

LONG-ACTING METHYLPHENIDATE FOR THE TREATMENT OF ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Introduction

Attention deficit hyperactivity disorder (ADHD) is widely recognised as one of the most common and heritable behavioural disorders in childhood, affecting around 3 to 5% of school age children (Smalley, 1997; Taylor et al., 1991). It is characterised by severe impairments of attention span, and/or marked hyperactive and impulsive behaviours that have serious consequences for social, academic and behavioural development of children and adolescents (American Psychiatric Association, 1994). Longitudinal studies indicate that one-third to two-thirds of children with ADHD go on to have significant behavioural and psychiatric problems in adult life (Barkley et al., 1990; Biederman et al., 1996; Gitelman et al., 1985; Mannuzza et al., 1991; Taylor et al., 1996; Weiss et al., 1985).

Although child and adolescent psychiatrists widely acknowledge the need to identify and treat ADHD, adult psychiatrists have been reluctant to follow suit. This is surprising given the considerable psychiatric morbidity associated with adult ADHD and the existence of effective treatments in the form of stimulant medications and psychological interventions. An increasing load on adult psychiatrists is likely to develop as adolescents become adults while still receiving treatment for ADHD and more adults recognise themselves as disabled by ADHD. Furthermore, Courts of Law increasingly wish to know whether adults with ADHD will benefit from treatment, preventing misdemeanours resulting from impulsive behaviour (e.g. shop-lift-

ing, verbal abuse, fighting) or inattentive behaviours (e.g. inadequate parenting, driving accidents).

Adults with ADHD are likely to present with relationship difficulties, academic failure and work instability that stem from persistent problems with concentration, disorganisation, forgetfulness, procrastination, impulsiveness and anger control (Wilens et al., 1995). Affective instability with hour-to-hour fluctuations in mood is also common (Weiss et al., 1985; Wender et al., 1997; Wender and Garfinkel, 1989). These symptoms overlap with those of personality disorder, anxiety and affective disorders that can lead to difficulties in diagnosis and treatment. For example, individuals diagnosed in adulthood with borderline or anti-social personality disorder are more likely to have had a history of childhood ADHD (Biederman, 1998; Fossati et al., 2002). What is less well established is whether ADHD symptoms in these cases respond to stimulant medication. Another problem is the unsuccessful treatment of disorders with overlapping symptom profiles, such as anxiety, depression and hypomania, in adult ADHD patients who respond well to stimulants.

Nevertheless, where symptoms overlap between ADHD and other disorders it is usually possible to make the distinction. ADHD differs from adolescent or adult onset disorders since symptoms causing clinical impairment start early in life (before the age of 7 years), persist over time and do not tend to fluctuate. In this respect they may be considered to be more trait-like than symptoms that are a change from a pre-morbid state. There

may of course be difficulties in obtaining accurate accounts of childhood behaviours in adult patients, although parents or older relatives can often provide such information. Certainly, many individuals with adult ADHD will not have received the diagnosis as a child, often because the condition was less widely recognised when they were young.

Despite more than 200 controlled studies of stimulant efficacy in children (Biederman and Spender, 2002) treatment of adult ADHD remains controversial. Controlled randomised studies in adults using stimulants, such as methylphenidate have, however, shown comparable response rates, around 50% to 70% (Iaboni et al., 1996; Mattes et al., 1985; Spencer et al., 1995; Wender et al., 1981, 1985; Wilens et al., 1996; Wood et al., 1976), and stimulant medication is the main treatment used for ADHD in adults. For many adults with ADHD, it appears that remembering to take methylphenidate several times a day (some experts recommend every two to three hours) is problematic, thus reducing its usefulness in routine clinical practice. Poor compliance is perhaps not surprising given that the condition involves poor concentration and attention, and that adults with ADHD often do not have a caregiver to administer their medication. Successfully treated adults with ADHD experience less restlessness, improved concentration, less lability in mood, fewer extreme anger outbursts, greater organisational ability, and reduced stress sensitivity and impulsivity (Wender, 1997).

A recent advance in the treatment of children with ADHD has been the introduction of a once a day formulation of methylphenidate, which has been made possible by the development of an osmotic controlled-release system (Concerta® XL) (Modi et al., 2000). Thus far the use of this medication has only been documented in children where the once daily dose regime is clearly an advantage (Keating et al., 2001). Additional benefits have been reported due to the smoothing of dose fluctuations by

the controlled release system that provides an optimal dosage profile throughout the day (Modi et al., 2000). Here, we detail the improvement of two adults with ADHD treated with Concerta® XL. This report highlights some of the issues when making the diagnosis of ADHD in adults and why this formulation may be considered to be suitable for some adults.

Case Reports

Case 1

Mrs A is a 23 year old housewife who was referred by her GP for assessment of inattentive and disorganised behaviour. At the time of referral her ability to look after her children was in question and the Court of Law was seeking advice on whether treatment for ADHD would improve her ability to cope. She attended the first consultation accompanied by a social worker who explained that she often failed to remember appointments and probably would be unable to make her own way to the clinic. Her main complaints were of poor concentration and failing to complete tasks; she reported marked distractibility, difficulty following verbal instructions and forgetfulness, so that she frequently forgot where she put objects and what she was meant to be doing. While she was able to give a clear account of these symptoms, she played down their impact on her life. In contrast, accounts from both her social worker and mother were consistent in describing considerable difficulties relating mainly to marked inattentiveness. She had considerable problems prioritising and organising everyday tasks such as those required to look after the house and her children. She tended to put things off and often failed to complete tasks that she had started. Another problem was her inability to listen and follow instructions. She was de-

scribed as distractible, often losing the thread of conversations and appearing not to listen. Thus, these behaviours had several serious consequences. Her house was in chaos and unhygienic and she was unable to attend appropriately and consistently to the physical needs of her children. Psychological testing showed her verbal intelligence quotient (IQ) was 76, although performance, at IQ 105, was slightly above average. There was evidence of an impulsive style of responding. Other psychiatric disorders and neurological conditions that could explain her current behaviour were excluded.

Mrs A had been a destructive child who showed poor memory and appeared 'dreamy'. From a young age she appeared to be rather irritable, and had a volatile mood with angry or tearful outbursts. Her problems began in primary school due to lack of concentration and global learning difficulties. She was first diagnosed with attention deficit disorder at the age of 15 and treated with methylphenidate (Ritalin®) 5mg three times a day. Stimulant medication helped her concentration and there was a marked improvement in her mood swings. However, it was difficult to get consistent benefit from the medication because she did not always remember to take the medication. The other major problem was obtaining a regular prescription once she grew older, and this was stopped when she was no longer under the supervision of child psychiatrists. She left school at 16 and has only ever had a brief period of employment. Mrs A married at an early age and had three young children. Although her husband who is a cleaner had no special complaints, her disorganisation and inability to manage the home has since resulted in the children being taken into care because it was thought that she was unable to provide the level of care that they required.

Following assessment, the diagnosis of DSM-IV ADHD (American Psychiatric Association, 1994), inattentive subtype was confirmed. Diagnosis was made on descriptions of her early childhood behaviour, which were

consistent with the DSM-IV combined subtype of severe inattentive, overactive and impulsive behaviours at home and at school. These symptoms had persisted through most of her childhood and adolescence. At the time of the assessment there were no apparent symptoms of over-activity, although she showed an impulsive style when problem solving and had marked inattention. Improvement in hyperactive/impulsive but not inattentive symptoms is typical of the developmental progression of ADHD into adult life. Her previous good response to stimulant medication was also consistent with the diagnosis of ADHD and suggested that further treatment was likely to be beneficial.

Further treatment with stimulants was initiated but with a once daily formulation to minimise previous problems arising from non-compliance and to provide effective cover throughout the day, without the normal peaks and troughs in behavioural benefits sometimes seen with short acting preparations. Mrs A was started on methylphenidate (Concerta® XL) 36mg once daily. At the time of writing she had been taking this medication daily for the last six months. Four follow-up contacts with her and her husband have confirmed consistent improvement over this period. Her opinion is that her life is 'totally different'. She reports that she no longer forgets things and is now taking everyday tasks in her stride. Her husband confirms symptomatic and behavioural improvements. The family are in regular contact with their children and hopeful that they will be returning home later in the year. Unfortunately, Court procedures are very slow and they will have to wait for another four months for their case to be reviewed. The recommendation will be that she has responded well to medication and is now far more able to cope than previously. Importantly, she is now able to take in information and follow advice more easily, enabling her to respond to support from social workers and other support teams.

Case 2

Mr B was 46 years of age when first referred by a consultant psychiatrist to the ADHD clinic over a year ago. On presentation in the clinic, he was over-talkative, and constantly interrupted questions, fidgeted constantly with his hands and jiggled his legs up and down. He described crowded and uncontrolled thoughts, by which he meant a constant flow of thoughts and multiple different thoughts that crowded one on top of the other. He was easily distracted but was keen to demonstrate that he could focus when motivated, although he had difficulty sustaining attention for more mundane tasks. Mr B detailed problems arising from over-activity and inattention, which have persisted since early childhood and showed little variation over time. He admitted to brief periods of low mood in the past and to having a quick temper. Psychological testing found his IQ was in the high-average range and he adopted a slow and accurate style of response in tests, suggesting a strategy favouring accuracy over speed, which is consistent with an attention problem.

His mother confirmed the account that Mr B gave of his life. She described him as an exhausting child from about 2 years who was 'always on the go and into things' and had to be constantly reminded to focus on what he was doing. He went to a boarding school from the age of 7 years, although his inability to concentrate seriously hampered his academic progress. He frequently disrupted the class, played pranks and was difficult to control. He finally left school at 16 having been to 14 different schools. He has moved between many different jobs and several failed business adventures, and more recently was imprisoned for smuggling alcohol through customs. Mr B had used alcohol fairly heavily on a regular basis and cocaine occasionally, had separated from his wife due to financial problems, and had a son who had recently been diagnosed with ADHD.

Mr B's behaviour and mental state was consistent with a diagnosis of DSM-IV ADHD, combined subtype. Although he reported some affective symptoms these were trait-like, with a chronic low level of irritable and slightly volatile mood. There were some similarities between his thought processes and those seen in hypomania but these were more consistent with the diagnosis of ADHD. Unlike hypomania they were not speeded up, did not make unusual logical connections, were not grandiose, and he reported this as his usual state of mind for as long as he could recall. Treatment with stimulants was initiated with dexamfetamine (Dexdrine®). His response was poor, after the initial dose of 5 mg he felt out of control as if on 'speed', had sleep problems and lost his appetite.

Mr B was then given a trial of short acting methylphenidate at a low dose of 5 mg once daily, increasing to twice and occasionally three times daily. He tolerated this medication well and reported considerable subjective and objective improvements. The most striking change was his report that for the first time in his life he felt relaxed and calm, his thoughts were focused, and he no longer experienced ceaseless mental activity. He was able to sleep better at night. Objectively, his ex-wife and son both reported a marked change; he appeared more relaxed, less agitated and more able to sit and focus on one thing at a time. Despite these benefits, he reported considerable ups and downs throughout the day that appeared to be related to the short acting nature formulation of the medication, and he was having difficulties in managing this constant change in his mental state. Mr B was therefore started on once-daily methylphenidate (Concerta® XL) 18 mg. He has been far more stable with the controlled-release preparation that achieved the aim of stabilising the beneficial effects of methylphenidate. He has been stabilised on this regime for over one year and reports a consistent benefit over that period.

Discussion

The clinical history of these cases is compatible with childhood ADHD persisting into adulthood. For both individuals clear accounts were obtained of hyperactive, impulsive and inattentive behaviours that began in early childhood and persisted into adult life. The degree to which these symptoms affected their ability to cope with and manage their lives was considerable, with clear impact on the quality of life for them and their families. We concluded that their current behaviours and symptoms fulfilled DSM-IV criteria for ADHD; inattentive subtype in Case 1 and combined subtype in Case 2 (TABLE I).

Both subjects had difficulties obtaining appropriate diagnosis and treatment before referral to our specialist ADHD clinic. Hesitation in making the diagnosis is typical for many individuals subsequently diagnosed with adult ADHD. The lack of clinical expertise and service provision for this population

is widely recognised by child and adolescent psychiatrists who are aware that ADHD frequently persists into adulthood and is often seen in parents of children with ADHD (Faraone et al. 2000). Moreover, a major justification for use of pharmacotherapies in childhood ADHD is the observation that childhood ADHD predicts adult mental health problems (Biederman et al., 1996; Gitelman et al., 1985; Institute of Health, 1998; Mannuzza et al., 1991; Weiss et al., 1985; Wood et al., 1976). One of the difficulties involved in diagnosis stems from the high rate of co-morbid conditions in adults with ADHD (e.g. depressive and anxiety disorders, antisocial personality disorder, alcohol and drug abuse/dependence), which are themselves associated with symptoms such as inattention, restless agitation and impulsiveness (American Academy of Child and Adolescent Psychiatry, 2002; Biederman, 1998; Fossati et al., 2002; Seidman and Biederman, 1998; Shaffer, 1994). Thus, individuals suffering from de-

TABLE I
DSM-IV diagnostic criteria for ADHD

Inattention	Hyperactivity/Impulsivity	
Careless	Squirms and fidgets	Blurts out answers
Difficulty sustaining attention in activity	Can't stay seated	Can't wait turn
Doesn't listen	Runs/climbs excessively	Intrudes/interrupts others
No follow through	Can't play/work quietly	
Avoids/dislikes tasks requiring sustained mental effort	"On the go" or acts as if "Driven by a motor"	
Can't organise	Talks excessively	
Loses important items		
Easily distractible		
Forgetful in daily activities		

A: Six (or more) of the symptoms of either inattention or hyperactivity/impulsivity that have persisted for at least 6-months to a degree that is maladaptive and inconsistent with the developmental level.

B: Some of the symptoms that caused impairment were present before age 7

C: Impairment from symptoms is present in two or more settings

D: There must be clear evidence of clinically significant impairment in social, academic or occupational functioning

pression can show impairments in concentration and task completion, and disturbances in mood, sleep and energy. Abnormal thought processes such as those described in Case 2 may be difficult to differentiate from hypomania or anxious worrying. Overlapping symptoms between ADHD and other disorders and the increased rate of psychiatric comorbidity can therefore increase the difficulty in making the diagnosis (Shaffer, 1994; Wender and Garfinkel, 1989).

Further problems arise from DSM-IV criteria and their interpretation since they were written for children and do not take into account developmental progression of the disorder. For example, hyperactive/impulsive behaviours reduce with age and adults with ADHD often devise strategies to cope with symptoms such as inattentiveness and forgetfulness. For this reason, it is likely that some adults who do not meet operational diagnostic criteria will still be impaired by ADHD symptoms. Review of prospective follow-up studies supports the view that childhood ADHD often persists into adult life, not always as a categorical diagnosis, but often as a contribution to poor social adjustment and personality problems (Biederman et al., 1996; Gittelman et al., 1985; Institute of Health, 1998; Mannuzza et al., 1991; Weiss et al., 1985; Wood et al., 1976).

Another feature of ADHD is the increased risk to close family members; around three to five fold the general population risk (Schachar and Wachsmuth, 1990; Smalley, 1997). The risk to first-degree relatives is around 15-20% (Faraone et al., 2000) and numerous twin studies demonstrate that the familial risk is due predominantly to genetic factors (Thapar et al., 1999). It is therefore not unusual that adults with ADHD, such as Case 2, have one or more children with ADHD.

In the cases presented here, symptoms of ADHD were not controlled until stimulant medication in the form of methylphenidate was received regularly and at sufficient dose.

Stimulants have been shown to be far more effective than other drugs such as antidepressants in reducing ADHD symptoms (Spencer et al., 1996). Although the efficacy of various psychotherapeutic interventions remains to be established, a retrospective assessment of adults with ADHD indicated that traditional insight orientated psychotherapy is not particularly helpful (Ratey et al., 1992). Cognitive/behavioural strategies are likely to be a useful adjunctive intervention and are appreciated by patients.

Studies of the short-term benefits of stimulants on the symptoms of ADHD constitute the largest body of evidence on any childhood onset psychiatric disorder (American Academy of Child and Adolescent Psychiatry, 2002). Studies of stimulant-treated adults show a wide range in drug efficacy (23-78%) (Wilens and Biederman, 1992). Variability in the outcome of these studies may result from differing diagnostic and assessment methods, the effects of psychiatric comorbidity, and variation in the dose of stimulant medication used. Controlled investigations using higher methylphenidate doses (≥ 1 mg/kg/day) resulted in more robust outcomes (Spencer et al., 1995) than those using lower doses (< 0.7 mg/kg/day) (Rappoport et al., 1987, 1989).

Published drug trials may not help the clinician choose a dose for a particular patient as they do not report dose response curves; most treat all patients with the same stimulant medication dose adjusted for the patients weight. Mg per kg is not particularly useful in everyday clinical practice. The minimum starting doses of methylphenidate is 5 mg given two or three times a day in children and adolescents with a maximum total daily doses of 60 mg. In our experience, similar dosage regimens are effective in adults, although there is a wide range of effective doses, i.e. from 5 mg twice daily to as high as 30 mg three or four times daily. As with children, dose should be tailored for each individual by titration

against clinical response rather than depend on mg/kg criteria.

Notably, the immediate-release preparations of methylphenidate have a brief duration of action with a clinical response that lasts around 4-6 hours. Plasma concentration levels are characterised by fluctuations with peaks and troughs associated with dosing and several doses are required during the day to maintain behavioural improvement. Traditional sustained release formulations of methylphenidate provide a constant plasma level but are associated with a decline in efficacy throughout the day. In contrast, Concerta® XL produces an ascending plasma drug level generated by the tablet's osmotically released, timed drug delivery system. It is this that is thought to be important in maintaining the therapeutic response throughout the day (Modi et al., 2000). Recent studies suggest that plasma drug levels need to increase throughout the day to maintain constant effect because short-term tolerance to methylphenidate develops by the second dose given in the same day (Swanson et al., 1999). This phenomenon of acute tolerance does not however lead to long-term tolerance because of the very short half life of methylphenidate. In both immediate- and sustained-release preparations this effect appears to contribute to their shorter duration of action (Swanson et al., 1999).

This report describes the improvement of two adults with ADHD treated with the osmotic controlled-release once a day formulation of methylphenidate. It highlights why the diagnosis of ADHD is problematic in adults and the obvious advantages of the osmotically-released formulation of methylphenidate for patients that do not always remember to take their treatment or have difficulties coping with multiple dosing and the fluctuating effects of shorter acting preparations.

Summary

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental syndrome characterised by inattentiveness, distractibility, impulsivity, and hyperactivity. It negatively affects the educational, social and occupational lives of those who suffer from its symptoms. Opinion regarding the diagnosis of ADHD in adults remains controversial, although research reports suggest that adult ADHD is a relatively common disorder that is under-identified in adult psychiatry clinics. We detail the improvement of two adults with ADHD treated with an osmotic controlled-release once-a-day formulation of methylphenidate. This report details symptomology, and highlights both why the diagnosis of ADHD is problematic in adults and why this formulation may be considered to be suitable for some adults.

Philip Asherson and Susan E. Libretto

***Susan E. Libretto, PhD**

Medical Writer and Publications Manager
UK, Janssen-Cilag Ltd., PO Box 79,
Saunderton, High Wycombe,
Buckinghamshire HP14 4HJ, UK
Tel: +44 (0)1494 567873
Fax: +44 (0)1494 567445
E-mail: slibrett@jacgb.jnj.com

Dr. Philip Asherson, MRCPsych, PhD

Senior Lecturer in Molecular Psychiatry and
Consultant Psychiatrist, MRC Social Genetic
Developmental Psychiatry Centre, Institute of
Psychiatry, De Crespigny Park, London,
UK

** For Correspondence*

References

- American Academy of Child and Adolescent Psychiatry.** (2002). Practice parameter for the use of stimulant medications in the treatment of children, adolescents and adults. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 26S-49S.
- American Psychiatric Association.** (1994). *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed. Washington DC: American Psychiatric Association.
- Barkley, R.A., Fischer, M., Edelbrock, C.S. and Smallish, L.** (1990). The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29, 546-557.
- Biederman, J.** (1998). ADHD : a life-span perspective. *Journal of Clinical Psychiatry*, 59, 4-16.
- Biederman, J., Faraone, S.V., Milberger, S., Guite J., Mick, E., Chen, L., Mennin, D., Marris, A., Ouellette, C., Morre, P., Spencer, T., Norman, D., Wilens, T., Kraus, I and Perrin, J.** (1996). A prospective four-year follow-up study of attention deficit hyperactivity and related disorders. *Archives of General Psychiatry*, 53, 437-446.
- Biederman J. and Spender T.** (2002). Methylphenidate in treatment of adults with attention-deficit/hyperactive disorder. *Journal of Attention Disorders*, 6, S101-S107.
- Faraone, S.V., Biederman, J. and Monuteaux, M.C.** (2000). Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genetic Epidemiology*, 18, 1-16.
- Fossati, A., Novella, L., Donati, D., Donini, M. and Maffei, C.** (2002) History of childhood attention deficit/hyperactivity disorder symptoms and borderline personality disorder: a controlled study. *Comprehensive Psychiatry*, 43, 369-377.
- Gitelman, R., Mannuzza, S., Shenka, R. and Bonagura, N.** (1985). Hyperactive boys almost grown-up I: Psychiatric status. *Archives of General Psychiatry*, 42, 937-947.
- Iaboni, F., Bouffard, R., Minde, K. and Hechtman, L.** (1996) *The efficacy of methylphenidate in treating adults with attention deficit/hyperactivity disorder*. In: Scientific Proceedings of the American Academy of Child and Adolescent Psychiatry, Philadelphia, PA.
- Institute of Health.** (1998). Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD). *NIH Consensus Statement*, 16, 1-37.
- Keating, G.M., McClellan, K. and Jarvis, B.** (2001) Methylphenidate (OROS® formulation). *CNS Drugs*, 15, 495-500.
- Mannuzza, S., Klein, R.G., Bonagura, N., Malloy, P., Giampino, T. L. and Addalli, K.A.** (1991). Hyperactive boys almost grown up V: Replication of psychiatric status. *Archives of General Psychiatry*, 48, 77-83.
- Mattes, J.A., Boswell, L. and Oliver, H.** (1985). Methylphenidate effects on symptoms of attention deficit disorder. *Archives of General Psychiatry*, 41, 1059-1063.
- Modi, N.B., Lindemulder, B. and Gupta, S.K.** (2000). Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation. *Journal of Clinical Pharmacology*, 40, 379-388.
- Rappaport, M.D., Jones, J.T., DuPaul, G.J., Kelly, K. L., Gardner, M. J., Tucker, S. B. and Schea, M.** (1987). Attention deficit disorder and methylphenidate: Group and single-subject analyses of dose effects on attention in clinic and classroom settings. *Journal of Clinical Child Psychology*, 16, 329-338.
- Rappaport, M.D., Quinn, S.O., DuPaul, G.J., Quinn, E.P. and Kelly, K.L.** (1989). Attention deficit disorder with hyperactivity and methylphenidate: The effects of dose and mastery level on children's learning performance. *Journal of Abnormal Child Psychology*, 17, 669-689.
- Ratey, J.J., Greenberg, M.S., Bemporad, J.R., and Lindem, K.** (1992). Unrecognized attention-deficit disorders in adults presenting for outpatient psychotherapy. *Journal of Child and Adolescent Psychopharmacology*, 2, 267-275.

- Schachar, R. and Wachsuth, R.** (1990). Hyperactivity and parental psychopathology. *Journal of Child Psychology and Psychiatry*, 31, 381-392.
- Seidman, L. and Biederman, J.** (1998). Neuropsychological function in adults with ADHD. *Biological Psychiatry*, 44, 260-268.
- Shaffer, D.** (1994). Attention deficit hyperactivity disorder in adults. *American Journal of Psychiatry*, 151, 633-638.
- Smalley, S.** (1997) Genetic influences in childhood-onset psychiatric disorders: Autism and Attention-Deficit Hyperactivity Disorder. *American Journal of Human Genetics*, 60, 1276-1282.
- Spencer, T., Biederman, J., Wilens, T.E., Harding, M., O'Donnell, D. and Griffin, S.** (1996). Pharmacotherapy of attention deficit disorder across the life cycle. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 409-432.
- Spencer, T., Wilens, T.E., Biederman, J., Faraone, S.V., Ablon, S. and Li, T.** (1995) A double blind crossover comparison of methylphenidate and placebo in adults with childhood onset ADHD. *Archives of General Psychiatry*, 52, 434-443.
- Swanson, J., Gupta, S., Guinta, D., Flynn, D., Agler, D., Lerner, M., Williams, L., Shoulson, I. And Wigal, S.** (1999). Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clinical Pharmacology and Therapeutics*, 66, 295-305.
- Taylor, E.** (1991). *The epidemiology of Childhood Hyperactivity*. Maudsley Monographs No. 33. Oxford University Press.
- Taylor, E., Chadwick, O., Heptinstall, E. and Danckaerts, M.** (1996). Hyperactivity and conduct problems as risk factors for adolescent development. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 1213-1226.
- Thapar, A., Holmes, J., Poulton, K. and Harrington, R.** (1999). Genetic basis of attention deficit and hyperactivity. *The British Journal of Psychiatry*, 174, 105-111.
- Weiss, G., Hechtman, L., Milroy, T. and Perlman, T.** (1985). Psychiatric status of hyperactives as adults: A controlled prospective 15 year follow-up of 63 hyperactive children. *Journal of the American Academy of Child Psychiatry*, 42, 211-220.
- Wender, P.** (1997). ADHD in adults: a wide view of a widespread condition. *Psychiatric Annals*, 27, 556-562.
- Wender, P. H. and Garfinkel, B.D.** (1989). Attention deficit hyperactivity disorder: adult manifestations. In: H.I. Sadock and B.J. Kaplan. (Eds.). *Comprehensive Textbook of Psychiatry*. Baltimore, Md: Williams & Wilkins.
- Wender, P.H., Reimherr, F.W. and Wood, D.R.** (1981). Attention deficit disorder ('minimal brain dysfunction') in adults: A replication study of diagnosis and drug treatment. *Archives of General Psychiatry*, 38, 449-456.
- Wender, P.H., Reimherr, F.W., Wood, D.R. and Ward, M.** (1985). A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *American Journal of Psychiatry*, 147: 547-552.
- Wilens, T.E. and Biederman, J.** (1992). The stimulants. *Psychiatry of Clinical North America*, 15, 191-222.
- Wilens, T., Biederman, J., Spencer, T.J. and Prince, J.** (1995). Pharmacotherapy of Adult Attention Deficit/Hyperactivity Disorder: A Review. *Journal of Clinical Psychopharmacology*, 15, 270-279.
- Wilens, T., Frazer, K., Prince, J., Spencer, T., Bostic, J., Hatch, M., Abrantes, A., Sienna, M., Soriano, J., Millstein, R. and Biederman, J.** (1996) *A double blind comparison of pemoline in adults with ADHD*. In: Scientific Proceedings of the American Academy of Child and Adolescent psychiatry, Philadelphia, PA.
- Wood, D.R., Reimherr, F.W. and Wender, P.H.** (1976) Diagnosis and treatment of minimal brain dysfunction in adults. *Archives of General Psychiatry*, 33, 1453-1460.