiple regression analysis, and controlling for sex, age and FDF-score. This finding is in agreement with Van der Meere et al.'s (1991) study, who found that the more pervasively hyperactive the child, the slower and more variable his PPCT cancellation time. This finding was considered by Van der Meere et al. (1991) to validate the assumption that pervasiveness is linked to cognitive defect.

We conclude that a group classification with respect to pervasiveness, based on parent, teacher, and clinic observation measures, is meaningful in order to detect cognitive defects in subgroups of hyperactive children within the heterogeneous group of children diagnosed as DSM-III-R ADHD.

Secondly, we found that as the PPCT proceeded the mean cancellation time increased (a sustained attention effect). However, this effect did not appear specifically in the ADHD children. Hence, there was no support for a deficit in sustained attention in hyperactivity. This finding is in agreement with earlier studies (Schachar et al., 1988; Van der Meere et al., 1991), making the hypothesis of a sustained attention deficit in hyperactive children increasingly untenable.

Thirdly, we found significant correlations between GPO during PPCT and PPCT performance (r ranged between .36 and .64). Using a multiple regression analysis and controlling for sex, age and PMA-score, we found that the higher GPO score a child obtained during PPCT testing, the more variable his cancellation time was and the worse his error percentage (with adjusted R squares of .51 and .06 respectively; table 4.6.4f). Thus, PPCT performance was found to be linked to the child's behavior during testing. This can be seen as an argument for the PPCT having some ecological validity. Barkley (1991) suggested that paper and pencil versions of Continuous Performance Tasks (CPTs) such as the PPCT may have a somewhat greater degree of ecological validity than briefer, mechanical CPTs, because of their greater length, stimulus complexity, and closer proximity to actual academic work than computer-administered CPTs.

Finally, using a multivariate linear regression analysis with PPCT performance as the dependent variable, and hyperactivity and aggressiveness as the independent variables, we found a significant relation between teacher reported hyperactivity (TRF Nervous-Overactive factor score) and PPCT mean cancellation time and variability of cancellation time. However, the adjusted R squares that we found with this model were very small (.03 and .04 respectively).

7.4 Clinical effects and adverse effects of clonidine and methylphenidate

This is the first controlled trial comparing the effects of clonidine and methylphenidate on hyperactivity. In an 8-weeks, parallel-group, double-blind, placebo-controlled trial, we found that for ADHD children without either Pervasive Developmental Disorder or

Tic Disorder (n=3x24) significantly more children showed a clinically significant improvement during treatment with clonidine or methylphenidate than during treatment with placebo. The percentage of responders were 50%, 50%, and 13% respectively. In this sample, an analysis of rating scale scores during the 7 weeks of treatment showed a significant effect of both clonidine and methylphenidate on hyperactivity in all three situations (home, school, clinic), and on teacher reported acting-out behavior, when compared with placebo. With respect to the effects on home/school hyperactivity, we found no differences between clonidine and methylphenidate. However, methylphenidate, but not clonidine, gave a significant improvement of both parent and teacher target problem behaviors, when compared with placebo. Moreover, the effect of methylphenidate on teacher target problem behaviors was significantly greater than the effect of clonidine. Finally, methylphenidate, not clonidine improved "social positive" behavior when compared with placebo.

After 7 weeks of treatment, 52% of the clonidine treated children showed physical adverse effects. The percentage of children showing physical adverse effects was 58% in the methylphenidate group, and 37% in the placebo group. However, annoying adverse effects were more frequent in the methylphenidate group than in the placebo and clonidine groups (21%, 7%, and 5% respectively). During methylphenidate treatment alarming behavioral or physical adverse effects were reported in 17% of the subjects, whereas this percentage was 21% in the placebo group, and 0% in the clonidine group.

Methylphenidate

In his review of stimulant drug research with hyperactive children, Barkley (1977) reported a mean percentage of hyperkinetic children responding to methylphenidate treatment of 77% (range 51%-94%, 14 studies), and an average improvement rate of 39% for placebo treatments (range 8%-67%, 8 studies). Therefore, our response rates for both methylphenidate and placebo are lower than the mean percentages reported in literature. This difference may be attributed to several possible factors, such as criteria for respondership, dosage, treatment duration, patient characteristics, etc.

Barkley (1990) has recently investigated the prevalence of parent reported adverse effects to placebo and to methylphenidate (0.5 mg/kg/day) in a sample of 82 children with ADHD. It was found that over half of the sample exhibited decreased appetite, insomnia, anxiousness, irritability, or proness to crying. Our ADHD children exhibited less insomnia than Barkley's (1990) children, and more drowsiness during treatment with placebo. These differences can probably be attributed to our trial design in which the parents also anticipated clonidine adverse effects (especially drowsiness).

Clonidine

We tested whether our study results showed signs of tolerance to the beneficial effects of clonidine developing. Although the development of tolerance has been noted in the antihypertensive effect in adults during treatment with high-dose clonidine (Hunt et al., 1991a), there are also reasons to suspect that tolerance can occur during low-dose

treatment:
(1) Cohen et al. (1980) observed the emergence of treatment resistance in GTS patients after five or more months of treatment with clonidine; (2) whereas acute single doses of clonidine give a suppression of central adrenergic activity, this suppression has not been observed during long-term clonidine treatment (see section 7.5); (3) the emergence of tolerance after three months of treatment with clonidine 4 µg/kg/day has been reported in mentally retarded children (see section 3.4.4, Leventhal, 1991); and (4) in open treatment we have often observed that the beneficial effects of clonidine decreased after several months of treatment. We must be cautious with the latter observation, because in general the requirements of ADHD or GTS children with respect to their medication needs, seem to change in the long-term. This might be attributed to tolerance, but might also be attributed to their altered "disease state" (effects of maturation, the development of a new "tic wave").

In our study, it was found that the effect of clonidine (compared to placebo) was time dependent with respect to "problems parents" in the children of trial group 3: the medication effect was significant after 3 weeks of treatment, but was not significant anymore after 5, and after 7 weeks of treatment. Possibly, this finding is caused by clonidine's transient sedative side effects. However, another possibility is, that tolerance developed with regards to the clonidine effect.

Leckman et al. (1991) reported on adverse effects during a 12 weeks parallel-group, placebo-controlled trial with clonidine in patients with Tourette's Disorder (GTS), including both children and adults. "Dry mouth" was reported much more frequently in Leckman et al.'s (1991) study than in our trial (57% and 5% respectively). Hunt et al. (1991a) reported that the anticholinergic effects of clonidine (dry mouth, constipation, urinary retention) are much less serious in children than in adults. It is our clinical experience that dry mouth is an infrequent adverse effect in ADHD/GTS children treated with clonidine.

Leckman et al. (1991) reported that the adverse effects during clonidine treatment were limited to the first 6 weeks of the trial, and that only 9% of the patients required a reduction in clonidine dosage because of adverse effects. In our study, 52% experienced adverse effects after 7 weeks of treatment with clonidine, and dosage adjustments had been necessary in 10% (n=4).

We had to diminish the dosage to less than 3.25 µg/kg/day in two of the subjects needing a dosage adjustment. Comings (1990) reported that he used dosages of only 25-100 µg/day to attain a good clinical response in GTS patients (both children and adults): "Usually, if there is no response at a dose of 25 µg, 3 times a day, clonidine is unlikely to be successful". In our study, children aged 7 (weight approximately 24 kg) already got a dosage of 100 µg/day (4 µg/kg/day). It is our clinical impression (although based on small numbers of patients) that dosages of only 2 µg/kg/day often are beneficial in ADHD/GTS patients who do not tolerate a dosage of 4 µg/kg/day.

Comings (1990) reported that about 10% of patients with tics, hyperactivity, irritability, and conduct problems became actually worse during treatment with clonidine. Goetz

et al. (1987) reported that 37% of their GTS patients complained of restlessness during treatment with clonidine. A clinically significant deterioration was observed in our sample in 3 of the 42 patients that were treated with clonidine (7%). These children all became more restless during treatment.

Hunt et al. (1991a) reported that clonidine can induce depression in about 5% of the patients. These had been patients with some definite depressive symptoms before treatment or who had a prior history of depression themselves or in the family history. We had 3 subjects with a DSM-III-R diagnosis of Dysthymia or Depressive Disorder NOS in our study, who were treated with clonidine. We observed no worsening of depressive symptoms in these patients during treatment.

We found a statistical reduction of both systolic and diastolic sedentary blood pressure for trial group 3 subjects in comparison with placebo. These subjects showed a mean decrease in systolic pressure of 11%, and in diastolic pressure of 14%. We never observed complaints suggestive of orthostatic hypotension in our subjects during treatment. Hunt et al. (1991a) found a 10% decrease in systolic pressure in over 100 children, treated with clonidine. This rarely produced clinical symptoms or discomfort.

Children with Tic Disorder

For the group of ADHD children with Tic Disorder (n=2x16, "TD+ADHD"), the percentage of children who showed a clinically significant improvement during treatment with clonidine did not differ from the responder percentage during placebo. However, an analysis of rating scale scores during the 7 weeks of treatment showed that clonidine significantly improved both hyperactivity and extraversion in the school situation when compared with placebo.

Of the children who had tics when clonidine treatment was started (n=14), the tics remained unchanged in 11, became worse in 2 patients, and improved in one patient. Although it was not our aim to investigate the effects of clonidine on tics, we may conclude that no beneficial effects of clonidine on tics were observed after 7 weeks of treatment. However, 7 weeks is probably too short a duration of treatment to evaluate the effect of clonidine on tics. Leckman et al.'s (1991) parallel-group trial of GTS patients had a 12-weeks duration of treatment. Their results indicated that clonidine was more effective than placebo in reducing some of the tic and other behavioral symptoms associated with GTS. They found that clonidine was more effective than placebo in reducing symptoms of impulsivity and hyperactivity in their GTS subjects. The effect of clonidine on impulsivity and hyperactivity was independent of its effects on tics in their study.

The effects of clonidine on hyperactivity in TD patients were beneficial less frequently in the trial compared to our earlier experiences with the same dosage of clonidine (4 µg/kg/day). After at least three months of open treatment with clonidine we had observed a clinically significant improvement in 45% of the non-hyperactive TD patients, and in 72% of the hyperactive TD patients (Gunning et al., 1990). In our trial we had only 25% responders in our clonidine TD+ADHD group (and 31% responders on placebo).

There are some reasons why it seems inadvisable to conclude from our study that clonidine does not benefit TD+ADHD patients with respect to their hyperactivity:
(1) this was the first study to study specifically the effects of clonidine on hyperactivity in TD+ADHD patients;
(2) in our pooled analysis of rating scale scores during the course of treatment, we found a beneficial effect of clonidine on both hyperactivity and extraversion in the school situation;
(3) TD+ADHD patients may need a longer duration of treatment before the effects of clonidine on hyperactivity become evident;
(4) the evaluation of hyperactivity in TD+ADHD patients is often obscured by the waxing and waning of the presence of the tics. When a parent or teacher reports that a TD child is quieter, he/she usually means that the child has less tics whereas when it is reported that a TD child is more hyperactive, this often primarily means that he has more tics.

Therefore, further research is needed to evaluate the effects of clonidine on hyperactivity in patients in whom both TD and ADHD are present.

In our study, ADHD children without TD with a family history of TD were treated with methylphenidate. At the time the study was planned inclusion of these children in trial group 3 seemed justified. Although there were several reports documenting the onset of tics after the administration of stimulant medication for the treatment of hyperkinesis (Lowe et al., 1982), there were more recent reports in which it was concluded that stimulants did not play a significant role in precipitating TD (Comings & Comings, 1987). More recently, Golden (1988) recommended a conservative use of stimulants in hyperkinetic children with a family history of TD: "If a trial of stimulants is initiated, the patient should be monitored very closely, and if tics are precipitated, the stimulant should be discontinued". Jacobvitz et al. (1990) criticized Comings and Coming's (1987) study because the finding that treatment with stimulants did not affect the gap between the onset of hyperkinesis and the onset of tics in GTS patients, had been based on retrospective data and thus did not fully resolve the issue. Jacobvitz et al. (1990) recommended that stimulants should not be used on hyperkinetic children with a first-degree relative with GTS and should be terminated at the onset of tics in children who were previously tic-free. Our present day course of action is as follows: if pharmacological treatment seems to be appropriate in a hyperkinetic child with TD or in a hyperkinetic child with a family history of TD clonidine should be used first. If the effect of clonidine on hyperactivity is insufficient, methylphenidate (or d-amphetamine) should be cautiously tried at the lowest effective dose possible. If tics are then precipitated, the stimulant medication should immediately be stopped. Although generally symptoms revert to baseline level when the drug is discontinued, a few cases have been reported in literature where the tics apparently did not diminish in frequency and severity following the termination of treatment (Golden, 1988).

The use of the GPO in the evaluation of drug effects

The GPO was first used in our study in the evaluation of drug effects. In using the GPO as an observation measure of the children's behavior during standardized playroom sessions, it was found to be sensitive to drug effects: (1) Both clonidine and methylphenidate gave a significant effect on GPO when compared with placebo; and (2) the effect of clonidine on GPO did not differ significantly from the effect of methylphenidate.

We used standardized playroom sessions with tasks similar to those given at home or school that typically elicit the ADHD symptoms. Barkley (1990) recorded the behavior of hyperkinetic children while accessed alone in a clinic playroom and provided with a package of sums to complete. The difference between Barkley's playroom setting and ours is that our behavioral observations included the child's interaction with an examiner who gave instructions, thus increasing the chance that the child might show defiant and oppositional behavior in addition to ADHD symptoms. When the purpose is only to assess ADHD symptoms, it is better to place the child in the playroom alone. We purposely included an interaction with an examiner in our playroom sessions, because: (1) interactions were of special interest for our ethological analyses (not reported in this thesis); and (2) including the possibility of defiance was clinically relevant: most ADHD children not only show ADHD symptoms but also defiant behavior which makes them difficult to handle. This applied to our subjects (trial group 3) of whom 76% were scored as "mild" to "moderate" on the symptom severity score "antisocial, aggressive behavior". However, with respect to significant drug effects we cannot differentiate to what degree these effects concern the ADHD symptoms or to what degree the defiant and oppositional behavior. In addition, the GPO rating cannot be regarded as a measure of ADHD symptoms because the raters knew that the children met the criteria for ADHD.

For future research, a better differentiation is advised between observation measures of ADHD symptoms and measures of defiance. This can be accomplished by:
(1) dividing the playroom sessions into two parts; one part when the child is alone and the other when the child interacts with an examiner; and (2) making a study design in which the examiner is blind with respect to whether the child meets the criteria for ADHD or not.

Predictors of drug responsiveness

A methodological problem in detecting factors that are possibly predictive with respect to a favorable medicinal response in ADHD, is that any parameter which is highly correlated to hyperactivity ratings will show improvement under medication that improves hyperactivity. In addition, there is the problem that changes are always correlated to each other: Even when two variables show a low correlation to each other, high scores on both these variables will have the tendency of a regression to the mean.

Taylor et al. (1987), in their methylphenidate crossover trial calculated correlations between baseline measures and the change in response measures. It was found that change in home and classroom hyperactivity correlated significantly with younger age, poor attentional test performance, low IQ, and hyperactivity at the clinic. Barkley (1990)

states that it is hardly surprising to find that behavioral and psychophysiological measures relating to attention span in many studies have been found to be the best and most reliable predictors of improvement during stimulant drug treatment. For stimulants have their primary mode of action on attention span.

When a factor that has not been expected to correlate with respondership, shows such a relation in the results of a study, it is precarious to conclude that the particular factor is predictive. It is better to hypothesize that the factor might be predictive and test this hypothesis in another study. We tested the relation between patient characteristics (e.g., "defiance", "emotional disorder", and "MND") and responder status (section 5.6). However, the number of subjects in each of the trial-group/drug conditions was too small to draw any conclusions. This was due to the parallel-group design of the trial.

7.5 The neurochemical results

The interpretation of our neurochemical results is hindered by the fact that plasma MHPG and urinary MHPG levels have been determined at different laboratories and the group of plasma MHPG controls was not the same as the group of urinary MHPG controls. Moreover, the urinary MHPG levels of the controls have been determined at another laboratory than the urinary MHPG levels of the patients. Although these two laboratories only had slight differences in determination method, these differences might have influenced the results. The determination of plasma MHPG levels has been performed in the same laboratory both for patients and controls.

The collection method for controls and patients was the same for plasma. This also was the case for 24-hr urines. The method that was employed to collect the 24-hr urines might also be criticized. MHPG excretion is so variable, that Shekim (Shekim et al., 1983; Serfontein et al., 1988) recommended that three 24-hr urinary samples of each child be collected. Shekim admits children to a clinic research center for 7 days, places the children on a standardized diet and makes sure that they don't lose urine, including a male external catheter for enuretic children (Shekim et al., 1979; Serfontein et al., 1988). In this study it was already difficult enough for the parents to collect 24-hr urines not to mention a 7-days admittance to a clinic.

We found that ADHD children excreted significantly less MHPG/24hrs than normal controls. This finding supports the findings of Shekim et al. (1977, 1979, 1983), Yu-cun and Yu-feng (1984), and Serfontein et al. (1988), who also demonstrated a significantly lower urinary MHPG excretion in hyperkinetic boys than in normal controls. Although we were hindered by different control groups and different laboratories, the fact that we found a significantly lower MHPG both in plasma and in 24-hr urine suggests that these lower MHPG values in comparison with normal controls represented a real trend. Shekim et al. (1979) suggested that reduced plasma and urinary MHPG levels in hyperkinetic children indicate that these children have decreased rates of synthesis, turnover, or neuronal discharge of NE (Shekim et al., 1979). Supposing that Shekim et al.'s hypothesis is valid, our findings support this view.

One study reported a subgroup of hyperkinetic children, who had high baseline MHPG levels and showed a good clinical response to methylphenidate (Serfontein et al., 1988). In our patients we neither found such subgroups, nor did we find a relationship between baseline plasma / urinary MHPG levels and clinical improvement to either clonidine or methylphenidate.

Plasma MHPG and urinary MHPG levels showed no significant correlation in our patients. Young et al. (1981b) found a correlation of .87 between plasma and 24-hr urinary MHPG levels for 8 normal boys. However, Young et al. admitted these boys to a clinic in order to sample plasma and 24-hr urines on the same day, while we organized the urine sampling during the weekends and the plasma sampling during the week following that weekend. Because MHPG levels have quite a large variation within subjects across time (Leckman et al., 1980, 1981), this might be the reason that we did not find a high correlation between plasma MHPG and urinary MHPG levels in our patients. However, it is also possible that plasma MHPG and urinary MHPG generally do not correlate so well as was found in Young et al.'s (1981) study. For instance, Leckman et al. (1983a) observed a disparity between the urine and plasma MHPG responses to clonidine before and after chronic treatment with clonidine.

A decrease of plasma MHPG (and not of urinary MHPG) was found, both following clonidine treatment and following treatment with methylphenidate. We have considered two explanations for the disparity between plasma and urinary MHPG response following drug treatment:

(1) Tang et al. (1981) have reported that MHPG plasma levels, and not urinary MHPG levels, were increased after exercise. Therefore, MHPG plasma levels in our study might have decreased, because the treatment ameliorated the motor restlessness present in our patients. However, we found that the change in plasma MHPG levels did not differ between responders and nonresponders in any of the three treatment groups. Therefore, it seems unlikely that a medication effect on hyperactivity had indirectly effect on the MHPG plasma levels;

(2) In urine we measured total MHPG. Total urinary MHPG consists of free MHPG, MHPG sulfate and MHPG glucuronide. More MHPG sulfate than MHPG free and glucuronide fractions in urine are of central origin (Peyrin & Pequignot, 1983; Filser et al., 1988). Perhaps we found no decrease of urinary MHPG because we chose a measure (total MHPG) that is more influenced by peripherally released NE than MHPG sulfate.

Clonidine effects

Following treatment with clonidine a significant decrease in plasma MHPG was found, when compared with placebo. Clonidine in low doses reduces the firing rate and the release of NE from neurons in the locus coeruleus, and modulates indirectly the firing of DA neurons in the ventral tegmental area (Leckman et al., 1991). A chronic agonistic effect of clonidine on the α_2-presynaptic receptors results in down regulation of these receptors (Wesseling et al., 1990). After abrupt clonidine withdrawal rebound phenomena occur: an increase in heart rate, blood pressure and, in GTS patients, an increase

in GTS symptoms. The neurochemical mechanisms responsible for these withdrawal symptoms are thought to include a rebound increase in the activity of central noradrenergic neurons and of the sympathetic nervous system following clonidine withdrawal coupled with subsensitivity of presynaptic α_2-receptors and/or postsynaptic supersensitivity (Leckman et al., 1986). Whereas after an acute single-dose of clonidine a decrease of plasma MHPG was reported (Lal et al., 1975; Leckman et al., 1980; Hunt et al., 1984), no apparent suppression of either central noradrenergic activity or sympathetic nervous system function was observed during long-term clonidine treatment in GTS patients (Leckman et al., 1983a, 1986; Silverstein et al., 1985). Possibly, the absence of noradrenergic suppression during long-term clonidine treatment reflects complex compensatory mechanisms which adapt to the effects of long-term clonidine therapy (hyposensitive presynaptic α_2-receptors and/or hypersensitive postsynaptic receptors) (Leckman et al., 1986). Silverstein et al. (1985) did a similar observation as Leckman et al. (1986). In five boys with GTS, both plasma NE, and specific binding of ^{3}H-yohimbine to receptors on platelet membranes were measured before and after treatment with clonidine. Plasma NE levels are strongly correlated with CSF NE levels. Yohimbine is a selective α_2-adrenoreceptor antagonist. Platelet α_2-receptors, despite their peripheral location, share important biochemical regulatory characteristics with their brain counterparts. It was found that the maximum number of specific binding sites (Bmax) for ^{3}H-yohimbine in the GTS patients was similar to those for a group of normal controls. After two weeks of treatment there was some improvement of behavior but not of tics, while in most patients both the number of binding sites for ^{3}H-yohimbine and plasma NE levels had decreased. Over the next six months of treatment all the patients continued to improve clinically (tics), but both indices of noradrenergic activity returned towards baseline values. It was suggested that clonidine's action might be independent of its prominent effects on α_2-adrenergic receptors and NE release.

We have considered how to interpret our finding of a decreased plasma MHPG after 7 weeks of treatment with clonidine. Supposing it were so that clonidine has similar biochemical effects in hyperkinetic patients as in GTS patients, a plausible explanation might be that the compensatory mechanisms as hypothesized by Leckman et al. (1986) did not develop in our patients and the decrease in MHPG reflects continued noradrenergic inhibition by clonidine. However, our study is the first to report effects of chronic clonidine treatment on noradrenergic functioning in hyperkinetic patients. Therefore, it is better first to await further research and to be cautious with conclusions. Our results do not corroborate a hypothesis (Silverstein et al., 1985) that clonidine's (longterm) action might be independent of its effects on NE release, at least after 7 weeks of treatment.

Methylphenidate effects

Following treatment with methylphenidate a significant decrease in plasma MHPG was found, when compared with placebo. Methylphenidate produces its effects primarily by increasing the concentrations of DA and NE at postsynaptic receptors

through the release of DA and NE from presynaptic stores (Wesseling et al., 1990; Hunt et al., 1991a). Just as our patients, Yu-cun and Yu-feng's (1984) hyperkinetic patients had a low MHPG excretion, as compared with controls. MHPG excretion was lowest in patients with a positive family history of hyperkinesis (in our sample we did not find such a relation). In Yu-cun and Yu-feng's study, the MHPG excretion further diminished following treatment with methylphenidate. The more marked the clinical improvement, the greater was the reduction in MHPG excretion (in our sample we did not find such a relation). Yu-cun and Yu-feng (1984) suggested that the negative correlation between the clinical effect and the urinary MHPG excretion might indicate that methylphenidate increased NE activity at the synapses, while inhibiting NE degradation. The results of Serfontein et al.'s (1988) study are in accordance with the results of Yu-cun and Yu-feng's (1984) study. Serfontein et al. found a low MHPG excretion, as compared with controls. They also found that the greater the reduction in MHPG excretion the more marked the clinical improvement was following treatment with methylphenidate. Our findings are contradictory to the results of Hunt et al. (1984), who did not find a significant change of mean plasma MHPG levels in hyperkinetic children after treatment with methylphenidate. Zametkin et al. (1985a) also did not find a significant change in MHPG excretion after treatment with methylphenidate. Elia et al. (1990) found a significant decrease both in plasma and urinary MHPG and in whole body NE turnover following treatment with d-amphetamine, but did not observe significant MHPG changes after treatment with methylphenidate.

We have considered how to interpret these findings with respect to methylphenidate. After acute d-amphetamine treatment there was found an increase in MHPG levels. This is most likely due to the increase in NE release (Maas & Leckman, 1983). After chronic treatment with d-amphetamine, however, a decrease of MHPG excretion has been observed, especially in children who showed clinical improvement (Shekim et al., 1979; Brown et al., 1981; Elia et al., 1990). It has been suggested that in chronic d-amphetamine treatment an excessive stimulation of adrenergic receptors probably reduces NE release via feedback inhibition, thus reducing the MHPG levels to normal (Maas & Leckman, 1983). Therefore, the most plausible explanation for our finding of decreased plasma MHPG levels following chronic methylphenidate treatment seems that excessive stimulation of adrenergic receptors caused a reduction of NE release via feedback inhibition. However, as long as the findings of plasma and urinary MHPG changes following treatment with methylphenidate are inconclusive, it is safer to await further studies which might corroborate earlier findings, before drawing conclusions.

Evaluation

One encounters many difficulties when trying to elucidate differential neurochemical mechanisms of action of stimulants and clonidine in hyperkinesis, using peripheral measures of NE metabolism. The most important are:

(1) We do not know to what degree plasma and urinary MHPG levels reflect central noradrenergic processes (Maas & Leckman, 1983; Filser et al., 1988). This does not

effect the validity of the findings, but makes it difficult to determine the basis of any alterations found (Deutsch & Kinsbourne, 1990);
(2) Both MHPG excretion and MHPG plasma levels have been reported to be quite variable (Serfontein et al., 1988; Leckman et al., 1980, 1981). This makes it difficult to interpret results.
(3) Recent pharmacological findings suggest that hyperkinetic children suffer a disorder of homeostasis of neurotransmitter systems (Kinsbourne, 1985). Perhaps what is deficient at the biochemical level is not a static overactivity or underactivity of a neurotransmitter system, but a system of reciprocal balances. Stimulant medication (and possibly also clonidine) may then correct the imbalance, not by changing neurotransmitter levels directly, but by facilitating stabilizing feedback mechanisms.

7.6 Recommendations for the use of clonidine and methylphenidate in hyperkinesis

Hyperkinesis is a child psychiatric condition, which is usually accompanied by impairment of social and school functioning and is associated with a poor long-term outcome. Thus far, psychological treatments alone have not been shown to induce clinically meaningful behavioral changes in hyperkinetic children. Several studies have corroborated the beneficial effects of stimulant medication in hyperkinesis. In clinical practice, we consider a trial of "hyperactivity medication" useful when hyperactive symptoms have caused severe chronic impairment in social, emotional and/or cognitive functioning and other treatments have proved to be insufficient. The more severe the dysfunction, the clearer the indication for medication. The threshold for treatment depends on the degree of dysfunction of the child and the effects and adverse effects of the medication. In our study we compared clonidine and methylphenidate with respect to effectiveness and profile of adverse effects.

Our study shows that clonidine is hardly less effective than methylphenidate in the treatment of hyperkinetic children without tics and without a pervasive developmental disorder but has a safer profile of adverse effects. Both clonidine and methylphenidate had significant beneficial effects on hyperactivity at school/home, and on acting-out (defiant) behavior at school. It did not affect anxiety-withdrawal symptoms at school. Methylphenidate improved the target problem behaviors as formulated by parents/teacher and improved cooperative behavior in the school situation, compared with placebo. Clonidine gave significantly less improvement of target behavior problems in the school situation compared to methylphenidate. After 7 weeks of treatment both drugs showed adverse effects in more than half of the subjects (placebo 37%). However, after treatment with methylphenidate these adverse effects were more frequently annoying than after treatment with clonidine (21% and 5% respectively; placebo 7%). During treatment with clonidine no clinically alarming behavioral or physical adverse effects were observed. Whereas clinically alarming behavioral or physical adverse effects were

found in 17% during treatment with methylphenidate (and in 21% during treatment with placebo). We found no predictors with respect to drug responsiveness.

Hunt et al. (1991a) in an open treatment study found that clonidine was slightly less effective than methylphenidate in hyperkinetic children. They reported a similar pattern and incidence of side effects during treatment with clonidine and methylphenidate.

Practical considerations will determine the choice for an initial medication trial with either clonidine or methylphenidate in a hyperkinetic patient. The following data will help to make a decision:

A comparison of effects and adverse effects of clonidine and methylphenidate in the treatment of hyperkinetic children.

Clonidine:	**Methylphenidate:**
- significant effect on home/school hyperactivity, and on defiance at school, compared to placebo	- significant effect on home/school hyperactivity, and on defiance at school, compared to placebo
- nonsignificant effect on target problems parents/ teacher compared to placebo	- more effective than placebo on target problems parents/ teacher. More effective than clonidine on problems teacher
	- more cooperative at school compared to placebo
- effect equable	- duration of action 3-4 hrs
- lack of evening rebound	- often rebound hyperactivity
- sometimes restlessness increases	- sometimes impulsivity increases
- nightly awakenings	- difficulty falling asleep
- drowsiness	- decreased appetite
- clinically alarming adverse effects rare	- clinically alarming adverse effects rather frequent
	- contraindicated as initial treatment when: tics, PDD, or (recent) seizures.

Our clinical data indicate that when a hyperkinetic child does not respond to either clonidine or methylphenidate, this does not indicate that there is no chance of the child responding to the other drug. Physicians who prescribe "hyperactivity medication" should only give medication after careful appraisal, take all necessary precautions and should know what kind of follow-up has to be carried out. The physician should control

if the child clearly benefits from the drug, not only when the medication is first prescribed, but also intermittently during the entire time that the child remains on the medication (Weiss, 1991). Medication should never be given without appropriate additional nonpharmacological treatment and physicians should try to discriminate the effects of medication from the effects of nonpharmacological treatments. Medication which is not effective anymore or gives either "annoying" adverse effects or chronic "acceptable" adverse effects should be stopped.

The fact that no enduring beneficial effects of stimulants have thus far been demonstrated in hyperkinetic children (Weiss, 1984) poses serious medical-ethical problems. The evaluation of the long-term efficacy of stimulant medication is fraught with methodological difficulties (Hinshaw, 1989). Research is needed to investigate the long-term effects and adverse effects of both clonidine and stimulants. Until research has demonstrated long-term benificial effects and safety, the use of medication in hyperkinesis will remain an area of controversy.

Studies on the long-term effects of clonidine are scarce. An important reason to start such studies is the reports on the development of tolerance. Longitudinal studies are needed not only to demonstrate tolerance but also to investigate the relation between tolerance and differences between short- and long-term effects of clonidine on noradrenergic mechanisms.

The design of our study may not have been appropriate to demonstrate the effectiveness of clonidine on hyperactivity in hyperkinetic children with tic disorder. In these children, the hyperactive symptoms are often the principal problem in need of treatment. Because of the reports about a substantial risk of exacerbation of tics during treatment with methylphenidate, a new controlled trial is needed to demonstrate the effectiveness of clonidine with respect to hyperactivity in these patients. For a new trial we recommend a longer treatment duration (at least 12 weeks) and a thorough evaluation of both tics and hyperactivity during the course of treatment.

Too few hyperkinetic children with a DSM-III-R classification Pervasive Developmental Disorder (PDD) entered our trial to draw any conclusions about the effectiveness of clonidine with respect to their hyperactivity. In open treatment we observed that these children frequently were good responders to clonidine (Gunning et al., 1990: 10 out of 16 hyperkinetic PDD patients were good responders). Since this category of patients is often seen in child psychiatric practice and often shows functional impairment caused by their hyperactivity, we recommend a controlled trial in a sample of hyperkinetic PDD children. In order to exclude a too short treatment duration as a cause for not finding effects, we recommend a treatment duration of at least 12 weeks.

As long as the effectiveness of clonidine on hyperactivity has not clearly been demonstrated in both hyperkinetic children with tic disorder, and in hyperkinetic PDD children, we recommend that the use of clonidine in these patients be restricted with respect to the indication of hyperactivity.

Appendices

Appendices

Appendix 3.2.2 Summarizing report

The summarizing report included:

(1) The reason(s) why the parents sought help and/or why other adults were worried about the child's behavior.

(2) Information about the child's living circumstances (home, school), including information about family relationships, problem behaviors or somatic complaints in siblings and parents, and environmental influences outside the home.

(3) A detailed description of all problem behaviors, both as they were reported (by the parents, child, teacher, etc.) and as they were assessed in the clinic. The standardized child and parent interviews helped to systematically question all areas of functioning and potential psychopathology. For any description the informant and the situation were mentioned. The frequency and intensity of the problem behaviors were described, and indications for the sort and degree of functional impairment at school, at home, etc. When available information was given on the precipitants and contingencies of each problem behavior, information about the ease with which the problem behavior could be elicited or subsequently stopped by the environment, and information on the meaning the problem behavior might have to the child himself; to his family; to his teacher, etc. Details concerning prior help (medical or otherwise) were also reported.

(3) Areas that were considered important for differential diagnosis (including DSM-III-R classification) were also mentioned in detail. In the case that a diagnosis Conduct Disorder might be considered for example: the absence of stealing, truancy, lying, fire-setting, smashing, physical fights and cruelty. The report included detailed behavior descriptions to give the rater as much raw material as possible to base his DSM-III-R classification on. However, even when the rater has all the information that he considers necessary for being sure of his DSM-III-R classification, raters can differ in their judgment. For example: "Is the particular problem behavior present in this patient?"; "Is this behavior considerably more frequent than that of most people of the same mental age?"). By giving behavior descriptions (rather than interpretations) we wanted to reduce possible interpretative influences to a minimum.

(4) The child's functioning at home, at school, in his peergroup, and in leisure activities, including details on the areas in which the patient functioned well.

(5) Rating scale scores: did the child obtain high scores on hyperactivity scales at home and/or at school?

(6) Information on the course of the child's development (motor, speech, psychological, social development, etc.), including information about the child's problem behaviors over a period of time.

(7) Information on the child's medical history.

(8) Information on the occurrence of (similar) problem behaviors or learning disabilities

in family members (the parents, when they were a child), and the degree of functional impairment over a period of time. The occurrence in the family of tics, epilepsy, mental retardation, (minor) physical anomalies, etc.
(9) A report on the diagnostic interview sessions with the child (including relevant information from the CAS).
(10) A report on the physical examination, including the developmental-neurological examination.
(11) A descriptive diagnosis, including a description of the degree of functional impairment and a consideration of possible aetiological factors. A DSM-III-R classification was not mentioned in the report.
(12) A section with details on the sort of treatment, that had been advised to the parents, and the course of action. For patients partipating in the clonidine trial, the start of new treatments other than medication was postponed until after the trial in order not to interfere with the evaluation of the medication effect.

Appendix 3.2.3 ***DSM-III-R ADHD Rating Scale***

(DuPaul, unpublished 1990; see Barkley, 1990).

Scoring:

1 not at all = not present.

2 just a little = few, if any symptoms, only minimal or no impairment in school and social functioning.

3 pretty much = symptoms or interference with functioning between "mild" and "severe".

4 very much = many symptoms, significant, pervasive or widespread impairment in functioning at home and school and with peers.

Instruction: Circle the number in the one column which best describes the child.

	Not at all	**Just a little**	**Pretty much**	**Very much**
1. Often fidgets or squirms in seat	1	2	3	4
2. Has difficulty remaining seated	1	2	3	4
3. Is easily distracted	1	2	3	4
4. Has difficulty awaiting turn in groups	1	2	3	4
5. Often blurts out answers to questions	1	2	3	4
6. Has difficulty following instructions	1	2	3	4
7. Has difficulty sustaining attention to tasks	1	2	3	4
8. Often shifts from one uncompleted activity to another	1	2	3	4
9. Has difficulty playing quietly	1	2	3	4
10. Often talks excessively	1	2	3	4
11. Often interrupts or intrudes on others	1	2	3	4
12. Often does not seem to listen	1	2	3	4
13. Often loses things necessary for tasks	1	2	3	4
14. Often engages in physically dangerous activities without considering consequences	1	2	3	4

Appendix 3.3.3a ***Minor physical anomalies and scoring weights, according to Waldrop and Halverson (1971).***

Head

Fine electric hair: no (0), fine hair that is soon awry after combing (1), very fine hair that will not comb down (2).

Head circumference outside the normal range: no (0),
> 1.0 SD (84th percentile) $\leq$ 1.5 SD (90th percentile) (1),
> 1.5 SD (90th percentile) (2).

Eyes

Epicanthus: no (0), partly covered (1), deeply covered (2).

Hypertelorism: inner canthal distance < 32 mm (0),
32-34 mm (1), > 34 mm (2).

Ears

Low-set ears: no (0), bottom ears in line with area between mouth-nose (1), bottom ears in line with mouth or lower (2).

Adherent ear lobes: no (0), lower edges of ears extend straight back toward rear of neck (1), lower edges of ears extend upward and back toward crown of head (2).

Malformed ears: no (0), yes (1).

Asymmetrical ears: no (0), yes (1).

Mouth

High palate: no (0), roof moderately high (1), steepled (2).

Furrowed tongue: no (0), yes (1).

Hands

Fifth finger: straight (0), slightly curved inwards (1), markedly curved inwards (2).

Single transverse palmar crease: no (0), yes (1).

Feet

Third toe: shorter than 2nd toe (0), equal in length to 2nd toe (1), longer than 2nd toe.

Partial syndactyly of two middle toes: no (0), yes (1).

Big gap between 1st and 2nd toe: no (0), yes (1).

Appendix 3.3.3b ***Cluster profile of the neurological examination according to Touwen*** *(1979; Hadders-Algra, 1987).*

Cluster:	Compound of:	Criteria for the presence of a deviant cluster:
1 **Posture and muscle tone**	* Posture during sitting, standing, walking and lying * Muscle tone	* Consistent changes of muscle tone * Postural deviations such as collaps, asymmetries, hyperextension
2. **Reflexes**	* Biceps * Knee * Ankle * Footsole response	* Increased or decreased intensities/thresholds * Asymmetries * Babinski sign
3. **Coordination and balance**	* Finger-nose test * Fingertip-touching test * Diadochokinesis * Kicking * Knee-heel test * Reaction to push (sitting, standing) * Romberg * Tandem gait * Standing on one leg	* Two or more tests inappropriate for age
4. **Fine manipulative ability**	* Finger-opposition test, smoothness * Finger-opposition test, transition * Follow-a-finger test * Circle test	* Two or more tests inappropriate for age
5. **Choreiform dyskinesia**	* During spontaneous motility * Test with extended arms * Face, eyes, tongue	* Marked choreiform movements of distal and facial muscles * Slight or marked chor. movements of proximal muscles, eyes or tongue
6. **Rarely occurring miscellaneous dysfunctions**	* Motility of facial musculature * Position and movements of eyes * Associated movements during diadochokinesis finger-opposition test, walking on toes, heels	* VIth and VIIth nerve palsy * Excessive amount of associated movements (for age)

Appendix 3.3.4.3a ***Groningen Behavior Observation scale, parent version*** *(Groninger Ouder Observatielijst, GOO; Boorsma, 1990):*

Instruction: One always has to fill in
one of the four answer categories given:
1 = this does not apply
2 = more "no" than "yes"
3 = more "yes" than "no"
4 = yes, this does apply
ANSWER ALL ITEMS.

1.	Is very impulsive; starts immediately without thinking first	1	2	3	4
2.	Has more trouble concentrating at the end of the day	1	2	3	4
3.	Is very talkative during meals, spends more time talking than eating	1	2	3	4
4.	Is constantly moving his/her legs or tilting his/her chair during meals	1	2	3	4
5.	Easily gives up, sometimes irritated when doing something he/she finds hard to accomplish	1	2	3	4
6.	Often doesn't think before talking, blurts out all kind of remarks	1	2	3	4
7.	Wants to continue talking even after having been asked to be quiet	1	2	3	4
8.	Is easily distracted, even when engaged in something he/she finds interesting	1	2	3	4
9.	Repeatedly leaves the table during meals	1	2	3	4
10.	Is always occupied by other things when having to prepare for school; has to be urged to wash, brush his/her teeth, dress, etc.	1	2	3	4
11.	Talks whenever possible	1	2	3	4
12.	Is unable to be engaged in the same activity for longer periods of time, for instance changes toys every five minutes or wants to play outdoors	1	2	3	4
13.	Always touches everything	1	2	3	4
14.	Is very playful for his/her age	1	2	3	4
15.	Is constantly fidgeting	1	2	3	4

Appendix 3.3.4.3b ***Groningen Behavior Observation scale, teacher version*** *(Groninger Basisschool Observatielijst, GBO; Vaessen, 1990):*

Instruction: One always has to fill in
one of the four answer categories given:
1 = this does not apply
2 = more "no" than "yes"
3 = more "yes" than "no"
4 = yes, this does apply
ANSWER ALL ITEMS.

1.	Starts the task immediately without trying to form an overall picture	1	2	3	4
2.	Becomes increasingly more restless as the day proceeds	1	2	3	4
3.	Has to be warned often because of talking	1	2	3	4
4.	Makes a lot of unnecessary movements during the execution of a task	1	2	3	4
5.	Gives up easily if something does not succeed	1	2	3	4
6.	Makes a lot of irrelevant (blurts out all sorts of) remarks while working	1	2	3	4
7.	Wants to continue talking after a small chat when lesson starts again	1	2	3	4
8.	Interrupts ongoing activities at the slightest disturbance	1	2	3	4
9.	Can hardly sit still when engaged in self-directed work	1	2	3	4
10.	Demonstrates a growing impatience during the course of the day	1	2	3	4
11.	Talks whenever possible	1	2	3	4
12.	Is unable to remain engaged in the same task for longer periods of time	1	2	3	4
13.	Without asking takes materials from other children's table	1	2	3	4
14.	Is more playful than task oriented	1	2	3	4
15.	Fidgets constantly	1	2	3	4

Appendix 3.3.4.5 **Conners Teacher Rating Scale 39-item version** (Werry et al., 1975; translated into Dutch by Blöte & Curfs, 1986).

Instruction: Listed below are descriptive terms of behavior. Place a check mark in the column which best describes this child. Answer all items.

	Not at all	Just a little	Pretty much	Very much
1. Fidgeting	1	2	3	4
2. Hums and makes other odd noises	1	2	3	4
3. Demands must be met immediately, gets frustrated	1	2	3	4
4. Poor coordination	1	2	3	4
5. Restless	1	2	3	4
6. Excitable, impulsive	1	2	3	4
7. Inattentive, distractible	1	2	3	4
8. Fails to finish things he starts (short attention span)	1	2	3	4
9. Sensitive to criticism	1	2	3	4
10. Serious or sad	1	2	3	4
11. Daydreams	1	2	3	4
12. Sullen or sulky	1	2	3	4
13. Cries	1	2	3	4
14. Disturbs other children	1	2	3	4
15. Quarrelsome	1	2	3	4
16. Moods change quickly	1	2	3	4
17. Acts "smart"	1	2	3	4
18. Destructive	1	2	3	4
19. Steals	1	2	3	4
20. Lies	1	2	3	4
21. Temper outbursts	1	2	3	4
22. Isolates himself from other children	1	2	3	4
23. Appears to be unaccepted by group	1	2	3	4
24. Appears to be easily led	1	2	3	4
25. No sense of fair play	1	2	3	4
26. Appears to lack leadership	1	2	3	4
27. Does not get along with the opposite sex	1	2	3	4
28. Does not get along with the same sex	1	2	3	4
29. Teases other children or interferes with their activities	1	2	3	4
30. Submissive	1	2	3	4
31. Defiant	1	2	3	4
32. Impudent	1	2	3	4
33. Shy	1	2	3	4
34. Fearful	1	2	3	4
35. Excessive demands for teacher'sattention	1	2	3	4
36. Stubborn	1	2	3	4
37. Anxious to please	1	2	3	4
38. Uncooperative	1	2	3	4
39. Attendance problem	1	2	3	4

Appendix 3.4.7 Informed consent

The study protocol was approved by the Medical Ethical Committee Academic Hospital Rotterdam and by Boehringer Ingelheim B.V., The Netherlands.

An informed consent was obtained from the parent(s) of the child both in writing and orally, considering the following guide-lines: (1) Declaration of Helsinki 1964 (World Medical Association, revised version 1975): "Recommendations guiding physicians in bio-medical research involving human subjects"; (2) Clinical Trials in Children (Working Party of Committee for Proprietary Medicinal Products October 1987; Boehringer Ingelheim B.V. The Netherlands); and (3) FDA Informed Consent guidelines (Pocock, 1983).

In the informed consent were included: (1) An explanation of the purposes and procedures, including an identification of what was experimental; (2) Foreseeable discomforts and risks; (3) Benefits; (4) A disclosure of appropriate alternative procedures; (5) Confidentiality; (6) Whom to contact for answers to pertinent questions about the research and the subject's rights, and in the event of a research-related injury; (7) Participation was voluntary, and subjects were free to terminate participation without prejudice at any time.

The informed consent included the following information: (1) The reason why the child was considered eligible for participation in the study (i.e., hyperactivity symptoms, functional impairment, medication try considered meaningful, medication can be a "stepping-stone" if it works without giving troublesome adverse effects);

(2) The purpose of the study: "Methylphenidate is the standard medicine for hyperkinesis; however, methylphenidate causes troublesome adverse effects in some children, and in other children it is not effective or contraindicated; therefore we welcomed the first clinical experiences with clonidine ameliorating hyperactivity symptoms; clonidine (a registered medicine, although not for the indication hyperactivity) appears to cause less adverse effects than methylphenidate, and has been used in our department for hyperactivity for the last five years. However, we don't know how effective it is with respect to hyperactivity when compared to placebo; that comparison is important when introducing a new medicine as placebo also often gives strong treatment effects as well; therefore a controlled trial was needed".

(3) "Participation in the study implies the following for the child":

(a) A thorough physical and psychiatric examination, including blood and urine tests, followed by:

(b) A medication treatment period (8 weeks, double-blind, trial procedures; considering the child's "staying-power" and the parents' possibilities to come to the clinic; rating scales have to be filled in by the parents and the teacher independently; video-tapes are only used for the study).

(4) "Participation implies the following for the parents/teacher": appointments with the project-leader (dr. Gunning) and the research-assistants; filling-in rating scales; expla-

nation of procedure, including instructions with respect to the medicines (see section "information given to parents, etc.).
(5) Patients enter the trial as out-patients of the Sophia Children's Hospital, department of Child and Adolescent Psychiatry with dr. Gunning as the child's attending physician. The project-leader effected a No Fault Clinical Trial Insurance for all subjects, for all risks during the treatment period, which were not covered by the patient's health insurance, or the University's/Hospital's liability insurance, or Boehringer Ingelheim B.V.'s product-liability (Boehringer Ingelheim B.V. is the producer of Dixarit^{R}, clonidine).
(6) Participation is voluntary, and free to be terminated at any time without prejudice. "Please contact dr. Gunning in advance in order to guard safety".
(7) The study protocol has been approved by the Medical Ethical Committee of the Academic Hospital Rotterdam.
(8) "Dr. Gunning will continue to help you with your child's problem behaviors after completion of the trial (realizing treatments, sometimes at the Sophia Children's Hospital, sometimes elsewhere)".

Information given to parents, teacher, and child

With regards to the medicines the following instructions were given to both parents (both orally and written) and teachers (written): "We would not have advised to give your child this medicine if there was chance of harming his health"; "unfortunately, medicines which ameliorate, often also have side effects"; double-blind principle; "only the pharmacist knows the code; we will wait untill after the treatment period before asking him the code"; "some children get only clonidine dragees, other children get both clonidine dragees and methylphenidate capsules" (explanation of verum/placebo); a good compliance is very important; abrupt withdrawal of medicine often gives problems (rebound hypertension, tics, behavioral effects); instructions (written) for gradual instalment of dosage, instructions about dosage times, and for gradually tapering off.

With regards to clonidine the following information and cautions were given: "It often occurs that the child tires sooner and/or gets drowsy especially the first weeks; accompany your child to and from school as long as he/she is drowsy (the project-leader helps to organize this if necessary; do not let the child go out alone in the traffic, including on his bike "through the neighbourhood"); sometimes insomnia occurs; sometimes feelings of dizziness; sometimes dry mouth; sometimes headaches".

With regards to methylphenidate the following information and cautions were given: "It often occurs, especially the first weeks, that the child tires sooner and/or gets drowsy (followed by instructions for traffic, see clonidine); sometimes insomnia occurs; sometimes decreased appetite; sometimes headaches".

"Dosage adjustments are possible" (we decide after ten days of treatment, if necessary earlier); if you have any questions, contact dr. Gunning; if you are uneasy about something possibly concerning the treatment, contact dr. Gunning, or telephone the child psychiatrist on-duty (who is informed about all aspects of the study procedure, and will try to contact the project-leader, or othwerwise will help you him/herself).

Appendix 4.2 *The Rotterdam SKZ-PI study*

Introduction

Five out of the 109 children who took part in the trial were referred as a result of a collaborative research project of the department of Child and Adolescent Psychiatry, Sophia Children's Hospital (SKZ), and the Pedological Institute Rotterdam (PI). The aims of the "SKZ-PI study" were:

(1) to investigate the prevalence of behavioral/emotional problems of learning disabled children in schools for special education. These results have been reported elsewhere (Jongbloed et al., 1991; Gunning et al., submitted).

(2) to select children who showed a considerable degree of both hyperactivity and problem behaviors, both in the school situation and at home and were suitable for the trial. These results will be presented here.

Methods and results

Five schools for special education in Rotterdam, comprising a total of 435 children aged 5-13, were asked to cooperate in the SKZ-PI-study. These were schools for non-mentally retarded and non-physically handicapped children with learning disabilities: Two schools for children with learning disabilities and mild behavioral problems ("Leer- en Opvoedingsmoeilijkheden": LOM), 2 schools for children who are difficult to educate ("Zeer Moeilijk Opvoedbare Kinderen": ZMOK), and one school for pupils with learning disabilities and developmental problems (Pedological Institute: PI). After informed consent had been obtained, the parents of all the pupils were asked to complete the CBCL and the GOO, and the teachers were asked to complete the TRF, the CTRS and the GBO. Questionnaires were completed for 313 of the children (72%). Eighty percent of the parents who did not respond were non-Caucasian (Surinam, Antillian, Turkish, Maroccan or Cap-Verdian), whereas the percentage of non-Caucasian parents who did respond was 15%. Therefore it is plausible to assume that many parents of foreign origin did not participate because they experienced difficulties in understanding the Dutch language of consent forms and questionnaires.

The children aged 6-11 with a full scale IQ score of more than 80 were retained for the study (n=172: 127 boys and 45 girls). We selected 6-11-year-olds to compare with Achenbach et al.'s (1983) CBCL norms for ages 6-11. We retained the children with a full scale IQ score of more than 80 to exclude children experiencing academic problems due to mental retardation. In this sample (n=172), we found that:

(1) 54% of the boys, and 49% of the girls had CBCL total problem scores in the clinical range (table app.4.2a).

(2) 37% of the boys, and 33% of the girls had TRF total problem scores in the clinical range (table app.4.2a).

(3) 36% of the boys, and 40% of the girls had CBCL Hyperactive factor scores in the clinical range (table app.4.2a).

(4) 4% of the boys, and 7% of the girls had TRF Inattentive factor scores in the clinical range. Two percent of the boys, and 11% of the girls had TRF Nervous-Overactive factor scores in the clinical range (table app.4.2a).

Table app. 4.2a Percentages of children (SKZ-PI-study) who had CBCL/TRF total problem/Internalizing/ Externalizing scores[a] or factor scores[b] in the clinical range.

CBCL:	% children who scored in the clinical range:	**TRF:**	% children who scored in the clinical range:
Boys (n=127):		**Boys** (n=124):	
Tot.probl.score	53.5	Tot.probl.score	37.1
Internal.score	48.0	Internal.score	38.7
External.score	58.3	External.score	33.9
CBCL factors:		TRF factors:	
Schizoid-Anx.	23.6	Anxious	8.1
Depressed	23.6	Social Withdr.	13.7
Uncommunic.	27.6	Unpopular	9.7
Obsess-Comp.	26.0	Self-destruct.	12.1
Somatic Compl.	8.7	Obsess-Comp.	4.0
Social Withdr.	33.1	Inattentive	4.0
Hyperactive	36.2	Nerv-Overact.	2.4
Aggressive	37.0	Aggressive	10.5
Delinquent	27.6		
Girls (n=45):		**Girls** (n=45):	
Tot.probl.score	48.9	Tot.probl.score	33.3
Internal.score	40.0	Internal.score	11.1
External.score	60.0	External.score	37.8
CBCL factors:		TRF factors:	
Depressed	22.2	Anxious	0
Social Withdr.	28.9	Social Withdr.	4.4
Somatic Compl.	0	Depressed	13.3
Schiz-Obsess.	11.1	Unpopular	15.6
Hyperactive	40.0	Self-destr.	4.4
Sex Problems	24.4	Inattentive	6.7
Delinquent	6.7	Nerv-Overact.	11.1
Aggressive	24.4	Aggressive	20.0
Cruel	8.9		

[a] CBCL/TRF Total-problem/Internalizing/Externalizing scores above the 90th percentile for nonreferred USA boys/girls[cd] were considered "in the clinical range" (i.e. T-scores > 63).

[b] CBCL/TRF factor scores above the 98th percentile for nonreferred USA boys/girls[cd] were considered "in the clinical range" (i.e. T-scores > 70).

[c] CBCL norms given by Achenbach and Edelbrock (1983).

[d] TRF norms given by Achenbach and Edelbrock (1986).

(5) 9% of the boys, and 27% of the girls had CTRS hyperactivity factor scores above the 90th percentile of Blöte and Curfs's (1986) Dutch normative sample.
(6) 27% of the boys, and 23% of the girls had GOO scores above the 90th percentile of Vaessen and Van der Meere's (1990) Dutch normative sample, and 17% of the boys, and 32% of the girls had GBO scores above the 90th percentile of Vaessen and Van der Meere's (1990) Dutch normative sample.
(7) 22% of the children had both CBCL and TRF total problem scores in the clinical range, and 22% of the children had GOO/GBO scores above either the 90th percentile or the 75th percentile of Vaessen and Van der Meere's (1990) normative sample (table app.4.2b).

Table app. 4.2b Percentages of children (SKZ-PI-study, n=172) who had CBCL/TRF total problem scores in the clinical range[a] and/or had GOO/GBO scores above the 75th/90th percentile[b].

CBCL and TRF total problem scores in the clinical range:	21.9% (n=37)
GOO score > P90 and GBO score > P75, or GOO score > P75 and GBO score > P90:	22.2% (n=37)
CBCL and TRF total problem scores in the clinical range, and GOO score > P90 and GBO score > P75 or GOO score > P75 and GBO score > P90:	16.3 % (n=27)

[a] CBCL/TRF norms given by Achenbach and Edelbrock (1983, 1986).
[b] GOO/GBO norms given by Vaessen and Van der Meere (1990).

Selection of children for the trial

Sixteen percent (n=27) of the subjects had both CBCL/TRF total problem scores in the clinical range and GOO/GBO scores above either the 90th percentile or the 75th percentile of Vaessen et al.'s (1990) normative sample (table app.4.2b). Judging from scores on rating scales that measure hyperactivity as well as problem behaviors, these 27 children showed both a considerable degree of hyperactivity, and significant problem behaviors, at school as well as at home. Subsequently, the school-doctors asked both the school staff and the parents of these children if they considered the level of functional impairment so poor, and the contribution of the hyperactivity in this functional impairment so obvious, that they wanted to try medication. Thereupon, 7 children were referred to the project-leader, who did a child psychiatric and medical assessment, screening the children for possible inclusion in the trial. Five children entered the trial. The two other children were classified (DSM-III-R) as Conduct Disorders without at the same time meeting the criteria for ADHD, and were excluded from the study. Of the

remaining 20 children, 9 did not meet the inclusion criteria because they either used clonidine medication already (n=4), or lived in a residential facility (n=5), and 11 were not referred because the school staff and/or the parents refused medication or preferred another form of treatment, or did not consider the child hyperactive and 'problematic'.

Another seven children from the SKZ-PI study sample, having scores below the cut-offs on CBCL, TRF, GOO and/or GBO, were referred to the clonidine trial because the school-doctors, school staff and/or the parents considered them as "very hyperactive and problematic" and wanted to try medication. Of these children, 5 fulfilled the DSM-III-R inclusion criteria and entered the trial. The two other children were classified as Conduct Disorder without at the same time meeting the criteria for ADHD.

All in all, 14 children were referred to the project-leader from the SKZ-PI-study. Of these children, 10 fulfilled the inclusion criteria, and entered the trial. No parents refused the advice to participate.

Discussion

The aim of the study was to identify potentially 'hyperactive and problematic' children, using teacher and parent questionnaires. Subsequently, first the school staff and parents judged if they considered a "hyperactivity medication try" meaningful, and then the project-leader checked if these children fulfilled the inclusion criteria for the trial.

The trial had been designed for children fulfilling the ADHD criteria, including situationally hyperactive children but for medical-ethical reasons we employed the strict criterion that the children had to be pervasively hyperactive in the SKZ-PI study. Although only 5 children entered the trial, the selection procedure was considered useful by the school doctors and their school staff, because it was impossible for them to select pervasively 'hyperactive and problematic' on account of 'impressions'.

As far as we know there is only one earlier study that collected parent as well as teacher ratings in a large sample of special school children. Mattison et al. (1986) assessed 90 boys aged 6-12 referred for possible placements in classrooms for the socially and emotionally disturbed (SED), using the CBCL and the CTRS (Werry et al.'s version, 1975). SED placement was recommended for 50 boys. Of these boys, 46% had scores in the clinical range on the CBCL Hyperactive factor, and 57% had scores above the 98th percentile on the CTRS Hyperactivity factor (USA validation). Mattison et al. (1986) do not mention the percentage of children who scored above the 98th percentile on both CBCL and CTRS hyperactive factors.

Mattison et al. (1986) found higher percentages of both parent and teacher reported hyperactivity than we found in the SKZ-PI study. However, a comparison with our results is difficult, because: (1) Mattison et al.'s (1986) study refers to the USA special school situation which is quite different from the Dutch; and (2) they used the USA CTRS factors, which differ from the Dutch CTRS factors. The USA CTRS Hyperactivity factor (Trites et al., 1982) refers to a wider range of externalizing problem behaviors than the Dutch factor (Blöte & Curfs, 1986; Werry et al's version, 1975). Possibly the Dutch CTRS Hyperactivity factor selects more "purely" hyperactive children, whereas the

USA factor selects many hyperactive conduct disordered children as well. This problem needs to be explored further in an epidemiological study with a second level of diagnostic confirmation.

Table app. 4.2c Percentages of boys/girls (SKZ-PI-study, n=172, 127 boys and 45 girls) who had scores above the cut-offs on the CBCL Hyperactive factor, TRF Inattentive and Nervous-Overactive factors, CTRS Hyperactivity factor, GOO and GBO. Cutoff (raw) scores are given for GOO, CTRS and GBO.

	boys %	cutoff score[a]	**girls** %	cutoff score[a]
Parent reported ratings:				
CBCL Hyperactive factor score >P98:	36.2		40.0	
GOO score >P90:	27.4	42[b]	22.7	42[b]
Teacher reported ratings:				
TRF Inattentive factor score >P98:	4.0		6.7	
TRF Nervous-Overact.fact.sc.>P98:	2.4		11.1	
CTRS Hyperactivity fact.sc.>P90:	8.8	17[c]	26.7	12[c]
GBO score >P90:	16.8	40-49[b]	31.8	35-43[b]

[a] upper limit of "normal" range.
[b] GOO/GBO norms given by Vaessen and Van der Meere (1990). GBO percentile points adapted for age and sex.
[c] CTRS norms ('GLO-groep') given by Blöte and Curfs (1986). CTRS percentile points adapted for sex. NB: skewed distribution of scores in the normative sample.

In the SKZ-PI sample, more girls than boys scored above the cutoff points on teacher ratings of hyperactivity. This was not the case for parent ratings of hyperactivity (table app.4.2c). The percentages of parent reported hyperactivity for boys/girls are in accordance with the percentages found by Bruck (1989) in a sample of 502 learning disabled children aged 6-11 using the CBCL. As far as we know there are no studies comparing special school boys and girls using the TRF. In Dutch schools for special education, girls are underrepresented compared with boys. Further research, including a second level of diagnostic confirmation, is needed to compare problem behaviors of boys and girls in schools for special education.

Appendix 4.3.1.a ***An example of a descriptive diagnosis and DSM-III-R calssification***

(subject No.95; less important details have been altered to make the case history unrecognizable):

Diagnosis: "Severe hyperkinesis[a], at the moment still mild but increasing oppositional and aggressive behavior problems[b], chronic mild motor tics and urges[c], sleeping problems[d], and bedwetting[e] in a 7;7 years old boy of an estimated average (to below average?) intelligence, with a disturbed personality development with predominantly preoedipal-features and with moderate impairment of fine manipulative ability. This boy is a pupil in group 4 of a regular school".

Details: [a] does not seem to "listen", "is not sensitive for punishment", running and rushing about all the time, is not able to "wait", overactive, impulsive and inattentive at school, at home, and at the clinic; [b] is getting pretty "smart" at home as well as at school, e.g. refuses to do things he "has to", slaps peers easily, swears at his parents; [c] shaking of the head, pinching his eyelids, turning up his nose, an urge to turn his hair and to pull skin from his fingers; [d] falls asleep late after frequently getting out of his bed, awakens early; [e] less than once a month.

Functional impairment: "The patient's functional impairment is severe and persistent, and his personality development is unfavorable: e.g. he has no friends and is never invited to children's parties, peers are teasing him (they only want to play with him if he gives them sweets), he does not like reading (although he is able to) or anything he "has to do". The school advised special education two years ago, but the parents refused. The situation is now becoming urgent, because of his disruptive behavior at school and his worsening school results".

Etiological consideration: "Both instrumental deficiencies and deficiencies in the upbringing appear to be etiologically important. Arguments for instrumental deficiencies: this boy is an ex-premature/small-for-date, was late in gross motor development, has been extremely overactive since the age of 2½, has tics since the age of 5, and father has vocal tics. Signs indicating deficiencies in the upbringing: the father has ill-health after years of alcoholic abuse, the mother is overstrung through worrying about her husband, and about her son's behavior and sleeping problems. However, the parents deny their son's functional impairment with the exception of his hyperactive and oppositional behavior at school, which has caused complaints from other parents and the school. The parents' up-bringing stategies are inadequate in relation to what the boy needs, and the house as well as the district where the family lives are unfavoroble".

Course of action: "The parents had refused parent guidance and wanted to try medication first, hoping that a favorable medication effect would make a switch to special education no longer necessary. It was agreed upon to await the medication effect, but subsequently to take a decision regarding a school for special education, and also with regards to treatment in a day-center for children with problem behaviors (including a behavior modification program and parent guidance)". Thereupon medication was tried in accordance with the protocol of the trial.

DSM-III-R classification: The project-leader classified this patient as ADHD and Chronic Motor Tic Disorder. Next the raters both classified ADHD, Chronic Motor Tic Disorder, as well as Oppositional Defiant Disorder. Two of the three raters agreed on the classification: ADHD, Chronic Motor Tic Disorder, and Oppositional Defiant Disorder. Therefore this classification was chosen.

Consensus procedure: A consensus procedure was necessary for cases, for which no two raters agreed on the classification.
These were: (1) Sjnrs 23 and 85: a discussion if these patients had Tourette's Disorder or Chronic Motor Tic Disorder; and
(2) Sjnr 48: one rater classified Conduct Disorder (apart from ADHD), and one rater classified Oppositional Defiant Disorder.

Appendix 4.3.1.b: ***DSM-III-R classification, symptom severity scores, and MND-classification for each of the subjects.***

Sjnr [a]	sex M/F	age yrs	Trial group[b]	DSM-III-R[c]	Sympt.Sev.Score[d] H	CD	E	MND[e]	ADHD[f]	RB[f]	
1	M	8	2	ADHD,GTS,ODD	3	2	1	3	14	14	*
2	F	7	3	ADHD	3	0	1	2	12	11	*
3	F	10	1	PDD NOS	3	0	0	2	11	8	*
4	M	10	2	ADHD,TTD	3	2	3	3	13	13	*
5	M	7	3	ADHD,ODD	3	2	2	1	14	14	*
6	F	11	2	ADHD,GTS,Anx	2	1	3	1	10	9	*
7	F	8	3	ADHD,Anx	3	0	2	2	13	8	*
8	M	7	2	ADHD,GTS	2	1	2	3	9	4	
9	M	7	3	ADHD	2	2	1	4	11	10	*
10	M	10	3	ADHD,ODD	2	2	1	3	14	13	*
11	M	9	3	ADHD	3	1	2	3	14	13	*
12	F	8	3	ADHD	3	2	2	3	12	11	*
13	M	9	3	ADHD,ODD	1	2	0	3	12	10	*
14	M	8	3	ADHD	2	0	1	1	13	10	*
15	M	14	3	ADHD,CD	3	3	1	3	12	12	*
16	M	7	1	PDD NOS	3	2	3	1	12	12	*
17	M	7	3	ADHD,ODD	3	2	1	3	12	11	*
18	M	8	3	ADHD,CD	2	3	2	3	13	12	*
19	M	10	3	ADHD,CD	3	3	0	1	12	8	
20	M	8	3	ADHD	3	1	2	2	13	11	*
21	F	9	2	ADHD,GTS	3	0	3	2	13	13	*
22	M	7	3	ADHD	3	1	2	3	13	7	
23	M	8	2	ADHD,CMT,ODD	2	2	1	3	9	9	
24	M	9	3	ADHD,Depr	2	0	3	1	10	10	*
25	M	7	2	ADHD,CMT	2	1	2	3	11	10	*
26	M	13	2	ADHD,GTS,ODD	2	2	2	3	11	9	
27	M	9	3	ADHD,ODD	3	2	1	3	10	9	
28	M	10	3	ADHD	2	2	2	3	12	8	
29	F	8	3	ADHD	3	1	1	1	13	12	*
30	M	10	3	ADHD	2	1	2	3	11	11	*
31	M	6	3	ADHD,ODD	2	2	0	1	11	11	*
32	M	9	3	ADHD	2	0	2	3	9	8	
33	M	10	2	ADHD,GTS,ODD	1	2	0	3	10	9	
34	M	7	3	ADHD,ODD	3	2	1	1	11	11	*
35	M	10	3	ADHD,ODD	2	2	1	3	9	7	
36	M	8	3	ADHD,Dysth	3	0	3	3	14	13	*
37	M	7	3	ADHD,ODD	3	3	0	3	12	11	*
38	F	7	3	ADHD	1	0	2	3	10	9	*
39	M	9	3	ADHD	2	0	2	3	9	9	
40	M	7	3	ADHD	2	1	1	1	13	13	*
41	M	10	3	ADHD	2	0	2	1	10	7	

42	M	10	2	ADHD,GTS	2	1	0	3	13	13	*
43	M	7	3	ADHD	3	0	0	3	11	10	*
44	M	11	2	ADHD,GTS	2	0	3	1	11	10	*
45	M	7	3	ADHD	3	2	0	2	14	12	*
46	F	6	3	ADHD,Dysth	3	1	2	3	12	11	*
47	M	11	2	ADHD,GTS	2	0	1	1	11	9	
48	M	8	3	ADHD,ODD	3	3	0	3	13	13	*
49	M	7	3	ADHD	3	0	1	1	12	10	*
50	M	10	2	ADHD,GTS	3	1	2	2	12	12	*
51	M	9	2	ADHD,TTD	3	1	1	1	14	14	*
52	M	8	1	PDD NOS	2	0	2	3	13	9	
53	F	6	2	ADHD,TTD,CD	2	2	1	3	13	12	*
54	M	8	3	ADHD,ODD	3	1	0	3	13	11	*
55	M	8	3	ADHD,ODD	3	2	0	3	13	13	*
56	M	13	3	ADHD	2	1	0	3	13	11	*
57	M	14	2	ADHD,GTS	2	0	1	4	11	8	
58	F	7	3	ADHD,ODD,Depr	3	1	3	3	13	11	*
59	M	7	3	ADHD	3	0	1	3	12	11	*
60	M	9	3	ADHD	3	1	0	3	14	13	*
61	M	7	3	ADHD,ODD	3	2	0	1	14	13	*
62	M	7	2	ADHD,GTS	2	0	0	3	12	11	*
63	F	7	1	PDD NOS	2	1	3	2	12	12	*
64	M	8	3	ADHD,ODD	3	2	0	3	13	13	*
65	M	11	3	ADHD,ODD	3	2	0	3	14	11	*
66	M	11	3	ADHD	3	1	2	1	12	12	*
67	M	6	2	ADHD,TTD,CD	3	3	1	3	13	13	*
68	M	8	3	ADHD	2	1	0	1	10	10	*
69	M	7	3	ADHD,ODD	3	1	0	3	14	13	*
70	M	8	3	ADHD	2	0	2	1	12	12	*
71	M	10	3	ADHD	2	1	0	3	11	10	*
72	M	11	3	ADHD	1	1	0	1	8	7	
73	M	10	3	ADHD,ODD	3	1	0	2	11	11	*
74	F	9	3	ADHD	2	0	0	1	9	9	*
75	M	12	3	ADHD	2	1	0	3	14	13	*
76	M	15	3	ADHD,CD	3	3	2	3	11	11	*
77	M	7	3	ADHD	1	0	0	1	8	6	
78	F	12	2	ADHD,GTS	2	0	2	3	12	12	*
79	F	12	3	ADHD,CD	2	2	1	3	12	11	*
80	M	9	3	ADHD	1	0	0	1	10	6	
81	M	11	2	ADHD,GTS,ODD	3	2	0	1	14	14	*
82	M	7	3	ADHD,ODD	3	3	1	3	12	12	*
83	M	8	2	ADHD,GTS	3	1	1	3	10	10	*
84	M	12	3	ADHD	2	2	1	3	13	12	*
85	M	9	2	ADHD,CMT	3	0	2	3	10	10	*
86	M	10	3	ADHD,ODD	3	2	2	3	12	12	*
87	M	9	3	ADHD	3	1	2	1	13	13	*
88	M	7	2	ADHD,GTS	2	1	0	3	12	9	
89	M	8	2	ADHD,GTS,ODD	3	2	0	1	14	12	*
90	M	14	3	ADHD,CD	3	3	0	3	12	10	*

91	M	8	3	ADHD,ODD	2	2	1	3	11	10 *
92	M	7	3	ADHD,ODD	2	2	0	3	11	11 *
93	M	7	3	ADHD	3	1	1	3	13	13 *
94	M	8	2	ADHD,CMT,ODD	1	1	2	1	10	7
95	M	7	2	ADHD,CMT,ODD	3	1	0	3	9	9
96	M	10	2	ADHD,GTS	1	0	2	3	9	9
97	M	8	3	ADHD,ODD	3	3	0	3	14	14 *
98	M	8	3	ADHD,ODD	3	2	1	3	11	11 *
99	M	9	1	PDD NOS,GTS	2	2	2	1	12	10 *
100	M	8	2	ADHD,CMT	2	0	0	3	9	9
101	M	8	3	ADHD	2	1	1	3	12	12 *
102	F	9	3	ADHD	1	0	0	3	9	9 *
103	M	9	3	ADHD,CD	3	3	0	3	12	12 *
104	M	11	3	ADHD	1	1	1	3	8	7
105	M	9	2	ADHD,GTS,ODD	2	2	1	3	12	11 *
106	M	9	3	ADHD,CD	2	2	0	3	11	9
107	M	14	2	ADHD,TTD	1	0	0	3	8	5
108	M	10	2	ADHD,GTS,Dysth	2	0	2	1	9	7
109	M	12	2	ADHD,CMT	1	0	1	3	8	8

[a] Sjnr = subject number.

[b] Trial: 1 = ADHD + PDD; 2 = ADHD + Tics, no PDD; 3 = ADHD, no Tics or PDD.

[c] DSM-III-R classifications: ADHD = Attention-deficit Hyperactivity Disorder; PDD NOS = Pervasive Developmental Disorder; GTS = Tourette's Disorder; CMT = Chronic Motor Tic Disorder; TTD = Transient Tic Disorder; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder; Anx = Overanxious Disorder; Dysth = Dysthymia; Depr = Depressive Disorder. The diagnoses enuresis, encopresis and stuttering have not been included in this table.

[d] Symptom Severity Score: Scales "hyperactivity" (H), "conduct disorder" (CD) and "emotional disorder" (E); a 4 point rating scale was used for each of these dimensions: 0="absent", 1="mild", 2="moderate", 3="severe".

[e] Minor Neurological Dysfunction (Touwen): 1 = MND-1; 2 = MND-2; 3 = normal; 4 = abnormal.

[f] ADHD = ADHD Rating Scale: count of DSM-III-R ADHD items, meeting criterion (≥ score 2); a subject with a count of ≥ 8-of-14 meets ADHD criteria; RB = Russell Barkley's (& DuPaul's) 1990 criteria for the ADHD Rating Scale: count of items with score ≥ 3; * = meets criteria for ADHD according to Barkley's criteria: ≥ 8-of-14 for girls, ≥ 10-of-14 for boys.

Appendix 4.5.1a ***Comparison of CBCL mean total problem T-scores[a] of subjects with referred and nonreferred USA boys/girls[b].***

Trial group:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 1+2+3:	72.83 (7.93) (N=109)	n.a.	n.a.
Boys (6-11 yrs)	73.01 (7.76) (n=82)	68.5 (8.8) (n=300)	50.5 (9.6) (n=300)
Boys (12-15 yrs)	71.20 (11.36) (n=10)	68.5 (8.8) (n=250)	50.5 (9.6) (n=250)
Girls (6-11 yrs)	72.75 (6.89) (n=16)	68.9 (9.5) (n=300)	50.6 (9.5) (n=300)
Trial 1:	73.40 (4.34) (n=5)	n.a.	n.a.
Trial 2:			
Boys (6-11 yrs)	73.04 (8.20) (n=23)		
Trial 3:			
Boys (6-11 yrs)	73.00 (7.82) (n=56)		
Girls (6-11 yrs)	71.30 (8.26) (n=10)		

[a] CBCL total problem T-scores have a potential range from 30 to 100 (clinical range > 63).
[b] taken from norms given by Achenbach and Edelbrock (1983).

Appendix 4.5.1b ***Comparison of TRF mean total problem T-scores[a] of subjects with referred and nonreferred USA boys/girls[b].***

Trial group:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 1+2+3:	66.72 (6.04) (N=109)	n.a.	n.a.
Boys (6-11 yrs)	66.70 (5.27) (n=82)	65.6 (8.9) (n=300)	51.5 (10.2) (n=300)
Boys (12-15 yrs)	64.20 (10.57) (n=10)	64.0 (10.0) (n=250)	51.7 (10.1) (n=250)
Girls (6-11 yrs)	68.69 (6.01) (n=16)	63.2 (10.4) (n=300)	50.6 (8.6) (n=300)
Trial 1:	69.20 (3.63) (n=5)	n.a.	n.a.
Trial 2:			
Boys (6-11 yrs)	66.43 (3.60) (n=23)		
Trial 3:			
Boys (6-11 yrs)	66.66 (5.86) (n=56)		
Girls (6-11 yrs)	69.10 (7.55) (n=10)		

[a] TRF total problem T-scores have a potential range from 30 to 100 (clinical range > 63).
[b] taken from norms given by Achenbach and Edelbrock (1986).

Appendix 4.5.1c ***Comparison of CBCL mean Internalizing/Externalizing T-scores[a] of subjects with referred and nonreferred USA boys/girls[b].***

Trial group/ scale:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 1+2+3:			
Internalizing	68.06 (8.16)	n.a.	n.a.
Externalizing	73.80 (7.02)	n.a.	n.a.
	(N=109)		
Boys (6-11 yrs):			
Internalizing	68.24 (8.23)	65.6 (8.9)	51.2 (9.1)
Externalizing	74.09 (6.80)	68.1 (8.7)	51.0 (9.3)
	(n=82)	(n=300)	(n=300)
Boys (12-15 yrs):			
Internalizing	66.80 (8.38)	64.7 (8.2)	51.3 (9.0)
Externalizing	73.20 (10.02)	66.2 (8.1)	51.4 (8.9)
	(n=10)	(n=250)	(n=250)
Girls (6-11 yrs):			
Internalizing	67.75 (8.38)	67.0 (9.1)	51.3 (9.1)
Externalizing	73.25 (6.19)	68.1 (9.5)	51.0 (9.4)
	(n=16)	(n=300)	(n=300)
Trial 1:			
Internalizing	64.20 (12.60)	n.a.	n.a.
Externalizing	75.60 (2.07)	n.a.	n.a.
	(n=5)		
Trial 2:			
Boys (6-11 yrs):			
Internalizing	70.43 (6.84)		
Externalizing	72.65 (7.77)		
	(n=23)		
Trial 3:			
Boys (6-11 yrs):			
Internalizing	67.48 (8.39)		
Externalizing	74.55 (6.52)		
	(n=56)		
Girls (6-11 yrs):			
Internalizing	67.00 (8.69)		
Externalizing	72.30 (7.53)		
	(n=10)		

[a] CBCL Internalizing/Externalizing T-scores have a potential range from 30 to 100 (clinical range > 63).
[b] taken from norms given by Achenbach and Edelbrock (1983).

Appendix 4.5.1d ***Comparison of TRF mean Internalizing/Externalizing T-scores[a] of subjects with referred and nonreferred USA boys/girls[b].***

Trial group/ scale:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 1+2+3:			
Internalizing	62.47 (6.55)	n.a.	n.a.
Externalizing	66.77 (6.52)	n.a.	n.a.
	(N=109)		
Boys (6-11 yrs):			
Internalizing	62.66 (5.33)	62.2 (8.7)	52.3 (8.3)
Externalizing	67.09 (6.44)	65.6 (8.9)	52.2 (9.2)
	(n=82)	(n=300)	(n=300)
Boys (12-15 yrs):			
Internalizing	63.60 (10.81)	63.6 (10.7)	51.8 (8.9)
Externalizing	63.90 (9.48)	62.5 (9.7)	52.4 (9.8)
	(n=10)	(n=250)	(n=250)
Girls (6-11 yrs):			
Internalizing	60.63 (8.97)	59.1 (9.3)	51.4 (7.5)
Externalizing	67.38 (4.30)	62.8 (9.9)	51.6 (7.5)
	(n=16)	(n=300)	(n=300)
Trial 1:			
Internalizing	64.80 (3.70)	n.a.	n.a.
Externalizing	67.20 (6.22)	n.a.	n.a.
	(n=5)		
Trial 2:			
Boys (6-11 yrs):			
Internalizing	63.57 (4.45)		
Externalizing	66.52 (5.18)		
	(n=23)		
Trial 3:			
Boys (6-11 yrs):			
Internalizing	62.05 (5.65)		
Externalizing	67.25 (6.90)		
	(n=56)		
Girls (6-11 yrs):			
Internalizing	59.90 (11.29)		
Externalizing	68.50 (5.15)		
	(n=10)		

[a] TRF Internalizing/Externalizing T-scores have a potential range from 30 to 100 (clinical range > 63).
[b] taken from norms given by Achenbach and Edelbrock (1986).

Appendix 4.5.1e ***Comparison of CBCL mean factor T-scores[a] of subjects aged 6-11 with referred and nonreferred USA boys/girls[b].***

Trial group:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 2/boys (6-11 yrs):	n=22	n=300	n=300
Schizoid-Anx.	66.59 (9.59)	64.8 (8.5)	57.7 (4.7)
Depressed	67.41 (8.20)	66.8 (9.1)	57.3 (4.4)
Uncommunic.	69.27 (10.20)	67.9 (10.2)	57.9 (5.3)
Obsess-Comp.	72.77 (7.90)	65.2 (8.2)	57.4 (4.5)
Somatic Compl.	64.45 (7.93)	61.6 (7.4)	57.9 (4.7)
Social Withdr.	68.59 (10.84)	67.1 (8.9)	57.9 (4.9)
Hyperactive	73.64 (8.93)	68.5 (9.3)	57.6 (4.8)
Aggressive	73.95 (11.82)	68.7 (10.7)	57.1 (4.8)
Delinquent	66.27 (8.60)	68.4 (8.5)	57.7 (4.6)
Trial 3/boys (6-11 yrs):	n=56	n=300	n=300
Schizoid-Anx.	65.09 (8.83)		
Depressed	67.39 (8.45)		
Uncommunic.	67.80 (10.45)		
Obsess-Comp.	68.34 (8.17)		
Somatic Compl.	61.50 (7.08)		
Social Withdr.	71.41 (9.94)		
Hyperactive	76.57 (9.06)		
Aggressive	77.07 (10.26)		
Delinquent	68.30 (8.60)		
Trial 3/girls (6-11 yrs):	n=10	n=300	n=300
Depressed	69.60 (13.00)	69.3 (10.5)	57.2 (4.5)
Social Withdr.	70.00 (10.79)	68.8 (9.9)	57.7 (4.6)
Somatic Compl.	64.00 (6.63)	63.2 (8.1)	57.6 (4.3)
Schiz-Obsess.	59.70 (5.62)	64.7 (7.6)	58.0 (4.6)
Hyperactive	76.50 (7.91)	69.5 (9.6)	57.4 (4.5)
Sex Problems	62.80 (9.53)	64.2 (9.6)	58.3 (5.4)
Delinquent	63.70 (8.41)	66.6 (8.9)	59.1 (4.3)
Aggressive	74.40 (12.08)	69.5 (10.6)	57.4 (4.7)
Cruel	64.00 (9.76)	65.8 (8.8)	58.5 (4.4)

[a] CBCL factor T-scores have a potential range from 55 to 100 (clinical range > 70).
[b] taken from norms given by Achenbach and Edelbrock (1983).

Appendix 4.5.1e ***Comparison of CBCL mean factor T-scores[a] of subjects aged 6-11 with referred and nonreferred USA boys/girls[b].***

Trial group:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 2/boys (6-11 yrs):	n=22	n=300	n=300
Schizoid-Anx.	66.59 (9.59)	64.8 (8.5)	57.7 (4.7)
Depressed	67.41 (8.20)	66.8 (9.1)	57.3 (4.4)
Uncommunic.	69.27 (10.20)	67.9 (10.2)	57.9 (5.3)
Obsess-Comp.	72.77 (7.90)	65.2 (8.2)	57.4 (4.5)
Somatic Compl.	64.45 (7.93)	61.6 (7.4)	57.9 (4.7)
Social Withdr.	68.59 (10.84)	67.1 (8.9)	57.9 (4.9)
Hyperactive	73.64 (8.93)	68.5 (9.3)	57.6 (4.8)
Aggressive	73.95 (11.82)	68.7 (10.7)	57.1 (4.8)
Delinquent	66.27 (8.60)	68.4 (8.5)	57.7 (4.6)
Trial 3/boys (6-11 yrs):	n=56	n=300	n=300
Schizoid-Anx.	65.09 (8.83)		
Depressed	67.39 (8.45)		
Uncommunic.	67.80 (10.45)		
Obsess-Comp.	68.34 (8.17)		
Somatic Compl.	61.50 (7.08)		
Social Withdr.	71.41 (9.94)		
Hyperactive	76.57 (9.06)		
Aggressive	77.07 (10.26)		
Delinquent	68.30 (8.60)		
Trial 3/girls (6-11 yrs):	n=10	n=300	n=300
Depressed	69.60 (13.00)	69.3 (10.5)	57.2 (4.5)
Social Withdr.	70.00 (10.79)	68.8 (9.9)	57.7 (4.6)
Somatic Compl.	64.00 (6.63)	63.2 (8.1)	57.6 (4.3)
Schiz-Obsess.	59.70 (5.62)	64.7 (7.6)	58.0 (4.6)
Hyperactive	76.50 (7.91)	69.5 (9.6)	57.4 (4.5)
Sex Problems	62.80 (9.53)	64.2 (9.6)	58.3 (5.4)
Delinquent	63.70 (8.41)	66.6 (8.9)	59.1 (4.3)
Aggressive	74.40 (12.08)	69.5 (10.6)	57.4 (4.7)
Cruel	64.00 (9.76)	65.8 (8.8)	58.5 (4.4)

[a] CBCL factor T-scores have a potential range from 55 to 100 (clinical range > 70).
[b] taken from norms given by Achenbach and Edelbrock (1983).

Appendix 4.5.1f ***Comparison of TRF mean factor T-scores[a] of subjects aged 6-11 with referred and nonreferred USA boys/girls[b].***

Trial group:	Trial subjects T-score (SD)	Referred children T-score (SD)	Nonreferred children T-score (SD)
Trial 2/boys (6-11 yrs):	n=23	n=300	n=300
Anxious	60.96 (5.43)	61.0 (7.2)	57.3 (4.5)
Social Withdr.	66.83 (6.14)	66.0 (9.1)	58.0 (5.4)
Unpopular	64.13 (5.66)	65.6 (8.2)	57.6 (5.0)
Self-Destruct.	66.00 (4.99)	65.4 (7.7)	58.0 (5.4)
Obsess-Comp.	67.91 (5.44)	65.7 (9.5)	57.9 (5.2)
Inattentive	66.17 (4.46)	65.8 (8.4)	57.7 (5.3)
Nerv-Overact.	69.26 (4.52)	65.7 (9.1)	57.8 (5.2)
Aggressive	64.83 (6.73)	65.8 (9.8)	57.6 (5.4)
Trial 3/boys (6-11 yrs):	n=56	n=300	n=300
Anxious	60.34 (5.06)		
Social Withdr.	64.14 (6.27)		
Unpopular	66.95 (8.17)		
Self-Destruct.	64.80 (6.40)		
Obsess-Comp.	63.66 (5.64)		
Inattentive	65.39 (5.94)		
Nerv-Overact.	66.89 (7.05)		
Aggressive	66.71 (8.36)		
Trial 3/girls (6-11 yrs):	n=10	n=300	n=300
Anxious	62.30 (8.63)	60.6 (7.6)	56.9 (3.9)
Social Withdr.	61.80 (8.51)	63.1 (8.3)	57.4 (4.3)
Depressed	71.80 (8.42)	64.5 (9.4)	57.1 (3.7)
Unpopular	66.20 (5.49)	65.3 (9.5)	58.8 (3.9)
Self-Destr.	64.40 (4.93)	62.6 (6.1)	59.4 (3.1)
Inattentive	66.00 (5.85)	64.0 (9.0)	56.9 (4.1)
Nerv-Overact.	70.70 (10.57)	63.7 (10.4)	57.3 (4.5)
Aggressive	69.50 (5.84)	63.9 (10.0)	57.0 (4.0)

[a] TRF factor T-scores have a potential range from 55 to 100 (clinical range > 70).
[b] derived from Achenbach and Edelbrock (1986).

Appendix 4.5.1g ***Proportions of subjects, who had CBCL Hyperactive (HFS), TRF Inattentive (IFS), or TRF Nervous-Overactive (NOFS) factor T-scores in the clinical range (i.e. above the 98th percentile for nonreferred USA boys/girls[a], T-score > 70).***

	Trial 1 n/N	Trial 2 n/N (%)	Statist.comp. trial 2 vs 3 (Fisher's[b])	Trial 3 n/N (%)	Trial 1+2+3 n/N (%)
Boys aged 6-11:					
HFS clin. range	3/3	13/22 (59.1%)	(ns)	37/56 (66.1%)	53/81 (65.4%)
IFS clin. range	1/3	3/23 (13.0%)	(ns)	7/56 (12.5%)	11/82 (13.4%)
NOFS clin. range	0/3	3/23 (13.0%)	(ns)	9/56 (16.1%)	12/82 (14.6%)
Both HFS and (IFS or NOFS) cl.range	0/3	2/22 (9.1%)	(ns)	3/56 (5.4%)	5/81 (6.2%)
Neither HFS nor (IFS or NOFS) in the cl.range	0/3	8/22 (36.4%)	(ns)	17/56 (30.4%)	25/81 (30.9%)
Boys aged 12-15:					
HFS clin. range	n.a.	2/4		6/6	8/10 (80%)
IFS clin. range	n.a.	1/4		0/6	1/10 (10%)
Both HFS and IFS in the cl.range	n.a.	0/4		0/6	0/10 (0%)
Neither HFS nor IFS clin.range	n.a.	1/4		0/6	1/10 (10%)
Girls aged 6-11:					
HFS clin. range	2/2	3/4		7/10	12/16 (75%)
IFS clin. range	0/2	0/4		2/10	2/16 (12.5%)
NOFS clin. range	0/2	2/4		4/10	6/16 (37.5%)
Both HFS and (IFS or NOFS) cl.range	0/2	0/4		2/10	2/16 (12.5%)
Neither HFS nor (IFS or NOFS) in the cl.range	0/2	1/4		2/10	3/16 (18.8%)

[a] taken from norms given by Achenbach and Edelbrock (1983, 1986).

[b] statistical comparison trial groups 2 and 3 (p-value Fisher's exact test, two-sided): * = $p < 0.05$.

Appendix 5.3.2a Rating scale scores during treatment

Improvement corresponds with a lower score on the GOO, GBO, and CTRS, and with a higher score on the problems parents or problems teacher scales. Rating scale scores were obtained at baseline (t_0), after 3 weeks of treatment (t_3), after 5 weeks of treatment (t_5), and after 7 weeks of treatment (t_7). The CTRS, GGGS and GGBS were only used at t_0 and t_7.

Trial groups 1+2+3, clonidine:

	N t_0	mean score t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	42	44.1	41.0	39.7	38.3	41
GBO:	42	41.4	37.9	36.8	36.7	39
CTRS ActOut f.:	42	26.6	n.a.	n.a.	24.2	39
CTRS hyp. f.:	42	14.4	n.a.	n.a.	12.4	39
CTRS AnxWdr.f.:	42	13.5	n.a.	n.a.	13.4	39
CTRS sum score:	42	78.9	n.a.	n.a.	74.0	39
problems parents:	42	26.3	38.7	40.1	45.4	42
problems teacher:	40	24.2	37.2	41.9	40.7	38

Trial groups 1+2+3, placebo:

	N t_0	mean score t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	43	46.4	43.9	43.0	43.5	42
GBO:	43	43.2	43.2	41.7	41.9	40
CTRS ActOut f.:	43	28.1	n.a.	n.a.	28.5	40
CTRS hyp. f.:	43	14.8	n.a.	n.a.	14.4	40
CTRS AnxWdr.f.:	43	14.6	n.a.	n.a.	13.9	40
CTRS sum score:	43	83.0	n.a.	n.a.	82.8	40
problems parents:	43	22.9	26.8	33.7	35.4	42
problems teacher:	42	25.9	33.7	36.0	34.9	40

Trial group 2, clonidine:

	N t_0	mean score t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	16	43.1	40.8	40.0	38.4	15
GBO:	16	39.8	37.3	37.9	37.3	15
CTRS ActOut f.:	16	26.3	n.a.	n.a.	24.3	15
CTRS hyp. f.:	16	14.6	n.a.	n.a.	12.5	15
CTRS AnxWdr.f.:	16	13.9	n.a.	n.a.	13.7	15
CTRS sum score:	16	79.7	n.a.	n.a.	74.4	15
problems parents:	16	29.7	37.5	41.1	47.6	16
problems teacher:	15	22.5	41.7	39.2	39.6	14

Trial group 2, placebo:

	N t_0	mean score t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	16	45.9	42.6	41.6	43.3	16
GBO:	16	41.9	42.1	41.1	41.4	16
CTRS ActOut f.:	16	27.1	n.a.	n.a.	27.4	16
CTRS hyp. f.:	16	14.6	n.a.	n.a.	14.6	16
CTRS AnxWdr.f.:	16	14.2	n.a.	n.a.	13.4	16
CTRS sum score:	16	81.9	n.a.	n.a.	82.1	16
problems parents:	16	17.3	24.8	29.6	31.3	16
problems teacher:	15	25.2	36.1	39.2	39.0	15

Trial group 3, clonidine:

	N t_0	mean score t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	24	44.9	41.4	39.6	38.2	24
GBO:	24	42.5	38.4	35.9	36.6	22
CTRS ActOut f.:	24	26.0	n.a.	n.a.	24.0	22
CTRS hyp. f.:	24	14.2	n.a.	n.a.	12.2	22
CTRS AnxWdr.f.:	24	13.0	n.a.	n.a.	13.2	22
CTRS sum score:	24	77.0	n.a.	n.a.	73.3	22
problems parents:	24	23.9	39.3	39.0	44.0	24
problems teacher:	23	24.7	32.8	42.5	40.3	22

Trial group 3, placebo:

	N s t_0	mean core t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	24	46.4	44.1	43.4	43.4	23
GBO:	24	45.1	44.4	42.3	42.8	21
CTRS ActOut f.:	24	29.2	n.a.	n.a.	29.6	21
CTRS hyp. f.:	24	15.3	n.a.	n.a.	14.2	21
CTRS AnxWdr.f.:	24	14.4	n.a.	n.a.	13.6	21
CTRS sum score:	24	84.1	n.a.	n.a.	83.1	21
problems parents:	24	27.8	29.0	39.2	40.2	23
problems teacher:	24	27.4	34.0	36.2	33.9	22

Trial group 3, methylphenidaat:

	N t_0	mean score t_0	mean score t_3	mean score t_5	mean score t_7	N t_7
GOO:	24	45.3	42.0	39.7	40.9	23
GBO:	24	45.8	41.3	39.2	37.8	22
CTRS ActOut f.:	24	31.1	n.a.	n.a.	25.8	22
CTRS hyp. f.:	24	15.7	n.a.	n.a.	12.3	22
CTRS AnxWdr.f.:	24	13.6	n.a.	n.a.	12.9	22
CTRS sum score:	24	86.1	n.a.	n.a.	73.6	22
problems parents:	24	25.8	41.0	48.9	45.7	23
problems teacher:	24	22.7	38.4	48.4	52.2	22

Appendix 5.3.2b ***Time x baseline interaction, time x treatment interaction, and estimated medication effect for treatment groups.***

The models, used in the repeated measures ANOVA, mathematically formulated:
(1) time-by-baseline interaction; and
(2) time-by-treatment group interaction.

Model 1: $y_t = \alpha_t + \Gamma + \beta_t y_0 + \varepsilon_t$.

y_t = effect measurement at time t (3, 5, 7 weeks).
α_t = time dependent intercept.
β_t = time dependent regression effect.
Γ = average medication effect.
ε_t = error term.

Model 2: $y_t = \alpha + \Gamma_t + \beta y_0 + \varepsilon_t$.

α and β are now time independent,
Γ is time dependent.

Treatment groups, medication:	time x baseline interaction: p-value	time x treatment interaction: p-value	medication effect/S.E.	p-value medic. effect:
Trial groups 1+2+3, clonidine/placebo (n=42 and n=43 respectively):				
GOO:	0.770 ns	0.242 ns	-1.28/0.98	0.192 ns
GBO:	0.471 ns	0.733 ns	-4.14/1.20	0.001 **
CTRS ActOut f.:	n.a.	n.a.	-3.55/1.14	0.003 **
CTRS hyp. f.:	n.a.	n.a.	-1.85/0.58	0.001 **
CTRS AnxWdr.f.:	n.a.	n.a.	0.18/0.51	0.727 ns
CTRS sum score:	n.a.	n.a.	-6.56/2.10	0.002 **
GGGS factors:				
1. social pos.:	n.a.	n.a.	0.78/0.45	0.080 ns
2. extravert:	n.a.	n.a.	-0.32/0.35	0.367 ns
3. hyperactive:	n.a.	n.a.	-1.84/0.55	0.001 **
4. social neg.:	n.a.	n.a.	-0.55/0.59	0.351 ns
5. introvert:	n.a.	n.a.	0.49/0.40	0.220 ns
GGBS factors:				
1. extravert:	n.a.	n.a.	0.56/0.40	0.163 ns
2. introvert:	n.a.	n.a.	-0.29/0.45	0.515 ns
3. social neg.:	n.a.	n.a.	-1.39/0.73	0.056 ns
4. taskor.good:	n.a.	n.a.	0.94/0.33	0.004 **
5. taskor.weak:	n.a.	n.a.	-1.23/0.53	0.020 *

* $p < .05$; ** $p < .01$.

Appendix 5.3.2b (continued).

Treatment groups, medication:	time x baseline interaction: p-value	time x treatment interaction: p-value	medication effect/S.E.	p-value medic. effect:
Trial group 2, clonidine/placebo (n=16 and n=16 respectively):				
GOO:	0.442 ns	0.392 ns	0.51/1.27	0.686 ns
GBO:	0.300 ns	0.667 ns	-2.93/2.03	0.150 ns
CTRS ActOut f.:	n.a.	n.a.	-2.56/1.78	0.161 ns
CTRS hyp. f.:	n.a.	n.a.	-2.06/0.90	0.022 *
CTRS AnxWdr.f.:	n.a.	n.a.	0.53/0.80	0.510 ns
CTRS sum score:	n.a.	n.a.	-6.22/3.44	0.070 ns
problems parents:	0.870 ns	0.413 ns	4.77/4.30	0.266 ns
problems teacher:	0.093 ns	0.243 ns	6.19/6.01	0.303 ns
GGGS factors:				
1. social pos.:	n.a.	n.a.	1.10/0.77	0.153 ns
2. extravert:	n.a.	n.a.	-0.74/0.64	0.254 ns
3. hyperactive:	n.a.	n.a.	-1.14/0.93	0.220 ns
4. social neg.:	n.a.	n.a.	-0.37/0.76	0.630 ns
5. introvert:	n.a.	n.a.	0.64/0.74	0.382 ns
GGBS factors:				
1. extravert:	n.a.	n.a.	1.39/0.62	0.024 *
2. introvert:	n.a.	n.a.	-1.29/0.74	0.081 ns
3. social neg.:	n.a.	n.a.	-1.12/0.84	0.181 ns
4. taskor.good:	n.a.	n.a.	0.68/0.63	0.282 ns
5. taskor.weak:	n.a.	n.a.	-0.77/0.83	0.351 ns

* $p < .05$; ** $p < .01$.

Appendix 5.3.2b (continued).

Treatment groups, medication:	time x baseline interaction: p-value	time x treatment interaction: p-value	medication effect/S.E.	p-value medic. effect:
Trial group 3, clonidine/placebo (n=24 and n=24 respectively):				
GOO:	0.658 ns	0.341 ns	-2.10/1.41	0.137 ns
GBO:	0.034 *	0.928 ns[a]	-4.57/1.60	0.004 **
CTRS ActOut f.:	n.a.	n.a.	-4.26/1.64	0.013 *
CTRS hyp. f.:	n.a.	n.a.	-1.44/0.80	0.073 ns
CTRS AnxWdr.f.:	n.a.	n.a.	0.41/0.72	0.564 ns
CTRS sum score:	n.a.	n.a.	-5.56/3.01	0.065 ns
problems parents:	0.978 ns	0.020 *[b]	t_3:11.41/5.53	0.039 *
			t_5: 0.86/5.67	0.884 ns
			t_7: 5.61/5.95	0.347 ns
problems teacher:	0.062 ns	0.146 ns	3.38/3.38	0.317 ns
GGGS factors:				
1. social pos.:	n.a.	n.a.	0.48/0.60	0.425 ns
2. extravert:	n.a.	n.a.	-0.21/0.46	0.639 ns
3. hyperactive:	n.a.	n.a.	-2.20/0.74	0.003 **
4. social neg.:	n.a.	n.a.	-0.64/0.91	0.478 ns
5. introvert:	n.a.	n.a.	0.02/0.46	0.974 ns
GGBS factors:				
1. extravert:	n.a.	n.a.	-0.03/0.59	0.963 ns
2. introvert:	n.a.	n.a.	0.52/0.56	0.355 ns
3. social neg.:	n.a.	n.a.	-1.49/1.17	0.203 ns
4. taskor.good:	n.a.	n.a.	1.21/0.38	0.002 **
5. taskor.weak:	n.a.	n.a.	-1.40/0.77	0.070 ns

* $p < .05$; ** $p < .01$.

[a] As the time-by-treatment interaction was not significant, we conclude that model 1 is the valid model.

[b] As the time-by-treatment interaction was significant, we followed model 2. The medication effect is significant at t_3 (t=2.06, p=0.039), but is not significant any more at t_5 (t=0.151, p=0.884), and at t_7 (t=0.943, p=0.347).

Appendix 5.3.2b (continued).

Treatment groups, medication:	time x baseline interaction: p-value	time x treatment interaction: p-value	medication effect/S.E.	p-value medic. effect:
Trial group 3, methylphenidate/placebo (n=24 and n=24):				
GOO:	0.104 ns	0.574 ns	-1.95/1.45	0.179 ns
GBO:	0.018 *	0.467 ns[a]	-3.72/1.69	0.028 *
CTRS ActOut f.:	n.a.	n.a.	-6.00/1.96	0.004 **
CTRS hyp. f.:	n.a.	n.a.	-2.31/0.84	0.006 **
CTRS AnxWdr.f.:	n.a.	n.a.	-0.38/0.75	0.612 ns
CTRS sum score:	n.a.	n.a.	-11.69/3.67	0.001 **
problems parents:	0.006 *	0.531 ns[a]	10.61/4.24	0.012 *
problems teacher:	0.001 *	0.059 ns[a]	9.43/3.63	0.009 **
GGGS factors:				
1. social pos.:	n.a.	n.a.	1.14/0.55	0.036 *
2. extravert:	n.a.	n.a.	-0.24/0.44	0.589 ns
3. hyperactive:	n.a.	n.a.	-1.55/0.79	0.049 *
4. social neg.:	n.a.	n.a.	-0.44/0.82	0.594 ns
5. introvert:	n.a.	n.a.	0.78/0.56	0.165 ns
GGBS factors:				
1. extravert:	n.a.	n.a.	-0.46/0.63	0.463 ns
2. introvert:	n.a.	n.a.	0.70/0.53	0.188 ns
3. social neg.:	n.a.	n.a.	-1.53/1.08	0.157 ns
4. taskor.good:	n.a.	n.a.	1.41/0.48	0.003 **
5. taskor.weak:	n.a.	n.a.	-1.88/0.75	0.013 *

* $p < .05$; ** $p < .01$.

[a] As the time-by-treatment interaction was not significant, we conclude that model 1 is the valid model.

Appendix 5.3.2b (continued).

Treatment groups, medication:	time x baseline interaction: p-value	time x treatment interaction: p-value	medication effect/S.E.	p-value medic. effect:
Trial group 3, clonidine/methylphenidate (n=24 and n=24):				
GOO:	0.086 ns	0.294 ns	0.32/1.46	0.827 ns
GBO:	0.258 ns	0.791 ns	-0.01/1.74	0.994 ns
CTRS ActOut f.:	n.a.	n.a.	-1.97/1.84	0.290 ns
CTRS hyp. f.:	n.a.	n.a.	1.03/0.87	0.232 ns
CTRS AnxWdr.f.:	n.a.	n.a.	-0.83/0.64	0.199 ns
CTRS sum score:	n.a.	n.a.	6.92/3.25	0.033 *
problems parents:	0.046 *	0.005 *	t_3:-0.61/6.22	0.921 ns
			t_5:-9.14/5.57	0.101 ns
			t_7:-1.25/6.59	0.849 ns
problems teacher:	0.188 ns	0.717 ns	-8.00/3.72	0.032 *
GGGS factors:				
1. social pos.:	n.a.	n.a.	-0.81/0.49	0.095 ns
2. extravert:	n.a.	n.a.	0.05/0.51	0.919 ns
3. hyperactive:	n.a.	n.a.	-0.69/0.94	0.465 ns
4. social neg.:	n.a.	n.a.	-0.20/0.91	0.824 ns
5. introvert:	n.a.	n.a.	-0.77/0.55	0.160 ns
GGBS factors:				
1. extravert:	n.a.	n.a.	0.33/0.63	0.601 ns
2. introvert:	n.a.	n.a.	-0.30/0.54	0.579 ns
3. social neg.:	n.a.	n.a.	0.00/1.10	0.998 ns
4. taskor.good:	n.a.	n.a.	-0.33/0.46	0.477 ns
5. taskor.weak:	n.a.	n.a.	0.53/0.85	0.532 ns

* $p < .05$; ** $p < .01$.

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Summary

SUMMARY

In Chapter 1 the background and the aims of the study are described. It is important to develop effective treatment strategies for children with the hyperkinetic syndrome, also called hyperkinesis, because it usually involves impaired social and school functioning, and in the majority of cases persists throughout childhood. Medication should be used as a stepping-stone for nonpharmacological treatment of these children. Many hyperkinetic children show a beneficial response to stimulants, but other children do not benefit from stimulants or have a contraindication against the use of this sort of medication. In the past few years an alternative for the latter group has presented itself in the form of the specifically noradrenergic drug clonidine. Encouraging results of both a small-scale, controlled trial and clinical experiences in open treatment justified a large-scale, controlled trial. The primary aim of the study was to compare the efficacy and safety of clonidine with those of placebo and methylphenidate in relation to short-term effects on hyperactivity in children with a DSM-III-R classification Attention-deficit Hyperactivity Disorder (ADHD). Because methylphenidate is contraindicated in ADHD children with Tic Disorder (TD) or a Pervasive Developmental Disorder (PDD), we had to confine ourselves to a comparison with placebo for these groups.

In Chapter 2 a review of the literature on hyperkinesis reveals general discontent about the delimitation of the hyperkinetic syndrome, as operationalized in ICD-9 and DSM-III-R, from other child psychiatric disturbances with respect to etiology, pathogenesis and outcome. Many children with a DSM-III-R diagnosis ADHD also have a Conduct Disorder or an Oppositional-defiant Disorder.

Chapter 3 describes the way in which the child psychiatric, medical, and psychological assessments were carried out and the methods of the trial.

The child psychiatric assessment included standardized child and parent interviews, history taking, playroom observations, and information obtained from parent and teacher behavioral rating scales. The medical examination included a limited pediatric examination, an assessment of minor physical anomalies, and a developmental neurological examination. The psychological assessment included the Primary Mental Ability test (PMA), the WISC-R Freedom from Distractibility Factor (FDF), and the Bourdon-Wiersma paper-and-pencil cancellation test (PPCT).

The trial design was double-blind, placebo-controlled, and assigned the subjects to parallel groups. The inclusion criteria were: (1) age 6-15 years; (2) not mentally retarded; (3) not institutionalized, and school-going; (4) meeting the DSM-III-R criteria for ADHD; (5) ADHD symptoms impeding development and existing treatments insufficient; (6) no earlier use of stimulants or clonidine, and no use of psychoactive medications during the previous 6 months; (7) no medical contraindications; (8) no

important changes in school or home situation, or in psychological treatment during the trial.

In Chapter 4 the results of the diagnostic assessment are presented. A total of 109 children entered the trial (93 boys and 16 girls). Most children had been referred by the school-doctor, the general practitioner, or a child psychiatrist. Fifty-nine percent of them attended a school for special education. All had been given prior assistance for behavioral problems. On the basis of their DSM-III-R classification, they were assigned to one of three trial groups: (1) ADHD + PDD (n=5); (2) ADHD + TD, and no PDD (n=32); or (3) ADHD, and no PDD or TD (n=72). Both the parents and the teacher were asked to formulate treatment targets in terms of observable behavior. For 98% of the subjects these targets referred to hyperactivity symptoms, and for 69% of the subjects to oppositional-defiant behavior. DSM-III-R classifications were made by three child psychiatrists, independently of one another. Thirty-nine percent of the children were given a classification Oppositional-defiant Disorder or Conduct Disorder in addition to ADHD, and 6% had an emotional disorder besides ADHD. On the basis of the developmental neurological examination, 34% of the children were classified as Minor Neurological Dysfunction and 2% as neurologically abnormal. From behavioral rating scale scores it appeared that 33% of the children was pervasively hyperactive (i.e., hyperactive both at school and at home). Using the PMA test, 31% of the children were diagnosed as learning-disabled. All children were classified according to the degree of pervasiveness of their hyperactivity using parent/teacher behavioral rating scores and behavior observation scores during psychological testing as criteria for pervasiveness. The results from the PPCT were then compared with those of normal controls. We found that the pervasively hyperactive children had a more variable PPCT cancellation time than normal controls, and that this variability of cancellation time was moderately high correlated with the child's behavior during PPCT testing. Moreover, mean cancellation time decreased with task duration, but this effect did not appear specifically in the ADHD children.

In Chapter 5 the results of the trial are presented. All children but one completed treatment. The statistical analyses of the results were performed according to the "intention to treat" principle. Each child was treated with medication for 8 weeks. The parents' and teacher's judgments were used to determine whether a child had shown a "clinically significant improvement" during the treatment period. Those who had improved were the "responders". In the trial groups 1 and 2, the difference between the clonidine-treated, and the placebo-treated children, was nonsignificant with respect to responder status. In trial group 3, the percentage of responders in the clonidine-treated group was as high as in the methylphenidate-treated group (50%), and significantly higher than in the placebo treated group (13%). A statistical analysis of the behavioral ratings during treatment showed similar results. Slight nuances could be observed: (1) in trial group 2, clonidine had a significant effect on hyperactivity in the school situation

compared with placebo; (2) methylphenidate, not clonidine, improved both the parents' and teacher's target problem behaviors. After 7 weeks of treatment high numbers of children showed adverse effects: 52% in the clonidine group, 37% in the placebo group, and 58% in the methylphenidate group. In the latter group, the percentage of annoying adverse effects was much higher than in the clonidine and placebo groups (21%, 5%, and 7% respectively). We did not find child characteristics predictive of a favorable drug response.

Chapter 6 presents a review of the literature on biochemical studies of hyperkinesis, followed by the results of our biochemical study. The aims of our biochemical study were: (1) to compare the ADHD children with normal controls with respect to free plasma MHPG and 24-hours total urinary MHPG; and (2) to compare the differential effects of clonidine and methylphenidate on MHPG. Only the children of trial group 3 were investigated with respect to MHPG. This group had significantly lower levels of MHPG than the controls, both in 24-hours urine and in plasma. They also had a significant decrease in plasma MHPG following both clonidine and methylphenidate treatment, compared with placebo.

Chapter 7 discusses the total study. The study has demonstrated the efficacy of clonidine in ADHD children without either PDD or TD. Moreover, we found that clonidine is hardly less effective than methylphenidate in this group of ADHD children, but has a safer profile of adverse effects. This means that clonidine can be added to the treatment arsenal as an alternative to stimulants. Our advice is to have the choice for an initial medication try with either clonidine or methylphenidate depend on that profile of effects and adverse effects which best suits the patient's needs. Neither for ADHD children with PDD, nor for ADHD children with TD, our study has demonstrated the efficacy of clonidine. However, we did find arguments suggesting that a possible efficacy should not be ruled out. We therefore recommend further research aimed at (a) the efficacy of clonidine on hyperactivity in hyperkinetic PDD and TD children, and (b) the long-term effects of clonidine on behavior and on biochemical measures in hyperkinetic children.

SAMENVATTING

In hoofdstuk 1 wordt beschreven waarom het onderzoek is verricht. Bij kinderen met een hyperkinetisch syndroom is er over het algemeen sprake van een ernstig dysfunctioneren op sociaal-emotioneel en cognitief vlak. Medicatie heeft in de behandeling van deze kinderen de betekenis van een ruggesteun bij het op gang brengen van niet-medicamenteuze behandelingsvormen. Veel hyperkinetische kinderen vinden baat bij psychostimulantia zoals methylfenidaat. Er zijn echter ook veel kinderen, die geen baat vinden bij psychostimulantia of bij wie deze soort van medicatie gecontraïndiceerd is. Voor deze kinderen lijkt er de laatste jaren een alternatief aanwezig in de vorm van het specifiek noradrenerg aangrijpende clonidine. De resultaten met clonidine bij hyperkinetische kinderen waren zowel in een klein gecontroleerd onderzoek als in open behandeling bemoedigend en rechtvaardigden een grote gecontroleerde trial. Het doel van het onderzoek was de werkzaamheid en neveneffecten van clonidine met betrekking tot hyperactiviteitssymptomen te vergelijken met die van placebo en methylfenidaat bij kinderen met een DSM-III-R diagnose Aandachtstekortstoornis met hyperactiviteit (ADHD). Omdat methylfenidaat gecontraïndiceerd is bij ADHD kinderen met tevens een DSM-III-R diagnose Diffuse Ontwikkelingsstoornis (PDD) of Tic Stoornis (TD), kon de vergelijking voor deze groepen enkel plaatsvinden met placebo.

In hoofdstuk 2 wordt het onderwerp hyperkinesie uitgewerkt in de vorm van een literatuuroverzicht van onderzoeksbevindingen op dit terrein. Men blijkt alom ontevreden over de mate waarin het op dit moment mogelijk is om het hyperkinetisch syndroom, zoals geöperationaliseerd in de classificatiesystemen DSM-III-R en ICD-9, af te grenzen van andere kinderpsychiatrische ziektebeelden ten aanzien van oorzaken, pathogenese en ziektebeloop. Bij veel kinderen met een DSM-III-R diagnose ADHD is er tevens sprake van een Gedragsstoornis of van Oppositioneel-opstandig gedrag.

In hoofdstuk 3 worden de methoden van de kinderpsychiatrische, medische en psychologische beoordeling besproken en van de trial. Het kinderpsychiatrisch onderzoek bestond uit een gestandaardiseerd kind- en ouderinterview, anamnestische gesprekken, spelkameronderzoek en informatie uit door leerkracht en ouders ingevulde gedragsvragenlijsten. Het medisch onderzoek bestond uit een beperkt pediatrisch onderzoek, een onderzoek op dysmorfe kenmerken en een ontwikkelingsneurologisch onderzoek. Het psychologisch onderzoek bestond uit de Primary Mental Ability test (PMA), de WISC-R Freedom from Distractibility Factor (FDF) en de Bourdon-Wiersma aandachtstest (PPCT).

De trial was dubbelblind, placebo-gecontroleerd van opzet en werkte met parallelle groepen. De inclusiecriteria waren: (1) leeftijd 6-15 jaar; (2) niet zwakzinnig; (3) niet-geïnstitutionaliseerd en schoolgaand; (4) voldoen aan de criteria voor de DSM-III-R diagnose ADHD; (5) duidelijke negatieve invloed van ADHD symptomen op de

ontwikkeling en reeds toegepaste behandeling bood onvoldoende soulaas; (6) geen eerder gebruik van clonidine, methylfenidaat, of (het laatste half jaar) psychoactieve stoffen; (7) geen medische contraïndicaties; (8) geen belangrijke veranderingen in leefsituatie of overige behandeling.

In hoofdstuk 4 worden de resultaten van de diagnostische beoordeling van de patiënten besproken. In totaal hebben 109 kinderen deelgenomen aan de trial (93 jongens en 16 meisjes). De meeste kinderen waren verwezen door de schoolarts, de huisarts, een kinder- en jeugdpsychiater of een RIAGG jeugdteam. Van de kinderen bezocht 59% een school voor speciaal onderwijs en was er in alle gevallen eerder sprake geweest van hulpverlening voor gedragsproblemen. Op grond van hun DSM-III-R classificatie werden de kinderen ingedeeld in drie trialgroepen: (1) ADHD + PDD (n=5); (2) ADHD + TD en geen PDD (n=32); en (3) ADHD en geen PDD of TD (n=72). De ouders zowel als de leerkracht werd gevraagd om behandeldoelen te formuleren in termen van concreet waarneembaar gedrag. Voor 98% van de patiënten lagen deze doelen op het hyperactiviteitsvlak en voor 69% van de kinderen lagen deze op het vlak van oppositioneel-opstandig gedrag. Er vond een controle plaats op de DSM-III-R classificatie door middel van een onafhankelijke beoordeling door drie kinderpsychiaters. Bij 39% van de kinderen was er naast ADHD tevens sprake van een Gedragsstoornis of van Oppositioneel-opstandig gedrag en bij 6% was er naast ADHD tevens sprake van een emotionele stoornis. Op grond van het ontwikkelingsneurologisch onderzoek werd 34% van de kinderen geclassificeerd als Minor Neurological Dysfunction en bleek 2% neurologisch afwijkend. Afgaande op de gedragsvragenlijstscores kon eenderde van de kinderen worden gekenschetst als pervasief hyperactief (d.w.z. zowel thuis als op school hyperactief). Op grond van de PMA test was er bij 31% van de kinderen sprake van een specifieke leerstoornis. De kinderen werden ingedeeld naar de mate waarin hun hyperactiviteit pervasief was op grond van ouder/leerkracht scores en observatiescores tijdens testafname. De resultaten op de PPCT werden vervolgens vergeleken met die van een controlegroep. Vergeleken bij normale controlepersonen bleken pervasief hyperactieve kinderen een meer variabele regeltijd te hebben op de PPCT. Deze variabiliteit bleek bovendien vrij sterk gecorreleerd met het gedrag van het kind tijdens testafname. Voorts bleek dat de taakprestatie verminderde naarmate de test langer duurde. Dit effect trad echter niet specifiek bij de ADHD kinderen op.

In hoofdstuk 5 staan de resultaten van de trial vermeld. Op één na hebben alle kinderen de behandeling afgemaakt. De statistische analyses van de resultaten vonden plaats volgens het principe "intention to treat". De kinderen zijn ieder 8 weken behandeld met medicatie. Voor ieder kind werd beoordeeld of er naar de mening van de ouder en/of de leerkracht sprake was van een (nader gedefinieerde) "klinisch zinvolle verbetering". Dit bleek in de trial groepen 1 en 2 bij de met clonidine behandelde kinderen niet vaker het geval dan bij de met placebo behandelde kinderen. In trial groep 3 bleek het percentage kinderen dat tijdens behandeling met clonidine "klinisch zinvol" verbeterde even groot

als het percentage dat op methylfenidaat verbeterde (beide 50%), terwijl dit percentage significant hoger was dan het percentage op placebo verbeterende kinderen (13%). Op grond van een statistische analyse van de gedragsvragenlijstscores tijdens de behandeling werden soortgelijke resultaten verkregen. Kleine nuanceringen konden worden aangebracht: (1) in de trial groep 2 bleek er een effect te zijn van clonidine vergeleken bij placebo ten aanzien van hyperactiviteit in de schoolsituatie; en (2) methylfenidaat bleek effect te hebben op de door ouders en leerkracht geformuleerde gedragsdoelen. Voor clonidine bleek dat niet het geval. Na zeven weken behandeling werden hoge percentages bijwerkingen gevonden: 52% in de met clonidine behandelde groep, 37% in de placebogroep, en 58% in de met methylfenidaat behandelde groep. In de met methylfenidaat behandelde groep lag het percentage hinderlijke bijwerkingen duidelijk hoger dan in de clonidine en placebo groep (resp. 21%, 5% en 7%). Er werden geen kindkenmerken gevonden met een voorspellende betekenis ten aanzien van een gunstige medicatierespons.

In hoofdstuk 6 wordt eerst een literatuuroverzicht gegeven van biochemisch onderzoek bij hyperkinetische kinderen. Op grond daarvan wordt vervolgens geformuleerd waarom in dit onderzoek metingen zijn meegenomen van MHPG in plasma en 24-uurs urine. De verschillen met normale controlepersonen zijn onderzocht en er is gekeken naar de differentiële effecten van clonidine en methylfenidaat op MHPG. Alleen de kinderen uit trial groep 3 zijn op MHPG onderzocht. Deze groep kinderen bleek significant lagere MHPG waarden te hebben in zowel plasma als 24-uurs urine vergeleken met de controlegroep. Vervolgens bleek dat zowel de met clonidine als de met methylfenidaat behandelde groep gedurende de behandeling een significante daling te zien gaf in plasma MHPG, vergeleken met de verandering in de placebogroep.

Hoofdstuk 7 sluit het proefschrift af met een discussie van de onderzoeksresultaten. Het onderzoek heeft aangetoond dat clonidine werkzaam is op hyperactiviteit bij ADHD kinderen zonder PDD en zonder TD en dat deze werkzaamheid nauwelijks onderdoet voor die van methylfenidaat. Dit betekent dat clonidine aan het medicamenteuze behandelarsenaal kan worden toegevoegd als een alternatief voor stimulantia. Of men een hyperkinetisch kind in eerste instantie met methylfenidaat dan wel met clonidine wil behandelen, dient men af te laten hangen van het bij het kind meest gewenste profiel van effecten en bijwerkingen. Noch voor ADHD kinderen met TD noch voor ADHD kinderen met PDD heeft het onderzoek de werkzaamheid van clonidine aangetoond. Er is echter reden om de werkzaamheid van clonidine bij deze kinderen vooralsnog niet uit te sluiten. Daarom wordt geadviseerd vervolgonderzoek te doen, gericht op de werkzaamheid van clonidine op hyperactiviteit bij hyperkinetische PDD en TD kinderen, en onderzoek gericht op de lange termijn effecten van clonidine op het gedrag en op biochemische parameters bij hyperkinetische kinderen.

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Even belangrijk als de samenwerking met de ouders en de scholen was het contact met de mede-behandelaars op de Boddaertcentra en de Praktisch Pedagogische Thuishulp. Zij hebben menig (ex)-trial-kind in behandeling gehad. Deze vorm van hulpverlening is een bijzonder belangrijke en naar mijn mening ook effectieve bij hyperkinetische kinderen. Dankbaar denk ik aan de kundige en betrokken inzet van ondermeer Rob van Everdingen, Marja Hodes en Martijn Akkermans.

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Het hyperkinesieproject werd levensvatbaar door potentiële trial-patiëntjes zo spoedig mogelijk na verwijzing te zien, door een kwalitatief zo goed mogelijke zorg te leveren en door in afspraken en het afwerken van procedures volstrekt betrouwbaar te zijn. Om dit laatste al in de opzet van het onderzoek in te bouwen, is de bijdrage van Karin Brouwer de Koning-Breuker (medisch-ethische commissie AZR) en van Bharat Tewarie (medische dienst Boehringer Ingelheim B.V.) heel belangrijk geweest. Ook de samenwerking met Hayo Graatsma (apotheker AZR) en Paul Mulder wil ik op dit punt noemen. Enkele personen hebben de centrale "clan" gevormd met wie de betrouwbaarheid gestalte kon

worden gegeven. Irma Huijbrechts is de volle duur van het project als student-assistente bij het onderzoek betrokken geweest. Zij wist uitstekend met de kinderen om te gaan, heeft de psychologische tests en spelkamerobservaties ook onder moeilijke omstandigheden zo goed mogelijk volgens protocol uitgevoerd, was zeer accuraat met haar data en stond klaar ook op momenten dat het tempo dat ik aan het onderzoek gaf, kwam te lijken op "slavendrijverij". Ook Annemarie Illsley-de Jonge en Inge Putter-Demmendaal maakten deel uit van de clan, die het onderzoek deed draaien. Annemarie doordat zij naar aanleiding van telefoontjes van ouders feilloos taxeerde wanneer ik moest worden gewaarschuwd en me dan ook belde. Inge doordat zij steeds binnen de week mijn op diskette aangeleverde "weekend-stapel" huisartsenbrieven eruit wist te werken, waardoor de zo noodzakelijke communicatie met verwijzers en medebehandelaars goed liep. Veel zorg voor de trial-kinderen heeft op de eigen polikliniek plaatsgevonden. Om aan ons aantal te komen, hebben we op ons neuropsychiatrisch spreekuur ongeveer vier keer zoveel nieuwe patiëntjes moeten zien als nodig waren voor de trial. In de diagnostiek en behandeling hebben Marijke Uleman en Willeke de Haan als psychologen een belangrijke rol gespeeld, en de behandelingen waren nooit mogelijk geweest zonder de deskundige bijdrage van de maatschappelijk werkenden Margo Rigterink, Dien de Jong-van Hof en Ariane Wolfensberger-Reesink. Dank ook aan de arts-assistenten, die in de loop der jaren meewerkten in het neuropsychiatrisch spreekuur en in het begin van het onderzoek ouderinterviews deden. Aad Moerman ben ik tenslotte zeer dankbaar dat hij de vele video-opnames heeft willen maken.

Mary Schoon-Aston dank ik voor de vele uren in korte tijd, die zij heeft gestoken in het zorgvuldig verbeteren van haar moedertaal (al deed ik die geweld aan door te kiezen voor Amerikaanse termen en spelling). Ook dank aan To Molenaar-Oosterbaan en Cor Hagoort, die de summary reviseerden, en aan Marianne Haages, op wie ik op mijn eerste werkdag in Amsterdam om kwart voor acht 's ochtends al een beroep mocht doen om van het proefschrift nette prints voor de promotoren te maken. Dank gaat tenslotte uit aan Gerben van der Meulen, die bereid was de lay-out te verzorgen.

Diegenen, die parallel aan dit promotie-onderzoek mij vormden binnen de psychoanalytische opleiding wil ik nadrukkelijk bedanken. Ik heb ervaren, dat een meer biologisch georiënteerde benadering binnen de kinder- en jeugdpsychiatrie heel goed kan samengaan met een psychoanalytische.

Tenslotte wil ik mijn vrouw Fleur bedanken. Het is niet eenvoudig om een echtgenoot te hebben, die steeds weer besluit om zoveel tijd aan "de kliniek" te besteden. De zeker in de trial-periode onredelijk grote druk, die dit thuis veroorzaakte, heb jij op bewonderenswaardige wijze weten op te vangen. Hoewel de druk van de kliniek zal blijven, hebben jij en onze dochters er recht op mij wat vaker thuis (beschikbaar) te hebben. Het afgelopen jaar maakten Myrna, Eline en Saskia hun pappa soms alleen aan het ontbijt mee en wilden zij de namen "Jannie" en "Frank" niet meer horen.

Curriculum vitae

De schrijver van dit proefschrift werd op 20 april 1953 te Oegstgeest geboren. Hij bezocht het Marnix College te Ede en het Stedelijk Gymnasium te Nijmegen, alwaar hij in 1972 het eindexamen gymnasium bèta behaalde. Hij was een jaar adelborst voor de zeedienst aan het Koninklijk Instituut voor de Marine te Den Helder. Hij studeerde geneeskunde aan de Rijksuniversiteit te Leiden en deed artsexamen in januari 1980 (cum laude). Tijdens zijn studie was hij student-assistent bij de vakgroep Psychiatrie (begeleider: Prof.Dr.R.E.Abraham) en begeleidde hij een gespreksgroep diabetespatiënten onder supervisie van Prof.Dr.J.J.Groen.

Van begin 1980 tot begin 1985 specialiseerde hij zich tot zenuwarts. Tot begin 1983 werd hij opgeleid tot neuroloog in de Kliniek voor Neurologie van het Academisch Ziekenhuis Utrecht (opleider: Prof.Dr.A.Kemp, in 1980 opgevolgd door Dr.J.J.Jansen). Hij doorliep ondermeer een stage kinderneurologie (hoofd: Prof.Dr.J.Willemse) en was een jaar gedetacheerd op de afdeling Neurologie van het St.Antonius Ziekenhuis te Utrecht (opleider destijds: Jhr.Dr.A.E.M. van der Does de Willebois). Vanaf begin 1983 werd hij opgeleid tot psychiater in de Kliniek voor Psychiatrie van het Academisch Ziekenhuis Utrecht (opleider: T.Franswa, in 1985 opgevolgd door Prof.Dr.M.Kuilman).

Van maart 1985 tot juli 1986 was hij als zenuwarts-jeugdpsychiater verbonden aan het Orthopedagogisch Behandelingscentrum voor Moeilijk Lerende Jongeren Groot Emaus te Ermelo (vanaf juli 1985 parttime). Van juli 1985 tot juli 1986 volgde hij de opleiding tot kinder- en jeugdpsychiater in de Kliniek voor Kinder- en Jeugdpsychiatrie van het Academisch Ziekenhuis Utrecht (opleider: Prof.Dr.H.van Engeland).

Van juli 1986 tot september 1991 was hij staflid op de afdeling Kinder- en Jeugdpsychiatrie van het Academisch Ziekenhuis Rotterdam/Sophia Kinderziekenhuis te Rotterdam (hoofd: Prof. Dr.J.A.R.Sanders-Woudstra, in april 1987 opgevolgd door Prof.Dr.F.C.Verhulst). Op de polikliniek van deze afdeling vond het promotieonderzoek plaats (januari 1989 tot januari 1991). Van 1987 tot 1991 was hij tevens voor enkele uren per week als consulent werkzaam bij de Afdeling Sociaal Psychiatrische Werkeenheid van de Stichting Reclassering Arrondissement Rotterdam.

In september 1991 werd hij staflid bij de afdeling Kinder- en Jeugdpsychiatrie van het Academisch Ziekenhuis bij de Universiteit van Amsterdam (hoofd ad interim: Prof.Dr.J.A.R. Sanders-Woudstra). Op 1 januari 1992 volgde hij Professor Sanders-Woudstra op als afdelingshoofd ad interim.

Hij is opleidingscandidaat van de Nederlandse Vereniging voor Psychoanalyse, gewoon lid van de Vereniging voor Gedragstherapie en de Vereniging voor Kinder- en Jeugdpsychotherapie. Hij is lid van de NWO deelwerkgemeenschap Gedrag en Farmaca en maakt deel uit van de GHIGV kerngroep Biologische Psychiatrie. Tenslotte is hij lid van de adviesraad van de Stichting Gilles de la Tourette.

Stellingen

(1) Bij de behandeling van hyperkinetische kinderen blijkt de werkzaamheid van clonidine na zeven weken behandeling significant groter dan die van placebo en vrijwel even groot als die van methylfenidaat.
(dit proefschrift)

(2) Het percentage kinderen, dat na zeven weken behandeling last heeft van hinderlijke bijwerkingen, ligt hoger bij behandeling met methylfenidaat dan bij behandeling met clonidine.
(dit proefschrift)

(3) Oppositioneel gedrag wordt door ouders dan wel leerkracht genoemd als één van de hoofdproblemen bij ruim tweederde van de hyperkinetische kinderen. Zowel clonidine als methylfenidaat geven, in vergelijking met placebo, een verbetering van oppositioneel gedrag te zien bij hyperkinetische kinderen.
(dit proefschrift)

(4) Het feit dat bij hyperkinetische kinderen een vrij sterke samenhang wordt gevonden tussen de taakprestatie op de Bourdon-Wiersma aandachtstest en het gedrag van het kind tijdens testafname, wijst erop dat deze papier-en-potlood-taak een zekere mate van ecologische validiteit bezit.
(dit proefschrift)

(5) Door middel van een gedragsmaat, die gescoord wordt naar aanleiding van gestandaardiseerd spelkameronderzoek, kan men in een randomized clinical trial medicatie-effecten vaststellen bij hyperkinetische kinderen.
(dit proefschrift)

(6) Clonidine geeft bij hyperkinetische kinderen na zeven weken behandeling nog steeds een remming van het noradrenerge systeem. Dit lijkt er op te wijzen, dat er na zeven weken nog geen sprake is van de compensatie-mechanismen zoals die bij langdurige behandeling met clonidine wel zijn waargenomen.
(dit proefschrift)

(7) Een betere integratie in de kinder- en jeugdpsychiatrie van biologische kennis en vaardigheden, zal leiden tot een oordeelkundiger gebruik van medicatie.

(8) Het consulteren van de kinderarts/-neuroloog bij hyperkinetische kinderen ontslaat de kinderpsychiater niet van de plicht om het kind ook zelf somatisch te onderzoeken zodat hij/zij in de loop van een medicamenteuze behandeling niet voor verrassingen komt te staan bij de evaluatie van effecten en bijwerkingen.

(9) Het is een misvatting, dat een somatisch onderzoek door de kinderpsychiater de vertrouwensrelatie met het kind schaadt.

(10) Een met de ouders overeengekomen informed consent garandeert niet dat het kind zelf voldoende zorgvuldig door ouders en onderzoeker in de informed consent wordt betrokken.
(R.J.Levine, Respect for children as research subjects. In M.Lewis, Child and adolescent psychiatry: A comprehensive textbook. pp. 1229-1238. Baltimore: Williams & Wilkins, 1991)

(11) Ouders, die bij hun kind een samenhang vermoeden tussen het gebruik van voedseladditieven en probleemgedrag, zijn gebaat bij een samenwerking van kinderarts, diëtiste en kinderpsychiater teneinde misbruik van diëten te voorkomen.

(12) Zolang er geen gunstige effecten van langdurig gebruik van medicatie bij hyperkinetische kinderen zijn vastgesteld, dient men langdurig gebruik te vermijden of dient een dergelijke behandeling in overleg met collega's plaats te vinden.

(13) Juist omdat de opleiding zo breed van opzet is, dienen wij, kinder- en jeugdpsychiaters, te waken voor oppervlakkigheid.

Stellingen behorend bij het proefschrift "A controlled trial of clonidine in hyperkinetic children" van W.B.Gunning, Rotterdam, 11 maart 1992.