

Ritalin and Attention Deficit Disorder: History of its Use, Effects and Side Effects.

By Susan McCrossin, 1995.

**Learning Enhancement Center, 3704 N 26th Street, Boulder CO 80304.
Phone (303) 449 1969, Fax (303) 449 0747**

Ritalin and Attention Deficit Disorder.

Introduction

Attention deficit disorder (ADD) is a behavioral disorder in children who display in common characteristics of developmentally inappropriate levels of inattention, impulsiveness and in some cases hyperactivity (Barkley et al., 1991; Wolraich et al., 1990). ADD has been further defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R) to indicate the presence of hyperactivity. The abbreviation ADD+H indicates ADD children with hyperactivity while the abbreviation ADD-H indicates those without hyperactivity. Emotionally, children with ADD often have low self-esteem or self-confidence and frequent low mood states. Socially, they often have peer problems with many described as loners or having no friends (Hechtman, 1985).

Since an American psychiatrist Charles Bradley (1937, 1950) and his associates (Bradley & Green, 1940) first reported improvement in behavioral disordered children treated with CNS stimulant drugs, these drugs have been frequently administered in America to ADD children with and without hyperactivity symptoms, while they are rarely used in the UK (Barkley et al., 1978; Murray, 1987). While ADD's etiology is still unclear, the most frequently prescribed of these drugs in recent years is methylphenidate (Ritalin®) which is an amphetamine derivative. Ritalin, or generic methylphenidate, is more commonly used because it is thought to be less likely than other amphetamines to cause euphoria or psychosis (Garfinkel et al., 1975). While Ritalin's action is not well understood, it is assumed to affect the brain's reticular system, the sensory nuclei in the thalamus and multiple neurotransmitters (Murray, 1987).

ADD was originally thought to be a short-term syndrome that discontinues at puberty and so drug therapy was initially accepted as a short-term therapy. However, evidence has shown that ADD problems persist into adolescence and adulthood (Krager & Safer, 1974; Murray, 1987; Safer & Krager, 1985; 1988).

Prevalence of Treatment

Safer and Krager (1988) who analyzed the results of nine biannual surveys of Baltimore County's public and private schools for 1971 to 1987 have reported the prevalence of medication treatment for hyperactivity/inattentiveness. Their findings indicated a consistent doubling of the rate of medication every 4 to 7 years. By 1987 the use of medication had risen from 1.07 to 5.96% of all public elementary school students, that is between one and two students per class. Methylphenidate increased from 40 to 93% of the medication prescribed indicating that while it had been a minor treatment approach in the 1960s, it had become a 'dominant child mental health intervention' in the US by the late 1980s. They also reported that medication treatment rates consistently peaked in the third grade and dropped throughout the primary school years. However, by the late 1980s and early 1990s, there were increasing rates of stimulant drug treatment in secondary school students. This increased stimulant use in

secondary students was based on evidence that stimulants were as useful for teenagers as for their primary school counterparts in increasing attentiveness and subduing impulsive behaviors (Varley, 1983).

Early research

The original research conducted by Bradley through the 1930s to 1950s used Benzedrine (an earlier amphetamine derivative) on children with behavioral disorders severe enough to have warranted hospitalization at the Emma Pendleton Bradley Home, a children's psychiatric hospital. Many of these children were long term residents and the hospital provided educational and sporting facilities as well as psychiatric treatment. His first study, in 1937, consisted of 30 children who were patients at the hospital. Twenty of these had been examined with EEG measurements and definite brain rhythm abnormalities were found in 11 of them, 8 of which showed symptoms of 'petit mal' epilepsy and one was schizophrenic. The other children varied considerably and included specific educational disabilities with secondarily disturbed school behavior. The intelligence of all the children was considered to be in the normal range. Dosage was given orally and commenced at 10 mg gradually increasing until a 'change in behavior was noticed'. The average dose was 20 mg with a few requiring 30 mg and some remained on 10 mg as increases from that level resulted in gastro-intestinal distress sufficient to disturb all of the child's reactions. On the basis of subjective observations by nurses and teachers it was reported that the responses of the subjects ranged from a decrease in motor function and being emotionally subdued to increased activity including agitation and over-stimulation, while others became worried and fearful. Physiological observations included increased blood pressure, mild sleep disturbances, loss of appetite, nausea, malaise and epigastric distress. Bradley concluded that half the group showed a striking response at school and favorable mood changes. The school improvement was, however, limited to changes in arithmetic performances only as measured by teachers' observations. No performance tests were conducted.

In a later study (Bradley & Green, 1940) used a battery of psychomotor tasks such as finger tapping, reaction time to a visual stimuli and the Revised Stanford-Binet Intelligence Test on their subjects to assess if stimulant therapy had an effect on any of these measures. This study comprised of 21 children from the same psychiatric hospital and they were divided into two groups. Group 1 were those who showed definite school improvement and group 2 were those who showed little or no school improvement. Individual children showed consistent results on all of the psychomotor and intelligence tests, before and after stimulant therapy, indicating no significant change. Bradley and Green concluded that administration of stimulant therapy may cause an apparent intellectual improvement in some situations by its positive effect on the emotional attitude toward the task.

Also in 1940, Bradley and Bowen investigated the suggestion that intellectual performance was accelerated indirectly by stimulant therapy due to the effect of the drug on the emotional state of the subject. They conducted a retrospective study looking at behavior, arithmetic progress and spelling progress. Behavior was measured by subjective observation by the teacher. Arithmetic progress was measured in terms of the number of pages in a standard elementary textbook thoroughly learned each month and spelling progress was measured in terms of the number of 'lists' of five words in a standard text thoroughly learned each month. The results indicated that although all of the subjects were assessed as improving in attitude and behavior during school, and the majority improved in their arithmetic progress, less than half of the subjects completed more spelling while on the drug. Individual performance in all areas varied considerably. However, 58% of the children showed *decreased* performance in one or other subject while taking the drug in spite of their improved attitude toward schoolwork.

Bradley and Bowen (1940) were unable to find any correlations between improvement in one or both school subjects with IQ, dosage, grade placement, the interval time between the control and medicated period and the predominant clinical diagnosis. While they acknowledged that they were using a group of severely maladjusted children, many of whom had missed a great deal of school, they could not explain why some children appeared to improve dramatically while others did not, or in some cases even regressed. Their suggestion was that spelling, which requires visual imagery and memory, may not be as hampered by wandering attention as arithmetic, a more cumulative subject. Since the drug only enables children to be more attentive it does not address other issues necessary to improve spelling.

A later study by Bradley in 1950 investigated change in children medicated with Benzedrine or Dexedrine (a dextro-rotatory isomer of Benzedrine considered to be more potent) and this time the subjects were grouped according to their psychiatric problems. While he acknowledged that he was hampered by a lack of generally accepted classification criteria for children's psychiatric disorders, he did group them according to four criteria: psychogenic disorders, epileptic or convulsive disorders, psychopathic personality and schizoid personality. The behavioral responses that were observed for both drugs were that 50-60% of children became more subdued, 15-25% showed no change at all, 20% increased in their activity levels and 5% showed an acceleration in school progress only, as assessed by observation, no quantitative tests were conducted. As a clinical response these reactions indicated 60-75% showed symptomatic improvement, 15-25% showed no change and 10-15% showed unfavorable responses. Children of all types of clinical diagnoses were seen to have benefited, with those diagnosed as psychopathic personalities showing the largest percentage improvement at 84% of a group of 25 subjects. Bradley concluded that the drugs influenced children's behavior by altering their emotional reactions to distressing situations.

By 1950, Bradley had had 12 years clinical experience using Benzedrine and Dexedrine on 350 individual psychiatrically maladjusted children. His results consistently indicated that when medicated with either stimulant the most dramatic observable effect in children was 'subdued' behavior. That included walking instead of running, speaking in normal or lowered tones of voice, avoiding the expression of differences of opinion and spending their leisure time quietly playing or reading instead of annoying others. The most commonly reported side effects were appetite suppression, insomnia, elevated blood pressure, pallid face, peripheral vasoconstriction and fine tremors of the extremities.

Recent Research

Analysis of more recent studies is made difficult by the fact that experimental designs vary in many respects (Barkley & Cunningham, 1978; Barkley et al., 1991; Hechtman, 1985; McBride, 1988; Murray, 1987). Firstly, subjects have often been selected on differing criteria, for example, attentional deficits, delinquent behavior, learning disorders without associated behavioral problems or neurological conditions such as epilepsy, psychiatric disorders such as schizophrenia or psychopathic personality and some were currently taking single or multiple doses of other medications. The age of subjects varies from pre-school through adolescence to adult, although school age children made up the largest group. Intelligence varied from below normal to normal and often was not described (Hechtman, 1985; Wolraich et al., 1990).

Dosage, when stated, also varies widely from a per kilogram per day dose of 0.3 mg to 1 mg (Ahmann et al., 1993; Barkley et al., 1990; McBride, 1988) or a per day dose of 5 to 50 mg with body weight not mentioned (Barkley et al., 1991; Bradley, 1937, 1950; Bradley & Green,

1940; Rapport et al., 1982). Since the age of subjects used in the drug trials varies typically from 5 to 19 years, a 30 mg dose for a 5 year old represents a significantly different dose on a per kilogram basis than the same 30 mg dose to a 19 year old. Research has indicated that Ritalin has a dose-related efficiency (Rapport et al., 1985) and therefore, the lack of standard dose presentation may confound comparison of results between studies. Dosage is usually slowly increased until an 'effect' is noticed. Rapport et al., however, express concern that since this 'effect' is judged by parents and teachers who are more likely to base their judgements on children's social behavior, the 'effect' noticed may not reflect improvement in learning and impulsivity.

A number of research studies express concern at the level of controls and experimental designs used in many of the studies. Rapport et al. (1982) note that many studies have small numbers of subjects which is insufficient to provide statistical significance. Barkley and Cunningham (1979) state that studies should be using placebo controlled, double blind, randomized, cross-over design and very few have done so. In fact placebo controls and double blind design has only become customary since the 1970s. Non compliance and medication discontinuance by children and especially adolescents was not considered in many studies (Charles et al., 1981; Hechtman, 1985; Murray, 1987; Weiss et al., 1975). In only a small minority of studies was compliance or the method of compliance mentioned, which is highly significant since effects can only be related to the drug if the subjects are actually taking it. For instance, Satterfield et al.'s (1981) study used pill counts at the end of each week and a urine test for ritalinic acid to confirm that subjects had complied with the drug regime. Without the assurance of compliance the results of many of the other studies may well contain biases not considered in the interpretation of the results.

A further problem that relates both to compliance and parent reporting is that some parents have expressed an overt resistance to the drug therapy in the first place, which may present a problem when interpreting negative results (Murray, 1987; Sleator, 1985). Safer & Krager, 1992, suggest that sensational media coverage of Ritalin use and its side effects had led to parent's concern with regard to its use and safety and potential lack of compliance.

According to Barkley and Cunningham (1979), a major problem in many of the research designs, was the consistent use of subjective opinions of teachers and parents on achievement performance, as opposed to more objective measures. This may have led to bias in reporting of the results because of the assumption by parents and teachers that behavioral improvements indicate academic gains. Their concern was that the perceived improvement in behavior may lead teachers to overlook real academic disabilities that lie underneath the overt behavioral problems with these children. The latter contention is supported by studies reviewed by Safer and Krager (1988) that show the vast majority of studies using stimulant treatment by itself does not result in maintained or long term achievement gains, even though such drugs improve attention and the amount of school work completed by affected students.

Reid and Borkowski (1984) conducted a repeated measures placebo controlled study on 12 children aged from 8 to 13 years of age. Using battery of efficiency tasks they found that while stimulant medication generally improved attention to task behavior by decreasing their activity level, it did not necessarily increase their task scores. They state that using objective measures of academic performance reveal few positive short term or long term effects. In a review of 17 studies that analyzed academic performance by using combinations of measures of arithmetic, spelling, reading and vocabulary, they found that only two studies showed significant positive change in arithmetic, another two showed significant change in spelling and reading, one showed word analysis improvement, and one showed vocabulary improvement, while 11

found no significant drug effect. Barkley and Cunningham reported that only 5 of the studies used placebo controlled, randomized, crossover designs. Of these, three of the studies showed no effect, one showed an increase in word analysis and one showed an increase in vocabulary. The observers of the two studies that showed improvement (Rie, Rie, Stewart & Ambuel, 1976), however, attributed these inconsistent findings to improved attention during the test procedure rather than improved achievement skills and concluded that stimulant therapy appeared to have no substantial impact on the academic performance of any of the children.

While much of the research has revealed inconsistent results, the principal effect of stimulant medication in many of the studies indicates that between 50 to 75% of subjects experience a reduction in activity level, distractibility and impulsive behavior. This results in improved attention to task behavior (Bradley, 1949, 1950; Barkley & Cunningham, 1979; Barkley et al., 1991; Rapport et al., 1972; Reid & Borkowski, 1984) thus improving classroom and home manageability by rendering the subjects more subdued and less disruptive.

Adolescent Outcome

To assess if stimulant treatment in childhood affects adolescent outcome, Hechtman (1985) reviewed nine follow-up and outcome studies. Only studies that clearly used stimulant therapy as their primary treatment for hyperactivity in childhood, and in which the subject's age at follow-up was adolescence (13-19 years of age) were included. An analysis of the study methods revealed that the availability of treatments other than stimulants varied widely, from no other treatment to elaborate multimodal intervention in two studies (Feldman et al., 1979; Satterfield et al., 1981). Usually other interventions were not mentioned, and when they were, frequency and duration of the intervention methods were not specified. Most studies had a 4-5 year follow-up time and evaluation varied from official police records to interviews with the child and/or the family, sometimes teacher and parent rating scales and occasionally educational assessments. The conclusions suggest that while the ADD+H symptoms decrease in some (this is thought to occur in some due to maturation effect) the symptoms are still present in many. Despite early stimulant therapy, antisocial behavior still exists in 20-30% of subjects, which is the same rate as subjects who do not receive stimulant therapy, and there was continuing low self-esteem and poor peer relationships. Academically, hyperactive adolescents are approximately two grade levels behind their peers in core subjects such as reading and mathematics. Hechtman concluded that early stimulant therapy does not appear to result in positive adolescent outcomes.

The two studies that combined stimulant therapy with several other types of intervention suggested a more positive outcome with fewer subjects still requiring academic help in adolescence. In this study (Satterfield et al., 1981) combined stimulants with several other types of interventions such as individual and group psychotherapy, educational therapy and family therapy for both subjects and parents. The subjects (100 boys) were arbitrarily divided into two groups with differing lengths of the combined treatment, those that had been medicated with Ritalin for more than 2 years and those that medicated for less than 2 years. The group that received the longer treatment was more academically advanced, less antisocial in behavior, more attentive and better adjusted at home and at school than the group that received the shorter treatment. Because there was no control group in which the other modes of intervention were used without Ritalin, it is difficult to arrive at any conclusion about the effects of Ritalin versus the effects of the other modes of intervention.

Side Effects

Despite the large amount of published research on stimulant medication and children with ADD, Barkley et al., (1990) found they were unable to locate any studies that specifically and

systematically evaluated the behavioral and physiological side effects of stimulant medication. Most studies fail to mention side effects at all in their results and those that did mention side effects reported only anecdotal information about the more obvious side effects. In a previous review of 29 studies up until 1976 that anecdotally reported behavioral and physiological side effects of stimulant medication Barkley (1977) found that the most frequently mentioned side effects were insomnia (26 studies), decreased appetite (23 studies), irritability (13), weight loss (12), abdominal pains (11) and headaches (10).

In an attempt to systematically study the incidence of side effects, Barkley et al. (1990) used a triple blind, placebo controlled design on 85 ADD+H children (aged 5 to 13 years) undergoing methylphenidate therapy. Two therapeutic doses were used, 0.3 and 0.5 mg/kg twice a day. Side effects were rated by teachers and parents weekly, at the end of each drug condition. The results indicated that three children (3.6%) had side effects severe enough to warrant immediate discontinuation of treatment. In the remaining group parent ratings indicated the side effects of decreased appetite, insomnia, stomachaches and headaches increased significantly in frequency and severity when compared to the placebo while taking the two levels of medication. Although Barkley et al. report in their abstract that stimulant medication “results in few, generally mild side effects”, their results state that while only 15% of the 82 subjects experienced insomnia on the placebo, this increased to 52% and 56% in low- and high-dose conditions respectively, with 18% registered as severe for both doses. Appetite suppression was 40% for the placebo condition and increased to 62% and 68% in low- and high-dose conditions. Stomachaches increased from 18% in placebo conditions to 39% and 35% in low- and high-dose conditions, and headaches increased from 11% in placebo conditions to 26% and 21% in low- and high-dose conditions with only a small percent being severe for both doses.

Ahmann et al. (1993) conducted a placebo controlled evaluation of Ritalin side effects by parent reports using the Barkley Side Effects Questionnaire (BSEQ), an 18-item list of behaviors rated on a 10-point scale from 0 = absent to 9 = severe. The eligibility criteria for subjects to participate was also much more stringent than in most previous studies in that children in this study had to meet the DSM-III-R criteria for ADD+H as assessed by both their physician and neuropsychologist. The Hyperactivity Index (as measured by the Conners' Teachers' Rating Scale and Conners' Parent Rating Scale) had to be 2 or more standard deviations from the mean as well as showing no history of seizures, mental retardation, Tourette's syndrome or other significant neurological history. The number of subjects used was also considerably larger than most previous studies, consisting of 234 children. Their results indicated increases on 5 of the BSEQ items with Ritalin therapy. These were insomnia, decreased appetite, stomachache, headache and dizziness. Ahmann et al. state that decreased appetite occurred even at the relatively low dose of 0.3 mg/kg/dose and were nearly twice as likely to be experienced at the higher dose. Four BSEQ items decreased during the Ritalin therapy; these were daydreaming, irritability, anxiety and nailbiting. The authors suggest that because these items had high baseline levels, they are not side effects of Ritalin therapy, but rather, symptoms or behaviors related to ADD+H which may have benefited by stimulant therapy. The remaining 9 items did not vary, euphoria, sadness, crying, talking less, disinterest, drowsiness, nightmares, motor tics and vocal tics. Four children (1.7%) experienced severe side effects and had to be withdrawn from treatment.

In their clinical practice and from anecdotal reports of colleagues elsewhere, Ahmann et al., (1993) also observed that a difference in effectiveness may exist between Ritalin and generic methylphenidate. Generic methylphenidate appeared less consistent in its dose effectiveness than Ritalin because research has shown the absorption rates for the two chemical

formulations differ. Therefore, they suggest, that the two drugs may not be bioequivalent and this may need to be taken into account in future research and clinical practice.

Summary

Based on parent and teacher subjective reports, the results of earlier studies were interpreted as showing an improvement in mood and subdued overt negative behavior. When measured improvements in academic performance were limited to changes in arithmetic performance, over half of the subjects showed decreases in other types of academic performance. Comparisons of early studies, however, are difficult due to differences in experimental design, dosage rates, small numbers of subjects and lack of controls in most studies.

The most consistent results of Ritalin treatment in more recent, somewhat better controlled, studies showed that 50-75% of subjects experienced a reduction in activity levels, distractibility and impulsive behavior. This appeared to improve attention to task resulting in improved classroom and home manageability by rendering the subjects more subdued and less disruptive. Studies in which subjects were followed up later in adolescence indicated that there was some, but limited, long term effective drug treatment on academic performance and antisocial behavior. Multimodal intervention, when used in conjunction with drug treatment, produced the best long-term outcomes. However, there are only two studies using this approach and one was uncontrolled.

Most earlier studies fail to mention side effects at all in their results, and those that did, anecdotally mention insomnia, decreased appetite, irritability, weight loss, abdominal pains and headaches in decreasing order of reporting. More recent studies using more stringent criteria for ADD and analysis of side effects found insomnia, appetite suppression, stomachaches and headaches to be increased relative to placebos. Based on clinical experience and anecdotal observation authors of one study suggest a difference in the consistency of effect may exist between Ritalin and generic methylphenidate and that this may need to be considered in future studies.

References

- Ahmann, P A, Waltonen, S J, Olson, K A, Theye, F W, Van Erem, A J & LaPlant, R J (1993). Placebo-controlled evaluation of Ritalin side effects. *Pediatrics*, *91*, 6, 1101-1106.
- American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., revised. Washington, DC: American Psychiatric Association, 1987.
- Barkley, R A & Cunningham, C E (1979). Do stimulant drugs improve the academic performance of hyperkinetic children? *Clinical Paediatrics*, *17*, 1, 85-92.
- Barkley, R A, DuPaul, G J & McMurray, M B. (1991). Attention deficit disorder with and without hyperactivity: Clinical response to three dose levels of methylphenidate. *Pediatrics*, *87*, 519-531.
- Barkley, R A, McMurray, M B, Edelbrock, C S & Robbins, K (1990). Side effects of methylphenidate in children with attention deficit hyperactivity disorder: a systematic, placebo-controlled evaluation. *Pediatrics*, *86*, 2, 184-192.
- Bradley, C (1937). The behavior of children receiving benzedrine. *American Journal of Psychiatry*, *94*, 577-585.
- Bradley, C (1950). Benzedrine and dexedrine in the treatment of children's behavior disorders. *Pediatrics*, *5*, 24-37.
- Bradley, C & Bowen, M (1940). School performance of children receiving amphetamine (benzedrine) sulphate. *American Journal of Orthopsychiatry*, *X*, 782-788.
- Bradley, C & Green, E (1940). Psychometric performance of children receiving amphetamine (benzedrine sulphate). *American Journal of Psychiatry*, *97*, 388-394.
- Charles, L & Schain, R (1981). A four-year follow up study of the effects of methylphenidate on the behavior and academic achievement of hyperactive children. *Journal of Abnormal Child Psychology*, *9*, 495-505.
- Feldman, S, Denhoff, E & Denhoff J (1979). Attention disorders and related syndromes outcome in adolescence and young adult life in minimal brain dysfunction: A developmental approach. In: Denhoff, E & Stern, L (eds.), *Minimal brain dysfunction: A developmental approach*. New York: Masson Publishing Co. pp. 144-148.
- Funk, J B, Chessare, J B, Weaver, M T & Exley, A R (1993). Attention deficit hyperactivity disorder, creativity, and the effects of methylphenidate. *Pediatrics*, *91*, 4, 816-819.
- Garfinkel, B D, Webster, C D & Sloman, L (1975). Methylphenidate and caffeine in the treatment of children with minimal brain dysfunction. *American Journal of Psychiatry*, *21*, 237-242.
- Hechtman, L (1985). Adolescent outcome of hyperactive children treated with stimulants in childhood: a review. *Psychopharmacology Bulletin*, *21*, 2, 178-191.

- McBride, M (1988). An individual double-blind crossover trial for assessing methylphenidate response in children with attention deficit disorder. *Pediatric Pharmacology and Therapeutics*, *113*, 1, 137-145.
- Murray, J B (1987). Psychophysiological effects of methylphenidate (Ritalin). *Psychological Reports*, *61*, 315-336.
- Rappport, M D, Murphy, H A & Bailey, J S (1982). Ritalin vs. response cost in the control of hyperactive children: a within subject comparison. *Journal of Applied Behavior Analysis*, *15*, 205-216.
- Rappport, M D, Stoner, G, DuPaul, G J, Birmingham, B K & Tucker, S (1985). Methylphenidate in hyperactive children: differential effects of dose on academic learning, and social behavior. *Journal of Abnormal Child Psychology*, *13*, 227-243.
- Reid, M K & Borkowski, J G (1984). Effects of methylphenidate (Ritalin) on information processing in hyperactive children. *Journal of Abnormal Child Psychology*, *12*, 1, 169-186.
- Rie, H, Rie, S, Stewart, I H & Ambuel, J (1976). Effects of methylphenidate on underachieving children. *Journal of Consulting Clinical Psychology*, *44*, 250-263.
- Safer, D J & Krager, J M (1988). A survey of medication treatment for hyperactive/inattentive students. *JAMA*, *260*, 15, 2256-2258.
- Safer, D J & Krager, J M (1992). Effect of a media blitz and a threatened lawsuit on stimulant treatment. *JAMA*, *268*, 8, 1004-1007.
- Satterfield, J, Satterfield, B & Cantwell, D (1981). Three year multimodality treatment study of 100 hyperactive boys. *Journal of Pediatrics*, *98*, 650-655.
- Sleator, E K (1985). Measurement of compliance. *Psychopharmacology Bulletin*, *21*, 1089-1093.
- Varley, C K (1983). Effects of methylphenidate in adolescents with attention deficit disorder. *Journal of American Academic Child Psychiatry*, *22*, 351-354.
- Weiss, G, Kruger, E, Danielson, U & Elman, M (1975). Effect of long term treatment of hyperactive children with methylphenidate. *Canadian Medical Association Journal*, *112*, 159-165.
- Wolraich, M L, Lindgren, S, Stromquist, A, Milich, R, Davis, C & Watson, D (1990). Stimulant medication use by primary care physicians in the treatment of attention deficit hyperactivity disorder. *Pediatrics*, *86*, 1, 95-101.