PHYTOMEDICINES AS PHARMACOLOGICAL ALTERNATIVES IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN

A thesis submitted in fulfilment of the requirements for the degree of
Master of Applied Science

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DECLARATION

I certify that except where due acknowledgement has been made, this work is that of the author alone; this work has not been previously submitted, in whole or in part, to qualify for any other academic award; the content of this thesis is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and the required ethics procedures and guidelines have been followed.

Fiona T. Dey
March 2011
DEDICATION

This work is dedicated to the memories of my mother and my maternal grandmother.

Two strong women.
ACKNOWLEDGEMENTS

I would like to offer my sincere thanks to the families and teachers who participated in this project, and to my senior supervisor Associate Professor Andrew Francis for his commitment to innovative research and herbal medicine. I also thank Andrew for reading my drafts, and for supporting the extension applications and periods of leave that were required as a result of the unexpected project obstacles, and the subsequent personal traumas and other problems, that badly affected my progress.

I thank Jacques Duff for acting as second supervisor, and thanks are also due to Adjunct Associate Professor Kerry Bone for undertaking the role of project consultant. In addition, I thank Adjunct Associate Professor Reg Lehmann for his technical support regarding the trial products, and MediHerb Pty Ltd for donating the trial products and the funding for the objective measures.

I wish to thank Associate Professor John Reece, my research student co-ordinator, for his support and advice in relation to candidature matters, and for his guidance regarding the data analysis. I would also like to thank Dr Pauline McCabe for inspiring me to do a higher degree, although it was my own mad decision to do a herbal clinical trial.

Thanks are also offered to Adrienne Patterson for her help with ethics procedures, Maria Pizzi for her legal advice, and Andrew McKenzie for his IT support. I appreciated the help of Dr Mandy Kienhuis regarding the rating of the line graphs, and I acknowledge the work that Dr Melinda Polimeni and Rohan Dempster did as Andrew’s students in developing the Sleep Diary.

Finally, thank you to those who gave me moral support during the periods of heavy personal stress that I endured during my prolonged candidature. I am particularly grateful to the friends who have been helping me since the onset of chronic health problems in 2008.
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<td>Attention Deficit Disorder</td>
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<tr>
<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>APA</td>
<td>American Psychiatric Association</td>
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<tr>
<td>APS</td>
<td>Australian Psychological Society</td>
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<tr>
<td>BNC</td>
<td>Behavioural Neurotherapy Clinic</td>
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<td>CAM</td>
<td>Complementary and Alternative Medicine</td>
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<td>CAP</td>
<td>Child Attention Problems</td>
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<td>CBCL</td>
<td>Child Behavior Checklist</td>
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<td>CEO</td>
<td>Catholic Education Office</td>
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<td>CPRS-R:S</td>
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<td>Conners’ Rating Scales-Revised</td>
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<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<td>CTN</td>
<td>Clinical Trial Notification</td>
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<td>CTRS-R</td>
<td>Conners’ Teacher Rating Scale-Revised</td>
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<td>CTRS-R:L</td>
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<tr>
<td>CTRS-R:S</td>
<td>Conners’ Teacher Rating Scale-Revised:Short Form</td>
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<td>DEET</td>
<td>Department of Education, Employment and Training</td>
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<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>EFAs</td>
<td>Essential Fatty Acids</td>
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<td>ESCOP</td>
<td>European Scientific Cooperative On Phytotherapy</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FFAs</td>
<td>Free Fatty Acids</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>GABA</td>
<td>Gamma Amino Butyric Acid</td>
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<td>GAS</td>
<td>Goal Achievement Scale</td>
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<tr>
<td>HIC</td>
<td>Health Insurance Commission</td>
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<td>HREC</td>
<td>Human Research Ethics Committee (RMIT University)</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>JAMA</td>
<td>Journal of the American Medical Association</td>
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<tr>
<td>LC-PUFAs</td>
<td>Long-chain Polyunsaturated Fatty Acids</td>
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<tr>
<td>MAO</td>
<td>Monoamine Oxidase</td>
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<tr>
<td>MJA</td>
<td>Medical Journal of Australia (The)</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NCCAM</td>
<td>National Center for Complementary and Alternative Medicine</td>
</tr>
<tr>
<td>NHAA</td>
<td>National Herbalists Association of Australia</td>
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<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NTA</td>
<td>Number of Times Awake</td>
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<td>OSQ</td>
<td>Overall Sleep Quality</td>
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<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PLMS</td>
<td>Periodic Limb Movements in Sleep</td>
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<td>PLS</td>
<td>Plain Language Statement</td>
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<td>PS</td>
<td>Phosphatidylserine</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>PUFAs</td>
<td>Polyunsaturated Fatty Acids</td>
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<td>QEEG</td>
<td>Quantitative Electroencephalography</td>
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<td>rCBF</td>
<td>Regional Cerebral Blood Flow</td>
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<tr>
<td>RLS</td>
<td>Restless Legs Syndrome</td>
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<tr>
<td>RT</td>
<td>Reaction Time</td>
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<td>SL</td>
<td>Sleep Latency</td>
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<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TMM</td>
<td>Test Method MediHerb</td>
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<tr>
<td>TOVA</td>
<td>Test of Variables of Attention</td>
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<tr>
<td>TST</td>
<td>Total Sleep Time</td>
</tr>
<tr>
<td>TTA</td>
<td>Total Time Awake</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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ABSTRACT

The research reported in this thesis investigated the use of herbal medicines (phytomedicines) for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) and associated sleep problems in children in terms of safety, tolerability, and efficacy. Herbal medicines are commonly used for the treatment of ADHD, yet scientific research on this topic is scarce. The aim of the present study was to address this situation, especially in view of the controversies surrounding the use of the relevant medical drugs, and the fact that there is no generally accepted pharmacological treatment option for the children who do not respond to such drugs, or cannot tolerate them. ADHD is a chronic disorder, and it has also been linked with substance abuse and other adverse outcomes, hence the vital need to investigate other possible treatment options. Furthermore, numerous scientific studies have investigated the relevant medical drugs, however during the initial planning phase of this project in late 1999 and early 2000 no scientific research was found regarding the use of herbs.

A randomised placebo-controlled double blind parallel clinical trial was conducted, and it consisted of four phases: baseline, treatment, post-treatment, and follow-up. The treatment phase lasted for 3 months, and the total duration of the trial was 7.5 months. The participants were children aged from 8 to 16 years who had been diagnosed with ADHD based on DSM-IV criteria. They had also received a medical clearance allowing them to be involved. Despite extensive recruitment efforts, only six participants enrolled in the study, and only five of them completed it. All of the participants were male, and three of them were concurrently using orthodox ADHD medication.

Eight herbs were used in the trial, and they were administered in two combinations, with each combination consisting of four herbs. One combination was given in the morning for the treatment of daytime behaviour, and the other was given the evening for the treatment of sleep problems. The daytime combination contained ginkgo, bacopa, paony, and St John’s Wort, and the night-time formula contained valerian, skullcap, passionflower, and chamomile. Both of the combinations were administered as tablets. Dosage for each participant was calculated based on body weight.
Eight measures were used to assess the effect(s) of the herbal tablets. Six subjective measures were included: five for the assessment of daytime behaviour, and one for the assessment of sleep. The daytime measures were the Child Behavior Checklist (CBCL), the Conners' Parent Rating Scale-Revised (CPRS-R), the Conners' Teacher Rating Scale-Revised (CTRS-R), a Side Effects Rating Scale, and the Child Attention Problems (CAP) scale for teachers. The sole night-time measure was a Sleep Diary. Two objective measures were used in the study: the Test of Variables of Attention (TOVA) and Quantitative Electroencephalography (QEEG). Information was also obtained from the parents by using the Goal Achievement Scale (GAS) at the conclusion of the initial face-to-face interview, and at the end of the treatment phase. Due to the small sample size the major method of data analysis consisted of the visual analysis of line graphs. In addition, statistical analyses were performed for the five prime sleep variables derived from the Sleep Diary: Sleep Latency (SL), Number of Times Awake (NTA), Total Time Awake (TTA), Total Sleep Time (TST), and Overall Sleep Quality (OSQ).

The research question addressed by the study was: 'Do the trial herbs have a beneficial effect on daytime behaviour and sleep problems in children with ADHD?'. It was hypothesised that there would be a positive effect on daytime behaviour. As some improvements in daytime behaviour occurred in the children who took the active tablets, this hypothesis was partially supported. Regarding sleep problems, it was hypothesised that there would be a positive effect on sleep. However, as the sleep data were highly variable, and were inconclusive for the participants who were randomised to the active tablets, this hypothesis was not supported. The overall results of the trial in terms of efficacy are inconclusive.

Regarding safety, there did not appear to be any adverse reactions to the herbal tablets. One participant withdrew from the trial due to his behaviour becoming worse however he was taking the placebo tablets, and there were confounding circumstances. In relation to tolerability, one child had a lot of difficulty taking the tablets at the start of the trial, despite them being crushed and various suggestions being made to the parents. However, the other participants did not experience such problems.

Since the commencement of this project a few other herbal trials have been published regarding children with ADHD, however as far as the author of this thesis is aware the present trial is still the first major study of its type. Indeed, due to the nature of the other research that has been conducted on this topic it is extremely difficult to compare results.
In terms of strengths, the present project was an innovative study. Herbal medicines are often used in the treatment of children with ADHD, and also in the treatment of children with other health complaints. However, as noted in the literature, data directly obtained from paediatric studies are extremely rare in the field of complementary and alternative medicine (CAM) (Ernst, 2006). Furthermore, the present trial involved qualified herbalists whose education and experience extends beyond just herbal medicine, and a rigorous design was employed. Unfortunately, as noted in the final chapter, there are several limitations concerning this work. For example, there were a number of factors that affected recruitment, and also various methodological issues arose during the course of the study. These are discussed in detail in the final chapter prior to the thesis concluding with suggestions for future work.

*Note.* In this thesis the term "children" is used for children and adolescents as the author is normally referring to an age range that covers both age groups. In addition, the term "phytomedicines" has been used in the title as it is the term that is usually employed in relation to the scientific use of herbal medicines.
CHAPTER 1
INTRODUCTION

1.1 An overview of ADHD

1.1.1 Prevalence
ADHD is typically diagnosed in young children and is estimated to affect millions of children throughout the world. It has been investigated in several countries, and despite a common perception encountered by the author of this thesis it is not a disorder that only occurs in America (Faraone, Sergeant, Gillberg, & Biederman, 2003). The prevalence of ADHD in many countries is in the same range as the prevalence for the disorder in the United States. Although figures relating to prevalence vary in the literature, ADHD is generally considered to affect between 2% and 9% of children (Barkley, 1998a). The average figure given is 5%, a figure that is also described as “approximately one child in every classroom” (Rapport, 1995, p. 353). The disorder occurs more frequently in boys, and they are generally considered to outnumber girls at about 3:1 (Barkley, 1998a). The age of onset can vary but the behaviour patterns that characterise ADHD usually start at between 3 and 5 years of age (Barkley, 1998a).

Two studies have investigated the prevalence of ADHD in Australia. A Victorian study of parents and teachers in Melbourne and Ballarat found that the prevalence for primary school children was 9.9% as rated by parents (with a ratio of 2.5:1 in favour of boys) and 8.8% as rated by teachers (with a ratio of 3.3:1 in favour of boys) (Gomez, Harvey, Quick, Scharer, & Harris, 1999). A national study of parent data for children and adolescents revealed that the prevalence of the disorder was 7.5% (Graetz, Sawyer, Hazell, Arney, & Baghurst, 2001). These figures are comparable to the figures given in the above paragraph.

1.1.2 History
ADHD is not a new disorder. Hippocrates is said to have described a similar disorder in which the patient had quickened responses to sensory experience, and then quickly moved on to the next impression (Baumgaertel, 1999). In the early 1860s the German physician Hoffman wrote a poem about a hyperactive child ‘Fidgety Phil’ (Barkley, 1998b). Part of it reads:
Phil stop acting like a worm, the table is no place to squirm. Thus speaks the father to his son, severely say it, not in fun. Mother frowns and looks around, although she doesn’t make a sound. But Phillip will not take advice, he’ll have his way at any price. He turns and churns he wriggles and jiggles here and there on the chair. Phil these twists I cannot bear. (Weiss, 1996, p. 544)

The disorder was described by Still in a series of lectures presented to the Royal College of Physicians of London in 1902. Still described children in his clinical practice who exhibited defective moral control. He noted various qualities, or behaviours, in the children, for example, wanton mischievousness-destructiveness, and stated that:

Some of these qualities, it will be observed, are natural to children at a certain age and to a certain extent; it is their persistence in a degree unusual for the particular age and not corresponding to the influences of environment which constitutes their abnormality in these children. (Still, 1902, p. 1009)

As understanding of the disorder increased, and the diagnostic criteria were refined, the names of the disorder changed. Over the years the condition has been labelled, in turn, ‘minimal brain damage’, ‘minimal brain dysfunction’, hyperactivity, and attention deficit disorder or ADD. It was named Attention Deficit Hyperactivity Disorder or ADHD in 1987 (Barkley, 1998b) and in 1994 this was changed to Attention-Deficit/Hyperactivity Disorder (Faraone et al., 2003).

1.1.3 Key features and diagnostic criteria
Children with ADHD have chronic difficulties with inattention, impulsivity, and overactivity. These are the three key features of the disorder. All children exhibit such behaviours. However, in children with ADHD they are considered to be inappropriate for their age or developmental level, and they are displayed across a variety of situations (Barkley, 1998b). The behaviours are more severe and pervasive, and they persist.

Although it is typically diagnosed in young children it should be noted that ADHD persists into adolescence and adulthood. Approximately 80% of children diagnosed in childhood continue to meet the diagnostic criteria, and to display symptoms, as adolescents (Rapport, 1995). Up to 70% of children with ADHD will continue to have symptoms as adults (Barkley & Murphy, 1998). Thus, ADHD is a chronic disorder. It has been linked with substance
abuse, and adverse effects on academic performance, vocational success, and social and emotional development (National Health & Medical Research Council [NHMRC], 1996; National Institutes of Health [NIH], 2000).

The diagnostic criteria for ADHD are presented in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* or *DSM-IV* (American Psychiatric Association [APA], 1994) and the subsequent Text Revision or *DSM-IV-TR* (APA, 2000) and they are as follows:

A. Either (1) or (2):

(1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

**Inattention**

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

(b) often has difficulty in sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

(e) often has difficulty organizing tasks and activities

(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)

(h) is often easily distracted by extraneous stimuli

(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often “on the go” or often acts as if “driven by a motor”
(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

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

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder). (APA, 2000, pp. 92-93)

The DSM-IV-TR defines three types of ADHD: Combined Type, Predominantly Inattentive Type, and Predominantly Hyperactive-Impulsive Type. In Europe the 10th revision of the International Classification of Diseases or ICD-10 is used. The ICD-10 diagnostic criteria for the disorder are similar to the diagnostic criteria outlined in the DSM-IV and DSM-IV-TR (Barkley, 2006).
ADHD frequently overlaps with other disorders, and one or more of these may also be present. Anxiety disorder, depressive disorder, oppositional defiant disorder, conduct disorder, and learning disabilities have all been noted as common comorbid conditions (Guevara & Stein, 2001). Finally, children with ADHD are often said to have problems with sleep (Barkley, 1998b) and these will be considered in the following section.

1.2 Sleep problems in children with ADHD

Sleep problems are not listed in the current diagnostic criteria for ADHD, however they were included in the DSM-III diagnostic criteria for ADD (Corkum, Tannock, & Moldofsky, 1998). Parents of children with ADHD report child sleep issues such as delayed sleep onset, waking during the night, shorter duration of sleep, and morning fatigue (Day & Abmayr, 1998; Owens, Maxim, Nobile, McGuinn, & Msall, 2000). In addition, children taking stimulants have been reported to have a higher prevalence of sleep problems than those not taking stimulants (Owens et al., 2000; Stein, 1999). More recently, it has been noted that night-time awakenings and restless sleep are the most commonly reported sleep problems in children with ADHD, although there does not appear to be a difference between children with ADHD and children without ADHD for sleep latency, and total sleep time (Sheldon, 2005).

1.2.1 Normal sleep in children

Children aged from 5 to 13 years require about 10 hours of sleep per night, while for those aged from 14 to 18 years the figure is 8 hours (Heussler, 2005). The average sleep duration at 10 years of age is 8 to 10 hours, and in mid-adolescence it is 8.5 hours (Stores, 2001). In one study of healthy children aged from 6 to 12 years the results revealed that they spent 8 to 9.5 hours in bed, and that they were asleep for 95% of this time (Anders, Sadeh, & Appareddy, 1995). Their sleep latency was 20 to 25 minutes, and they had an average of one to three brief awakenings during the night. Children in this age range usually have fewer problems going to sleep and staying asleep compared with younger children, and adolescents. Sleep is mainly sound between about 5 years of age and puberty, and waking at night is unusual. In contrast, high rates of sleep problems are reported in adolescence (Stores, 2001).

1.2.2 Sleep in children with ADHD

Many studies have investigated the nature of sleep in children with ADHD. Two ongoing issues in the literature have been the differences between subjective data and objective data, and the question of cause and effect.
Subjective data versus objective data

Subjective sleep data is typically collected during interviews with parents, and via the use of questionnaires and sleep logs or sleep diaries. Objective sleep data is derived from techniques such as polysomnography (PSG), actigraphy, and video monitoring. The instruments used in the assessment of sleep will be discussed in sub-section 1.10.2.

A 1995 review found that subjective parental reports and objective data from PSG studies revealed different results. The parental reports indicated that ADHD was associated with sleep disturbance, while most of the PSG studies found that this was not the case (Ball & Koloian, 1995). In contrast, a study that used parental reports and actigraphy to compare the sleep quality of 12 children with ADHD with 12 control children revealed that the parental reports did not indicate reduced sleep quality, yet the actigraphic measures showed that the children with ADHD experienced sleep difficulties. No significant difference was found regarding sleep onset time or sleep duration, however sleep efficiency was significantly lower in the experimental group compared to the control group. In addition, activity levels were significantly higher in the children with ADHD (Dagan et al., 1997).

In a systematic review, Corkum et al. (1998) found differences between subjective data and objective data, and inconsistent findings for objective studies. Consideration of clinical and parental information found no epidemiological evidence of an association between sleep disturbances and ADHD. Some studies that used questionnaires and sleep diaries revealed more night-time awakenings in children with ADHD compared with control children, but no differences were noted for sleep latency and total sleep time. The review of objective studies covered 12 PSG studies and two actigraphic studies. These studies involved a total of 91 children with ADHD. Nine of the studies investigated sleep latency with mixed results. Three studies found longer sleep latency in children with ADHD compared with controls, while two found shorter, and four found no difference. Ten objective studies examined total sleep time. Of these only one found a difference between children with ADHD and controls, namely a longer total sleep time in the experimental group. The remaining nine found no difference. Overall, the reviewers noted that children with ADHD tend to be more restless during sleep. They also discuss the methodological issues regarding the studies reviewed, in particular small sample sizes, variations in control procedures, and variations in accounting for medication use.
Cause and effect

The relationship between ADHD and sleep has been described as a conundrum that may manifest in different ways. ADHD may be associated with or exacerbate sleep problems, and stimulant medications may cause sleep disturbance. However, sleep problems may also produce ADHD-like symptomatology, or they may aggravate underlying ADHD symptoms (Owens, 2005). Further investigation is required in order to ascertain whether dysfunctional sleep is a cause or effect of ADHD in some individuals (Sheldon, 2005), or whether indeed a reciprocal relationship exists.

Given the varied phenomenology of ADHD, and its related sleep problems, it is not surprising that different theories have been proposed regarding aetiology. These will be discussed in section 1.3.

1.3 The aetiology of ADHD

An extensive amount of research has been conducted looking for the cause(s) of this disorder, including studies that have investigated neuroanatomy, neurochemistry, genetics, and diet. This section commences with a summary of the relevant neuroanatomy and neurochemistry. This is followed by an overview of the different types of research studies, and their results.

Much of the neurological research investigating the aetiology of ADHD has concentrated on the basal ganglia, and the frontal areas of the brain. The basal ganglia consist of the caudate nucleus, putamen, and globus pallidus. The caudate nucleus and the putamen are sometimes referred to as the striatum. The basal ganglia are located in the central regions of the cerebral hemispheres, above and surrounding the thalamus. Cortical inputs from the striatum funnel into the globus pallidus, and fibres from the globus pallidus lead into the thalamus. The basal ganglia are involved in the initiation and execution of movement, and have also been implicated in cognitive functioning, and learning. The basal ganglia receive input from the prefrontal cortex. The prefrontal cortex is involved in attending to actions, and appears to play a role in the use of working memory and language in the control of action (Thompson, 2000; Toates, 2007; Ward, 2006).

The relevant neurotransmitters are the catecholamines: dopamine and noradrenaline (norepinephrine). The dopamine-containing cells that are located in a midbrain area known as the substantia nigra project directly to the basal ganglia. This dopamine system is involved in the regulation of movement. The norepinephrine pathways in the brain arise from a collection
of cells in the brain stem, and project to virtually all forebrain structures. This system is thought to be involved in arousal (Thompson, 2000; Toates, 2007).

1.3.1 Neuroimaging studies
Numerous imaging studies have been conducted using techniques that provide structural imaging, functional imaging, or both.

**Computed tomography (CT)**
The early imaging studies used CT scans, which are a type of structural imaging. Shaywitz, Shaywitz, Byrne, Cohen, and Rothman (1983) compared CT scans in two groups of children, a cohort of children with ADD, as the disorder was then called, and a control group, and found no differences between the groups.

However, an emission CT study that assessed regional cerebral blood flow (rCBF) in children with dysphasia and/or ADD [sic] compared with children who served as controls (mainly siblings of those in the study group) showed that those with ADD had hypoperfusion in the white matter of the frontal lobes. Furthermore, most of the participants with ADD also showed hypoperfusion in the caudate nuclei region (Lou, Henriksen, & Bruhn, 1984). A later study by the same research group found hypoperfusion in the striatal regions (Lou, Henriksen, Bruhn, Børner, & Nielsen, 1989). The authors noted that in both of these studies the stimulant drug methylphenidate increased blood flow to the hypoperfused areas. Methylphenidate will be discussed in sub-section 1.4.1.

In a 1986 study 24 young male adults with a childhood history of hyperactivity and other ADHD behaviours showed a significantly greater frequency of cerebral atrophy than 27 matched male controls. However, all had been treated with stimulants in childhood and some also had a history of alcohol abuse, leading the authors to suggest that these issues may have confounded their results (Nasrallah et al., 1986).

**Positron emission tomography (PET)**
PET is a form of functional imaging. An oft-cited PET study investigated cerebral glucose metabolism in adults who had a history of hyperactivity since childhood compared to controls (Zametkin et al., 1990). Each member of the patient group was a biologic parent of a child with hyperactivity. None of the patient group had used stimulants, and none had a history of substance abuse, however they all had difficulty with restlessness and inattentiveness.
Glucose metabolism, both global and regional, was reduced, and the largest reductions were in the premotor cortex and the superior prefrontal cortex. These are areas that are involved in the control of attention and motor activity.

Some other PET studies have investigated cerebral glucose metabolism in adolescents and adults with ADHD, and these have found a decrease in metabolism in cells of the basal ganglia (Zametkin & Liotta, 1998).

A more recent PET study examined dopamine receptor binding and reaction time (RT) in children who had been assessed for rCBF at pre-term birth, and who subsequently displayed attention deficit. The study found that a high level of dopamine receptor availability ('empty receptors') was linked with increased RT, and RT variability. The authors concluded that these results support the concept of a dopaminergic role in ADHD symptomatology (Lou et al., 2004).

**Magnetic resonance imaging (MRI)**

Several structural MRI studies have been conducted in children and adolescents, and all have reported differences between the ADHD and control groups (Zametkin & Liotta, 1998). Most of the findings have involved the basal ganglia.

In a major study, Castellanos et al. (1996) compared 57 boys with ADHD with 55 healthy matched controls aged from 5 to 18 years. The participants with ADHD were found to have a smaller total cerebral volume; loss of the normal right>left asymmetry in the caudate; smaller right globus pallidus, right anterior frontal region, and cerebellum; and reversal of the normal lateral ventricular asymmetry. The authors noted that their results were consistent with their hypothesis that dysfunction of the right-sided prefrontal-striatal systems is involved in ADHD. Regarding such studies Castellanos (2001) points out that, with one exception, all study groups have found reduced volumes (or areas) that are consistent with the theory that certain brain regions are hypofunctioning in ADHD.

**Functional magnetic resonance imaging (fMRI)**

This technique imparts both structural and functional information, and it is a more recent imaging method that has been used to study ADHD (Zametkin & Liotta, 1998). An early fMRI study of 7 adolescents with ADHD and 9 controls found that the patient group exhibited hypofrontality during the performance of certain tasks. One of the tasks was a ‘stop’ task, a
task that requires response inhibition (Rubia et al., 1999). The findings lead the authors to conclude that ADHD is associated with subnormal activation of the prefrontal systems that are responsible for higher-order motor control.

A study that was conducted using a newer fMRI technique discovered that ADHD symptoms may be due to functional abnormalities of the putamen. This is an area of the brain that is mainly involved in the regulation of motor behaviour (Teicher et al., 2000).

**Single photon emission computed tomography (SPECT)**

SPECT is a functional imaging technique that has only been introduced into ADHD research in recent years (Zametkin & Liotta, 1998). A study by Sieg, Gaffney, Preston, and Hellings (1995) produced results that suggested abnormalities of blood flow and metabolism in the frontal lobe.

Another SPECT study (Amen & Carmichael, 1997) compared children and adolescents with ADHD with a psychiatric control group, both at rest and performing a task. The results revealed that 65% of the ADHD group had decreased perfusion in the prefrontal cortex with intellectual stress, compared to only 5% of the control group. Furthermore, when the ADHD participants who did not have decreased perfusion were assessed most of them exhibited markedly decreased activity in the prefrontal cortices at rest. As the functions of the prefrontal lobe include attention span, concentration, judgement, activity level, critical thinking, and impulse control, the authors suggested that hypoperfusion in the prefrontal cortex may result in a loss of inhibition, and that this could cause the hyperactive, impulsive, and inattentive behaviours that characterise ADHD.

**Neuroimaging reviews and meta-analyses**

Given the various types of neuroimaging studies that have been conducted over a number of years, some more recent work has focused on producing reviews and meta-analyses in an attempt to clarify findings. In a review of structural imaging studies Seidman, Valera, and Makris (2005) assessed study findings according to the brain regions that were investigated. Regarding the prefrontal cortex, they noted that all of the studies that measured at least one component of this region found smaller volumes in children with ADHD compared with controls. They also noted the increasing amount of evidence that supports the involvement of the basal ganglia and the cerebellum in ADHD. A meta-analysis of structural imaging findings found that the regions of interest with the largest significant reductions relative to
controls were the cerebellum, the splenium of the corpus callosum, total and right cerebral volume, the right caudate, and various frontal areas (Valera, Farone, Murray, & Seidman, 2007).

A review of functional imaging studies found that convergent data suggest that fronto-striatal abnormalities are involved in the symptomatology of ADHD (Bush, Valera, & Seidman, 2005). A meta-analysis of functional imaging research concluded that the most consistent findings are deficits in neural activity within fronto-striatal and fronto-parietal circuits (Dickstein, Bannon, Castellanos, & Milham, 2006).

The consistency of findings from different research groups, and also from different types of imaging studies, is obviously of great interest, however there are recognised limitations regarding the imaging literature. Most imaging studies have used small sample sizes. Studies also differ in terms of how they address issues such as the use of medications, and the existence of comorbidities. In addition, female participants are usually underrepresented.

1.3.2 Neurochemistry studies
Neurochemistry research has investigated the catecholamine neurotransmitters dopamine and noradrenaline (norepinephrine). Studies have been conducted by measuring the neurotransmitters and their metabolites in blood, urine, and cerebrospinal fluid (CSF), or by assessing response to ADHD medications. Results for the first type of study have not found consistent differences between children with ADHD and controls (Levy, Barr, & Sunohara, 1998). However, some evidence from studies of CSF in children with ADHD indicates that they have decreased brain dopamine (Barkley, 1998b).

The results for the second type of study are conflicting. The beneficial effects of stimulants implicate dopamine, however the beneficial effects of clonidine and desipramine implicate norepinephrine (Anderson & Cohen, 1996). Studies on the site of action of methylphenidate implicate dopamine as the main neurotransmitter involved in ADHD (Swanson, Castellanos, Murias, LaHoste, & Kennedy, 1998). The relevant medical drugs will be considered in section 1.4.

Dopaminergic therapy has been investigated in 7 children with ADHD and restless legs syndrome/periodic limb movements in sleep (RLS/PLMS) (Walters et al., 2000). Five of the children were treated with levodopa and the remainder were treated with the dopamine
agonist pergolide. PSG and behavioural testing were administered at baseline and after 6 months. After treatment 3 children no longer met the criteria for ADHD. In addition, ADHD behaviours had improved in all of the participants. Five of the children had previously been treated with stimulants however they were ineffective or caused side effects. The authors concluded that the beneficial effects of dopamine may be due to improved sleep as a result of the amelioration of the RLS/PLMS, or that ADHD and RLS/PLMS may involve a common dopaminergic deficit.

1.3.3 Genetic studies
There is no evidence to suggest that ADHD is due to chromosomal abnormalities however different lines of research strongly suggest that it has high hereditability (Barkley, 1998b). About 10% to 35% of immediate family members of children with ADHD are also likely to have the disorder. For siblings the figure is around 32%, and if a parent has ADHD the risk to offspring is 57% (Barkley, 1998b). The results of adoption studies show a strong possibility of significant hereditary contribution (Barkley, 1998b).

In addition, numerous twin studies have suggested that there are substantial genetic influences that affect ADHD. The research findings have been consistent despite the fact that the twin samples that have been investigated differ in age, the assessment methods and instruments used, geographical location, and referral status (Waldman & Gizer, 2006). Several molecular genetics studies have been conducted in order to find the gene(s) that are responsible. Studies on two dopamine sites (the dopamine transporter and the D4 receptor) have shown an association with ADHD (Swanson et al., 1998). Indeed, the authors of a systematic review paper on dopamine genes and ADHD concluded that the implication of these genes in ADHD “appears to be one of the most replicated in psychiatric genetics and strongly suggests the involvement of the brain dopamine systems in the pathogenesis of ADHD” (DiMaio, Grizenko, & Joober, 2003, p. 27).

1.3.4 Neuropsychology
A large body of literature has revealed that individuals with ADHD, including children, exhibit relatively poor performance on neuropsychological tests of attention, and executive functions. Executive functions are cognitive processes that underlie self-regulation and goal-directed behaviour, including response inhibition, planning, working memory, and attention (Doyle, 2006). Several well-replicated findings have been confirmed by meta-analyses, and it appears that many neural networks are involved. However, at this stage it has not yet been
shown that neuropsychological deficits play a causal role in the development of ADHD (Nigg, 2005).

1.3.5 Complications of pregnancy and birth
Low birth weight and birth injuries have been associated with an increased risk of ADHD (Barkley, 1998b). A recent twin study that was conducted in Sweden found that low birth weight was a risk factor for the symptoms of ADHD, and that the association persisted despite the investigators controlling for genetic influences (Hultman et al., 2007).

Retrospective pregnancy and birth data have consistently shown a high incidence of adverse antenatal and perinatal events in relation to ADHD (Lou et al., 1989). The striatum is particularly vulnerable if circulation is compromised. Hypoxia is common in prematurity, and it is thought that this explains the high incidence of ADHD in children who were born preterm (Lou, 1996; Toft, 1999).

In addition, season of birth has been put forward as a possible risk factor for ADHD. A study that assessed all children born in Denmark from 1990 to 1999 for the incidence of various disorders, including Hyperkinetic Disorder, found no substantial variation regarding season of birth. Hyperkinetic Disorder, which is diagnosed as per the ICD-10, overlaps diagnostically with ADHD in relation to the symptoms of hyperactivity (Atladóttir et al., 2007). An earlier study that was conducted in the United States also failed to find evidence of a strong seasonal pattern. However, the results showed statistically significant peaks in September births for children with ADHD and comorbid learning disorders, and children with ADHD who did not have additional psychiatric comorbidity. The researchers suggested that exposure to Winter infections during the first trimester of pregnancy, a time when the central nervous system is developing rapidly, may account for some subtypes of ADHD (Mick, Biederman, & Faraone, 1996).

1.3.6 Toxins
Elevated body lead has a statistically significant relationship to the symptoms of ADHD (Barkley, 1998b). There is also a link between prenatal exposure to tobacco and alcohol, and inattention and hyperactivity, however, as with lead, it is correlational (Barkley, 1998b). There are a number of confounding variables, and Barkley (1998b) stresses that most studies on these substances have not evaluated or controlled for the presence of ADHD in the parents. However, in one study the authors found “a strong and significant positive association
between smoking by mothers during pregnancy and ADHD in their children that could not be attributed to socioeconomic status, parental ADHD, and parental IQ” (Milberger, Biederman, Faraone, Chen, & Jones, 1996, p. 1140).

1.3.7 Diet
The notion that ADHD is caused by certain dietary factors has often been controversial. However, Baumgaertel (1999) concluded that it is difficult to dismiss the findings that some children with ADHD respond favourably to individualised elimination diets. The main items that are excluded are one or more of the following: dairy, wheat, food additives, salicylates, sugar, and yeast. More recent reviews have concluded that some children may be sensitive to food additives, and that further investigation is warranted (Rojas & Chan, 2005; Stevenson, 2006).

1.3.8 Poor parenting
Parenting styles and discipline methods are thought to be a response to the child’s behaviours, and it has also been noted that the way in which parents manage children with ADHD may exacerbate behaviour. However, parenting factors are not considered to be the cause of the disorder (Barkley, 1998b; Green & Chee, 1997).

1.3.9 Conclusion regarding the aetiology of ADHD
The aetiology of ADHD appears to be multifactorial. Neuroimaging studies have consistently revealed results such as hypoperfusion, decreased glucose metabolism, and structural differences, regarding certain brain areas. Neurochemistry and genetic studies have highlighted the role of dopaminergic systems, while genetic research has also shown that the disorder is highly hereditary. In addition, analyses of pregnancy and birth data have found a high incidence of ADHD in relation to factors such as prematurity and low birth weight. Despite the apparently diverse nature of the disorder in terms of aetiology, medication is the main form of treatment. The major medical drugs that are prescribed for ADHD will be discussed in the following section.

1.4 The major medical drugs used to treat ADHD
Pharmacological treatment is the most commonly used form of treatment, as about 80% to 90% of children with ADHD receive medication (Australian Psychological Society [APS], 1997; Sheridan & Sanders, 1996). The main drugs used are the psychostimulants or stimulants. A stimulant drug was first used to treat behavioural disorders in children in 1937
(Bradley, 1937) and Ritalin has been used since 1957 (Green & Chee, 1997). Other relevant classes of drugs include the tricyclic antidepressants and the alpha-adrenergic agonists. The newer antidepressants and major tranquillisers may also be used depending on the child (Jarman, 1996).

1.4.1 Stimulants
Stimulants increase the level of arousal or alertness of the central nervous system (Barkley, 1998b). They exert their effects via the neurotransmitter systems that are involved in attention, inhibition, reward, and locomotion (Andersen, 2005). The relevant drugs are two related but pharmacologically distinct medications: methylphenidate hydrochloride and dexamphetamine sulphate.

Methylphenidate hydrochloride is marketed under several trade names in Australia, including Ritalin and Attenta. Its mode of action in humans is not fully understood (Mims Online, 2007). Like cocaine, it blocks the reuptake of dopamine and noradrenaline (Andersen, 2005).

There are many side effects associated with methylphenidate. Nervousness, insomnia, and irritability are noted as very common side effects. Common side effects include headache, drowsiness, dizziness, dyskinesia, anorexia, abdominal pain, nausea, vomiting, dry mouth, tachycardia, palpitations, and arrhythmias. Blurred vision and growth retardation are listed as rare side effects, while tics, psychosis, and abnormal liver function are classed as very rare. There have also been reports of suicide, suicide attempt, and suicidal ideation however no causal relationship has been established (Mims Online, 2007).

Dexamphetamine sulphate is marketed as Dexamphetamine. It is a sympathomimetic amine of the amphetamine group. The specific mode of action has not been established in humans. Amphetamines facilitate the action of dopamine and noradrenaline in animals by blocking reuptake from the synapse. They also inhibit the action of monoamine oxidase (MAO) and promote the release of catecholamines. Tolerance and dependence can develop, and there is a high potential for drug abuse. Side effects include palpitations, tachycardia, overstimulation, restlessness, dizziness, insomnia, dyskinesia, psychosis, tremor, headache, dry mouth, anorexia, and weight loss (Mims Online, 2007).
**Efficacy and safety**

The stimulants are considered to be highly effective. These drugs work quickly, and about 75% of children with ADHD display dramatic improvements in cognitive processing, behaviour, and academic performance. Some authorities say that the figure is higher, and is in fact closer to 90% (Diller, 1998). However, it is generally accepted that approximately 20% to 35% of children do not respond to these medications (NHMRC, 1996; Wilens & Biederman, 1992). There has also been ongoing discussion in the literature about various safety issues that are related to the use of stimulant drugs.

For example, there have been concerns about the long-term safety of stimulants in children as it has not been extensively studied, and little is known about the use of stimulants in adolescence (Bennett, Brown, Craver, & Anderson, 1999). Some authorities have also noted that most drug studies are short-term despite the fact that long-term treatment is indicated (NIH, 2000). However, as the research into stimulants has progressed some short-term studies have been followed by open-label studies that have lasted for 1 to 2 years (Pliszka, 2007).

Concerns have also been expressed about a possible link between methylphenidate and cancer. A study that was conducted in 12 children taking methylphenidate found that it induced chromosomal abnormalities that have been associated with an increased risk of cancer. The drug was prescribed within the therapeutic dose range, and cytogenetic evaluations were conducted on blood samples that were taken before the start of treatment, and after 3 months of treatment. Each child served as his or her own control. The researchers concluded that their results, and positive cancer bioassay data in laboratory animals, point to the need for further investigation of this drug (El-Zein et al., 2005).

Furthermore, in early 2006 the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) in the United States met to consider how to approach the study of the cardiovascular risks that are associated with stimulants. Following discussion of the level of stimulant use in the United States, and the adverse reactions that have been reported, including cases of sudden death in children, the committee put forward a recommendation to change the way in which stimulants are labelled. They proposed a black-box warning describing the cardiovascular risks that can result from the use of these drugs (Nissen, 2006). The prescribing guidelines for stimulants in Australia currently specify that children, adolescents, or adults with pre-existing cardiac abnormalities or other serious heart problems must be assessed by a cardiologist before treatment commences, and on an ongoing
basis (Mims Online, 2007). The FDA also recently reviewed the safety data for stimulants in relation to mania, psychotic symptoms, aggression, and suicidality. Changes in labelling were approved in order to promote awareness of the possibility of these rare adverse events (Pliszka, 2007). Other controversial issues regarding stimulants will be discussed in section 1.5.

1.4.2 Tricyclic antidepressants

Imipramine hydrochloride, which is marketed in Australia as Tofranil, and desipramine are the most commonly used tricyclics. The tricyclics are considered to be less effective than stimulants but of value for children with comorbid symptoms of anxiety or depression. Imipramine is preferred over desipramine because of a lower incidence of cardiovascular side effects, although desipramine has been noted as the best-studied tricyclic for ADHD treatment (Greenhill, 1992; Jarman, 1996). Desipramine is no longer available in Australia (B. Reed, personal communication, April 6, 2005).

The therapeutic actions of imipramine are thought to be due to its ability to inhibit the neuronal reuptake of serotonin and noradrenaline. Side effects include dry mouth, constipation, tremor, headache, dizziness, tachycardia, arrhythmias, nausea, vomiting, anorexia, drowsiness, sleep disorders, and allergic skin reactions (Mims Online, 2007).

Efficacy and safety
Tricyclics present more risks than stimulants. Despite the fact that several studies have demonstrated the efficacy of tricyclics, FDA approval for their use in the treatment of ADHD in the United States has not been sought due to safety concerns (Wolraich, McGuinn, & Doffing, 2007). There have been cases of sudden death in children taking desipramine (Cyr & Brown, 1998) and one death occurred in a child on high doses of imipramine (Weiss, 1996). The tricyclics now have a lesser role in the treatment of ADHD (Pliszka, 2007). Indeed, the current prescribing guidelines for Tofranil in Australia specify that it should not be used in children and adolescents younger than 18 years of age for the treatment of depression or other psychiatric disorders (Mims Online, 2007).

1.4.3 Alpha-adrenergic agonists
Clonidine hydrochloride is an antihypertensive drug that is marketed in Australia under the trade name Catapres. It is also used for the prophylaxis of migraine, and to treat menopausal flushing. Clonidine is often prescribed for treating ADHD, either alone or in combination
with stimulants, as it is considered useful for the control of aggressive behaviour, and for counteracting some stimulant side effects such as sleep disturbance and lack of appetite (Jarman, 1996). The alpha-adrenergic agonists are also said to have a valuable role in the treatment of comorbid tics (Pliszka, 2007). Clonidine acts by causing a decrease in sympathetic outflow. The side effects of this drug include drowsiness, dry mouth, nausea, vomiting, depression, irritability, sleep disturbances, and adverse cardiovascular effects (Mims Online, 2007).

**Efficacy and safety**

Although clonidine is widely used for ADHD there are relatively few studies that support its efficacy (Biederman, Spencer, & Wilens, 2004). In addition, FDA approval for the use of this drug class in the treatment of ADHD has not been sought in the United States (Wolraich et al., 2007). There are also safety issues associated with clonidine, notably the increase in the number of cases of clonidine overdose in children, a serious condition that requires treatment in an intensive care unit. The increased incidence of overdose has been related to the increased use of this drug for treating ADHD (Kappagoda, Schell, Hanson, & Hutchins, 1998). Indeed, a recent survey that was conducted in the United States investigated the prescribing patterns of 1,273 child and adolescent psychiatrists in relation to both prescription and non-prescription remedies for a variety of disorders, including ADHD (Owens, Rosen, Mindell, & Kirchner, 2010). The results showed that alpha-adrenergic agonists such as clonidine were the most commonly prescribed medications for insomnia in children with ADHD. Combining clonidine with other drugs is also a safety issue, as there have been several reported cases of sudden death in children treated with clonidine and methylphenidate (Biederman & Spencer, 1999).

**1.4.4 Other relevant drugs**

Atomoxetine hydrochloride is a centrally acting sympathomimetic that is marketed under the trade name of Strattera. It is considered to be particularly useful in children who do not respond to stimulants, or who exhibit comorbid anxiety or depression (Pliszka, 2007). This drug received FDA approval for use in the treatment of ADHD in 2003 (Wolraich et al., 2007). It has come onto the market in Australia in recent years, and it became available on the Pharmaceutical Benefits Scheme (PBS) on July 1, 2007. Strattera inhibits serotonin and dopamine uptake, and it is also an inhibitor of the presynaptic noradrenaline transporter. Side effects include anorexia, dizziness, hostility, mood swings, and suicidal ideation. The
prescribing guidelines for Stattera in Australia include a red-letter warning that patients must be closely monitored for suicidality (Mims Online, 2007).

The newer antidepressants, such as moclobemide and fluoxetine, have been studied in some children with ADHD, and major tranquillisers, such as thioridazine, have also been used (Jarman, 1996).

1.5 Controversies surrounding the use of medical drugs for ADHD
Despite the ongoing debate in the literature about safety issues, due to the high level of efficacy the benefit-risk ratio is still thought to be one that is favourable for the use of medical drugs to treat ADHD (Wolraich et al., 2007). However, in addition to the safety concerns outlined in the previous section there are three other controversial issues surrounding drug treatment: the increasing use of stimulants, the prescribing of psychotropics to preschoolers, and off-label prescribing.

1.5.1 The increasing use of stimulants
No other treatment in the disciplines of psychology, paediatrics, or psychiatry has generated more controversy than the use of stimulants for treating children with ADHD (Jarman, 1996). This is despite the fact that many clinical trials have investigated the use of these drugs. As Lawrence Diller states in his book “Over the past thirty-five years, ADD [sic] has been the most extensively studied pediatric psychiatric condition and Ritalin the most extensively studied psychotropic drug in pediatrics” (Diller, 1998, p. 42). The controversy continues yet the number of prescriptions for stimulants has increased dramatically in recent years, including in Australia.

A significant increase in the prescribing of stimulants in Western Australia and New South Wales occurred between 1988 and 1993 (Valentine, Zubrick, & Sly, 1996). From 1984 to 2000 the rate of consumption of these drugs in Australia increased by 26% per year, with an increase of 8.46-fold between 1994 and 2000 (Berbatis, Sunderland, & Bulsara, 2002). A newspaper article cited Health Insurance Commission (HIC) figures regarding prescriptions for Dexamphetamine that showed a 20-fold rise in Australia between 1992 and 1999 (“Parents Breeding Pillpoppers”, 2000). Dexamphetamine was apparently the main stimulant drug prescribed in Australia at the time due to its listing on the PBS (Mackey & Kopras, 2001). The author of this thesis is unable to cite figures directly from the HIC. Despite
contacting them on several occasions during the early stages of this project her request for information was denied.

1.5.2 Psychotropic drugs and preschoolers
Two papers that were published in 2000, one in the *Journal of the American Medical Association (JAMA)* and the other in *The Medical Journal of Australia (MJA)*, documented the rise in the prescribing of psychotropics to preschoolers. In the *JAMA* paper it was revealed that there was a dramatic increase in the prescribing of psychotropics to preschoolers in the United States between 1991 and 1995 (Zito et al., 2000). The *MJA* paper, which was published later in the year, expressed concern about such trends also occurring in Australia. Indeed, it is already happening here. Children aged as young as 2 years are being prescribed stimulants. The *MJA* authors stated that there:

> was a 12-fold increase in the number of preschool children treated with stimulants between 1990 and 1999. There are no Australian data about the use of other psychotropic drugs in this age group, but our clinical experience shows that antidepressants, antipsychotics and clonidine are being used. (Rey, Walter, & Hazell, 2000, p. 172)

An Australian survey that was completed by 435 general paediatricians and 187 child and adolescent psychiatrists confirmed the above. Regarding the youngest age for which they had ever prescribed certain drugs, or drug categories, 10% of respondents reported that they had prescribed clonidine for a child younger than 3 years of age. The results for other relevant medications for children in this age range were 8% for methylphenidate, 7% for dexamphetamine, and 3% for tricyclic antidepressants (Efron et al., 2003).

It is interesting to note that the current prescribing guidelines for stimulants advise that methylphenidate should not be used in children under 6 years of age, and dexamphetamine is not recommended for use in children under 3 years of age (Mims Online, 2007).

1.5.3 Off-label prescribing
Off-label prescribing refers to the use of a drug for an indication that is not listed in the product information. It appears to be common in the treatment of ADHD. For example, the prescribing guidelines for clonidine in Australia do not list ADHD as an indication, nor do they mention the use of this medication in children generally (Mims Online, 2007). However,
Efron et al. (2003) noted a high level of clonidine prescribing in their survey study, despite a lack of information and the safety concerns outlined in sub-section 1.4.3.

1.6 The use of complementary and alternative medicine (CAM) in treating ADHD
Given the side effects of the relevant medical drugs, the fact that not all children respond to them, and the controversies surrounding their use, it is not surprising that various forms of CAM are commonly used in the treatment of children with ADHD. A survey study that was conducted in the United States obtained data from 114 families out of 203 who were deemed to be eligible. All of the 114 children had been referred for assessment regarding ADHD, although only 64 met the *DSM-IV* criteria for diagnosis. The overall results showed that 62 families (54%) reported using CAM in the previous year, and 36 of these children (58%) met the *DSM-IV* criteria for ADHD. The main therapies used were expressive therapies such as art and dance, however vitamins, dietary modification, dietary supplements, and herbal remedies also featured in the results (Chan, Rappaport, & Kemper, 2003).

Two studies have investigated the level of CAM usage in Australia. A survey study of families in Western Australia found that 64% of the 290 who responded had used or were currently using an alternative therapy, with the most common therapy being dietary modification (Stubberfield, Wray, & Parry, 1999). Multivitamins and naturopathic products were also used. There was a similar level of usage of alternatives by children taking stimulants and children who were not taking stimulants.

The results of a survey study of 75 children (75 returned surveys) in Melbourne revealed that 67.6% of families reported current or previous use of CAM. The treatments that had been tried or were being used were dietary modification, vitamins, minerals, aromatherapy, dietary supplements, chiropractic, naturopathic treatment, and herbs (Sinha & Efron, 2005). Only 8% of the children surveyed were not taking any orthodox ADHD medication at the time of the study. The main reason given for using CAM was to minimise the symptoms of ADHD, and the authors noted that 64% of families had told their paediatrician about their use of CAM.

1.7 The major CAM pharmacological treatment options for ADHD
The major CAM pharmacological treatment options for ADHD that are mentioned in the literature will be outlined in this section. As this thesis is solely concerned with pharmacological treatment other forms of treatment will not be included.
1.7.1 Essential fatty acids (EFAs)

It has been proposed that at least some features of ADHD may reflect an abnormality of fatty acid metabolism. With regard to long-chain polyunsaturated fatty acids (LC-PUFAs) the authors of a review paper stated that:

The consistent findings of both clinical signs of fatty acid deficiency and blood biochemical indices of fatty acid abnormalities in at least a subset of ADHD children [sic] indicate that supplementation with LC-PUFAs might be helpful in at least some cases. (Richardson & Puri, 2000, p. 84)

They concluded that up to 3 months is needed for the benefits of such treatment to be seen, and they also stressed the need for further studies. However, a review that considered four supplementation studies of fatty acids for ADHD and related conditions noted mixed results (Hallahan & Garland, 2004).

Evening primrose oil and fish oil are the main supplements that are used, either on their own or in various combinations. For example, a product called Efalex™ is marketed for the treatment of ADHD. It contains evening primrose oil, fish oil, vitamin E, and thyme oil (Efalex™ Product Information, n.d.). The references given in the information sheet are three papers on fatty acids rather than clinical data on the product itself.

The National Health Service (NHS) in the United Kingdom has published a review of such products in response to claims that have been made in the media. The author noted that many studies are unpublished, that a number are uncontrolled, and concluded that:

There is limited evidence that supplementation with omega-3 and omega-6 PUFAs may improve behaviour and concentration in children with behavioural and/or learning problems. The evidence is insufficient to support the routine use of these supplements in the management of children with attention-deficit hyperactivity disorder (ADHD). (Sullivan, 2006, p. 3)

1.7.2 Minerals

Zinc

Zinc deficiency has been hypothesised as a cause of ADHD, however controlled studies are lacking (Baumgaertel, 1999). There has been some mention in the literature of a link between
EFAs and zinc. An investigation into serum free fatty acids (FFAs) and zinc was carried out in children with ADHD and controls. Results showed significantly lower levels for both FFAs and zinc levels in the ADHD group. There was also a statistically significant correlation in the ADHD group, but not in the control group, between decreased FFAs and zinc (Bekaroglu et al., 1996).

A study has been conducted to assess the relationship of zinc nutrition status to EFAs supplementation (Efamol) and stimulant effects (dexamphetamine) (Arnold, Pinkham, & Votolato, 2000). In a placebo-controlled double blind crossover treatment comparison, 18 participants were classified as adequate, borderline, or deficient regarding zinc status. The classification was based on three criteria: hair, red cell, and urine zinc levels. Efamol was only of benefit with borderline zinc levels. The researchers commented that their data suggest that zinc nutrition status may be important for the treatment of ADHD, and that if Efamol benefits children with ADHD it probably does so by improving or compensating for borderline zinc levels. They concluded that further studies are needed.

Magnesium

A study on magnesium found a deficiency in 95% of a group of children with ADHD. Magnesium levels were measured in hair, red blood cells, and serum (Kozielec & Starobrat-Hermelin, 1997). According to Baumgaertel (1999) the same researchers conducted another study which revealed that children with ADHD who had a concurrent magnesium deficiency showed behavioural improvement after 6 months of supplementation.

Iron

A case report of a 3-year-old boy has documented the use of an iron supplement to treat ADHD. The child met the DSM-IV criteria for the diagnosis of ADHD, and this was supported by an assessment of the information provided by his parents and kindergarten teachers. A blood test revealed that he was not anaemic, however his serum ferritin level was low. The iron supplement was prescribed for 8 months, and it lead to an improvement in daytime behaviour and sleep (Konofal, Cortese, Lecendreux, Arnulf, & Mouren, 2005).

1.7.3 Homoeopathic Remedies

There are anecdotal claims of homoeopathic remedies being effective for the treatment of ADHD (Baumgaertel, 1999). In brief, homoeopathy, also known as homeopathy, is a system of medicine that uses specially prepared remedies, and they are prescribed for patients on an
individual basis by matching the profile of the remedy to the profile of the patient. A systematic review of randomised controlled trials of homeopathy for the treatment of various ailments in children and adolescents identified three trials concerning ADHD. Two trials reported beneficial effects, while the third found no differences between groups (Altunç, Pittler, & Ernst, 2007). However, due to the nature of homoeopathic treatment it is difficult to test its efficacy under scientific trial conditions. For this reason the Swiss research group that conducted one of the beneficial trials has decided to investigate unconventional study designs in an attempt to enable further scientific evaluation of homoeopathic remedies for ADHD (Frei et al., 2007).

1.7.4 Phosphatidylerine (PS)
PS is a phospholipid that has been trialled for the treatment of dementia, and it is a constituent of some over-the-counter products for ADHD in the United States (Baumgaertel, 1999). It is available in Australia. A technical information sheet refers to ADD as a clinical application, however no ADD or ADHD research publications, or references specific to the disorder, are provided (Eagle Pharmaceuticals, n.d.). Two unpublished open pilot studies in children found that PS improved attention, learning, and behaviour in 15 out of 20 children aged 4 to 19 years. It is claimed to reinforce concurrent treatment such as Ritalin so presumably the children had ADHD but no further details are given (Kidd, 1999). A paper by the same author mentions an in-office physician study of 21 children with ADHD aged 4 to 19 years. PS resulted in improvement in over 90% of the children. The supplement was given for up to 4 months (Kidd, 2000).

1.7.5 Pycnogenol ®
Pycnogenol ® is a standardised extract derived from the bark of the French maritime pine tree (*Pinus pinaster*). It has been promoted as a miracle treatment for ADHD in the United States despite a lack of scientific evidence (Baumgaertel, 1999). According to a website clinical trials were being conducted in the United States however no details were provided (Fairborne Pycnogenol Monograph #2, 1996). In addition, claims said to be based on “scientific research in humans” state that it “alleviates the symptoms of ADD” [*sic*] however no references are given (Hyperhealth, 1998).

Some case reports have attested to its efficacy and a clinical trial has recently been conducted in Europe. A randomised placebo-controlled double blind parallel study investigated the use of Pycnogenol ® in 61 children aged from 6 to 14 years. The children were diagnosed
according to the *ICD-10* criteria for Hyperkinetic Disorder, Hyperkinetic Conduct Disorder, and Attention Deficit without Hyperactivity. The ratio for active treatment to placebo was 2.5:1, therefore 44 participants received Pycnogenol® and 17 received placebo. The trial lasted for 1 month, and the measures consisted of a psychiatric examination, and parent and teacher rating scales. The results revealed a significant reduction in hyperactivity, and an improvement in attention, concentration, and visual-motoric co-ordination in the treatment group. No positive effects were noted for placebo (Trebatická et al., 2006).

1.7.6 Herbs

Herbal medicines are popular remedies for ADHD, despite the fact that their use as a sole treatment or as a complementary treatment has not been systematically studied (Chan, Gardiner, & Kemper, 2000). Herbs that promote cognition are used to treat attention deficits; herbs that have relaxant or sedative effects are used for treating hyperactivity; and herbs that are classed as hypnotics are used for treating the sleep problems that often accompany the disorder.

*Herbs to promote cognition*

Ginkgo (*Ginkgo biloba*) is a cognition enhancer that has been extensively studied in adults for the treatment of conditions such as dementia. Due to its beneficial effects on cognition it is often used for treating ADHD. It is apparently used in Germany for this purpose (Chan et al., 2000).

Bacopa (*Bacopa monniera*) is a nootropic herb. The investigator is aware of anecdotal evidence from herbal practitioners suggesting that it is a “good” herb to use for treating ADHD. In addition, a survey of the prescribing patterns of 23 practitioners found that 31% nominated bacopa as their “first choice” herb for treating this disorder (Francis, 1999).

Herbs that are recommended for memory problems are also considered relevant for ADHD. For example, gotu kola (*Centella asiatica*), withania (*Withania somnifera*), basil (*Ocimum basilicum*), and rosemary (*Rosmarinus officinalis*) (Romm, 2004).

*Herbs that are relaxant, sedative, and/or hypnotic*

There are several plants in this category. Valerian (*Valeriana officinalis*), lemon balm (*Melissa officinalis*), chamomile (*Matricaria recutita*), passionflower (*Passiflora incarnata*), and hops (*Humulus lupulus*) are marketed as over-the-counter remedies for the nervous
system, and for the treatment of sleep problems associated with ADHD, in the United States (Chan et al., 2000). However, with regard to non-prescription products for treating insomnia associated with ADHD, herbal remedies such as valerian and chamomile were recommended by a relatively low number of the child and adolescent psychiatrists surveyed by Owens et al. (2010) in comparison to the prescribing rates for orthodox medical drugs.

Herbs such as oats (*Avena sativa*), skullcap (*Scutellaria lateriflora*), lavender (*Lavandula officinalis*), and wood betony (*Stackys officinalis*) may also be used to calm the nervous system, and to treat hyperactivity (Romm, 2004).

**Sources of herbal information regarding ADHD**

A survey study of herbal use in children with ADHD or depression in the United States found that almost 80% of the caregivers who had administered herbs supervised their child’s herbal treatment without communicating with a health care professional. Their choice of herbs was based on the recommendations of friends, relatives, or health food shop staff (Cala, Crison, & Baumgartner, 2003). Ginkgo and St John’s Wort (*Hypericum perforatum*) were the main herbs used.

It is not known if the same situation exists regarding caregivers in Australia. As per section 1.6, 64% of Melbourne families who were surveyed had told their paediatrician about their use of CAM. However, the author of this thesis does not know of any research showing how many children with ADHD receive herbal treatment that is prescribed by naturopaths and other qualified practitioners, and how many receive it as a result of information that is in the media, on the internet, provided by product manufacturers, or derived from other sources. These issues are of concern, especially given the possibility of interactions, however they are beyond the scope of the current study.

**1.8 The rationale for this research project**

This research project is an original study, and as far as the author of this thesis is aware it is still the first major study of its type. The initial idea for the topic arose out of her interest in the increasing use of medical drugs to treat ADHD. Despite the fact that she had never treated this condition during 10 years in clinical practice as a naturopath and herbalist, she had seen a media item regarding the increasing use of stimulants and wondered if herbs could play a role.
The project was originally going to focus on daytime behaviour, however a previous project that had been conducted at RMIT University had found some benefit regarding the herb Mexican valerian (*Valeriana edulis*) and the treatment of sleep problems in children with intellectual deficits and hyperactivity. Therefore the senior supervisor suggested that the study should include sleep. In addition, when the topic of ADHD was suggested to the project consultant it was found that MediHerb Pty Ltd was interested in supporting research in this area.

As per sub-section 1.1.3 ADHD is a chronic disorder, and as per section 1.4 medical drugs are the most commonly used form of treatment. However, not all children respond, and the medications that are used have many side effects. At present there is no generally accepted alternative pharmacological treatment option for the children who do not respond to the ADHD medical drugs, or cannot tolerate them.

Furthermore, numerous scientific studies have investigated the relevant medical drugs, especially the stimulants, whereas relatively few scientific studies have investigated the use of CAM for treating ADHD. During the initial planning phase of this project in late 1999 and early 2000 no scientific research was found regarding the use of herbs for treating this disorder. Thus the aim of this study was to see if certain herbal medicines (phytomedicines) could provide an alternative pharmacological treatment for ADHD symptomatology and associated sleep problems in terms of safety, tolerability, and efficacy.

### 1.9 The herbs used in this research project

This section consists of monographs for each of the eight herbs used in the project: ginkgo, bacopa, paony, St John’s Wort, valerian, skullcap, passionflower, and chamomile. The monographs focus on information that is relevant to the research topic. Other actions and indications for these plants, for example the use of St John’s Wort as an anti-viral agent, and the use of chamomile for the treatment of digestive disorders, have not been included. The monographs have been prepared using standard headings as follows:

- Herb names (common and Latin)
- Family
- Part used
- Relevant chemical constituents
- Actions
• Traditional use
• Indications
• Contraindications and drug interactions
• Adverse effects
• Use in children
• Rationale for use in this study

Various herbs were considered during the initial meetings that were held between the investigator, senior supervisor, and project consultant before the final selection was made. Herbal pharmacology, actions, and indications were areas that were canvassed. In addition, the scientific research that was available at the time regarding certain plants, traditional use, and the clinical experience of the project consultant in treating ADHD, were also discussed.

All of the trial herbs are commonly used in the practice of herbal medicine in Australia, and five have approved status in the Commission E monographs: ginkgo, St John’s Wort, valerian, passionflower, and chamomile. Commission E is the expert interdisciplinary committee for herbal drugs that was established by the German government. Their monographs have been published in English, and they are recognised internationally as a scientific herbal medicine reference text (Blumenthal et al., 1998).

The herbs were administered to the participants in tablet form. The rationale for this, and full details of the trial products, including constituent profiles, dosages, and the means of administration, will be presented in Chapter 2, sub-section 2.3.1. As the study was a clinical trial individual prescribing was not possible. Nor was making any adjustment regarding the level of dosage of individual herbs. Both are the norm in professional herbal practice irrespective of the condition that is being treated.

1.9.1 Ginkgo Ginkgo biloba

Family
Ginkgoaceae

Part used
The leaves.
**Relevant chemical constituents**

Ginkgo contains flavone glycosides and terpenoids (ginkgolides and bilobalide).

**Actions**

Ginkgo is an antioxidant, tissue perfusion enhancer, circulatory stimulant, and nootropic. It is likely that the pharmacodynamic effect of this herb results from a combination of free radical scavenging activity, platelet activating factor antagonistic effects, and the modulation of cholinergic function (Nathan, 2000).

**Traditional use**

Ginkgo leaves were not used in traditional herbal medicine (Mills & Bone, 2000).

**Indications**

Numerous clinical trials have been conducted on the standardised extract of ginkgo since the research into this herb commenced in the 1960s (Mills & Bone, 2000). The effects of ginkgo include increased cerebral blood flow, increased tissue oxygenation and nutrition, and enhanced memory and cognitive function. Based on clinical trials ginkgo is indicated in the treatment of disorders due to restricted cerebral blood flow, including memory and/or cognitive impairment. Nine randomised placebo-controlled double blind trials were assessed in a systematic review, and they were found to collectively suggest that ginkgo is more effective than placebo for treating dementia (Ernst & Pittler, 1999).

Some of the more recent research on this herb has studied its use as a nootropic in healthy populations. For example, a randomised placebo-controlled double blind study that investigated the cognitive effects of ginkgo in healthy university students found that acute administration resulted in an improvement in sustained attention, and memory (Elsabagh, Hartley, Ali, Williamson, & File, 2005). However, a recent systematic review of 15 randomised clinical trials found no convincing evidence of a beneficial effect from ginkgo products, either given as a single dose or administered over a longer period of time, on any aspect of cognition in healthy people aged less than 60 years (Canter & Ernst, 2007).

**Contraindications and drug interactions**

It is recommended that caution be exercised if patients are on anticoagulant or antiplatelet medication, and in individuals with coagulation disorders (Mills & Bone, 2005). The only
known contraindication for the use of ginkgo is hypersensitivity to ginkgo preparations (Blumenthal et al., 1998; Schulz, Hänsel, & Tyler, 1998).

**Adverse effects**

Ginkgo is well tolerated, and no toxic side effects have been reported (Weiss, 1988). Willard (1991) reports that despite extensive toxicity studies on this herb virtually none was found. Side effects are very rare, consisting of mild gastric upset, headache, or allergic skin reactions (Blumenthal et al., 1998; Schulz et al., 1998). A Cochrane review of randomised double blind controlled studies found no significant differences between the herb and placebo regarding the number of participants who experienced adverse events (Birks & Grimley Evans, 2002).

**Use in children**

There is a paucity of published information regarding the use of this herb in children as the extensive scientific research that has been conducted has mainly involved adults. Two case reports of boys with Down Syndrome found improvement in academic and social skills after 3 months of treatment with a standardised extract (Donfrancesco & Dell’uomo, 2004). One child exhibited better control of impulsiveness. An open-label trial has investigated the use of ginkgo in the treatment of dyslexia in 15 children aged from 5 to 13 years (Donfrancesco & Ferrante, 2007). The children were diagnosed according to the DSM-IV-TR criteria for the condition, and they were given 80 mg of ginkgo each morning for an average of 34.4 days. A statistically significant and clinically meaningful improvement was found, and at the end of the study some of the children no longer met the DSM-IV-TR criteria for dyslexia. The authors concluded that a randomised double blind trial should be carried out involving a larger number of participants, and including a repeat dose of ginkgo later in the day.

Ginkgo is often present in herbal remedies for ADHD although reports of benefit are anecdotal (Baumgaertel, 1999). A product called AD-FX™ was investigated in a Canadian pilot study (Lyon et al., 2001). This product is a capsule containing a combination of 200 mg of American ginseng (*Panax quinquefolium*) and 50 mg of ginkgo. The study was an open trial of 36 children aged from 3 to 17 years that lasted for 4 weeks. Only one measure was used, the long version of the Conners’ Parent Rating Scale-Revised (CPRS-R), and some beneficial effects were found.

More recently, two papers have been published concerning the use of ginkgo as a simple, or single herb, in the treatment of children with ADD and ADHD respectively. A small open
trial involving 6 participants who met the DSM-III-R criteria for ADD was conducted in a clinic setting (Niederhofer, 2010). The children were aged from 17 to 19 years, and they received a set dose of ginkgo for 4 weeks. Wender Utah ratings were used as the sole outcome measure, and at the end of the trial all patients reported significant improvement in their ADD symptoms. The author concluded that ginkgo might be beneficial for the treatment of ADD.

In contrast, a randomised double blind parallel trial compared ginkgo with methylphenidate in 50 children who had been diagnosed with ADHD according to DSM-IV-TR criteria (Salehi et al., 2010). The children were aged from 6 to 14 years, and the study lasted for 6 weeks. The main outcome measure was the Teacher and Parent ADHD Rating Scale-IV, and significant differences were observed between the two groups. However, the authors concluded that the results of their study do not support the use of ginkgo in the treatment of ADHD.

Rationale for use in this study

Ginkgo was chosen due to its beneficial effects on cerebral blood flow. As per sub-section 1.3.1, several neuroimaging studies have shown that children with ADHD have hypoperfusion in certain areas of the brain, for example, the striatum. In some of these studies the stimulant drug methylphenidate was administered, and this led to an increase in blood flow to the hypoperfused regions.

1.9.2 Bacopa *Bacopa monnieri* (also known as *Bacopa monniera and Herpestris monierra*)

*Family*

Scrophulariaceae

*Part used*

The whole plant.

*Relevant chemical constituents*

Bacopa contains saponins (bacosides A and B), bacosine, and flavonoids.

*Actions*

This herb is a nervine tonic, nootropic, and anxiolytic. Various animal studies have been conducted however the exact mechanism of action is uncertain. It has been suggested that bacopa results in cognitive enhancing and neuroprotective effects due to its ability to modulate the cholinergic system, and counteract oxidative stress (Russo & Borrelli, 2005).
Traditional use
Bacopa is the most important nerve tonic in Ayurveda (a form of traditional Indian medicine). Traditional use includes the treatment of epilepsy, debility, nervous breakdown, and insanity (Mills & Bone, 2005).

Indications
This herb is used to improve memory, concentration, and learning (Bone, 1996).

Contraindications and drug interactions
No information has been found.

Adverse effects
Adverse effects are not expected for therapeutic doses of bacopa (Morgan & Bone, 1999). The herb has been found to be well tolerated, and without side effects, in toxicological and pharmacological studies (Russo & Borrelli, 2005). The bacosides were well tolerated by healthy human volunteers in a double blind placebo-controlled trial (Singh & Dhawan, 1997).

Use in children
This herb is used in the treatment of children in Ayurveda (Mills & Bone, 2005). Placebo-controlled clinical studies have been conducted on its nootropic effects in children, and these have shown a beneficial effect (Abhang, 1993; Sharma, Chaturvedi, & Tewari, 1987).

A placebo-controlled study of children with mild to moderate “mental deficiency” found that bacopa significantly increased concentration ability, memory span, and overall mental performance. The herb was administered in syrup form, and it was given three times a day for a year (Agrawal, Pandey, & Dubey, 1993).

A randomised double blind placebo-controlled trial of a standardised extract of bacopa was conducted in 36 children with ADHD. The children were evaluated by using various tests, and there was a significant improvement in sentence repetition, logical memory, and paired associate learning after 12 weeks (Negi et al., 2000).

Rationale for use in this study
Bacopa was selected because of its long history of traditional use in Ayurveda, including a role in the treatment of children. In addition, as per sub-section 1.7.6, it also has a strong
anecdotal reputation amongst herbal practitioners as a valuable herb for the treatment of ADHD.

1.9.3 Paeony (also known as Peony) *Paeonia lactiflora* (also known as *Paeonia albiflora*)

*Family*
Ranunculaceae

*Part used*
The root.

*Relevant chemical constituents*
Paony contains a monoterpane glycoside called paeoniflorin.

*Actions*
Paony is a cognition enhancer (Bone, 1996). Paeoniflorin improved deficits in working memory that had been induced by the effects of scopolamine in an animal study. It was suggested that the mechanism of action involves the central cholinergic system (Ohta, Ni, Matsumoto, Watanabe, & Shimizu, 1993).

*Traditional use*
This herb is used in traditional systems of medicine to treat dementia (World Health Organization [WHO], 1999). It has been used for thousands of years in Chinese medicine (Foster & Chongxi, 1992). A search of the literature found reference to its use in various traditional combinations.

*Indications*
Paony is used to assist memory (Bone, 1996). It is used to treat epilepsy in Japan and China in combination with other herbs.

*Contraindications and drug interactions*
No information has been found.

*Adverse effects*
No information is available regarding adverse reactions to paony (WHO, 1999).
**Use in children**

A Chinese formula that contains paeony has been trialled in the treatment of “hyperkinesia” in children. The results revealed an improvement in behaviour and school marks, and a decrease in the rate of “soft neurotic signs” (Sun et al., 1994).

More recently, a randomised double blind placebo-controlled clinical trial of a compound herbal preparation recruited 120 children aged from 6 to 12 years (Katz, Adar Levine, Kol-Degani, & Kav-Venaki, 2010). The children were diagnosed with ADHD according to DSM-IV criteria. The study was a parallel trial of 4 months duration, and the compound herbal preparation was administered as a liquid product. It contained six primary herbs, including bacopa and paeony. No other herbs are listed, and no proportions are specified. The placebo product was also a liquid, and it was designed to be very similar to the active product in relation to taste, odour, and appearance. However, the formula for the placebo product is not provided. The test of variables of attention (TOVA) was used as the sole outcome measure, and there was a significant improvement in the treatment group. As there was no significant difference in TOVA scores for the control group the authors concluded that their product may be an effective treatment for ADHD.

**Rationale for use in this study**

Paeony was included due to its action as a cognition enhancer based on traditional use, and the research that has been conducted on the constituent paeoniflorin.

1.9.4 St John’s Wort (also known as Hypericum) *Hypericum perforatum*

**Family**

Guttiferae

**Part used**

The aerial parts.

**Relevant chemical constituents**

St John’s Wort contains naphthodianthrones (hypericin and pseudohypericin), flavonoids, and a phenolic compound called hyperforin.
**Actions**

This herb is an antidepressant and nerve tonic. Numerous *in vitro* and animal studies have been conducted in an attempt to elucidate the mechanism of action, and various effects have been found. For example, St John’s Wort weakly inhibits MAO activity, and it also inhibits the synaptosomal uptake of serotonin, dopamine, and noradrenaline. There is also increased affinity for gamma amino butyric acid (GABA) receptors, and an increase in the density of dopaminergic and serotonergic receptors (Butterweck, 2003; Rodriguez-Landa & Contreras, 2003).

A randomised double blind placebo-controlled crossover study of 16 healthy human participants found that St John’s Wort did not affect plasma concentrations of norepinephrine and its main metabolite dihydroxyphenylglycol. However, plasma concentrations of dihydroxyphenylacetic acid, the main metabolite of dopamine, increased in every participant, leading the authors to conclude that this finding might suggest a previously unknown mechanism of action that should be investigated by *in vitro* studies (Schroeder et al., 2004).

**Traditional use**

In traditional herbal medicine St John’s Wort was used for the treatment of nervous system complaints, particularly for conditions such as excitability (Mills & Bone, 2000).

**Indications**

Indications for use that are supported by clinical trials include the treatment of mild to moderate depression, and the treatment of anxiety (Kim, Streltzer, & Goebert, 1999; Schulz et al., 1998). The efficacy of this herb is comparable to that of antidepressant drugs (Mills & Bone, 2005).

**Contraindications and drug interactions**

According to Blumenthal et al. (1998) there are no known contraindications for St John’s Wort, and no known drug interactions. However, information that was published at a later date suggested that St John’s Wort might interact with certain medical drugs affecting their activity (Ernst, 1999). This information came to light during the initial planning of this study in 2000. To avoid any possibility of interaction the drugs concerned were listed in the exclusion criteria.
A recent case report has suggested that St John’s Wort should be used cautiously in individuals who are concurrently taking methylphenidate (Niederhofer, 2007). The report describes an adult patient aged 22 years who was taking methylphenidate for 6 months after being diagnosed with ADHD. The drug treatment resulted in a significant improvement in his ADHD symptomatology as measured by his “Conner’s score” [sic]. However, he began taking St John’s Wort on a self-prescribed basis, and his score deteriorated. Three weeks after ceasing the herbal product, which he apparently took for 4 months, his ADHD improved. The author of the report notes that there were no adverse events in relation to either the drug or the herb, however they comment that the herb appeared to decrease the efficacy of the drug.

**Adverse effects**

Adverse effects are rare from the use of St John’s Wort at normal dosages (Mills & Bone, 2000). This herb is well tolerated, with an incidence of adverse reactions in the literature that is similar to that of placebo (Ernst, Rand, Barnes, & Stevinson, 1998). The most common reactions are gastrointestinal symptoms, dizziness, confusion, and tiredness. Photosensitivity has been cited as a possible adverse reaction, especially in individuals with fair skin (Blumenthal et al., 1998). This condition can occur in light skinned grazing animals if they consume large amounts of St John’s Wort, however it is considered to be extremely rare in humans (Ernst et al., 1998). Indeed, severe skin reactions have not been reported in humans, and the overall safety profile of this herb as a standardised extract is more favourable than that of synthetic antidepressant drugs (Schulz, 2006).

**Use in children**

This herb is used in the treatment of enuresis and night terrors in children (Weiss, 1988). St John’s Wort products are approved for use as antidepressants in Germany, and this includes their labelling for use in the treatment of children (Fegert, Kölch, Zito, Gläcske, & Janhsen, 2006).

The majority of the research papers on St John’s Wort involve adults however three studies have been published regarding children with depression. A multi-centre post-marketing surveillance study investigated the use of St John’s Wort for a minimum of 4 weeks in 101 children under 12 years of age with symptoms of depression and psychovegetative disturbances. There was a beneficial effect for all symptoms, and no adverse events were reported (Hübner & Kirste, 2001). Two open-label pilot studies of major depressive disorder have been conducted in North America. Both studies were 8 weeks in duration. The first
study investigated 33 participants aged from 6 to 16 years, and it included medical monitoring in addition to psychometric measures. No changes in serotonin blood levels were found, however beneficial thymoleptic effects were observed (Findling et al., 2003). The second study enrolled 26 participants aged from 12 to 17 years, and 15 did not complete the study. However, the majority of those who did complete the study demonstrated clinical improvements (Simeon, Nixon, Milin, Jovanovic, & Walker, 2005). The authors of both papers concluded that St John’s Wort is well tolerated, and that placebo-controlled trials are indicated.

A randomised placebo-controlled double blind parallel clinical trial investigating the use of St John’s Wort in the treatment of ADHD in children has recently been conducted in the United States (Weber et al., 2008). It was supported by government grants (National Center for Complementary & Alternative Medicine [NCCAM], 2005), and 54 children aged from 6 to 17 years took part. The children were diagnosed with ADHD according to DSM-IV criteria, and they were randomised following a placebo run-in phase, with an equal number of participants in each group. The active and placebo products were both administered as capsules, and the herb group received one capsule (300 mg) of St John’s Wort three times a day. The trial lasted for 8 weeks, and the main outcome measures were the ADHD Rating Scale-IV, the Clinical Global Impression Improvement Scale, and an adverse events assessment. The St John’s Wort capsules had no additional effect beyond placebo, however the authors concluded that it is possible that this herb may work in conjunction with other CAM remedies. They also discuss the possibility of oxidation affecting the active product due to it being given in capsule form. There was no statistically significant difference between the two groups for adverse events.

Rationale for use in this study
St John’s Wort was selected due to its traditional use for nervous system complaints, and its demonstrated effects on neurotransmitters.

1.9.5 Valerian Valeriana officinalis

Family
Valerianaceae

Part used
The root and rhizome (underground stem).
Relevant chemical constituents
Valerian contains iridoids (valeropatriates), an essential oil, and a non-volatile cyclopentane sesquiterpene (valerenic acid). Recent research has identified other constituents including a flavone glycoside (linarin).

Actions
This herb is a hypnotic. It also acts as an anxiolytic and mild sedative (Mills & Bone, 2000). Considerable research has been undertaken in an attempt to identify the mechanism of action. It appears that the actions of valerian are due to the presence of various constituents, and the potentiating effects that are a result of their combination. For example, in animal studies linarin has shown sedative and sleep enhancing effects that are potentiated by the simultaneous use of valerenic acid (Fernández, Wasowski, Paladini, & Marder, 2004).

Traditional use
Valerian was traditionally used to promote sleep, and as an anxiolytic for nervous unrest.

Indications
Valerian improves sleep latency and sleep quality, lowers periods of wakefulness, and reduces anxiety (Mills & Bone, 2000). Clinical trials have provided some support for the indications of insomnia, restlessness, and nervous tension. A recent systematic review and meta-analysis of 16 randomised placebo-controlled trials for sleep found that valerian might improve sleep quality without causing side effects (Bent, Padula, Moore, Patterson, & Mehling, 2006). However, eight of the studies were small as they featured less than 25 participants. In addition, several methodological problems were noted, although the authors commented that methodological problems are also common in controlled trials of medical drugs used for the treatment of insomnia. They concluded that further studies investigating valerian should be given high priority.

Contraindications and drug interactions
There are no known contraindications or drug interactions (Blumenthal et al., 1998; Bradley, 1992).

Adverse effects
There are no known side effects for valerian (Blumenthal et al., 1998; Schulz et al., 1998; Scientific Committee of European Scientific Cooperative On Phytotherapy [ESCOP], 1997).
The authors of a clinical trial paper commented on the extremely low number of adverse events during the valerian treatment periods (Donath et al., 2000). The adverse events consisted of one attack of previously known migraine, one episode of gastrointestinal complaints, and one complaint relating to the use of PSG equipment. A systematic review of randomised placebo-controlled double blind trials found that reports of adverse events due to valerian were rare. In addition, the adverse events that occurred were mild, and they were similar to the events that resulted from the use of placebo (Stevinson & Ernst, 2000).

Use in children

There is a dearth of available scientific information regarding the use of this plant in children. Clinical trials have been conducted using a valerian tablet called Valdispert ®. The results have apparently confirmed the Commission E indications for valerian - restlessness, and sleeping disorders due to nervous conditions - however the original papers are published in German (Schücher, 1997).

An RMIT University study investigated the effect of a related plant known as Mexican valerian or Valeriana edulis on sleep problems in 5 children with intellectual deficits. A randomised placebo-controlled double blind crossover design was employed. The results showed reductions in sleep latency and time awake at night, and improvements in total sleep time and sleep quality. In addition, the improvements in sleep resulted in improvements in daytime behaviour, especially in relation to hyperactivity (Francis & Dempster, 2002). A tablet called Euvegal ® forte was investigated in an open multi-centre post-marketing surveillance study of 918 children (out of 938 recruited participants) aged less than 12 years with restlessness and dyssomnia. Each tablet contains 160 mg of valerian and 80 mg of lemon balm (Melissa officinalis). The children were treated for at least 4 weeks using a dosage level determined by the investigator. The treatment was found to be effective, and it was well tolerated (Müller & Klement, 2006).

Rationale for use in this study

Valerian was chosen due to traditional use, and the results of scientific research, including the beneficial effects that were found in the previous study that was conducted at RMIT University using a related species.
1.9.6 Skullcap *Scutellaria lateriflora*

*Family*
Labiatae

*Part used*
The aerial parts.

*Relevant chemical constituents*
Skullcap contains flavonoids (baicalein and scutellarein) and their glycosides (baicalin and scutellarin). Other flavonoids are also present (apigenin, hispidulin, and luteolin) (Wohlmuth, n.d.).

*Actions*
Skullcap is a mild sedative, and a nerve tonic (Mills & Bone, 2005). The scientific literature concerning this herb is limited as very little research has been conducted. An animal study investigated the anxiolytic properties of skullcap in rats, and beneficial effects were found. The authors propose that the anxiolytic effects are due to baicalein and baicalin, as these constituents bind to the benzodiazepine site of the GABA<sub>A</sub> receptor (Awad et al., 2003).

*Traditional use*
Skullcap has traditionally been used to treat insomnia, excitability, and restlessness (Willard, 1991).

*Indications*
This herb is used to treat nervous exhaustion, tension, anxiety, insomnia, and restless sleep (Fisher & Painter, 1996). A double blind placebo-controlled crossover study investigated the anxiolytic effects of skullcap in 19 “healthy volunteers”. A non-validated subjective rating scale was used to assess the influence of the treatment on energy, cognition, and anxiety. Three skullcap preparations were compared to placebo, and all showed beneficial effects regarding anxiety, and milder effects regarding energy and cognition (Wolfson & Hoffmann, 2003).

*Contraindications and drug interactions*
No information has been found.
Adverse effects

No information has been found. There have been several case reports of skullcap causing hepatotoxicity, however these are now recognised as cases of substitution or adulteration (Mills & Bone, 2005). There are no known cases of hepatotoxicity occurring as a result of the use of authenticated Scutellaria lateriflora (K. Bone, personal communication, September 30, 2000).

Use in children

Skullcap infusion, or tea, has some history of traditional use as a remedy for teething children (Mills & Bone, 2005).

Rationale for use in this study

Skullcap was used based on traditional indications. It was also included to stabilise the nervous system throughout the following day.

1.9.7 Passionflower Passiflora incarnata

Family

Passifloraceae

Part used

The aerial parts.

Relevant chemical constituents

Passionflower contains flavonoids (including apigenin and luteolin) and indole alkaloids (including harman). The levels of the various alkaloids appear to depend upon how the plant has been grown, and the stage of growth (Dhawan, Dhawan, & Sharma, 2004; Mills & Bone, 2005).

Actions

This plant is an anxiolytic. It is also a mild sedative, and a hypnotic (Mills & Bone, 2005). Scientific research regarding the pharmacology of passionflower, and its mechanism of action, is limited. An in vitro study of three receptor binding sites - benzodiazepine, dopamine, and histamine - provided no indication of how the herb acts at a molecular level (Burkard et al., 1997). A dose-related anxiolytic effect has been demonstrated in an animal study (Dhawan, Kumar, & Sharma, 2001).
Traditional use

Passionflower has traditionally been used to promote sleep (Schulz et al., 1998).

Indications

Passionflower is indicated in the treatment of insomnia, restlessness, and anxiety (Fisher & Painter, 1996) however little scientific research has been conducted. A randomised double blind trial compared passionflower with oxazepam in the treatment of generalised anxiety disorder in 36 participants. The participants received passionflower extract plus placebo tablets, or oxazepam plus placebo drops for 4 weeks. The study found no significant difference in efficacy between the two treatments. Passionflower was slower in terms of the onset of action, however it resulted in a lower incidence of problems that impaired work performance (Akhondzadeh, Naghavi et al., 2001). Another randomised double blind study compared clonidine and passionflower extract with clonidine and placebo in the detoxification treatment of outpatients undergoing opiate withdrawal. Both treatments were effective in terms of the physical symptoms of withdrawal, however the treatment that included passionflower demonstrated a significantly superior effect over clonidine on its own regarding the management of mental symptoms (Akhondzadeh, Kashani et al., 2001).

A case report has documented the use of a product called Calmanervin as a pre-medication prior to anaesthesia (Yaniv, Segal, Trau, Auslander, & Perel, 1995). Each tablet contains 250 mg of passionflower and 60 mg of valerian, in addition to 10 mg of thiamine and 10 mg of pyridoxine. The number of tablets administered is not specified, however the authors comment on the favourable sedation effect that was achieved without the side effects of the standard pre-medication drugs. More recently, a randomised double blind placebo-controlled study has investigated the use of passionflower on its own as a pre-medication (Movafegh, Alizadeh, Hajimohamadi, Esfahani, & Nejatfar, 2008). Sixty adult patients were randomised into two equal groups, and they received passionflower (500 mg) or placebo 90 minutes before surgery. Both products were administered as tablets. The patients in the active group demonstrated significantly lower levels of anxiety compared with the patients who were given the placebo. No side effects were noted.

Contraindications and drug interactions

There are no known contraindications or drug interactions (Blumenthal et al., 1998; Mills & Bone, 2005).
**Adverse effects**

Adverse reactions to passionflower are rare, and they are usually of an allergic nature (Mills & Bone, 2005). A case report has documented gastrointestinal and cardiovascular signs and symptoms in a woman 34 years of age who self-medicated using a passionflower product that she purchased from a supermarket. The product was apparently consumed within the therapeutic dose range, and it was later verified by government analysis. The authors noted that there are few reports of toxicity associated with the use of this herb (Fisher, Purcell, & Le Couteur, 2000).

**Use in children**

There is very little published information regarding the use of passionflower in children. It has been recommended as a tea for the treatment of nervous restlessness (Schilcher, 1997). Indeed, the author of an early paper wrote that:

> In cases of nervousness, the result of pain, the drug is of no use, but in those cases in which there is mental unrest, agitation, worry and exhaustion, when the patient sleeps restlessly or not at all, -- in those conditions of cerebral excitement, especially where there is a tendency to convulsions and this particularly in children, you will find in passiflora incarnata [sic] an excellent remedy. (Stapleton, 1904, p. 17)

A randomised double blind parallel trial has been conducted to investigate the use of passionflower in the treatment of ADHD in children (Akhondzadeh, Mohammadi, & Momeni, 2005). The trial compared passionflower tablets with methylphenidate, and 34 children aged from 6 to 13 years who were diagnosed with ADHD according to *DSM-IV* criteria participated. The randomisation resulted in an equal number of participants in both groups, and the dosage of both treatments was calculated based on body weight. The study lasted for 8 weeks, and the primary outcome measure was the Parent and Teacher ADHD Rating Scale. Both treatments were found to be effective, however there was a higher incidence of side effects, especially decreased appetite and anxiety/nervousness, in the methylphenidate group. The authors note that passionflower may be a novel agent for the treatment of ADHD, although they acknowledge the need for further research.

**Rationale for use in this study**

Passionflower was selected based on its traditional use to promote sleep. It was also included to help stabilise the nervous system during the next day.
1.9.8 Chamomile (German) *Matricaria recutita* (also known as *Chamomilla recutita*)

*Family*
Compositae

*Part used*
The flowers.

*Relevant chemical constituents*
Chamomile contains an essential oil and flavonoids (including apigenin) (Mills & Bone, 2005).

*Actions*
Chamomile is a mild sedative. Pharmacological research into its actions is limited, however an animal study found that apigenin is a ligand for the central benzodiazepine receptors with anxiolytic and sedative effects (Viola et al., 1995).

*Traditional use*
Chamomile has traditionally been used to treat restlessness and anxiety.

*Indications*
Chamomile is indicated in the treatment of mild sleep disorders (Bradley, 1992). According to the WHO (1999) the use of chamomile as a tea for the treatment of restlessness and mild insomnia due to nervous disorders is supported by clinical data.

Scientific research into the sedative effects of chamomile is scarce. A 1973 study investigated the haemodynamic properties of the herb as a tea in 12 patients with heart disease. The authors noted that approximately 10 minutes after ingesting the tea, 10 of the patients fell into a deep sleep. This was considered highly unusual, given the anxiety and discomfort produced by the cardiac catheterisation procedure that was conducted (Gould, Reddy, & Gomprecht, 1973).

*Contraindications and drug interactions*
The topical use of chamomile may cause allergic skin reactions in patients who are sensitive to plants in the Compositae family (Mills & Bone, 2000).
Adverse effects

Regarding internal use of chamomile, there have been a few reported cases of anaphylactic or allergic reactions, however they all involved the use of the herb as a tea. It has been stated that given the widespread consumption of this herb such reactions are extremely rare (Fisher & Painter, 1996; Mills & Bone, 2000). According to Blumenthal et al. (1998) there are no known side effects for chamomile.

Use in children

The traditional use of this herb includes the treatment of children (Mills & Bone, 2000), however the lack of relevant clinical studies has been noted in the literature (Hrastinger, Dietz, Bauer, Sagraves, & Mahady, 2005).

Rationale for use in this study

Chamomile was selected due to its long history of use for treating restlessness and mild sleep disorders. Furthermore, it is frequently used for the treatment of such conditions in children.

Having reviewed the relevant herbs, consideration will now be given to the instruments that are used to assess children with ADHD in terms of both daytime behaviour and sleep. This will be followed by an outline of the dependent variables that were used in this study, and the research question and hypotheses.

1.10 The assessment of children with ADHD

1.10.1 The assessment of daytime behaviour

Subjective assessment of behaviour

Child behaviour checklists and rating scales are widely used as instruments for the assessment of children with ADHD, and numerous scales are available for both parents and teachers. Despite the limitation that the responses that they elicit are opinions, they are considered to be a valuable means of obtaining a large amount of information in a relatively short time. There are several scales that offer excellent reliability and validity, and normative data, across a wide age range. Such scales also provide a means of quantifying information (Barkley, 2006).

The Child Behavior Checklist (CBCL) is used to assess social competence and behaviour problems. It has been described as the most well developed and empirically-derived rating scale, and it is considered useful for the initial assessment of children with ADHD (Barkley, 1990). The CBCL is a broad-range scale as it covers the major dimensions of child
psychopathology such as depression, aggression, and delinquent conduct, in addition to inattentive and hyperactive-impulsive behaviour (Barkley, 2006).

The Conners’ Rating Scales-Revised (CRS-R) are available as both long and short forms. They are used for obtaining behavioural information from parents (CPRS-R) and teachers (CTRS-R). These scales do not provide the same extent of coverage regarding child psychopathology as the CBCL (Barkley, 2006) however they have been used extensively in ADHD drug trials (Barkley, Fischer, Newby, & Breen, 1988; Conners, 1997; Conners, 1998). Apart from the CTRS-R, there are several other rating scales that are available for teachers (Weyandt, 2007). For example, the Child Attention Problems scale (CAP) is a teacher rating scale that was developed primarily for assessing stimulant drug effects (Barkley, 1990).

Numerous neuropsychological tests have been used in ADHD research. These include the Matching Familiar Figures Test, Wisconsin Card Sort Test, Stroop Word-Color Test, Tower of Hanoi, and various visual search and verbal fluency tasks. However, the findings for such tests have been highly inconsistent across different studies (Weyandt, 2007).

Finally, scales that allow for the recording of side effects are typically used in medication studies to obtain information about any side effects or adverse events (Barkley & Murphy, 1998).

**Objective assessment of behaviour**

Computer-based continuous performance tests (CPTs) may be used in the objective evaluation of ADHD. CPTs measure attention, impulsivity, and RT (Weyandt, 2007). The test of variables of attention (TOVA) is a CPT that can be used to monitor the effects of treatment over time. Regarding children with ADHD it is used to measure errors of omission (a measure of inattention) and errors of commission (a measure of impulsivity) (Greenberg, 2007). The TOVA can be easily administered, and it is automatically scored.

Quantitative electroencephalography (QEEG) is a computer-based technique that is used to measure brain-wave activity. QEEG may be used to compare children with ADHD and children without ADHD, as children with ADHD show elevated theta (slow wave) activity in the frontal regions of the brain. In addition, QEEG can be used to distinguish different subtypes of ADHD (Nash, 2000) and to monitor the effects of stimulants (Barkley, 2006). The disadvantages of QEEG are the cost involved due to the specialist equipment that is required,
the time that it takes regarding preparation, and the fact that some children cannot tolerate the procedure.

1.10.2 The assessment of sleep
As per sub-section 1.2.2, subjective sleep data is typically obtained during interviews with parents, and via the use of written instruments such as questionnaires and sleep logs or sleep diaries. Objective sleep data is derived from procedures such as PSG, actigraphy, and video monitoring.

Subjective sleep assessment instruments
A full sleep history may be obtained from parents during a research or clinical interview. Questionnaires may also be used as a means of obtaining information about sleep patterns from parents or children, however, as with questions posed at an interview, they have the disadvantage of being retrospective. In contrast, sleep diaries are completed by parents, or by older children, on a daily basis for 2 weeks or more in order to provide a prospective and systematically compiled record of sleep patterns. Such diaries usually include questions about the time of going to bed, the time of sleep onset, the time of waking, the details of any nighttime awakenings, and the details of any other relevant events such as illness. They are easily administered in the home environment, and they are reported to have high internal consistency (Stores, 2001; Wiggs & Stores, 1995). Furthermore, sleep diaries may be used when there is a need to assess sleep over an extended period of time, for example, over a number of months.

Objective sleep assessment techniques
PSG involves the recording of multiple physiological parameters, and it is usually conducted on an overnight basis in a sleep laboratory. It is a comprehensive technique that is considered to be the ‘gold standard’ against which other sleep assessment methods are compared. The major disadvantages of PSG are the time and expense involved. In addition, there are relatively few sleep laboratories that are specifically designed for children (Davey, 2005; Wiggs & Stores, 1995). This is an important point as having a PSG can cause anxiety in some individuals. The author of this thesis has previously been employed in a hospital sleep studies unit undertaking PSG preparation and recording for adults, and has directly observed the high degree of anxiety that some adult patients experience in relation to the procedure. The advantages of PSG are that it allows for the collection of a large amount of data in real time, and for the viewing of sleep stages and sleep architecture. However, given the complexities
involved, and the fact that PSG is not suitable for assessing sleep over prolonged periods of time, it is usually reserved for the investigation of complaints such as excessive daytime sleepiness, sleep apnoea, narcolepsy, and PLMS (Davey, 2005; Stores, 2001).

Actigraphy involves the wearing of a small device like a wristwatch on the wrist or leg, and it is useful for assessing body movements during sleep. It is a procedure that is preferred over PSG for children when details of sleep physiology are not required. The advantages of actigraphy are simplicity, automatic scoring, and the fact that it can be used in the child’s home (Stores, 2001; Wiggs & Stores, 1995). However, as with PSG, the cost and availability of equipment may be an issue with actigraphy.

Video monitoring may accompany PSG, actigraphy, or audio recording. It may be conducted in a hospital setting or in the home, using an infra-red light so as not to disturb the patient. Although it is a non-standardised procedure in the home setting, it is possible to obtain clinically useful information (Stores, 2001).

1.11 The dependent variables used in this research project
Following a review of the ADHD literature, especially in relation to drug trials, six dependent variables were chosen for this study by the investigator and the senior supervisor. Two other measures were chosen after a meeting with the second supervisor. All of the dependent variables were discussed in the previous section, and the details of their administration will be presented in Chapter 2, sub-sections 2.3.2 and 2.4.3. Consideration was given to factors such as cost, parental and teacher time constraints, ease of use, and the location of administration.

1.11.1 Subjective measures
Six subjective measures were used in this study: five for daytime behaviour, and one for sleep. The relevant daytime measures were the CBCL, the CPRS-R, the CTRS-R, a Side Effects Rating Scale, and the CAP. The sole night-time measure was a Sleep Diary. All of these measures were completed in the child’s home and school environments.

1.11.2 Objective measures
The TOVA and QEEG were selected as objective measures for this study following consultation with the second supervisor, Mr Jacques Duff. Mr Duff had been approached regarding his possible involvement in the project due to his extensive experience in testing
children with ADHD in his psychology practice. It was thought that having two objective
dependent variables would enhance the study. MediHerb Pty Ltd agreed to donate funding to
cover the use of the relevant equipment and disposables at Mr Duff's clinic. In turn, Mr Duff
agreed to train the investigator in the administration of these procedures, and to supervise the
analysis of the data, at no cost to the investigator or RMIT University.

The CPRS-R and CTRS-R were selected as the primary efficacy variables, and the secondary
efficacy variables were the TOVA, QEEG, and Sleep Diary.

1.12 The research question and hypotheses posed by this project
This project investigated the effects of selected herbal medicines on the symptomatology of
ADHD and related sleep problems in children with regard to safety, tolerability, and efficacy.
A clinical trial was conducted using eight herbs. The herbs were administered as two
combinations: one combination was given in the morning for the treatment of daytime
behaviour, and the other combination was given in the evening for the treatment of sleep
problems.

The research question addressed by the study was: ‘Do the trial herbs have a beneficial effect
on daytime behaviour and sleep problems in children with ADHD?’ It was hypothesised that
there would be a positive effect on daytime behaviour. It was expected that the children who
were assigned to the active tablets would exhibit an improvement in attention, and a reduction
in hyperactivity and associated behaviours, and that the children randomised to the placebo
tablets would not display these behavioural changes. Regarding sleep problems, it was
hypothesised that there would be a positive effect on sleep. It was expected that the children
who were assigned to the active tablets would exhibit a reduction in sleep latency, a reduction
in the number of night-time awakenings, a reduction in the total time awake during the night,
an increase in total sleep time, and an improvement in overall sleep quality. In addition, it was
expected that the children who received the placebo tablets would not display these changes.
CHAPTER 2
METHOD

2.1 Study protocol

2.1.1 The application for ethics approval
A randomised placebo-controlled double blind parallel clinical trial protocol was developed. Ethics approval for the trial was sought from the RMIT University Human Research Ethics Committee (HREC) at the start of 2001. It was granted in mid-2001, after a period of 5 months of full-time candidature had elapsed. The approved ethics application, minus attachments, is included as Appendix A. After HREC approval was granted (Appendix B), approval for teachers to be involved was obtained from the ethics committees of the Catholic Education Office (CEO), and the Department of Education, Employment and Training (DEET) (Appendices C and D). In addition, the trial was registered as a Phase 2 trial with the Drug Safety and Evaluation Branch of the Therapeutic Goods Administration (TGA) under the Clinical Trial Notification (CTN) Scheme. A complete copy of the approved ethics application was sent to the TGA after they requested a copy of the study protocol, and the investigator’s brochure. The TGA was also informed of subsequent drug amendments.

The major reasons for the delay in obtaining ethics approval
When the initial application for approval was discussed by the HREC in February 2001 they requested several changes. The major changes concerned the definition of the participant population regarding medical drugs, informing parents of the possibility of side effects, and the request in the plain language statement (PLS) to keep the names of the trial herbs confidential.

Definition of the participant population regarding medical drugs
It was the original aim of the investigator to recruit children who were not taking medical drugs for ADHD. It was hoped that parents of children who were recently diagnosed, and who did not want to place them on drugs, would be interested in participating. In addition, it was thought that including children concurrently taking medical drugs for ADHD would confound the study results. However, the senior supervisor felt that requiring the children to be drug-free would cause problems with recruitment. Therefore, in the first application that was submitted to the HREC, the inclusion criteria included the following sentence: “It is hoped that the subjects will be medication-free however it is anticipated that some will be under drug treatment for their condition”.

The HREC response to this in a letter dated February 13, 2001 was:

The Committee believed that the subject population should be defined more closely. For example it was noted that there was provision for children taking some medications to be included in the study. It was thought better to include only those who had never taken or who had stopped the drugs for an adequate (to be defined) washout time. If the investigator still wished to include those on some medications, these should be listed and the protocol should include a statement on how they would analyse the data to take account of this. It would also be necessary to stratify the randomisation to take account of those on other medication and those who were not.

A rationale should be given for both the exclusion and (if so) inclusion of participants taking particular drugs.

In response, the investigator wrote in a submission dated March 15, 2001:

The exclusion criteria have been altered to exclude children who are currently taking specific drugs or alternative treatments for ADHD. The alternative treatments have been added following a recent review of such products that was undertaken by the investigator. Please refer to the main document page 6 under "exclusion criteria". Should a child cease taking these for a period of one month they will be considered for inclusion.

The specific drugs added to the exclusion criteria were methylphenidate, dexamphetamine, imipramine, desipramine, and clonidine. The rationale for this was to avoid confounding the study results. The rationale for adding certain supplements to the exclusion criteria was the same. The one-month washout period was decided upon following discussion between the senior supervisor, the investigator, and the project consultant. The investigator also obtained feedback regarding the washout time from a colleague qualified in pharmacy, pharmacology, and herbal medicine (P. Rasmussen, personal communication, May 23, 2001).

Informing parents of the possibility of side effects
In the first application that was submitted to the HREC, the following paragraphs relating to possible side effects were included in the PLS:
Special care has been taken in the selection of these herbs. Although they are all regularly prescribed by naturopaths and herbalists this will be the first clinical trial of its type. There have been rare cases of side effects from these herbs, for example mild gastric upset. In addition St John's Wort has recently been thought to interact with certain medical drugs. If a child is taking any of the drugs concerned they will not be able to participate in the study.

No adverse effects are expected however as with any kind of medication there is always the risk of a side effect or adverse reaction. If such a reaction occurs you will be advised to stop the tablets immediately and to contact Dr Francis and your child's doctor.

In their February 13, 2001 response the HREC stated that:

The plain language statement should make clear possible side effects associated with each of the herbs (perhaps a table listing herbs and effects) and state that there is currently no data on their side effects in combination or with other medications. The phrase “No adverse effects are expected” should be removed.

In the approved PLS (Appendix E) there is a section on side effects, and it consists of a sentence or paragraph summarising the information for each herb at the time.

The request in the PLS to keep the names of the trial herbs confidential
The most time-consuming and difficult issue that had to be dealt with in obtaining HREC approval for the study was the issue of confidentiality of trial product. After the eight trial herbs were finalised in 2000, MediHerb Pty Ltd insisted that the names of the herbs, and all details regarding the trial products, remain confidential. Indeed, the section of the ethics committee application that contained the full details of the trial herbs was supplied to the HREC as a confidential document that was to be filed in a separate secure location. The PLS was included with it as an attachment, as it contained the common names of the eight herbs. The investigator had previously worked for 10 years in clinical practice as a naturopath and herbalist, and had always informed patients of what they had been prescribed. Therefore, in the first PLS that was considered by the HREC the herbs were named as follows:
The herbs which [sic] will be used in this study are ginkgo, bacopa, paeony, St John’s Wort, valerian, skullcap, passionflower and chamomile. They are all herbs that are commonly used in the practice of herbal medicine in Australia. As this is the first major research project of its type we ask that you keep the names of these herbs confidential.

In the HREC response of February 13, 2001 it was stated that:

In the section “What Herbs are being used?” the request to keep the herbs confidential created a problem for the Committee as parents may legitimately wish to seek advice of another party.

In her submission to the HREC dated March 15, 2001 the investigator responded that:

Mr Kerry Bone, of MediHerb Pty Ltd, has advised that he understands the concerns of the HREC however, to quote from an email, “telling the parents the formula will negate any intellectual property protection (e.g. patent) we may wish to establish”.

It should be noted that there is already considerable interest in this project from not only individuals, for example herbal students and practitioners, but also from other companies. Indeed, the investigator recently experienced persistent [sic] and direct questioning from representatives of another company who are trying to find out what is to be used in the trial.

In addition to the exchange of correspondence with the HREC, and with MediHerb Pty Ltd, the investigator and the senior supervisor attended the March 2001 HREC meeting in person in order to facilitate discussion of these issues. MediHerb Pty Ltd, and the investigator, put forward various suggestions as a way around the problem of confidentiality, and the HREC sought further advice. In the end, the HREC ruled that the herb names must be included in the PLS, and that the request to keep the herb names confidential must be removed, as per their letter of May 9, 2001:
At the last meeting the Committee noted that Mediherb [sic] wished to keep confidential the names of the herbs to be used in this proposal. Members believed that parents of the subjects should be told what the herbs were, and not be restrained from seeking advice by a request to keep the names confidential. It was agreed to seek further advice on this issue.

[Names and positions of advisors omitted.]

In the light of advice received and with further consideration of the issues by members since the last meeting, it was agreed that the investigators should still be required to name the herbs to be given to the participants in the plain language statement.

Members viewed the issue of safeguarding the formulation as one to be addressed by Mediherb [sic] and the investigator. It was noted that a preliminary patent application could be lodged and also that the ratios and dosage of the herbs did not have to be specified in the plain language statement.

In response to the above, MediHerb Pty Ltd decided to obtain a provisional patent for the trial products, in conjunction with RMIT University. The investigator and the senior supervisor were involved in writing the text for the provisional patent application. As this process continued, contracts were deemed to be necessary by MediHerb Pty Ltd, and RMIT University. Thus, there were further delays over several months in the second half of 2001 due to the provisional patenting process, and also due to investigator seeking legal advice, and clarification, after she was asked to sign a contract with RMIT University (a Student Participation Agreement) before the research could commence. A related contract between RMIT University and MediHerb Pty Ltd was also developed. As both contracts were being finalised the investigator had to take leave of absence due to distressing personal circumstances. The contracts were completed and signed after her return to RMIT University in mid-2002, thus allowing the study to proceed.
2.1.2 Amendments to the approved study protocol

A number of amendments were made to the approved study protocol over time. These pertained to various medical drugs, and the age range for the study.

Amendments regarding medical drugs

Following the large number of inquiries that arose from the first media release publicising the project in September 2002, the vast majority of which came from parents with children taking one or more of the standard ADHD drugs, an application was made to the HREC to amend the exclusion criteria. The amendment proposed including children taking methylphenidate, dexamphetamine, imipramine, desipramine, and clonidine, and allowing for whether or not a child was already taking one or more of these medications to be considered in the design. The investigator attended the September 2002 HREC meeting in person in order to discuss these matters with the committee.

At the meeting, the HREC expressed concern about the possible interactions between tricyclic antidepressants, such as imipramine and desipramine, and St John’s Wort. They were also concerned about any possibility of interaction between MAO inhibiting drugs and St John’s Wort, and MAO inhibiting drugs and ginkgo. HREC members had seen information regarding these drugs and St John’s Wort in the literature. The investigator responded by saying that children taking tricyclic antidepressants, or MAO inhibitors, would be excluded unless they ceased taking the drugs for a period of 1 month. The HREC sought further information regarding the randomisation strategy to be used to allow for the inclusion of children taking methylphenidate, dexamphetamine, and clonidine, and decided that the matter would be dealt with by delegation.

The investigator made a submission in writing that was considered at the following HREC meeting. It confirmed the above exclusion criteria regarding tricyclic antidepressants, and MAO inhibitors. It also contained the following suggestion regarding the inclusion of children taking methylphenidate, dexamphetamine, or clonidine:

Regarding the randomisation strategy to be used to include children on these medications the following is proposed. Children will be allocated into one of two groups according to their current medication status at the time of initial contact: “on medication” or “not on medication”. Dr Francis will then randomly assign them to placebo product or active herbal product within their particular group. The random
assignment of subjects to placebo product or active herbal product will be achieved through using random number tables as per my approved protocol.

The changes were approved by the HREC delegation, and all other relevant bodies were notified. The investigator also contacted all of the parents who had inquired about the study, and who had said that their child was taking one or more of these drugs, in order to inform them of the changes.

Other amendments regarding medical drugs occurred as further information came to hand. Drugs in the anticonvulsant and antipsychotic drug classes were later added to the exclusion criteria due to any possibility of interaction with St John’s Wort.

**Individual amendments regarding age range**

There were two applications to the HREC to include children who were just outside of the age range for the study. The children were 6 years old and 7 years old, and in both instances they were described by the parent who contacted the investigator as being “big” for their age. Both children were granted an age exemption, but did not proceed into the study.

### 2.2 Participants

An extensive, and prolonged, advertising campaign was undertaken for the purpose of participant recruitment. The aim of the campaign was to recruit up to 30 children, as per the Student Participation Agreement. The main form of advertising was via media release. Three media releases were conducted, on September 16, 2002, May 13, 2003, and December 8, 2003 respectively. Together they produced the largest number of inquiries, resulting in a total of 104 copies of the PLS being mailed out. Details of the other publicity strategies that were used, which resulted in additional copies of the PLS being sent out, are given in sub-section 2.4.1. Overall, most inquiries came from metropolitan Melbourne, or from within Victoria. A small number of inquiries came from people interstate and overseas. In this case the PLS was mailed or emailed to them, however they were informed that due to the ethics approvals in place they would not be eligible to be involved.

Despite considerable interest in the study, only 12 potential participants attended an initial face-to-face interview. Of these, 6 children were enrolled in the trial, and only 5 of them completed it. Issues concerning recruitment difficulties, and attrition, will be discussed in
Chapter 4. Information regarding participant gender, age, ADHD medication, other medication, supplements, and medical history is summarised in Table 2.1.

2.3 Materials

2.3.1 Trial tablets
All of the tablets for the trial were manufactured and donated by MediHerb Pty Ltd, a major manufacturer of practitioner-only herbal medicines. MediHerb Pty Ltd conducted a special production run at their manufacturing facility in Warwick, Queensland, in order to manufacture the tablets for this research project. Thus, there was no variation in batch numbers. The facility complies with the Code of Good Manufacturing Practice as per the requirements of the TGA.

MediHerb Pty Ltd also donated consultancy and technical support for the trial products. Despite the fact that liquids, for example, fluid extracts, are the most commonly used means by which herbs are prescribed in clinical practice, tablets were chosen as the form in which the trial herbs were to be administered. This was due to concerns about compliance. Children can have problems tolerating liquid herbs due to their taste, especially in a situation where high doses are required. Small, scored tablets that could be cut in half were initially proposed, however due to production issues MediHerb Pty Ltd realised that the tablets would be larger than expected. Therefore, they advised that the tablets could be crushed if a child had difficulty taking them.

Active tablets
Two herbal combinations were used in the treatment group, with each combination consisting of four herbs. The project herbs were chosen following discussions between the investigator, the senior supervisor, and the project consultant. One combination was given in the morning, and the other at night. The herbs in the morning formula were ginkgo, bacopa, paeony, and St John's Wort. The herbs in the night formula were valerian, skullcap, passionflower, and chamomile. Detailed monographs for each herb were presented in Chapter 1, section 1.9. The project consultant specified the amount of each herb per tablet (Table 2.2). Standardised, phytochemically-profiled extract was used wherever possible in the manufacturing process.
Table 2.1 Participant details regarding gender, age, ADHD medication, other medication, supplements, and medical history

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Gender</th>
<th>Age</th>
<th>ADHD medication</th>
<th>Other medication</th>
<th>Supplements</th>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Male</td>
<td>9</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Only one kidney due to past history of cancer; deaf in one ear</td>
</tr>
<tr>
<td>2.</td>
<td>Male</td>
<td>8 at the start of the study, turned 9 during it</td>
<td>Nil</td>
<td>Ventolin and steroid asthma drugs prn</td>
<td>Nil (ceased Efalex to go into the study)</td>
<td>Premature at birth (induced); eczema; asthma</td>
</tr>
<tr>
<td>3.</td>
<td>Male</td>
<td>8 at the start of the study, turned 9 during it</td>
<td>At baseline Ritalin 10 mg tds, and clonidine one nocté; from treatment phase Ritalin L.A. 30 mg daily during the week</td>
<td>Panadol and Ventolin prn</td>
<td>Nil</td>
<td>Migraines; asthma</td>
</tr>
<tr>
<td>4.</td>
<td>Male</td>
<td>14</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>No other health problems</td>
</tr>
<tr>
<td>5.</td>
<td>Male</td>
<td>11</td>
<td>Ritalin L.A. during the week</td>
<td>Nil</td>
<td>Nil</td>
<td>Anorexia due to Ritalin; eczema</td>
</tr>
<tr>
<td>6.</td>
<td>Male</td>
<td>8</td>
<td>Ritalin 10 mg tds every day</td>
<td>Nil</td>
<td>Nil (he ceased various supplements to go into the study)</td>
<td>Anorexia due to Ritalin; rapid pulse rate at times (thought to be due to Ritalin)</td>
</tr>
</tbody>
</table>

*Note. Abbreviations: L.A. long acting; nocté at night; prn when required; tds three times a day.*
Table 2.2 The amount of each herb per tablet for both herbal combinations

<table>
<thead>
<tr>
<th>Each morning tablet contained:</th>
<th>Each night tablet contained:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo</td>
<td>Valerian</td>
</tr>
<tr>
<td>1.5 g</td>
<td>300 mg</td>
</tr>
<tr>
<td>Bacopa</td>
<td>Skullcap</td>
</tr>
<tr>
<td>700 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>Paeony</td>
<td>Passionflower</td>
</tr>
<tr>
<td>500 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>St John’s Wort</td>
<td>Chamomile</td>
</tr>
<tr>
<td>900 mg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

The tablet dosage, as advised by the project consultant, was one tablet per 10 kg body weight in both instances, that is, for morning and night. The dosage was rounded down where the child’s body weight was, for example, 21 to 24 kg, and rounded up where the child’s body weight was, for example, 25 to 29 kg. Regarding the timing of administration, the morning tablets were given at breakfast time, within the time range of 5 a.m. to 9 a.m. The night tablets were given an hour before bedtime, within the time range of 5 p.m. to 9 p.m.

The morning tablets and night tablets were of the same appearance. They were oval in shape, and approximately 19 mm in length. The excipients were Calcium Hydrogen Phosphate BP2001, Cellulose Microcrystalline, Silica – Colloidal Anhydrous BP2001, and Magnesium stearate. The tablets were brown in colour, as they were coated with a brown film coat.

Placebo tablets

Only one placebo was manufactured, and the dosage and timing of administration were the same as for the herbal tablets. The placebo tablets were identical in appearance to the herbal tablets. They also contained the same excipients, however the excipients were present in higher amounts. This was due to the absence of any actives. A brown colouring agent was included in the placebo tablets to make them look like they contained actives when they were broken or crushed.

Packaging, labelling, and expiry dates

MediHerb Pty Ltd pre-packaged all of the trial tablets in sealed amber-glass containers, each containing 90 tablets, before they were shipped in boxes to RMIT University. The boxes, and the glass containers, were labelled with product codes known only to MediHerb Pty Ltd, and the senior supervisor. The boxes were kept in secure storage. Following the recruitment of a participant the investigator would provide the senior supervisor with the child’s name, their trial code number, and the details of any ADHD medications that they were taking, their body
weight, and the required number of tablets. The senior supervisor would then conduct the
randomisation procedure, and over-label the glass containers with the investigator's tablet
labels (Figure 2.1). The investigator would then note the date of dispensing, the child’s name
and code number, and the number of tablets to be taken, on the labels before providing the
tablets to the child’s parents. Further information regarding the randomisation procedure is
given in sub-section 2.4.3. The administration of trial tablets is also discussed in sub-section
2.4.3.

Morning tablets label:

MORNING TABLETS  Date:  F/DAL001-
Name:  
Take  tablets with breakfast between 5 a.m. and 9 a.m. Tablets may be crushed if necessary.

Store below 30°C away from direct sunlight and out of reach of children.

Department of Psychology and Disability Studies RMIT University
Ms Fiona Dey (Investigator) and Dr Andrew Francis (Senior Supervisor)
Telephone 9925-7376 (mobile 0408 511 437)

Night tablets label:

NIGHT TABLETS  Date:  F/DAL001-
Name:  
Take  tablets an hour before bedtime between 5 p.m. and 9 p.m. Tablets may be crushed if necessary.

Store below 30°C away from direct sunlight and out of reach of children.

Department of Psychology and Disability Studies RMIT University
Ms Fiona Dey (Investigator) and Dr Andrew Francis (Senior Supervisor)
Telephone 9925-7376 (mobile 0408 511 437)

Figure 2.1 The labels that were used by the senior supervisor to over-label the
containers of trial tablets before they were provided to the investigator

The tablets were manufactured in November 2001, and the designated expiry date was
November 2004. In 2004 MediHerb Pty Ltd conducted testing on the tablets with a view to
extending their shelf-life, as it was hoped that more children might be recruited by altering
the protocol to that of an open study. The expiry date for both the active and placebo tablets
was changed in 2004 to December 2005. The HREC reluctantly gave approval for the
change of protocol on the condition that any open study data would be analysed separately
to the data that had already been obtained, however the open study did not proceed due to
the constraints of candidature time. Following the cessation of recruitment MediHerb Pty
Lmt conducted further testing on the active tablets in order to determine the levels of various constituents. For each herb the appropriate Test Method MediHerb (TMM) was used. Bacopa was not included in these tests as the test method that is used for bacopa makes it impossible to test it when it is mixed with other herbs (R. Lehmann, personal communication, October 4, 2005). The results of the post-trial tests are summarised in Tables 2.3 and 2.4. The full report is provided in Appendix F.

Table 2.3 The results of the analysis of the daytime tablets (average of duplicate assays) at the end of the trial, excluding bacopa

<table>
<thead>
<tr>
<th>Herb</th>
<th>Compound</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo</td>
<td>Quercetin</td>
<td>17.05</td>
</tr>
<tr>
<td></td>
<td>Kaempferol</td>
<td>2.58</td>
</tr>
<tr>
<td></td>
<td>IsoRhamnetin</td>
<td>0.25</td>
</tr>
<tr>
<td>Pacony</td>
<td>Paeoniflorin</td>
<td>6.67</td>
</tr>
<tr>
<td>St John’s Wort</td>
<td>Rutin</td>
<td>5.69</td>
</tr>
<tr>
<td></td>
<td>Hyperoside</td>
<td>6.29</td>
</tr>
<tr>
<td></td>
<td>Isoquercitrin</td>
<td>2.95</td>
</tr>
<tr>
<td></td>
<td>Quercitrin</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>Hyperforin</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Table 2.4 The results of the analysis of the night-time tablets at the end of the trial

<table>
<thead>
<tr>
<th>Herb</th>
<th>Compound</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valerian</td>
<td>Valerenic acid</td>
<td>0.26</td>
</tr>
<tr>
<td>Passionflower</td>
<td>Vitexin</td>
<td>4.15</td>
</tr>
<tr>
<td>Skullcap</td>
<td>Baicalin</td>
<td>4.63</td>
</tr>
<tr>
<td></td>
<td>Oroxylin A -7-O</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>glucoside</td>
<td></td>
</tr>
<tr>
<td>Chamomile</td>
<td>Apigenin</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Apigenin-7-glucoside</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Luteolin-7-glucoside</td>
<td>0.85</td>
</tr>
</tbody>
</table>
2.3.2 Dependent variables

Eight measures were used in the study. As they were discussed in the previous chapter in sections 1.10 and 1.11 only a summary regarding procedure will be presented here. The administration points for each measure are further detailed in sub-section 2.4.3.

TOVA

For the TOVA the child was required to sit at a computer and pay attention to the screen whilst holding a push-button micro-switch. They were instructed to press the button when a target appeared, and not to press it when a non-target appeared. A short practice run, lasting 5 minutes, was undertaken before the test. The duration of the actual test is 24 minutes. Thus, the time taken for the whole test was approximately 30 minutes. The TOVA was administered at baseline and at post-treatment at the Behavioural Neurotherapy Clinic (BNC). The BNC is located in Doncaster, and an information sheet was developed for parents in order to inform them of what their child would be expected to do at the clinic (Appendix G).

QEEG

For the QEEG a fitted electrode cap was applied to the child’s head to allow for the recording to be taken. The child’s earlobes were wiped with a cleansing paste and a small quantity of conductive paste was applied to them. Conductive gel was then applied to each sensor in the cap using a syringe with a blunt needle. In order to obtain a low impedance level, which allows for a good recording to be taken, each sensor was checked following the application of the gel. If necessary the blunt needle was gently wiggled in the electrode to part the hair, and more gel was applied to ensure a good contact. The child was seated in a comfortable recliner chair for both the preparation and the recording. Once the preparation was completed an eye mask was put on so that 6 to 10 minutes of eyes-closed recording could be taken. The QEEG was administered at the BNC as per the TOVA (Appendix G). Allowing for preparation and recording, the procedure takes approximately 1 hour.

CBCL

The CBCL was completed by the parents at baseline, at the end of the treatment phase and at follow-up. The time taken to complete the checklist is 15-20 minutes. The CBCL that was used in this study covers children aged from 4 to 18 years. It has three Competence Scales: Activities, Social, and School. In addition, there are eight Problem Scales: Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention
Problems, Delinquent Behavior, and Aggressive Behavior (Achenbach, 1991). The data that are obtained may be hand-scored or computer-scored, and summarised on a profile form that shows the rating for each scale (Achenbach & Ruffle, 2000). The profile form also displays the normal range, borderline clinical range, and clinical range for each scale.

The CBCL is a standardised instrument. Regarding validity, its content validity has been demonstrated by its significant ability to discriminate between demographically matched referred and non-referred children (Achenbach, 1991). The construct validity for the CBCL is supported by its significant associations with comparable scales on other checklists, and its criterion-related validity has been shown by the ability of its quantitative scores to discriminate between referred and non-referred children after demographic effects are taken into account. In relation to reliability, inter-interviewer and test-retest reliabilities are demonstrated by intra-class correlations in the .90s for the mean item scores derived from different interviewers, and for parental reports, on two occasions 7 days apart. The test-retest reliability of the Competence Scales was supported by a mean r of .87 over 7 days, and the mean r for the Problem Scales was .89. Over periods of 1 year and 2 years, the changes in the mean values did not exceed the changes that would be expected due to chance (Achenbach, 1991).

CPRS-R and CTRS-R

The CPRS-R and CTRS-R were used to obtain information regarding the child’s behaviour from parents and teachers, respectively. Both of the scales are available in long and short forms. The long forms (CPRS-R:L and CTRS-R:L) were administered at the baseline and follow-up phases, and the short forms (CPRS-R:S and CTRS-R:S) were used during the treatment phase and at post-treatment. At baseline the forms were administered twice in accordance with the usual protocol that is recommended in the literature (Conners, 1997). The long forms take up to 20 minutes to complete, and the short forms up to 10 minutes.

The CPRS-R:L consists of 14 subscales: Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, Psychosomatic, Conners’ ADHD Index, Conners’ Global Index: Restless-Impulsive, Conners’ Global Index: Emotional Lability, Conners’ Global Index: Total, DSM-IV: Inattentive, DSM-IV: Hyperactive-Impulsive, and DSM-IV: Total. The CPRS-R:S contains only four of these subscales: Oppositional, Cognitive Problems/Inattention, Hyperactivity, and Conners’ ADHD Index. The CTRS-R:L has the same subscales as the CPRS-R:L, except that there is
no Psychosomatic Subscale. Finally, for the CTRS-R:S the subscales are the same as for the CPRS-R:S.

The CRS-R may be hand-scored or computer-scored. In order to hand-score the forms they are separated at the perforation so that the scoring key can be revealed (Conners, 1997). For the long forms the scoring is done on the form, and the scores are then transferred to a separate profile sheet. For the short forms the scoring key and the profile are both contained within the form. The CRS-R profile forms provide separate columns for different age groups. They also display the relevant T-scores, allowing for comparisons to be made across respondents and CRS-R parent and teacher forms.

The CRS-R are considered to be psychometrically sound as they were developed from earlier Conners’ scales using data collected from 11,000 respondents located at over 200 sites in North America (Conners, 1997). Extensive statistical analyses have examined the scales in terms of different types of validity. Regarding reliability, the CRS-R have been thoroughly assessed for internal reliability, and test-retest reliability. In relation to internal reliability for the CPRS-R:L, the reliability coefficients range from 0.728 to 0.942, while for the CPRS-R:S the range is 0.857 to 0.938. The ranges for the CTRS-R:L and CTRS-R:S are 0.773 to 0.958, and 0.882 to 0.952 respectively. Regarding test-retest reliability, moderate to high values were obtained for the CRS-R across the various forms.

**Sleep Diary**

The parents completed a daily Sleep Diary. The diary used in this study was essentially the same as the one that was used in other projects involving the senior supervisor. It takes approximately 5 minutes to fill out, and it was completed morning and night (Appendix H). The diary allowed the parents to record information regarding their child’s sleep, behaviour, and health, and whether or not the child had taken the trial tablets. It also included questions and spaces for comments in relation to the parents’ sleep, and their own well-being. The variables that were derived from the Sleep Diary for the purpose of data analysis will be discussed in sub-section 2.5.2.

**Side Effects Rating Scale**

The parents completed a Side Effects Rating Scale on a weekly basis (Appendix I). The investigator developed the scale based on her knowledge of common side effects that may occur on taking medical drugs, or herbs. It followed the format of the weekly Side Effects
Rating Scale for medical drugs that was published in Barkley and Murphy (1998). The scale took approximately 5 minutes to fill out.

**CAP**

The CAP scale for teachers is used primarily for assessing stimulant drug effects (Barkley, 1990). It was completed on a weekly basis, taking about 5 minutes (Appendix J). The CAP allowed the teachers to document information about the child’s attention, impulsivity, ability to sit still and to follow directions, and their ability to carry out tasks.

2.4 Procedure

2.4.1 Recruitment

Approval for the trial to be conducted was granted by the HREC in mid-2001. Some initial advertising for recruitment took place as the various bureaucratic and legal matters outlined in section 2.1 were underway during the second half of 2001. At that stage it was expected that the trial would commence at the start of the 2002 school year. MediHerb Pty Ltd had advised that they required 3 months notice for the manufacture of trial products, and that the manufacturing process could not commence until all of the required approvals were obtained. Further advertising to recruit took place following the investigator’s return to RMIT University in mid-2002 following a leave of absence, and it continued until late 2004. The recruitment advertising methods that were used in addition to the three media releases and the items listed in the Dissemination Details are presented in Table 2.5.
Table 2.5 The recruitment advertising methods that were used in addition to the three media releases and the items listed in the Dissemination Details

<table>
<thead>
<tr>
<th>Date</th>
<th>Details</th>
</tr>
</thead>
</table>
| 2001 | • contacted ADHD support groups, and other disability support groups, initially by telephone, and then by sending out flyers by email or mail  
      • organised a trial website  
      • contacted Family and Community Support at the Department of Human Services Victoria  
      • contacted the Australian Education Union  
      • flyers were placed on various community noticeboards, and in clinics (for example, medical and chiropractic clinics)  
      • various contacts in naturopathy, herbal medicine, and medicine were sent flyers, also various institutions and groups known to the investigator (such as the Australian Complementary Health Association)  
      • a message was posted on an ADHD internet discussion forum  
      • contacted WIRE – Women's Information and via them obtained the details of local community ADHD support groups  
      • an advertisement was placed in the newsletter of the National Herbalists Association of Australia (NHAA) (this was later repeated), also a message was posted on the NHAA full practitioner members email discussion list |
| 2002 | • letters were sent to all ADHD support groups, also various naturopathic professional associations and colleges, and other types of practitioner associations, and special schools  
      • posters were mailed to various practitioner colleagues known to the investigator, and were also placed on community noticeboards (for example, public libraries, and gymnasiums) |
| 2003 | • continued to publicise the project via contacts |
| 2004 | • conducted a mail-out via the second supervisor’s clinic to 100 people  
      • presented a talk at a community garden club |
As mentioned in section 2.2, the three media releases that were conducted produced the largest number of trial inquiries. They also led to other opportunities to promote the research. Following the first media release the investigator was contacted by paediatrician and ADHD researcher Dr Daryl Efron, and was invited to address a meeting of paediatricians at the Royal Children's Hospital in Melbourne. The second media release unfortunately went out just after a large amount of negative media publicity about herbal medicines, and other complementary medicines, as a result of the Pan Pharmaceuticals affair. This affair came to light due to problems with a medical drug that was manufactured by that company, not a herbal product. It was emphasised in the second release that MediHerb Pty Ltd had manufactured all of the tablets for the trial at their own facility.

In addition to generating enormous interest in the study from parents, teachers, and health professionals, the entire advertising campaign also produced inquiries from various media organisations. During the campaign, the investigator conducted telephone interviews with two newspapers ("The Australian" and "The Age"), Melbourne radio station FOX-FM, and a producer from ABC-TV.

Despite the trial herbs being named in the PLS, and despite the provisional patent, it should be noted that the investigator was restricted to talking openly about only three of the trial herbs: ginkgo, bacopa, and valerian. This was due to MediHerb Pty Ltd expressing ongoing concerns about confidentiality. Ginkgo, bacopa, and valerian were considered to be the obvious herbs. Throughout the entire duration of the research, the investigator was only permitted to speak in public about all eight of the trial herbs on one occasion, when she gave a presentation at a postgraduate conference for psychology students at RMIT University. The impact that this constraint had on recruitment will be considered in Chapter 4.

2.4.2 Screening
Parents who were interested in the research contacted the investigator, primarily by telephone. They were assessed against the inclusion and exclusion criteria for the trial during a telephone-screening interview. They were sent a copy of the PLS, unless one had already been sent out at the time of first contact. Due to the volume of calls, especially in response to the first and second media releases, some parents were sent the PLS first, and were then contacted later by the investigator in order to see if they had any further interest in the project, and/or if they would be willing to participate in a telephone-screening interview. Other parents participated in the telephone-screening interview at the outset, and the PLS
was sent to them afterwards. If a child appeared to meet the trial criteria, the parents were invited to attend an initial face-to-face interview at the RMIT University Psychology Clinic.

**Inclusion and exclusion criteria**

The inclusion criteria for the trial were kept broad, due to it being the first study of its type, and to assist with recruitment. The exclusion criteria consisted of a list of medical drugs and supplements. During the drafting of the research proposal in 2000, information started to appear in the literature regarding known or potential interactions between a variety of medical drugs and St John’s Wort. Due to this, the investigator proposed omitting this herb from the research, as she could foresee that its presence could prevent children on such drugs from taking part in the study. However, following correspondence with the project consultant, St John’s Wort remained as one of the trial herbs, and all of the relevant drugs were listed in the exclusion criteria.

**Inclusion criteria**

Children aged from 8 to 16 years, and diagnosed with ADHD based on *DSM-IV* criteria (APA, 1994) by a paediatrician, psychiatrist, or psychologist. In addition, the child must experience disturbance to their sleep that causes significant distress to the parents/caregivers or the child, or interferes significantly with the child’s functioning or well-being; for example, difficulties settling to sleep, night-time waking, or early morning waking. The child must receive a medical clearance to participate in the study from a registered medical practitioner.

**Exclusion criteria (as per the approved protocol)**

Children who are taking any of the following medications will be excluded due to the possibility of an interaction with St John’s Wort:

- HIV protease inhibitors (idinavir, nelfinavir, ritonavir, saquinavir)
- Immunosuppressants (cyclosporin, tacrolimus)
- HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, delavirdine)
- Warfarin
- Anticonvulsants (carbamazepine, phenobarbitone, phenytoin)
- Digoxin
- SSRI’s and related antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, nefazodone)
- Triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan)
- Oral contraceptives
Theophylline

Children who are taking the following will be excluded due to the caution concerning concurrent use of ginkgo:
Aspirin (except for occasional use)

Children who are currently taking any of the following medical drugs and/or alternative treatments for ADHD will be excluded to avoid confounding the study results:
Methylphenidate
Dexamphetamine
Imipramine
Desipramine
Clonidine
Zinc supplements
Magnesium supplements
Homoeopathic remedies
Phosphatidylserine
Efalex and other essential fatty acids supplements
Pycnogenol and/or grapeseed products
AD-FX (a product that contains ginkgo)
Any product containing one or more of the trial herbs
Should the child cease taking these for a period of one month they will be considered for inclusion.

Exclusion criteria (as per the amended protocol)
For a child to participate in this clinical trial they must not be concurrently taking any of the following drugs or supplements. If they are currently taking any of the following drugs and/or supplements they must cease taking it/them for a period of one month in order to be eligible to participate:

HIV protease inhibitors indinavir (Crixivan) nelfinavir (Viracept) ritonavir (Norvir)
saquinavir (Invirase)
Immunosuppressants cyclosporin (Neoral Sandimmun) tacrolimus (Prograf)
HIV non-nucleoside reverse transcriptase inhibitors efavirenz (Stocrin) nevirapine
(Viramune) delavirdine (Rescriptor)
Warfarin (Coumadin Marevan)
Anticonvulsants carbamazepine (Carbium Tegretol Teril) phenobarbitone phenytoin
(Dilantin) sodium valproate (Epilem)
Digoxin (Lanoxin)
SSRI antidepressants citalopram (Cipramil) fluoxetine (Auscap Erocap Fluohexal Lovan
Prozac Zactin) fluvoxamine (Faverin Luvox) paroxetine (Aropax) sertraline (Zoloft)
nefazodone (Serzone)
Tricyclic antidepressants amitriptyline (Endep Tryptanol) clomipramine (Anafranil
Clomipramine-BC Clopram DBL-Clopramamine GenRx-Clomipramine Placil) desipramine
dothiapen (Dothep Prothiaden) doxepin (Deptran Sinequan) imipramine (Melipramine
Tofranil) nortriptyline hydrochloride (Allegron) trimipramine (Surmontil)
Monoamine oxidase inhibitors moclobemide (Arima Aurorix Clobemix DBL-Moclobemide
GenRx-Moclobemide Maosig Moclobemide-BC Mohexal) phenelzine (Nardil)
tranylcypromine (Parnate)
Antipsychotics including haloperidol (Serenace) pericyazine (Neulactil) risperidone
(Risperdal)
Triptans sumatriptan (Imigran) naratriptan (Naramig) rizatriptan zolmitriptan (Zomig)
Oral contraceptives
Theophylline (Nuelin Theo-Dur)
Aspirin (except for occasional use)
Zinc supplements
Magnesium supplements
Homoeopathic remedies
Phosphatidylyserine
Efalex and other essential fatty acids supplements
Pycnogenol and/or grapeseed products
AD-FX or any product containing one or more of the trial herbs

Initial face-to-face interview
The main purpose of the initial face-to-face interview was to further clarify whether or not a
child was eligible to participate in the study. However, it also gave families the opportunity to
ask any additional questions, and/or to clarify any concerns that they had about being
involved. Their written consent was obtained before the interview could proceed (Appendix
K).
The interview followed a semi-structured format. Details of the child’s school, their ADHD diagnosis, their use of medical drugs and supplements (current and previous), and any other health problems were obtained. In addition, any allergies, any adverse reactions to herbs, details of their daytime behaviour, and details of their sleep, were noted. The parents were also asked the child’s weight so that the investigator could give them an indication of the number of tablets that they would be required to take twice a day. The interview form used by the investigator is included as Appendix L.

Information was also obtained from the parents regarding their ideals for their child’s behaviour using the Goal Achievement Scale (GAS) (Hudson, 1998). This was done in order to assess the clinical significance of any changes. The GAS involves selecting a problem behaviour and constructing a scale for it, so that post-intervention the changes, if any, in the problem behaviour can be expressed as a percentage. The investigator asked the parents to list three or four problem behaviours for both daytime and night-time. The current level of behaviour was taken as the baseline or zero, and then the parents were asked to give their opinion of what would be considered to be a 100% improvement. Attempts were also made to set 25%, 50%, and 75% levels of improvement. The GAS was repeated, where possible, at the end of the treatment phase.

The possibility of side effects or adverse reactions to the herbs was also discussed. The investigator informed the parents that they would be provided with her mobile telephone number in case any queries or problems arose. The HREC gave permission for the investigator to give her mobile telephone number to parents due to her background as a former registered nurse, and a qualified naturopath and herbalist. The investigator advised parents that if their child had any problems with the trial tablets, they should contact her immediately. In the case of serious problems such as an adverse reaction, they were advised to also contact their medical practitioner, or the nearest hospital emergency department, and Dr Francis, if they had not already done so. They were also told that if an adverse reaction occurred, their child would be withdrawn from the study, and that the trial code for their child would be broken by the senior supervisor in order for the matter to be reported to the HREC and the TGA. It was also emphasised to the parents that there was a 50% chance of their child receiving the placebo tablets, and that the investigator would be unaware of which product their child would be taking.
At the interview, the evidence of ADHD diagnosis form, medical practitioner clearance form, and informed consent form were provided to parents if necessary. That is, if they had not been mailed out to them with the PLS. An additional copy of the PLS was also provided to parents if necessary. The investigator explained to parents that she needed to write to the principal of the child's school in order to obtain their written permission for the child's teacher to be involved, even if the teacher had already consented verbally to them, and that this permission, and the other forms, needed to be in place before the child could commence the baseline phase of the trial. In addition, if the child was taking any drugs and/or supplements listed in the trial exclusion criteria, they were ceased at this time (if this had not already been done) in order to comply with the one-month washout period.

**Trial forms**

**Letter to school principal**

A letter was written to the child’s school principal seeking their permission for the child’s teacher to be involved in the study. It included a summary of the rating scales that the teacher would be asked to complete, with an estimate of the time involved. Copies of the PLS, the relevant education authority letter of approval, and the HREC letter of approval, were included as attachments. A sample letter is provided in Appendix M.

**Evidence of ADHD diagnosis form**

The evidence of diagnosis form was completed by the paediatrician, psychiatrist, or psychologist who had given the diagnosis of ADHD according to *DSM-IV* criteria (Appendix N). If this was not possible, it was completed by the child’s current practitioner.

**Medical practitioner clearance form**

The HREC emphasised that the parents would not be able to consult with a medical practitioner purely for the purpose of having this clearance form signed. This is because claiming a fee from Medicare for such a consultation is not allowed; therefore, the parents could not be bulk-billed. In addition, if they were required to pay the medical practitioner a fee, it would cause them to be out of pocket. Thus, the medical practitioner clearance form was provided to parents on the understanding that they would take it with them when they saw their general practitioner, or paediatrician, for a routine visit, or that they would leave it at the practitioner’s rooms for them to peruse it and sign it. A copy of the PLS was also provided, as in signing the clearance form the medical practitioner concerned was declaring that they had read a description of the research, and that they understood that participants may
be given herbal medicines. They were also attesting to the fact that in their opinion there was no medical problem present, and no current medications being taken, that suggested that the child should not participate (Appendix O).

*Informed consent form*

After the completion of the informed consent form (Appendix P), a copy was given or mailed to the parents, and the original was kept on file.

2.4.3 Study Design

*Overview*

The study was a randomised placebo-controlled double blind parallel clinical trial. A parallel design was used rather than a crossover design due to the duration of the treatment phase of the trial. As herbal medicines can be slower to take effect in comparison to orthodox remedies, it was felt that the treatment phase should last for 3 months. Given that the research participants were to be children, it was considered unlikely that they would persevere with taking tablets for longer than 3 months. Following the recruitment of a child, and the completion of the informed consent form, the senior supervisor conducted the randomisation procedure using random number tables. Thus, the child was allocated to one of two groups: the active herbal group, or the placebo group. The senior supervisor had no contact with the participants or their parents. All details concerning the randomisation were kept in a locked filing cabinet in his office at RMIT University. The investigator remained unaware of which group a child was in until the code was broken by the senior supervisor at the conclusion of the trial for the purpose of data analysis. As the trial was parallel, the child remained in the same group for the duration of the study. The entire trial for each child lasted for 7.5 months. The trial phases, and their duration, are given in Table 2.6.

<table>
<thead>
<tr>
<th>Trial Phase</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Treatment</td>
<td>3 months</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Between phases interval</td>
<td>3 months</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>
The outcome of the randomisation procedure, and the dosage of trial product for each participant, is presented in Table 2.7.

### Table 2.7 Participant details regarding ADHD medication status, weight, randomisation, and dosage of trial tablets

<table>
<thead>
<tr>
<th>Participant number</th>
<th>ADHD medication</th>
<th>Weight</th>
<th>Randomisation</th>
<th>Dosage of trial tablets&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Nil</td>
<td>39 kg</td>
<td>Active</td>
<td>Three tablets&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.</td>
<td>Nil</td>
<td>27 kg</td>
<td>Placebo</td>
<td>Three tablets</td>
</tr>
<tr>
<td>3.</td>
<td>On medication</td>
<td>21 kg</td>
<td>Active</td>
<td>Two tablets</td>
</tr>
<tr>
<td>4.</td>
<td>Nil</td>
<td>65 kg</td>
<td>Placebo</td>
<td>Seven tablets</td>
</tr>
<tr>
<td>5.</td>
<td>On medication</td>
<td>45 kg</td>
<td>Active</td>
<td>Five tablets</td>
</tr>
<tr>
<td>6.</td>
<td>On medication</td>
<td>22.5 kg</td>
<td>Placebo</td>
<td>Two tablets</td>
</tr>
</tbody>
</table>

<sup>a</sup>The dosage was the same morning and night. <sup>b</sup>This was a reduced dose due to him having only one kidney.

**Trial tablets administration, and trial record keeping**

After the first participant had difficulty taking the tablets, despite the verbal instructions from the investigator to his parents to crush them if necessary, a participant information sheet was devised in order to provide the instructions to other parents in writing. The investigator also obtained a sample of tablets from another trial from MediHerb Pty Ltd. It was used in the case of further inquiries, and face-to-face interviews, to illustrate the size of the trial tablets.

Due to some difficulty with data collection with the first child, for example, trial forms being completed by one parent to begin with, then by the other parent, written instructions regarding these issues were also devised. They were included on the same information sheet for parents as the instructions for tablets, and this is presented in Figure 2.2.
Regarding the rating scales and questionnaires:

It is best if they are all completed by the same parent or teacher (as applicable) for the entire trial. However, we understand that this may not be possible, especially for the sleep diary.

Please note that on some scales, for instance the Conners’ scales, the date is asked for in “American” style, that is “month, then day, then year”. To avoid any confusion it is preferable to write the date in “Australian” style, or to write it longhand, for instance “30 July 2004”.

Please return all forms, including any that are not completed.

Regarding trial tablets:

The trial tablets are coated, and can be swallowed whole, but they may be crushed if this is difficult. To do this a mortar and pestle should be used. The crushed tablets can then be mixed with something as a base in which to take them. For instance, mashed banana or other fruit.

The empty tablet containers, and any unused tablets, should be returned to Fiona Dey at the end of the treatment (i.e. tablet-taking) phase of the trial.
If you have any queries please contact:

Fiona Dey
Division of Psychology
RMIT University
telephone (03) 9925-7376 [mobile 0408 511 437]
facsimile (03) 9925-7303
e-mail s8210843@student.rmit.edu.au

Figure 2.2 Written instructions for parents regarding the completion of trial documents, and the administration of trial tablets
A case report/record form was used by the investigator for each participant in order to record the details of their progress through the trial, and any anomalies regarding their data collection (Appendix Q). Participant files were kept in a locked filing cabinet in the investigator’s office at RMIT University.

Details of the trial phases, and when the measures were administered

The trial commenced with a 2-week baseline phase. The trial tablets were commenced the day after the end of the baseline phase, and they were taken morning and night for 3 months. Immediately after the 3 months on tablets, that is, the treatment phase, there was a 2-week post-treatment phase. At the end of the post-treatment phase there was an interval of 3 months during which no data collection took place. It was followed by a 2-week follow-up phase that concluded the trial. The details of when the trial measures were administered are summarised in Table 2.8.

Table 2.8 Summary of the four trial phases, and when each of the eight measures was administered

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Post-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOVA</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>QEEG</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CPRS-R</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>CTRS-R</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

The TOVA and QEEG were conducted twice: at baseline, and at post-treatment. The testing was conducted at these points in order to give “before tablets” and “after tablets” data in line with the recommendation of the second supervisor.

The CBCL was used three times: at baseline, at the end of treatment, and at follow-up. The CBCL was used at baseline and at the end of treatment in order to give “before tablets” and
“after tablets” data. It was completed during the follow-up phase to see if the changes in daytime behaviour and sleep, if any, were maintained.

For the CPRS-R and the CTRS-R, the long forms were administered twice at baseline in accordance with the guidelines in the literature, and the second administration was used as the baseline (Conners, 1997). The long forms were also used once at follow-up as per the CBCL. The short forms were given on a monthly basis for each of the three treatment months as they take less time to complete, and they were also used once at post-treatment.

The Sleep Diary was completed on a daily basis across the entire study. It was used during each phase in order to obtain the maximum amount of data regarding sleep as it was the only night-time measure.

The Side Effects Rating Scale was completed on a weekly basis during the treatment phase, and weekly during the post-treatment phase. The scale was used weekly based on the example of the weekly side effects scale for medical drugs that was developed by Barkley and Murphy (1998).

The CAP is a weekly scale. It was used once at baseline, weekly during the treatment phase, once at post-treatment, and once at follow-up.

Three months after the conclusion of the trial, that is, 3 months after the end of the follow-up phase, the parents were telephoned by the investigator in order to ascertain their child’s well-being, and to see if any issues had arisen for them as a result of their involvement in the research.

Some participants missed the TOVA and QEEG due to their own commitments. The investigator conducted the TOVA and QEEG testing for the initial participants who did undergo those tests, however due to problems with the testing, and with the equipment, the staff of the BNC conducted the remaining tests.

The trial rating scales, the other forms, and the trial tablets, were either supplied to parents at meetings, or were sent to them by mail in advance. Forms were returned to the investigator at meetings, or via mail. The forms for the teachers were supplied to the teachers via the parents. For the most part, they were returned to the investigator via the parents until later in the study.
when some were returned directly by reply-paid mail following an amendment of the trial budget.

2.4.4 Monitoring of participants
The investigator contacted the parents by telephone on a weekly basis in order to ascertain compliance, answer questions, and to see if their child was experiencing any problems taking the trial tablets. As the trial proceeded it was found that some parents preferred to be contacted by email, or to have less frequent telephone calls. In those instances a schedule of contact was negotiated between the investigator and the parents.

Compliance
The investigator monitored compliance in the above manner regarding the taking of the trial tablets, and the completion of the trial measures. A question on the Sleep Diary allowed for parents to record any instances where the child had missed taking the trial tablets. It was also proposed that, if necessary, parents would return the tablet containers, and any unused tablets, to the investigator at the conclusion of the trial.

Side effects or adverse reactions
The incidence of side effects was monitored during the regular contact that the investigator had with the parents, as above. In addition, the parents completed a weekly Side Effects Rating Scale as per sub-section 2.3.2. The scale allowed for parents to record the incidence of the following signs and symptoms: stomachaches, nausea, vomiting, diarrhoea, lack of appetite, dizziness, headaches, sleepy in daytime, feverish, and skin rash. In addition, it was emphasised to the parents that if they had any concerns at all about their child, they could contact the investigator at any time, either at RMIT University or on her mobile telephone number, as per sub-section 2.4.2.

2.5 Data analysis
The data from the TOVA and QEEG were analysed by the staff of the BNC under the guidance of the second supervisor. The computer files containing the analyses were then provided to the investigator, in conjunction with reports summarising the results for each child.

For the other trial measures the investigator checked the various forms as they were received, and noted the date of completion, and any anomalies, in the child’s file. Data anomalies were
also noted in a computer file that did not contain any identifying information. The completed forms, and the participants' files, were kept in a locked filing cabinet in the investigator's office at RMIT University.

The forms for the CBCL, CPRS-R, CTRS-R, and CAP were hand-scored by the investigator. In addition, five prime sleep variables were derived from the Sleep Diary. The quantitative trial data were then entered into a Statistical Package for the Social Sciences (SPSS) data file, minus any identifying information. For missing data points the SPSS cells were left blank.

The SPSS data file was created using SPSS 11.0 for Windows at RMIT University, and this was also the location for the data entry. The completed data file was later transferred to SPSS Graduate Pack 11.0.2 for Macintosh OS X at the investigator's home for the purpose of analysis. Dr John Reece - the Advanced Research Methods lecturer for the Division of Psychology at RMIT University - provided guidance regarding the data analysis for the study.

Finally, the investigator checked the Side Effects Rating Scale forms as they were received, and any salient points were noted in the child's file. In addition, any information concerning the GAS was also noted.

2.5.1 Line graphs
Line graphs were produced in SPSS for all dependent variables except the TOVA and QEEG, the Side Effects Rating Scale, and the GAS. The line graphs displayed every data point of every scale, and subscale, for each participant across the trial phases. Means graphs were also generated for the active and placebo groups.

The investigator conducted a visual analysis of the line graphs in order to provide MediHerb Pty Ltd with the initial trial results in August 2005. The provisional patent was due for renewal in mid-September 2005, hence the need for the preliminary results of the study to be supplied to the company prior to that date.

Independent rating of line graphs
Following on from the initial stage regarding results, the investigator prepared a set of amended line graphs. These were provided to an independent rater who was not involved in the research for the purpose of visual analysis. The independent rater was unaware of the variables being considered as all such information had been removed from the graphs. They
were also blind as to which product each child had taken, and they had no knowledge of whether an increase or decrease in score represented an improvement, or deterioration, in behaviour. They were simply informed of the points at which the particular measure had been administered, and asked to give their assessment of change across the trial according to the following criteria: substantial change, moderate change, no change, variability, or cannot decide. The criteria were modified from Weiskopf, Richdale, and Matthews (2005). The definitions for each criterion have been provided below, and in Appendix R. The investigator also conducted a blind visual analysis of the amended graphs, and then the results of the visual analyses were compared. The means graphs for the two treatment groups were not included in the analysis of the amended graphs.

The criteria used for the independent rating procedure were as follows:

**Substantial change** (SC): Data showing that for the behaviour there was a significant and consistent change across the phases of the trial. That is, the graph shows that the behaviour increased or decreased significantly, and that the direction of change was maintained.

**Moderate change** (MC): Data showing that for the behaviour there was a consistent change across the phases of the trial, and that the direction of change was maintained. However, the magnitude of change is not great enough for it to be considered substantial.

**No change** (NC): Data showing that there was no change in the behaviour across the phases of the trial.

**Variability** (V): Data showing fluctuation, or fluctuations, in the behaviour across the phases of the trial. That is, the behaviour changes, but the direction of the change is not consistent.

**Cannot decide** (CD): Cannot classify the behaviour according to one of the above criteria.

In addition, the independent rater devised the criterion **Not enough data points** (NED), which they used as a rating, and/or as a comment. Due to the lack of data points on some graphs they expressed their concern about being unable to reliably assess change. They also expressed concern about the graphs that had scales that did not commence at zero. Therefore, they only gave ratings for seven sets of line graphs (that is, for seven measures) out of 64: CBCL Problems Scales Externalising, CAP, and the five prime sleep variables.
2.5.2 Statistical testing of the five prime sleep variables

Five prime sleep variables were derived from the Sleep Diary: sleep latency (SL), number of times awake (NTA), total time awake (TTA), total sleep time (TST), and overall sleep quality (OSQ). SL was calculated as being the difference in minutes between evening question four *What time did you leave your child for sleep tonight?* and evening question seven *What time do you think your child fell asleep?*. NTA was derived from morning question two *Did your child wake during the night?*. If the answer was yes, the parents were asked to list in a table the time of waking, the possible reason(s) for waking, and how long the child was awake. Thus, the number of times the child woke could be counted. TTA was also calculated from the answer to morning question two, by adding up how long the child was awake in minutes. TST was calculated in decimal hours as being the difference between the answers to morning question one *What time did your child wake up?* and evening question seven *What time do you think your child fell asleep?*. OSQ was derived from morning question seven *How would you rate your child's sleep last night?*. Parents were asked to circle a number on a six-point Likert scale that ranged from zero *Not restless at all* to five *Very restless*.

In addition to the visual analysis of line graphs for the sleep variables, a Kruskal-Wallis non-parametric analysis of variance (ANOVA) was conducted on the ranks associated with the scores. Some significant results were found. Post-hoc pairwise comparisons were conducted using Mann-Whitney *U* tests with a Bonferroni adjusted significance level of .008 in order to see where the significant effects occurred. In order to clarify the nature of the results, the investigator then conducted a further visual analysis of the relevant line graphs.
CHAPTER 3
RESULTS

3.1 Participant attrition

A total of 157 formal inquiries were received about the study in response to the participant recruitment advertising campaign described in Chapter 2. Some additional inquiries were received on an informal basis, for example from colleagues, and from herbal medicine students. The majority of formal inquiries were made by telephone, and the remainder were made by email. Of the 157 formal inquiries, 139 were made by a parent, or other relative, inquiring about the possible participation of a child. The remaining 18 came from health professionals, students, the media, and teachers’ aides.

Despite considerable interest in the study only 12 potential participants attended the initial face-to-face interview. Of these, 6 children proceeded to be enrolled in the trial. Five children completed the trial, and there was one withdrawal. The child who withdrew, participant 6, was taking the placebo tablets, and his behaviour deteriorated. It appears that he reacted to the chocolate product that MediHerb Pty Ltd had used to colour the placebo tablets in case they were broken or crushed, however there were confounding issues. The withdrawal report that was submitted to the HREC has been provided in Appendix S. The data that were obtained before he withdrew from the trial were analysed, and included in the results.

The biggest barrier to participation during the initial stage of recruitment advertising was having the standard ADHD medical drugs - methylphenidate, dexamphetamine, and clonidine - listed in the trial exclusion criteria. This situation was altered following an application to the HREC to amend the trial protocol, as outlined in the previous chapter in sub-section 2.1.2. The amendment allowed children who were taking one or more of these drugs to be considered for inclusion in the trial.

Other issues, and stated reasons, that affected recruitment were:

- the remaining exclusion drugs
- the 50% risk of receiving the placebo tablets
- the amount of time and effort involved
- wanting a treatment that “works”
- being unwilling to comply with the ADHD diagnosis requirement
• wanting to keep the child’s ADHD hidden from their teacher
• the other parent refused to allow the child to participate
• difficulty in getting back to the inquirer (for a very small number of calls)
• the constraint upon the investigator regarding confidentiality and trial products

These matters will be discussed in Chapter 4.

3.2 Participants and data analysis

Details of the trial participants were presented in Table 2.1. Three participants received the herbal tablets, and 3 participants received the placebo tablets, as per Table 2.7. As outlined in Chapter 2, section 2.5, the major method of data analysis consisted of the visual analysis of line graphs. This was due to the small sample size. Unfortunately some graphs could not be generated due to insufficient data. Summary tables derived from the blind graph ratings that were given by the investigator for all of the relevant variables are presented in section 3.3. Representative graphs have been included at the end of the present section to provide examples of the criteria that were used to derive the graph ratings. Detailed tables that include descriptive comments made by the investigator subsequent to the rating procedure, and during the preparation of this chapter, have been provided in Appendix T. These comments were made using a set of graphs that includes the full details of the variables. This was done in order to clarify the behavioural changes for each participant.

As per sub-section 2.5.1 in the previous chapter, the comments made by the independent rater were made when they rated a set of amended graphs without being aware of the details of the variables. Due to the lack of data points, and some of the scales not commencing at zero, the independent rater only gave ratings for seven sets of line graphs (that is, for seven measures) out of 64: CBCL Problems Scales Externalising, CAP, and the five prime sleep variables. Their ratings and comments have been included in Appendix T in separate tables. The details of the rating criteria have been provided in Chapter 2, sub-section 2.5.1.

In addition to the visual analysis of line graphs, statistical analyses were conducted for the five prime sleep variables derived from the Sleep Diary. Moreover, the staff of the BNC provided the results of the limited data obtained from the TOVA and QEEG testing, and the investigator collated the information obtained from the Side Effects Rating Scale and the GAS. Summaries of both individual and collective trial results will be presented at the end of the present chapter.
Figure 3.1 Example of a graph showing ‘substantial change’ (improvement) for the CPRS-R:L Subscale F. Social Problems

Figure 3.2 Example of a graph showing ‘moderate change’ (deterioration) for the CBCL Competence Scale Activities
Figure 3.3 Example of a graph showing ‘no change’ for the CBCL Competence Scale Social

Figure 3.4 Example of a graph showing ‘variability’ (improvement followed by deterioration) for the CBCL Competence Scale School
Figure 3.5 Example of a graph showing ‘variability’ for Sleep Latency across the entire trial (B=Baseline, T=Treatment, PT=Post-treatment, and F=Follow-up)

Figure 3.6 Example of a graph showing ‘cannot decide’ for the CTRS-R:S due to a missing data point following improvement at treatment month 3
3.3 Results of the visual analysis of line graphs

3.3.1 Results for the daytime measures

**CBCL**

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CBCL Competence Scales is presented in Table 3.1. These data show that there were three improvement ratings for the active tablets, and there were no improvement ratings for placebo. However, there were two deterioration ratings for the active tablets, and no deterioration ratings for placebo. Most of the ratings fitted other criteria.

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CBCL Problem Scales is presented in Tables 3.2 and 3.3. The data for the individual scales show that there were five improvement ratings for the active tablets, and there was one improvement rating for placebo. There were two deterioration ratings for the active tablets, and three deterioration ratings for placebo. Most of the ratings fitted other criteria. The data derived from more than one item show that there were two improvement ratings for the active tablets, and no improvement ratings for placebo. Furthermore, there were no deterioration ratings for either product. Most of the ratings fitted other criteria.

**CPRS-R**

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CPRS-R:L is presented in Tables 3.4 and 3.5. These data show that most of the ratings were for improvement on the active tablets, including some ratings of substantial rather than moderate change. There were a smaller number of deterioration ratings for the active tablets, and one active tablets rating of no change. Unfortunately all of the placebo graphs were blank due to insufficient data.

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CPRS-R:S is presented in Table 3.6. These data show there were three improvement ratings for the active tablets, and there were no improvement ratings for placebo. However, all of the remaining ratings fitted the variability and cannot decide criteria.
Table 3.1 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CBCL Competence Scales (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competence Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Competence Scale</td>
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<td>1</td>
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<td>Competence Scale</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.2 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CBCL Problem Scales [Scales I to VIII inclusive] (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale II Somatic Complaints</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale III Anxious/Depressed</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale IV Social Problems</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale V Thought Problems</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale VI Attention Problems</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale VII Delinquent Behaviour</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Problem Scale VIII Aggressive Behaviour</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>1</td>
</tr>
</tbody>
</table>
Table 3.3 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CBCL Problem Scales [Internalising, Externalising, and Total Score] \(N = 6\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>No Change</th>
<th>Deterioration</th>
<th>Variability</th>
<th>Cannot Decide</th>
<th>Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Internalising: the sum of Problem Scales I, II, and III, minus a duplicated item</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Externalising: the sum of Problem Scales VII and VIII</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total Score: the sum of all Problem Scale items</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

93
Table 3.4 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CPRS-R:L [Subscales A. to H. inclusive] (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale A. Oppositional</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale B. Cognitive Problems/Inattention</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale C. Hyperactivity</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale D. Anxious-Shy</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale E. Perfectionism</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale F. Social Problems</td>
<td>3**</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale G. Psychosomatic</td>
<td>3*</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Subscale H. Conners’ ADHD Index</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*Note.* The number of asterisks refers to the number of children rated as substantial change.
Table 3.5 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CPRS-R:L [Subscales I. to N. inclusive] (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Placebo</th>
<th>No Change Active</th>
<th>Placebo</th>
<th>Deterioration Active</th>
<th>Placebo</th>
<th>Variability Active</th>
<th>Placebo</th>
<th>Cannot Decide Active</th>
<th>Placebo</th>
<th>Blank Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale I. Conners’ Global Index: Restless-Impulsive</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale J. Conners’ Global Index: Emotional Lability</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale K. Conners’ Global Index: Total</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subscale L. DSM-IV: Inattentive</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Subscale N. DSM-IV: Total</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<td>0</td>
<td>0</td>
<td>3</td>
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</tbody>
</table>
Table 3.6 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CPRS-R:S (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>No Change</th>
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<th>Variability</th>
<th>Cannot Decide</th>
<th>Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale A. Oppositional</td>
<td>1 0</td>
<td>0 0</td>
<td>0 0</td>
<td>2 1</td>
<td>0 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Subscale B. Cognitive Problems/Inattention</td>
<td>1 0</td>
<td>0 0</td>
<td>0 0</td>
<td>2 1</td>
<td>0 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Subscale C. Hyperactivity</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>3 1</td>
<td>0 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Subscale D. Conners' ADHD Index</td>
<td>1 0</td>
<td>0 0</td>
<td>0 0</td>
<td>2 1</td>
<td>0 2</td>
<td>0 0</td>
</tr>
</tbody>
</table>
The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the T-scores for the CPRS-R across the entire trial is presented in Table 3.7. These data show that there were two improvement ratings for the active tablets, and no improvement ratings for placebo. All of the other ratings fitted the variability and cannot decide criteria. The use of the T-scores to obtain results for the CPRS-R across the entire trial will be discussed in Chapter 4, sub-section 4.3.2.

**CTRS-R**

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CTRS-R:L is presented in Tables 3.8 and 3.9. These data show that most of the ratings were for improvement on the active tablets, including some ratings of substantial rather than moderate change. There were also some deterioration ratings on the active tablets, including two that were substantial. Unfortunately, the graphs for two of the placebo participants were blank. The remaining placebo participant fluctuated between improvement, deterioration, and no change.

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CTRS-R:S is presented in Table 3.10. These data show that there were two improvement ratings for the active tablets, and no improvement ratings for the placebo. There was one deterioration rating for the active tablets, and there were no deterioration ratings for the placebo. The remaining ratings fitted the variability, cannot decide, and blank categories.

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the T-scores for the CTRS-R across the entire trial is presented in Table 3.11. There were two improvement ratings for the active tablets, and there were no improvement ratings for placebo. There was one deterioration rating for the active tablets, and there were no deterioration ratings for placebo. The remaining ratings fitted the variability and cannot decide categories. The use of the T-scores to obtain results for the CTRS-R across the entire trial will be discussed in Chapter 4, sub-section 4.3.2.

**CAP**

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the CAP is presented in Table 3.12. These data show that all of the participants were placed in the variability category.
Table 3.7 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CPRS-R T-scores \((N = 6)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale A. Oppositional</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subscale B. Cognitive Problems/Inattention</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subscale C. Hyperactivity</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subscales H. (long form) &amp; D. (short form) Conners' ADHD Index</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3.8 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CTRS-R:L [Subscales A. to H. inclusive] (**N** = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Placebo</th>
<th>No Change Active</th>
<th>Placebo</th>
<th>Deterioration Active</th>
<th>Placebo</th>
<th>Variability Active</th>
<th>Placebo</th>
<th>Cannot Decide Active</th>
<th>Placebo</th>
<th>Blank Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale A. Oppositional</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subscale B. Cognitive Problems/Inattention</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subscale C. Hyperactivity</td>
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<td>0</td>
<td>1</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subscale D. Anxious-Shy</td>
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<td>1</td>
<td>1</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subscale E. Perfectionism</td>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subscale F. Social Problems</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subscale H. Conners’ ADHD Index</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* The number of asterisks refers to the number of children rated as substantial change. There is no subscale G. for the CTRS-R:L.
Table 3.9 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CTRS-R:L [Subscales I. to N. inclusive] \((N = 6)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale I. Conners’ Global Index: Restless-Impulsive</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subscale J. Conners’ Global Index: Emotional Lability</td>
<td>2*</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subscale K. Conners’ Global Index: Total</td>
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<td>1</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subscale L. DSM-IV: Inattentive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subscale M. DSM-IV: Hyperactive-Impulsive</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Subscale N. DSM-IV: Total</td>
<td>2</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>2</td>
</tr>
</tbody>
</table>

*Note.* The number of asterisks refers to the number of children rated as substantial change.
Table 3.10 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CTRS-R:S ($N = 6$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale A.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oppositional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscale B.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cognitive Problems/Inattention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscale C.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Hyperactivity</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscale D.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conners’ ADHD Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.11 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CTRS-R T-scores (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement Active</th>
<th>Improvement Placebo</th>
<th>No Change Active</th>
<th>No Change Placebo</th>
<th>Deterioration Active</th>
<th>Deterioration Placebo</th>
<th>Variability Active</th>
<th>Variability Placebo</th>
<th>Cannot Decide Active</th>
<th>Cannot Decide Placebo</th>
<th>Blank Active</th>
<th>Blank Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscale A. Oppositional</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subscale B. Cognitive Problems/Inattention</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subscale C. Hyperactivity</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subscales H. (long form) &amp; D. (short form) Conners’ ADHD Index</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3.12 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the CAP (N = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>No Change</th>
<th>Deterioration</th>
<th>Variability</th>
<th>Cannot Decide</th>
<th>Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>CAP</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3.13 Number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding line graph ratings for the five prime sleep variables ($N = 6$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>No Change</th>
<th>Deterioration</th>
<th>Variability</th>
<th>Cannot Decide</th>
<th>Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NTA</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>3</td>
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<td>0</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
3.3.2 Results for the night-time measures

Sleep Diary

The number of participants who improved, did not change, deteriorated, or fitted other criteria, regarding the line graph ratings for the five prime sleep variables is presented in Table 3.13. These data show that there were no ratings for improvement or deterioration on either the active tablets or the placebo. Most of the ratings fitted the variability criterion, while a smaller number fitted no change and cannot decide.

3.4 Results of statistical testing of the sleep variables

The following sub-sections present the results of the statistical tests that were conducted for the five prime sleep variables derived from the Sleep Diary, as per sub-section 2.5.2 in the previous chapter.

3.4.1 Sleep latency

The initial analysis revealed a significant effect across the four phases for participant 2 (placebo) \( \chi^2 (3, N = 6) = 9.82, p = .020 \), participant 3 (active) \( \chi^2 (3, N = 6) = 9.34, p = .025 \), participant 4 (placebo) \( \chi^2 (2, N = 6) = 9.66, p = .008 \), and participant 5 (active) \( \chi^2 (3, N = 6) = 11.20, p = .011 \). There were also significant effects across the four phases for the mean of the active group \( \chi^2 (3, N = 6) = 8.12, p = .044 \), and the mean of the placebo group \( \chi^2 (3, N = 6) = 29.70, p < .001 \). The relevant means and standard deviations are presented in Table 3.14. The significant results of the post-hoc tests for SL have been summarised in Table 3.15.

3.4.2 Number of times awake

The initial analysis revealed a significant effect across the four phases for participant 3 (active) \( \chi^2 (3, N = 6) = 7.86, p = .049 \). The relevant means and standard deviations are presented in Table 3.16. The post-hoc tests did not reveal where the significant effect occurred.

3.4.3 Total time awake

The initial analysis found no significant effects across the four phases.

3.4.4 Total sleep time

The initial analysis revealed a significant effect across the four phases for participant 1 (active) \( \chi^2 (3, N = 6) = 19.29, p < .001 \), participant 4 (placebo) \( \chi^2 (2, N = 6) = 9.17, p = .010 \), and for the mean of the placebo group \( \chi^2 (3, N = 6) = 25.97, p < .001 \). The relevant means and
standard deviations are presented in Table 3.17. The significant results of the post-hoc tests for TST have been summarised in Table 3.18.

3.4.5 Overall sleep quality

The initial analysis revealed a significant effect across the four phases for participant 2 (placebo) $\chi^2 (3, N = 6) = 27.56, p < .001$, participant 3 (active) $\chi^2 (3, N = 6) = 28.23, p < .001$, participant 4 (placebo) $\chi^2 (2, N = 6) = 12.40, p = .002$, and participant 6 (placebo) $\chi^2 (1, N = 6) = 7.11, p = .008$. There were also significant effects for the mean of the active group $\chi^2 (3, N = 6) = 8.64, p = .034$, and the mean of the placebo group $\chi^2 (3, N = 6) = 20.46, p < .001$.

The relevant means and standard deviations are presented in Table 3.19. The significant results of the post-hoc tests for OSQ have been summarised in Table 3.20.

Table 3.14 The means and standard deviations for SL (minutes) for participants 2, 3, 4, and 5, and both groups across the trial phases

<table>
<thead>
<tr>
<th>Participants and groups</th>
<th>Value</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Post-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>18.08</td>
<td>13.65</td>
<td>10.00</td>
<td>14.62</td>
</tr>
<tr>
<td></td>
<td>Nights SD</td>
<td>13</td>
<td>89</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.09</td>
<td>5.53</td>
<td>.00</td>
<td>5.19</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Mean</td>
<td>26.43</td>
<td>17.84</td>
<td>27.14</td>
<td>18.21</td>
</tr>
<tr>
<td></td>
<td>Nights SD</td>
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<td>81</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.25</td>
<td>14.32</td>
<td>17.18</td>
<td>7.50</td>
</tr>
<tr>
<td>3. Active</td>
<td>Mean</td>
<td>31.54</td>
<td>20.73</td>
<td>—</td>
<td>28.46</td>
</tr>
<tr>
<td></td>
<td>Nights SD</td>
<td>13</td>
<td>52</td>
<td>—</td>
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</tr>
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<td></td>
<td>20.04</td>
<td>7.94</td>
<td>—</td>
<td>10.28</td>
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<td>123.75</td>
<td>108.45</td>
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</tr>
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<td>Nights SD</td>
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<td>71</td>
<td>14</td>
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<td>63.03</td>
<td>50.08</td>
<td>33.60</td>
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<td>40.37</td>
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<td>28.93</td>
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<td></td>
<td>Nights SD</td>
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<td>90</td>
<td>14</td>
<td>14</td>
</tr>
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<td></td>
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<td>24.85</td>
<td>21.39</td>
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<td>20.44</td>
<td>10.00</td>
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<td>9</td>
<td>14</td>
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<td></td>
<td>9.67</td>
<td>9.14</td>
<td>.00</td>
<td>6.23</td>
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Note. The dash indicates missing data.

*For the post-treatment phase the same figures were calculated for participant 2 (placebo) and the placebo group due to missing data.
Table 3.15 Summary of the significant results of the post-hoc tests for SL

<table>
<thead>
<tr>
<th>Participants and trial groups</th>
<th>Baseline vs treatment</th>
<th>Baseline vs post-treatment</th>
<th>Baseline vs follow-up</th>
<th>Treatment vs post-treatment</th>
<th>Treatment vs follow-up</th>
<th>Post-treatment vs follow-up</th>
</tr>
</thead>
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<td>2. Placebo</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3. Active</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Placebo</td>
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<tr>
<td>5. Active</td>
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<td>$p = .006 \downarrow$</td>
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</tr>
<tr>
<td>6. Placebo</td>
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<td></td>
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<td>Active group</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>$p &lt; .001 \downarrow$</td>
<td>$p &lt; .001 \downarrow$</td>
<td>$p = .005 \downarrow$</td>
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<td>$p &lt; .001 \downarrow$</td>
<td>$p &lt; .001 \uparrow$</td>
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</table>

*Note.*

$\uparrow$ longer

$\downarrow$ shorter
Table 3.16 The means and standard deviations for NTA for participant 3 across the trial phases

<table>
<thead>
<tr>
<th>Participant and group</th>
<th>Value</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Post-treatment</th>
<th>Follow-up</th>
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<td>.00</td>
<td>.00</td>
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</tr>
<tr>
<td></td>
<td>Nights</td>
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<td>82</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.27</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
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Table 3.17 The means and standard deviations for TST (decimal hours) for participants 1 and 4 and the placebo group across the trial phases

<table>
<thead>
<tr>
<th>Participants and groups</th>
<th>Value</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Post-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
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<td>Mean</td>
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<td>9.10</td>
<td>9.66</td>
<td>9.71</td>
</tr>
<tr>
<td></td>
<td>Nights</td>
<td>14</td>
<td>89</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>SD</td>
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<td>.66</td>
<td>.48</td>
<td>.38</td>
</tr>
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<td>4. Placebo</td>
<td>Mean</td>
<td>9.10</td>
<td>9.95</td>
<td>—</td>
<td>9.47</td>
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<tr>
<td></td>
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<td>53</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.49</td>
<td>.98</td>
<td></td>
<td>.16</td>
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<td>9.88</td>
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<td>Nights</td>
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<td>14</td>
</tr>
<tr>
<td></td>
<td>SD</td>
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<td>.43</td>
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*Note.* The dash indicates missing data.
Table 3.18 Summary of the significant results of the post-hoc tests for TST

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<th>Baseline vs post-treatment</th>
<th>Baseline vs follow-up</th>
<th>Treatment vs post-treatment</th>
<th>Treatment vs follow-up</th>
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<td>3. Active</td>
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<td></td>
<td></td>
</tr>
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<td></td>
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<td>6. Placebo</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
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<td>$p = .002 \uparrow$</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>$p &lt; .001 \downarrow$</td>
<td></td>
<td>$p = .005 \downarrow$</td>
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*Note.*

$\uparrow$ longer

$\downarrow$ shorter
Table 3.19 The means and standard deviations for OSQ for participants 2, 3, 4, and 6, and both groups across the trial phases

<table>
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<th>Participants and groups</th>
<th>Value</th>
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<th>Treatment</th>
<th>Post-treatment</th>
<th>Follow-up</th>
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</tr>
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<td>2.14</td>
<td>1.49</td>
<td>.22(^a)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Nights</td>
<td>14</td>
<td>89</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.29</td>
<td>1.03</td>
<td>.44</td>
<td>.85</td>
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<td>.86</td>
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<td>Nights</td>
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<td>14</td>
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<td></td>
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<td></td>
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<td>.72</td>
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<td>.93</td>
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<td>.06</td>
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<td>—</td>
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<td>Nights</td>
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<td>53</td>
<td></td>
<td>—</td>
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<td></td>
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<td>.41</td>
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<td>—</td>
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<td>1.94</td>
<td>1.49</td>
</tr>
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<td>90</td>
<td>14</td>
<td>14</td>
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<td></td>
<td>SD</td>
<td>.40</td>
<td>.55</td>
<td>.51</td>
<td>.59</td>
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<td>9</td>
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<td>SD</td>
<td>.65</td>
<td>.39</td>
<td>.44</td>
<td>.58</td>
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*Note.* The dashes indicate missing data.

\(^{a}\)For the post-treatment phase the same figures were calculated for participant 2 (placebo) and the placebo group due to missing data.
Table 3.20 Summary of the significant results of the post-hoc tests for OSQ

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<th>Participants and trial groups</th>
<th>Baseline vs treatment</th>
<th>Baseline vs post-treatment</th>
<th>Baseline vs follow-up</th>
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<td></td>
<td></td>
</tr>
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<td>3. Active</td>
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<td>$p &lt; .001$ ↑</td>
<td></td>
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</tr>
<tr>
<td>4. Placebo</td>
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</tr>
<tr>
<td>5. Active</td>
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<td></td>
</tr>
<tr>
<td>6. Placebo</td>
<td>$p = .008$ ↓</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Active group</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>$p = .002$ ↑</td>
<td></td>
<td></td>
<td>$p &lt; .001$ ↑</td>
<td></td>
<td>$p &lt; .001$ ↓</td>
</tr>
</tbody>
</table>

**Note.**

↑ improved

↓ deteriorated
3.5 Test of Variables of Attention

As per section 2.5 in the previous chapter, the staff of the BNC provided the results for the TOVA. The TOVA interpretation compares the participant’s test results with the test results of a large number of individuals who do not have attention problems. The ADHD score is a comparison of the participant’s TOVA performance to an age/gender specific group with ADHD. It is a measure of how similar the child’s performance is to the performance of others with ADHD (Greenberg, 2007).

3.5.1 Participant 1 - Active

The investigator conducted his baseline TOVA. The TOVA interpretation found that the results were not within normal limits, and were suggestive of an attention disorder. The ADHD score of -3.64 is not within the normal range.

The investigator also conducted his post-treatment TOVA. The TOVA interpretation was the same as for baseline. The ADHD score was -5.21. This is a deterioration compared to baseline.

3.5.2 Participant 2 - Placebo

He did not attend the BNC for testing.

3.5.3 Participant 3 - Active

The investigator conducted his baseline TOVA. The TOVA interpretation found that the results of the first half of the test were not within normal limits, and were suggestive of impulsivity (disinhibition) and/or behaviour problems. The ADHD score could not be calculated due to invalid quarters.

His post-treatment TOVA was conducted by the BNC. Despite repeated requests the file was not supplied, and no explanation was provided to the investigator.

3.5.4 Participant 4 - Placebo

His baseline TOVA was conducted by the BNC. The TOVA interpretation found that the results of the first half of the test were not within normal limits, and were suggestive of an attention disorder. The ADHD score could not be calculated due to invalid quarters.

He did not return for the post-treatment test.
3.5.5 Participant 5 - Active
His baseline TOVA was conducted by the BNC, and they stated that they were unable to locate the file.

He did not return for the post-treatment test.

3.5.6 Participant 6 - Placebo
His baseline TOVA was conducted by the BNC. The TOVA interpretation found that, overall, his TOVA was within normal limits. His ADHD score was 1.09, which does not fit the profile of ADHD, and is therefore deemed inconclusive. However, the test was administered after his usual ADHD medication, so this appears to have resulted in a performance that is considered to be within normal limits.

He withdrew from the study, thus he did not attend the clinic for the post-treatment test.

3.6 Quantitative Electroencephalography
As per section 2.5 in the previous chapter, the staff of the BNC provided the results for the QEEG. These consist of a graph that shows the theta/beta power ratio at CZ for the participant in comparison to the ratios for the normal mean and the ADHD cutoff, and a scale that illustrates the frontal beta power status at anterior sites. The interpretation of these results was also provided by the BNC.

3.6.1 Participant 1 - Active
The investigator conducted his baseline QEEG. Due to a procedural error at the time of the post-treatment test, when no warning was given regarding the file name, the baseline file was overwritten, and therefore it is unavailable.

The investigator also conducted his post-treatment QEEG. The results are shown in Figures 3.7 and 3.8.
Figure 3.7 The theta/beta power ratio at CZ for participant 1 at post-treatment

Figure 3.8 The frontal beta power status at anterior sites for participant 1 at post-treatment

The graph displayed in Figure 3.7 is not representative of an inattentive or combined ADHD subtype. However, the value shown in Figure 3.8 is representative of an overaroused or frontal beta excess subtype of ADHD, which is suggestive of excessive dopamine and norepinephrine neuromodulation (BNC, personal communication, June 8, 2006).

3.6.2 Participant 2 - Placebo
He did not attend the BNC for testing.

3.6.3 Participant 3 - Active
The investigator conducted his baseline QEEG. The results are shown in Figures 3.9 and 3.10.
Figure 3.9 The theta/beta power ratio at CZ for participant 3 at baseline

Figure 3.10 The frontal beta power status at anterior sites for participant 3 at baseline

The graph displayed in Figure 3.9 is representative of an inattentive or combined ADHD subtype, which is suggestive of an underaroused ADHD subtype due to low dopamine neuromodulation (BNC, personal communication, June 8, 2006). The value shown in Figure 3.10 is not representative of an overaroused or frontal beta excess subtype of ADHD.

The BNC conducted his post-treatment QEEG. The results are shown in Figures 3.11 and 3.12.
Figure 3.11 The theta/beta power ratio at CZ for participant 3 at post-treatment

Figure 3.12 The frontal beta power status at anterior sites for participant 3 at post-treatment

The graph displayed in Figure 3.11 is representative of an inattentive or combined ADHD subtype, which is suggestive of an underaroused ADHD subtype due to low dopamine neuromodulation (BNC, personal communication, June 8, 2006). The value shown in Figure 3.12 is not representative of an overaroused or frontal beta excess subtype of ADHD.

3.6.4 Participant 4 - Placebo
The BNC conducted his baseline QEEG. The results are shown in Figures 3.13 and 3.14.
Figure 3.13 The theta/beta power ratio at CZ for participant 4 at baseline

Figure 3.14 The frontal beta power status at anterior sites for participant 4 at baseline

The graph displayed in Figure 3.13 is representative of an underaroused inattentive or combined ADHD subtype. The value shown in Figure 3.14 is not representative of an overaroused or frontal beta excess subtype of ADHD (BNC, personal communication, June 8, 2006).

He did not return for the post-treatment test.

3.6.5 Participant 5 - Active

The BNC conducted his baseline QEEG. The results are shown in Figures 3.15 and 3.16.
Figure 3.15 The theta/beta power ratio at CZ for participant 5 at baseline

Figure 3.16 The frontal beta power status at anterior sites for participant 5 at baseline

The graph displayed in Figure 3.15 is not representative of an inattentive or combined ADHD subtype. In addition, the value shown in Figure 3.16 is not representative of an overaroused or frontal beta excess subtype of ADHD (BNC, personal communication, June 8, 2006).

He did not return for the post-treatment test.

3.6.6 Participant 6 - Placebo

The BNC conducted his baseline QEEG. The results are shown in Figures 3.17 and 3.18.
Figure 3.17 The theta/beta power ratio at CZ for participant 6 at baseline

Figure 3.18 The frontal beta power status at anterior sites for participant 6 at baseline

The graph displayed in Figure 3.17 is representative of an inattentive or combined ADHD subtype, which is suggestive of an underaroused ADHD subtype due to low dopamine neuromodulation (BNC, personal communication, June 8, 2006). The value shown in Figure 3.18 is not representative of an overaroused or frontal beta excess subtype of ADHD.

He withdrew from the study, thus he did not attend the clinic for the post-treatment test.

3.7 Side Effects Rating Scale

The Side Effects Rating Scale (Appendix I) consisted of a 5-point Likert scale ranging from 1 Not at All to 5 Frequent for the signs and symptoms listed in sub-section 2.4.4 in the previous chapter, and a section for comments. It was administered during the treatment phase and the post-treatment phase.

3.7.1 Participant 1 - Active

For week 3 of the treatment phase the mother noted that he had a cold and cough in the comments section, and for week 4 she circled 2 for stomachaches. Apart from this, all of the responses were 1, and no other comments were made.
3.7.2 Participant 2 - Placebo

For weeks 1 and 2 of the treatment phase the mother circled 3 and 2 respectively for lack of appetite. For week 3 she noted in the comments section that he had a cold but it had not turned into asthma, and in week 4 he had a small amount of asthma and needed Ventolin. Apart from this, all of the responses were 1, and no other comments were made.

3.7.3 Participant 3 - Active

In week 1 of the treatment phase the mother noted under comments that he had asthma, and that he required Ventolin for two days. No other comments were made, and all of the responses were 1.

3.7.4 Participant 4 - Placebo

For weeks 3, 6, 7, and 8 the father circled 2, 3, 4, and 2 respectively for headaches. Apart from this, all of the responses were 1, and no comments were made. The treatment phase forms beyond week 8, and the post-treatment phase forms, were not returned.

3.7.5 Participant 5 - Active

The mother completed the treatment phase forms as follows. For week 1 she circled 2 for nausea, 3 for lack of appetite, and 2 for headaches. For week 2 she circled 2 for lack of appetite, and 2 for headaches. For week 3 she circled 2 for nausea, and 2 for headaches. In week 4 she circled 2 for nausea, and 2 for lack of appetite, and for week 5 she circled 3 for skin rash, and in the comments section noted that he had sore arms and legs. In week 6 she circled 2 for skin rash, and commented that he had sore arms and legs but they had cleared up also the skin rash had gone. For week 8 she circled 2 for lack of appetite, and in the comments section she noted that this was due to Ritalin. In week 9 she circled 2 for stomachaches, and in week 10 she circled 2 for lack of appetite. For week 12 she circled both 1 and 2 for headaches. Apart from this, all of the responses were 1, and no other comments were made.

3.7.6 Participant 6 - Placebo

The mother completed the treatment phase forms as follows. For week 1 she circled 5 for lack of appetite, 3 for feverish, and 2 for skin rash, and commented that he had a cough and was on antibiotics. She also noted that he had a runny nose the day she completed the form, and he had been sneezing a lot. Also he had a rash on his legs but he had been rolling in grass. In week 2 she circled 2 for diarrhoea, and 5 for lack of appetite. In week 3 she circled 5 for lack of appetite. For week 4 she circled 5 for lack of appetite, and in the comments section she
noted that he had been sneezing a lot and his nose was running. For weeks 5, 6, 7, and 8 she circled 5 for lack of appetite. Apart from this, all of the responses were 1, and no other comments were made. No forms were completed beyond week 8 of the treatment phase as he withdrew from the study.

3.8 Goal Achievement Scale

3.8.1 Participant 1 - Active

*Initial interview*

*Daytime*

The mother set the following goals as the 100% goals for daytime: if he was more accepted by other kids at school, if he had more friends, to listen to his father and his sister (she yells at him), to remember things more (to be able to focus), and be better organised for school, to improve his short-term memory (for example, so he is not distracted on his way to clean his teeth), and for him to be more independent in order to get things done. The 25%, 50%, and 75% goals were not set as the mother stated that she needed to consider these.

*Night-time*

The night-time goals were not set as the mother was only concerned about his daytime behaviour.

*End of treatment phase*

The GAS was not done.

3.8.2 Participant 2 - Placebo

*Initial interview*

*Daytime*

The mother set the following goals as the 100% goals for daytime: more co-operative, more intuitive at school regarding what he is taught, less argumentative, and as he is very poor regarding his eating perhaps this could improve. The 25%, 50 %, and 75% goals were not set, and the mother wondered if we should ask his teacher about his behaviour at school for these, as he breaks things and snaps pencils.

*Night-time*

The mother set the 100% goal for night-time as he wakes up in a good mood. The 25%, 50 %, and 75% goals for night-time were not set.
**End of treatment phase**

This was done by email, and it was late as the mother had computer problems and was very busy.

**Daytime**

There was no change regarding being more co-operative, and the mother stated that he was still very difficult at school. Regarding being argumentative, she stated that he always has to have the last word. His very poor eating changed at first, but then it reverted back to how it was.

**Night-time**

The mother made no comment.

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**3.8.3 Participant 3 - Active**

**Initial interview**

**Daytime**

The mother set the 100% goals for daytime as follows: she wanted his swearing fixed, for him to stop climbing on furniture inappropriately, and, as he is constantly non-compliant and does not respond to instructions, for him to respond to at least some instructions. The 25%, 50%, and 75% goals were not set.

**Night-time**

The 100% goals for night-time were for him to get to sleep, for him to stay in bed when put in, as he gets in and out of bed if not asleep already, and to stop him getting up and going to the toilet “not in the toilet”, although this only happens occasionally. The 25%, 50%, and 75% goals were not set.

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**End of treatment phase**

This was done by email.

**Daytime**

There has been no improvement at all in his swearing, and it is probably worse. There has been no change regarding climbing on the furniture inappropriately. Regarding responding to instructions, he responds sometimes when the Ritalin has kicked in, but he is still very non-compliant.
Night-time
He is not too bad getting to sleep, and he seems to go to bed more willingly. He does not seem to get up as often as he used to once he is in bed. He has not gone to the toilet “not in the toilet” at all during the treatment phase.

3.8.4 Participant 4 - Placebo
Initial interview
Daytime
Both parents set the 100% goals for daytime as follows: that he can attend to things, that is, listen and then do things, that his attentiveness would improve a lot, also that his language improves, and that his violent aggression improves, as he directs it towards a lot of people. A 50% level for the first goal was that he listens to half what you say.

Night-time
The 100% goal was that he enjoys going to bed and can get to sleep without getting up and sneaking out to put the TV on.

End of treatment phase
This was done by email.

Daytime
There was no change at all in his attention, behaviour, or language.

Night-time
He still finds it hard to get to sleep, and although he goes to bed when asked he tends to stay up for hours before getting to sleep.

3.8.5 Participant 5 - Active
Initial interview
Daytime
The mother set the 100% daytime goals as better behaviour at school, that he does his school work, and that he enjoys school and is not so negative.
Night-time
She set the 100% goals for night-time as if he went to sleep at a decent time, if he didn’t argue about wanting to stay up and watch adult shows on TV, and if he ate a healthy dinner in the evening as he does not eat in the day and then he will not eat vegetables at night.

End of treatment phase
This was done by telephone.

Daytime
His behaviour at school was unchanged. He has improved a bit doing his school work, about a 25% improvement, which she then described as considerable. Regarding enjoying school, there was maybe a 5% improvement, but it was only a very small difference.

Night-time
Regarding going to sleep at a decent time, she said he goes through phases so it is hard to judge. She said he was not bad about a month ago but has now slipped. He is not waking in the night at all, so she estimated that at about a 10% improvement out of 100. Most times he goes to sleep, and he has not been having nights where he is up all night. The main complaint is getting him to sleep.

He still argues regarding the TV but she thinks it has improved a little bit. There is only a small improvement with it, then she said about 50:50. Regarding the nights that he wants to stay up now, once the TV is switched off he does not come back out to want it switched on again. He still comes out a little bit but not for this reason.

Regarding his eating, he is still much the same and he will not eat in the day but she makes him eat cut up fruit in the day and makes him have Rev milk. She has decreased his junk food, but he is still not eating much at breakfast or in the daytime.

3.8.6 Participant 6 - Placebo
Initial interview
Daytime
For daytime the parents set the main goals as follows: to improve his appetite, and to get him to eat a lot more, and to get him to come straight off the Playstation or computer without
having to entice him. They would also really love him to be able to socialise with other children at school, as they said he is starting to do this but he still goes off on his own.

Night-time
Their main goal for night-time was to stop him getting aggressive when they were trying to get him to bed, as he headbutts, hits, punches, and throws objects.

End of treatment phase
Not applicable as he withdrew from the trial.

3.9 Summary of individual results
3.9.1 Participant 1 - Active
For the CBCL Competence Scales Total Competence Score, this child’s behaviour was variable. His score improved between baseline and the end of treatment, however his follow-up score was the same as his baseline score. He exhibited improvement on two out of the eight CBCL Problem Scales, and also for the CBCL Problem Scales Total Score.

He showed an improvement in behaviour for 13 out of the 14 CPRS-R:L Subscales, however on the four Subscales for the CPRS-R:S his behaviour improved for one Subscale and it exhibited variability for the other three. Regarding his behaviour across the entire trial based on the T-scores for the CPRS-R, he displayed improvement on two of the four Subscales concerned, and his behaviour was variable on the remaining Subscales.

Out of the 13 Subscales for the CTRS-R:L, he showed improvement on 11, however the results for the CTRS-R:S were variable. On the T-scores for the CTRS-R across the entire trial, he showed variable behaviour on two Subscales, however no decision could be reached regarding the remaining Subscales. In addition, his behaviour was variable on the CAP, and there were some missing data points.

Regarding the Sleep Diary variables, his line graphs showed variability, and the statistical analysis revealed nothing apart from a significant effect for TST. The post-hoc tests found that this effect occurred at treatment versus follow-up, with his TST being longer at follow-up.
This child's TOVA showed a deterioration in behaviour, however there are concerns about how the TOVA and QEEG tests were conducted and these will be discussed in the following chapter. For the QEEG there are only results for the second test, therefore no comparisons can be made with the baseline test.

The Side Effects Rating Scale did not record any reactions to the trial tablets, and as there were no second measure point data for the GAS it is not possible to make any comparisons with his GAS baseline behaviour. Regarding the investigator's file notes for this participant, when the mother was contacted prior to the follow-up phase she mentioned that his kinesiologist wanted to make up the herbs for him if he had received the active product. This comment suggests that some positive changes had been observed. The mother was advised that as the trial was still running the code could not be broken at that point.

3.9.2 Participant 2 - Placebo
For the CBCL Competence Scales Total Competence Score this child's behaviour was variable as he deteriorated between baseline and the end of the treatment phase, and then he improved. His score at the follow-up point was better than his score at baseline. His results were mainly variable for the eight CBCL Problem Scales, and for the relevant Total Score. No graphs were derived from his CPRS-R:S forms due to missing data. He exhibited variable results on the CPRS-R:S, and also on the T-scores for the CPRS-R across the entire trial.

Regarding the 13 Subscales for the CTRS-R:L, he displayed improvement on six and deterioration on four. There were no changes for the other Subscales. The results for the CTRS-R:S and the T-scores for the CTRS-R across the entire trial were variable or fitted other criteria, and there were some missing data points. On the CAP his behaviour was variable, and some data points were missing.

His line graphs for the Sleep Diary variables showed fluctuations in the data. The statistical analysis of these variables revealed a significant effect on the initial analysis for SL, however the post-hoc tests did not reveal where this occurred. A significant effect was also found on the initial analysis for OSQ. The post-hoc tests revealed that his OSQ was better regarding the baseline versus post-treatment, and treatment versus post-treatment, comparisons.
He did not attend the BNC for the TOVA and QEEG, and his Side Effects Rating Scale did not reveal any reactions to the trial tablets. For the GAS there was no change in his daytime behaviour, and his mother made no comment in relation to night-time. Regarding the investigator's file notes, the mother stated that the first month of treatment made a difference to his behaviour in terms of an improvement, however in the second and third treatment months he reverted to his previous behaviour.

3.9.3 Participant 3 - Active

On the CBCL Competence Scales his behaviour was variable, however his Total Competence Score showed improvement. His results on the CBCL Problem Scales were also variable, although there were a number of improvements. His Total Score for the Problem Scales showed that he improved between baseline and the end of the treatment phase, and then at follow-up he deteriorated to a level that was about the same as his baseline score. For the 14 Subscales of the CPRS-R:I he exhibited improvement on 7 Subscales, and deterioration on 7 Subscales. His results on the CPRS-R:S and the *T*-scores for the CPRS-R across the entire trial were mostly variable, however there were some improvements.

Regarding the results for the 13 Subscales of the CTRS-R:L, he displayed a deterioration in behaviour on 12 Subscales, and there was no change for the remaining item. For the CTRS-R:S and the *T*-scores for the CTRS-R across the whole trial he exhibited fluctuations or variability in his behaviour. His behaviour on the CAP was also variable, and there were some missing data points.

The line graph results for the Sleep Diary variables showed mainly fluctuations, however some effects were noted on the statistical analysis. For SL and NTA the initial analyses revealed a significant effect, however the relevant post-hoc tests did not reveal where these effects occurred. For OSQ the initial analysis found a significant effect, and the post-hoc tests revealed four points of improvement: baseline versus post-treatment, baseline versus follow-up, treatment versus post-treatment, and treatment versus follow-up.

For his TOVA there is only information from the baseline test which is suggestive of impulsivity and behaviour problems, while there appears to be very little difference between baseline and post-treatment on his QEEG.
The Side Effects Rating Scale did not reveal any reactions to the trial tablets. For his GAS there were no marked changes in his daytime behaviour, however the mother noted that there had been some improvements regarding his sleep.

3.9.4 Participant 4 - Placebo

For the CBCL there were no data for the end of the treatment phase, and his scores for the baseline and follow-up phases varied for both the Competence Scales and the Problem Scales. No line graphs were generated for the CPRS-R:L due to a lack of data. He showed initial improvement on three out of the four CPRS-R:S Subscales, however the remaining data points are missing. The T-scores data for the CPRS-R are scarce, and the data that do exist are variable.

For the CTRS-R:L the line graphs were unable to be created due to missing data. He displayed initial improvement on three out of the four Subscales for the CTRS-R:S however the remaining data are missing. There is a lack of data regarding the T-scores for the CTRS-R, and the data that do exist are variable. He also showed variability on the CAP, and several data points were missing.

There is also a lack of data regarding the line graphs for the five prime sleep variables. Regarding the statistical analyses for sleep there was a significant effect on the initial analysis for SI, but the post-hoc tests did not reveal where this occurred. The initial analysis also found a significant effect for TST and OSQ. The post-hoc tests revealed that his TST was longer at treatment compared to at baseline, and his OSQ deteriorated at follow-up compared to the results for the treatment phase.

There are only objective measures results for the baseline phase. The TOVA was suggestive of an attention disorder, while the QEEG was representative of an inattentive or combined subtype of ADHD.

Some headaches were noted on the Side Effects Rating Scale, and some of the forms for this measure were not returned. For the GAS there was no change in his daytime behaviour, and his night-time behaviour was still causing problems.
3.9.5 Participant 5 - Active

His results for the CBCL Competence Scales were variable. His Total Competence Score showed variability as he deteriorated between baseline and the end of the treatment phase, and then improved at the follow-up point to a level almost the same as baseline. Most of his CBCL Problem Scales also showed deterioration followed by improvement, and the relevant Total Score showed variability. He exhibited improvement on 10 out of the 14 Subscales for the CPRS-R:L, and deterioration on the remaining four Subscales. For the CPRS-R:S, and for the $T$-scores for the CPRS-R across the whole trial, his behaviour displayed variability.

Regarding the 13 Subscales for the CTRS-R:L this child showed improvement on nine Subscales and deterioration on three Subscales. There was no change in his behaviour on the remaining Subscale. His scores on the CTRS-R:S and his $T$-scores for the CTRS-R across the entire trial showed a mixture of improvements and deteriorations. On the CAP his behaviour fluctuated and there were some missing data points.

For the five prime variables that were derived from the Sleep Diary his results showed mainly fluctuations in behaviour. He exhibited numerous awakenings, and the longest time he was awake for was 120 minutes. The statistical analyses for these variables only revealed a significant effect on the initial analysis for SL. The post-hoc tests found that his SL was shorter at treatment compared to at follow-up.

There were no results for the TOVA, and the baseline QEEG results were not representative of ADHD. On the Side Effects Rating Scale there were apparently no adverse reactions to the trial tablets. He had a lack of appetite due to Ritalin, and some instances of nausea and headaches were recorded. This child was in the treatment phase over Summer. According to his file notes, an early episode of nausea was relieved when he ate something. In addition, the first time that his mother mentioned that he complained of a headache she said it was only when he was at the pool. On the GAS for daytime his behaviour at school was noted as being unchanged, although he had improved in terms of doing his schoolwork. He still had problems getting to sleep at night.

3.9.6 Participant 6 - Placebo

No line graphs were generated for the CBCL and the CPRS-R:L due to insufficient data as he withdrew from the trial as per section 3.1. For the CPRS-R:S and the $T$-scores for the CPRS-R he deteriorated initially and the remaining data were missing.
No line graphs were available for the CTRS-R:L due to his withdrawal. On the CTRS-R:S and the $T$-scores for the CTRS-R there were some initial improvements, however the remaining data points are missing. The CAP data that were obtained showed fluctuations in behaviour.

Regarding the line graphs for Sleep Diary variables he had some early fluctuations, and some awakenings, before his withdrawal, and the initial statistical analysis only revealed a significant effect for OSQ. The post-hoc tests showed that his OSQ deteriorated at baseline versus treatment.

There were only objective measures results for the baseline phase due to his withdrawal. The TOVA was within normal limits due to his ADHD medication, and his QEEG was representative of an inattentive or combined ADHD subtype.

The Side Effects Rating Scale mainly recorded a lack of appetite due to his orthodox medication, however he later withdrew from the trial for behavioural reasons. No comparisons could be made on the GAS due to his withdrawal from the study.

3.10 Summary of collective results

3.10.1 Primary and secondary efficacy variables

As per section 1.11 in Chapter 1, the CPRS-R and CTRS-R were the primary efficacy variables for the study. Regarding the CPRS-R, there appears to be some beneficial effect from the herbs for the CPRS-R:L, however it is not possible to compare these results with the results for placebo as all of the relevant placebo graphs are blank due to insufficient data. For the CPRS-R:S, there appears to be a slight beneficial treatment effect, however most of the line graph ratings fitted the ‘variability’ and ‘cannot decide’ criteria. The results for the $T$-scores for the CTRS-R across the entire trial are inconclusive. For the CTRS-R, there appears to be some beneficial effect from the herbs for the CTRS-R:L, however the graphs for two of the participants who received placebo are blank due to insufficient data. For the CTRS-R:S, the results are inconclusive. Finally, the results for the $T$-scores for the CTRS-R across the entire trial are inconclusive.

The secondary efficacy variables were the TOVA, QEEG, and Sleep Diary. The results for the TOVA did not show evidence of a beneficial effect from the herbs. Indeed, there are full TOVA results for only one participant. He received the active tablets and he deteriorated. For
the QEEG there are also full results for only one participant, a child who received the herbal tablets, and there appears to be negligible difference. It should be noted that there are concerns about how both the TOVA and the QEEG were conducted, and these will be considered in the following chapter.

For the line graphs ratings for the Sleep Diary, most of the graphs were rated as exhibiting variability, while a smaller number were placed in the ‘no change’ and ‘cannot decide’ categories. In addition, the statistical analyses for the sleep variables produced inconclusive results.

3.10.2 Other variables
The other variables were the CBCL, CAP, Side Effects Rating Scale, and GAS. The results for the CBCL, for both the Competence Scales and the Problem Scales, are inconclusive. Most of the results fitted categories other than improvement or deterioration. For the CAP, all of the participants were rated in the ‘variability’ category. Regarding the Side Effects Rating Scale, there were apparently no side effects from the herbal tablets. The only participant who appeared to react adversely to the trial tablets was taking the placebo, and, as per section 3.1, he withdrew from the study. Finally, for the GAS there appears to be a slight beneficial effect regarding sleep for two of the participants who received the active products.
CHAPTER 4
DISCUSSION

The research reported in this thesis investigated the use of eight herbs for the treatment of ADHD and related sleep problems in children in terms of safety, tolerability, and efficacy. The herbs were administered as two combinations, with each combination consisting of four herbs. One combination was given in the morning for the treatment of daytime behaviour, and the other combination was given in the evening for the treatment of associated sleep problems. The ensuing findings will be discussed in this chapter, and compared with the findings of other studies. This will be followed by a consideration of the strengths and limitations of the present study, and the conclusions that may be drawn from it. Finally, this chapter will conclude with suggestions for future work.

4.1 Findings

4.1.1 Findings in relation to efficacy
The research question addressed by the present clinical trial was: ‘Do the trial herbs have a beneficial effect on daytime behaviour and sleep problems in children with ADHD?’ It was hypothesised that there would be a positive effect on daytime behaviour. It was expected that the children who were assigned to the active tablets would exhibit an improvement in attention, and a reduction in hyperactivity and associated behaviours, and that the children randomised to the placebo tablets would not display these behavioural changes. As some improvements in daytime behaviour occurred in the children who took the active tablets, this hypothesis was partially supported; although there are constraints on these conclusions to be discussed later.

Regarding sleep problems, it was hypothesised that there would be a positive effect on sleep. It was expected that the children who were assigned to the active tablets would exhibit a reduction in sleep latency, a reduction in the number of night-time awakenings, a reduction in the total time awake during the night, an increase in total sleep time, and an improvement in overall sleep quality. In addition, it was expected that the children given the placebo tablets would not display improvement regarding these parameters. As the sleep data were highly variable, and were inconclusive for the participants who were randomised to the active tablets, this hypothesis was not supported.
4.1.2 Findings in relation to safety and tolerability

Safety

Regarding the active tablets, there do not appear to have been any side effects or adverse reactions. In addition, two of the participants who received the herbal tablets were concurrently taking medical drugs, and no herb-drug interactions were noted. This is a pertinent point, as in recent years St John’s Wort has been found to interact with a range of orthodox medications. Regarding the standard medical drugs that are used to treat ADHD, a recent case report has suggested that St John’s Wort should be used cautiously in individuals who are concurrently taking methylphenidate (Niederhofer, 2007). However, this is not due to adverse reactions in relation to either the herb or the drug, rather it is due to the observation that the herb appeared to decrease the efficacy of the drug.

In relation to the placebo tablets for the present study, only one participant experienced problems and he withdrew from the trial as his behaviour deteriorated. It appears that he reacted to the colouring in the tablets, however, as per section 3.1 in Chapter 3, there were confounding issues. The report that was submitted to the HREC has been provided in Appendix S.

Tolerability

Some of the families who participated in this study had concerns about the size of the trial tablets and/or the number of tablets prescribed. The first participant had problems taking the tablets, despite them being crushed and various suggestions being made by the investigator. This child was not used to taking tablets, but in the end he took them crushed and in neat juice followed by water, accompanied by a countdown until the end of the treatment phase. His mother expressed concern about the number of tablets that would need to be administered to a teenager. In contrast, the second participant, who had taken capsules in the past, had no problems taking the tablets, and took them whole. The third participant also had no difficulties. The mother of participant four, who was a teenager, queried the number of tablets required, however her son had no problems taking them. Participant five took the tablets whole followed by a bribe, but finished the treatment phase five days early, at the end of a month, as he was sick of taking them. The sixth child took the tablets crushed to a fine powder and mixed in with his Milo.
4.2 How the present findings compare with other findings

As per the literature review that was presented in Chapter 1, few scientific studies have investigated the use of CAM for treating ADHD. Moreover, only a small number of the relevant studies have researched the use of herbs. Therefore other findings for the present topic are scarce. This situation, and the nature of the other projects that have been conducted, including that fact that some have involved female as well as male children, makes it extremely difficult to directly compare the findings of this research project with the findings of others.

As mentioned in sub-section 1.9.1, ginkgo is a constituent of a herbal product called AD-FX™. This product was investigated in a 4-week pilot study of 36 children with ADHD aged from 3 to 17 years (Lyon et al., 2001). The diagnosis of ADHD was made using DSM-IV criteria, and no changes were made regarding the use of other medications. Indeed, 25 of the participants were concurrently taking other medications. The CPRS-R:L was administered at baseline, after 2 weeks, and at the conclusion of the trial, and the participants T-scores were analysed for significant differences. After 2 weeks, 18 out of the 36 children had improved regarding hyperactive-impulsive behaviour, 20 had improved in relation to cognitive problems, and 23 had improved in terms of oppositional behaviour. After 4 weeks the corresponding figures are given as 22 out of 34 children, 18, and 21 respectively. The authors concluded that there was significant improvement in the three key areas of ADHD behaviour, however they conceded that it is difficult to ascertain whether there were differences regarding the study outcomes between those taking concomitant medications and those who were only taking AD-FX™.

There is some consistency between these findings and those of the current study. However, as AD-FX™ also contains four times the amount of another herb - American ginseng (Panax quinquefolium) - relative to the amount of ginkgo, it is unclear as to whether the beneficial effects were a result of one or other of the herbs, or the combination. It is also important to note that the AD-FX™ study was of short duration, only one subjective measure was used, and it was conducted on an open basis.

In addition, two papers have been published concerning the use of ginkgo on its own in the treatment of children with ADD and ADHD respectively. A small open trial involving 6 children who met the DSM-III-R criteria for ADD was conducted in a clinic (Niederhofer, 2010). The participants were aged from 17 to 19 years, and they received a set dose of ginkgo
for 4 weeks. The children were not taking other medications. Wender Utah ratings were used as the sole outcome measure, and at the end of the trial all of the children reported significant improvement in their ADD symptoms. This lead the author to conclude that ginkgo might be a beneficial treatment for ADD. Although this study had the same sample size as the current study it was conducted on ADD, and different ratings were used. It also involved the use of a single herb on an open basis, and the results were self-reported.

A randomised double blind parallel trial compared ginkgo with methylphenidate in 50 children who had been diagnosed with ADHD according to DSM-IV-TR criteria (Salehi et al., 2010). The participants were aged from 6 to 14 years, and the trial lasted for 6 weeks. The dosage for both treatments was based on body weight. The main outcome measure was the Teacher and Parent ADHD Rating Scale-IV, which was administered at baseline, at 3 weeks, and at 6 weeks. Both of the treatments produced benefit on both teacher and parent ratings for inattentive and hyperactive-impulsive behaviour, however ginkgo was less effective than methylphenidate. Indeed, the authors concluded that the results of their study do not support the use of ginkgo in the treatment of ADHD.

The findings of the current study varied for the same attributes for both parents and teachers, as measured on different scales. In addition, although this study involved a larger sample size than the current study it was of shorter duration, and it did not involve the use of a placebo.

Bacopa has been tested in a randomised double blind placebo-controlled trial in 36 children with ADHD, as per sub-section 1.9.2 (Negi et al., 2000). This trial has only been published in abstract form therefore information about it is limited. The aim of the study was to evaluate the memory enhancing properties of a standardised extract of bacopa in children diagnosed with ADHD according to DSM-IV criteria. Nineteen children received the active product and 17 were given a placebo. The active treatment was followed by 4 weeks on placebo, and the total duration of the trial was 16 weeks for both groups. Mean age was 8.3 years in the treatment group, and 9.3 years in the placebo group. The children were evaluated on a battery of tests before the trial, during the trial - at 4, 8, and 12 weeks - and at the end of the study. There was a significant improvement in sentence repetition, logical memory, and paired associate learning after 12 weeks on active treatment, and this improvement was maintained at 16 weeks. No information is provided regarding the use of medical drugs or any other products or treatments.
In this study bacopa was administered as a simple, that is, not as part of a combination of herbs. In addition, different parameters were measured in comparison to those that were assessed in the present clinical trial.

As noted in sub-section 1.9.3, a Chinese formula that includes paeony has been trialled in the treatment of 66 children with “hyperkinesia” (Sun et al., 1994). The age range for the study was 7 to 13 years, and the diagnosis was made based on DSM-III-R criteria, and the criteria that were stipulated at a Chinese symposium. The formula contained a total of 13 ingredients, and it was given as a syrup for at least 6 weeks. The average duration of treatment was 3.5 months, and all other Chinese and Western drugs had been discontinued. Twenty four children aged from 7 to 12 years served as a control group. The results revealed an improvement in scores for clinical behaviour and school marks, and a decrease in the incidence of “soft neurotic signs”. In addition, laboratory measurements were made for 24-hour urine specimens, and various changes in urinary biochemistry were noted. The general efficacy of the treatment was rated at 84.8%.

There are obviously differences in terminology between this study and the current study. Furthermore, paeony was combined with numerous other constituents in a Chinese formula, thus its role, if any, in producing the beneficial results is unclear.

More recently, a randomised double blind placebo-controlled clinical trial has investigated the use of a formula containing bacopa and paeony in 120 children aged from 6 to 12 years (Katz et al., 2010). The children were diagnosed with ADHD according to DSM-IV criteria. The study was a parallel trial of 4 months duration, and 80 children were randomised to the treatment group, and 40 children were randomised to the control group. The compound herbal preparation was administered as a liquid product. It contained six primary herbs, including bacopa and paeony, and it appears to have contained other herbs that are not listed. In addition, no proportions are specified. The placebo product was also a liquid, and it was designed to be very similar to the active product in relation to taste, odour, and appearance. However, the formula for the placebo product is not provided. The TOVA was used as the sole outcome measure, and there was a significant improvement in the treatment group. As there was no significant difference in TOVA scores for the control group the authors concluded that their product may be an effective treatment for ADHD.
Although the TOVA was used in this trial, and in the present study, it is not possible to compare the results of both. The trial conducted by Katz et al. (2010) had a much larger sample size than the current study. It also involved the use of liquid products, and the active formula contained various herbs in addition to bacopa and paeony. Furthermore, the authors acknowledge that a limitation of their study is the differential loss to follow-up in the two groups. Only 73 of the 80 children in the treatment group completed the trial, and only 19 of the 40 children in the placebo group finished the study. Katz et al. stress that the masking of treatment status was maintained. However, given the distinctive nature of liquid herbal products it would be interesting to know what was in the placebo, and how it was manufactured to be almost identical to the active product to the point where it is claimed that 20 medical students were unable to tell the difference.

As per sub-section 1.9.4, a randomised placebo-controlled double blind parallel clinical trial investigating the use of St John’s Wort in the treatment of ADHD in children has recently been conducted in the United States (Weber et al., 2008). The trial recruited 54 children aged from 6 to 17 years who were diagnosed with ADHD according to DSM-IV criteria, and it lasted for 8 weeks. The active and placebo products were both administered as capsules, and the herb group received one capsule (300 mg) of St John’s Wort three times a day. No ADHD medical drugs were allowed during the trial. The main outcome measures were the ADHD Rating Scale-IV, the Clinical Global Impression Improvement Scale, and adverse events, however a version of the CBCL and a version of the CPRS were also used. No significant differences were found between the groups. Although the herbal capsules had no additional effect beyond placebo, the authors concluded that it is possible that St John’s Wort may work in conjunction with other CAM remedies. They also discuss the possibility of oxidation affecting the herb due to it being given in capsule form.

This was a single herb study and the herb was given as capsules, however it involved the use of a later version of the CBCL than the present study, and what appears to be the long version of the CPRS. There is some inconsistency between the two studies regarding these measures. Weber et al. (2008) found no significant differences between the active group and the placebo group for both. However, in the current study there were some differences between the two groups for the CBCL, while on the long version of the CPRS-R improvements and deteriorations were noted in the active group, and there were no data for the placebo group.
As outlined in sub-section 1.9.5, an earlier RMIT University study investigated the effect of Mexican valerian (Valeriana edulis) on sleep problems in 5 children with intellectual deficits using a randomised placebo-controlled double blind crossover design (Francis & Dempster, 2002). The children were aged from 7 to 14 years, and they all had an intellectual disability or various intellectual disabilities in conjunction with severe sleep problems. The active treatment consisted of 500 mg valerian tablets, and the placebo tablets contained 25 mg of valerian in order to give the same appearance and odour as the active product. The dosage for the active product was 20 mg of valerian per kilogram body weight given as a single dose at night at least one hour before bed, and an 8-week Sleep Diary was completed by the parents. The Sleep Diary was an earlier version of the Sleep Diary that was used in the current study.

The group analyses revealed that the valerian treatment lead to a significant reduction in sleep latency and time awake at night, and improvements in total sleep time and sleep quality. In addition, the improvements in sleep resulted in improvements in daytime behaviour, especially in relation to hyperactivity. One of the children had a mild to moderate intellectual disability accompanied by daytime behavioural problems including hyperactivity. He exhibited a marked improvement in sleep latency and the number of times that he woke at night, as well as various improvements in his daytime behaviour. Another child had ADD, and hyperactive and aggressive behaviour. He was taking dexamphetamine and clonidine. While he was on the valerian tablets he exhibited a substantial reduction in sleep latency and his behaviour improved. Finally, another child had been diagnosed with ADHD and a learning disorder. He was taking methylphenidate and clonidine, and he had various sleep problems including difficult behaviour at bedtime, long sleep latency, and he was waking at night. His results showed a decrease in sleep latency and nocturnal time awake, an increase in total sleep time, and an improvement in sleep quality. In addition, behavioural changes in terms of his maturity and his interactions with family members were also noted.

There is no consistency between the group results of Francis and Dempster (2002) and the overall results of the current study, yet there is some consistency regarding the single case results of both studies as some improvements for the same sleep variables were noted in the single case results of the present trial. However, not all of the children in the Francis and Dempster study - which only investigated sleep - had been diagnosed with ADHD. Furthermore, only one herb was used, and it is a different species of valerian compared to the species that was used in the current trial.
Finally, a randomised double blind parallel trial has been conducted to investigate the use of passionflower in the treatment of ADHD in children, as per sub-section 1.9.7 (Akhondzadeh et al., 2005). The 8-week trial compared passionflower tablets with methylphenidate, and it recruited 34 children aged from 6 to 13 years. All of the participants were newly diagnosed with ADHD according to DSM-IV criteria, and the exclusion criteria included current treatment with psychotropic medications. The dosage of both treatments was calculated based on body weight, and the principal outcome measure was the Parent and Teacher ADHD Rating Scale. Both treatments produced significant improvement over the trial, and the trend was linear. Moreover, there were no significant differences between the herb and the drug, however there was a higher incidence of side effects in the methylphenidate group. It is not possible to make comparisons between the results obtained by Akhondzadeh et al. and the present study due to insufficient information about the behaviours that they assessed.

4.3 The strengths and limitations of the present study

4.3.1 Strengths
This project was an innovative study. As per section 1.8 in Chapter 1, during the initial planning phase of this clinical trial no scientific research was found regarding the use of herbs for treating ADHD in children. This is not surprising. Herbal medicines are often used in the treatment of children generally, however they are rarely tested in this age group (Ernst, 2003). Indeed, data directly obtained from paediatric studies are extremely rare in CAM (Ernst, 2006). In addition, relatively few herbal clinical trials involve qualified herbalists, and a rigorous design was employed.

4.3.2 Limitations
Unfortunately there are a number of limitations and methodological issues that need to be considered in relation to this study. Despite extensive effort, recruitment proved to be a major difficulty, due to the issues outlined in Chapter 2, sub-section 2.1.2, and the issues and stated reasons listed in Chapter 3, section 3.1. The factors that affected recruitment will now be discussed prior to a consideration of various methodological issues.

Recruitment issues
As per sub-section 2.1.2 in Chapter 2, some amendments were made to the trial exclusion criteria regarding medical drugs. The main change was the early amendment to allow children taking one or more of the standard ADHD medical drugs to be considered for inclusion in the study. This was done after a large number of inquiries were received in response to the first
media release, and most came from parents or caregivers who had a child taking one or more of these drugs. Obviously it would have been a different situation if the standard ADHD drugs had not been an issue when the first media release went out. Despite the investigator contacting people to advise them of the change in protocol, that is, to advise them that they could be considered for inclusion without a change to their child’s orthodox medication, it was difficult to maintain their interest in the project.

In addition, some of the remaining exclusion drugs, as per Chapter 2, sub-section 2.4.2, also caused difficulty for many interested families who had a child taking one or more them, and who did not wish to cease using the drug(s) in order to participate. These drugs were present in the amended exclusion criteria due to St John’s Wort being retained as a trial herb during the drafting of the research proposal, in spite of the suggestion by the investigator that it should be omitted after information concerning herb-drug interactions came to light. In hindsight, it would have assisted recruitment, at least in the initial inquiry stage, if St John’s Wort had been deleted from the daytime combination.

The 50% risk of receiving the placebo tablets also caused concern for many interested parents and caregivers. In 2003 MediHerb Pty Ltd suggested that the protocol of the trial should be changed to that of an open study due to their concerns about the small number of participants, and the amount of remaining trial product. However, after consideration of this option by the senior supervisor and the investigator, it was decided that the placebo-controlled protocol should be maintained, and that further efforts should be made in order to recruit more children into it before making the change. Once the decision was made to alter the protocol, in 2004, an application was made to the HREC. After some delays the HREC gave approval for the change, albeit reluctantly. The HREC felt that much of the value of the study would be lost if the placebo component was deleted. Despite their reservations, they agreed to approve the change on the condition that any open study data would be analysed separately to the data that had already been obtained. However, due to the length of the trial, and the fact that the investigator’s candidature had already been extended and in the meantime she had received a letter from RMIT University stating that further extension was unlikely, the approved switch to an open trial design did not proceed. Instead, recruitment was ceased. Given that a number of other issues had also affected recruitment it is questionable as to whether simply converting the trial to an open study at that time would have made a great deal of difference regarding participant numbers.
To return to general recruitment issues for the controlled study, the amount of time and effort involved for families was also a major barrier to recruitment. Participating in the project meant completing numerous forms and diaries, attending appointments, liaising with teachers, maintaining regular contact with the investigator, and administering a number of tablets to a child with behavioural difficulties twice a day for 3 months as part of a trial lasting for 7.5 months. In addition, some interested families, understandably, wanted a treatment that "works". They stated that they did not want to take part in the trial knowing that even if they received the active tablets their child would be taking an unproven remedy.

Being unwilling to comply with the evidence of ADHD diagnosis requirement also proved to be an issue for some families. In some cases their child had not received a formal diagnosis of ADHD. In others it had been made some time in the past, and the family had lost contact with the health professional concerned and they were unwilling to see someone else. A small number of interested families decided not to proceed beyond the initial inquiry stage for other reasons. For example, the child’s teacher was unaware of the child’s ADHD and the family wanted the diagnosis to remain hidden, or one parent wanted to be involved in the study but the other refused to allow the child to participate. Finally, during the entire recruitment campaign there were a very small number of calls where investigator was unable to contact the person who had inquired. This was despite trying to call them back on different days, both on weekdays and at weekends, and at different times of the day or evening, and leaving messages wherever possible.

**Confidentiality and trial products**

The constraint upon the investigator regarding confidentiality and trial products also played a role in impeding recruitment as it hampered efforts to publicise the research. Despite the provisional patent being in place, and having the common names of the herbs listed in the PLS, the investigator was restricted in terms of talking about the trial products. MediHerb Pty Ltd only permitted her to openly discuss three of the eight herbs - ginkgo, bacopa, and valerian - as these were considered to be the obvious herbs. There is no doubt that this constraint caused concern in the minds of many individuals as to what was being trialled, and why it could not be freely discussed and explained. This restriction also hindered the further opportunities to promote the research that arose during the recruitment campaign, as per Chapter 2, sub-section 2.4.1.
Further consideration of these matters, and the issues that caused lengthy delays during and subsequent to the application for ethics approval, as detailed in sub-section 2.1.1 at the start of Chapter 2, is beyond the scope of this thesis. However, it is important to note the negative impact that they had on the research in relation to both candidature time and recruitment efforts. Such issues would certainly need to be given detailed consideration in advance if any further herbal trials using formulated product(s) were to be undertaken by a higher degree student, irrespective of topic.

Methodological issues

Various methodological issues also arose during the course of the research, and others have been noted with the benefit of hindsight. For example, for the face-to-face interviews the child was present. This may have caused difficulty for the parents in discussing their child’s behaviour and sleep problems in front of them. For the early participants the teacher forms were returned to the investigator via the parents. This may have had an impact on the data that was provided by the teachers concerned. Furthermore, as per sub-section 4.1.2, some of the families who participated in the trial had concerns about the trial tablets in terms of the size of the tablets, and/or the number of tablets prescribed. The first participant had great difficulty taking the tablets despite them being crushed, and various suggestions being made to the parents. In addition, a reduced dosage was prescribed for him based on body weight due to him only having one kidney, and as he was assigned to the active group this may have affected his results.

Regarding the dependent variables, there were issues in relation to the TOVA and QEEG, the use of the CRS-R, the GAS, and general data collection. The initial TOVA and QEEG tests were conducted by the investigator, however due to her lack of familiarity with these procedures, and difficulty trouble-shooting when problems occurred with the equipment, the staff of the BNC conducted the remaining tests. In addition, for participant three there was a long delay between his baseline and the commencement of his treatment phase due to the situation with these tests. Further discussion of these matters is beyond the scope of this thesis, however if these tests were to be used in a future project they would need to be conducted by an individual thoroughly trained in their administration.

The CRS-R were administered to the parents and teachers on a remote basis. This is an important point, as remote administration was not used when these forms were standardised, thus any data obtained through their remote administration needs to be interpreted with
caution (Conners, 1997). Moreover, the long and short forms were used for each child at different times as they progressed through the trial, as per Chapter 2, sub-section 2.3.2. After the data were scored, difficulty arose in wanting to put the raw scores for the same subscales from the relevant long and short forms on the same line graphs. For example, the raw score for the oppositional subscale on the parent long form is derived from 10 questions. However, the raw score for the same subscale on the parent short form is derived from six questions. The investigator contacted Multi-Health Systems Inc. and was advised that the best situation would be to compare the relevant long forms to each other, and the relevant short forms to each other. Regarding the possible use of the T-scores to create the desired graphs, it was suggested that the T-scores could be used to put all of the scores for the same subscale on the same graph to get an idea of a child’s progress through the entire trial, however any comparisons would need to be made with caution (M.-L. Randazzo, personal communication, September 30, 2005).

There were also issues regarding the GAS. This was used during the initial face-to-face interview, and it was repeated, where possible, at the end of the treatment phase. However, some of the parents found it difficult to set goals in terms of a percentage of improvement, especially for the 25%, 50%, and 75% levels.

Moreover, there were some anomalies regarding data collection generally. For example, some forms were not administered at the exact time at which they should have been administered due to parent and/or teacher commitments, or the forms being lost in the outgoing mail and having to be re-sent. In the early days of the project, before written instructions were provided, some forms were completed by different parents at different times. There were also instances where the teacher forms were completed by different teachers during the trial, for various reasons. In addition, there were some missing parent and teacher data points due to school holidays, and other changes in the child’s routine.

Finally, regarding data analysis, attempts were made to obtain independent ratings of the line graphs, as per sub-section 2.5.1 in Chapter 2. However, the independent rater found it difficult to give ratings for most of the graphs due to the lack of data points. They also expressed concerns about some of the scales not commencing at zero. Therefore, the tabulated results of the visual analysis of the line graphs are based on the ratings produced by the investigator.
4.4 The conclusions that may be drawn from this research

4.4.1 An overview of the trial

As per Chapter 1, sub-section 1.7.6, herbal medicines are commonly used for the treatment of ADHD in children, yet scientific research on this topic is scarce. The aim of the present study was to address this situation, especially in view of the safety issues and controversies surrounding the use of the relevant medical drugs, as outlined in sections 1.4 and 1.5 in Chapter 1, and the fact that there is no generally accepted pharmacological treatment option for the children who do not respond to such drugs, or cannot tolerate them. Furthermore, ADHD is a chronic disorder that persists into adolescence and adulthood. It has also been linked with substance abuse and other adverse outcomes as per Chapter 1, sub-section 1.1.3, hence the vital need to investigate other possible treatment options.

The protocol for this study was a randomised placebo-controlled double blind parallel clinical trial consisting of four phases: baseline, treatment, post-treatment, and follow-up. It investigated the use of particular herbs for the treatment of ADHD and associated sleep problems in children aged from 8 to 16 years. Eight herbs were used in the project, and they were administered in two combinations. Each combination consisted of four herbs: one combination was given in the morning for the treatment of daytime behaviour, and the other was given the evening for the treatment of sleep problems. The daytime combination contained ginkgo, bacopa, paeony, and St John’s Wort, and the night-time formula contained valerian, skullcap, passionflower, and chamomile. Both of the combinations were administered as tablets, and the number of tablets taken by the participants was calculated based on body weight. The placebo tablets were identical in appearance to the active tablets, and the treatment phase of the study lasted for 3 months.

Eight measures were used to assess the effect(s) of the herbal tablets in terms of safety, tolerability, and efficacy. Six subjective measures were completed in the child’s home and school environments: five for the assessment of daytime behaviour, and one for the assessment of sleep. The daytime measures were the CBCL, the CPRS-R, the CTRS-R, a Side Effects Rating Scale, and the CAP, and the night-time measure was a Sleep Diary. In addition, two objective measures were used for the study: the TOVA and the QEEG. As these tests require specialised computer equipment they were conducted at a psychology clinic. With regard to efficacy, the CPRS-R and the CTRS-R were selected as the primary variables. The secondary efficacy variables were the TOVA, the QEEG, and the Sleep Diary. Information was also obtained from the parents by using the GAS at the conclusion of the
initial face-to-face interview, and at the end of the treatment phase. Despite extensive efforts in terms of recruitment, only six participants enrolled in the study, and only five of them completed it. All of the participants were male. Due to the small sample size the major method of data analysis consisted of the visual analysis of line graphs.

4.4.2 Conclusions
As per section 4.1, some improvements in daytime behaviour took place in the children who took the active tablets, however the sleep data for these children were highly variable. Due to this, and the small sample size, the overall findings for this trial do not allow firm conclusions to be made in relation to efficacy. Regarding safety and tolerability, it is also difficult to arrive at firm conclusions due to the small sample size. However, it is of interest to note the apparent lack of adverse reactions for the herbal tablets, especially in the children who were concurrently taking medical drugs. In addition, it is important to consider the feedback concerning tolerability for the sake of those who may participate in further studies. Indeed, given the dearth of research on this topic, the popularity of herbal medicines as remedies for ADHD, and the fact that the findings of the present study are inconclusive, it is imperative to consider suggestions for future work.

4.5 Suggestions for future work

4.5.1 Suggestions to facilitate recruitment
As per sub-section 4.3.2, the recruitment of participants proved to be a major problem, despite the extensive efforts that were outlined in section 2.2 and sub-section 2.4.1 in Chapter 2. This is not unusual as recruiting an adequate number of participants is one of the major challenges involved in conducting this type of research, even in orthodox medicine. In addition, recruiting children into randomised controlled trials is more difficult than recruiting adults (Caldwell, 2003). It should be noted that the publicity strategies that were used for the present study were effective as they generated an enormous amount of interest, and numerous inquiries. However, only a small number of interested families advanced to the initial face-to-face interview stage, and only half of those families proceeded into the trial.

In order to maximise the number of inquirers regarding such a project there should be no restrictions regarding confidentiality and the herb(s) being investigated. This would greatly assist in the promotion of any future studies. In relation to increasing the number of inquirers who proceed to the initial face-to-face interview stage, and then hopefully into a trial, it is suggested that matters should be simplified for any future studies on this topic. As the present protocol was a parallel trial, meaning that there was a 50% risk of receiving the placebo
tablets for the duration of the study, and this was a concern for some interested families, a
crossover design should be employed if another study of the same duration were to be
conducted. However, if a parallel design were to be used in future, shortening the duration of
the treatment phase might assist recruitment.

Some other herbal studies have now been undertaken using a parallel design, as per section
4.2: one of 6 weeks duration, and two trials that lasted for 8 weeks. However, in each case
only one herb was administered, and there are also other differences between the protocols of
these studies and the present clinical trial. For example, two of these studies did not involve
the use of a placebo as they compared a herb with methylphenidate. In addition, in the St
John’s Wort study, which was placebo-controlled, no ADHD medical drugs were permitted,
and washout periods were specified for these and other orthodox pharmaceuticals. However,
multivitamins and EFAs were allowed providing that the child had been taking the
supplement(s) for at least 3 months and was expected to maintain the same dose (Weber et al.,
2008). In future studies it is suggested that the orthodox ADHD medical drugs be permitted as
per the present trial, however it is also suggested that the approach to supplements that was
used by Weber et al. be adopted rather than a blanket exclusion regarding the concurrent use
of such remedies. As per the standard ADHD medical drugs, supplements such as EFAs are
commonly used in the treatment of ADHD, and families can be reluctant to cease their use.

Despite some concerns over the use of tablets for administering the herbs in the present study
it is suggested that tablets remain the preferred option over liquids or capsules. This is due to
concerns about compliance, and stability of product. One possible suggestion regarding
protocol is to only give tablets once a day in order to target either daytime behaviour or the
associated sleep problems. However, the medical treatment of ADHD often involves the
administration of the relevant pharmaceutical drugs on a twice a day basis or through the day.
For example, stimulants are commonly given early in the day, and these may be followed by
the administration of clonidine at night. Finally, reducing the number of dependent variables
is another idea to enhance recruitment, as it would reduce the amount of time and effort
involved.

4.5.2 Possible choices regarding herbs
As per the examples listed in sub-section 1.7.6 in Chapter 1, there are various herbs that are
used for treating ADHD and its associated sleep problems, and these could be trialled either
alone or in combination. Given that most of the families who inquired about the present study
were using one or more orthodox medications it is suggested that St John’s Wort not be used. This is due to the large number of medical drugs that cause this herb to be contraindicated. In addition it should be noted that in professional clinical practice herbal prescriptions are normally prepared and dispensed on an individual basis, however this is not possible in a clinical trial.

4.5.3 Possible choices regarding dependent variables

The instruments that are used to assess children with ADHD in terms of daytime behaviour and sleep were discussed in Chapter 1, section 1.10. With regard to cost, time constraints, ease of use, and the location of administration, it is suggested that the objective measures not be used in future studies. However, further use of the subjective measures is warranted, notably the CRS-R as these scales have been used extensively in trials that have tested medical drugs for ADHD.

4.5.4 Concluding remarks

Due to the increasing use of herbal medicines for the treatment of various paediatric conditions it is important to establish the efficacy and safety of such agents by means of conducting controlled clinical trials (Hrastinger et al., 2005). Furthermore, herbs are commonly used in the treatment of ADHD and associated sleep problems in children despite a distinct lack of scientific research in this area.

The present study was an innovative project, and, as far as the author of this thesis is aware, it is still the first major study of its type. It is unfortunate that many unexpected project and personal obstacles were encountered during the progress of this research. It is also unfortunate that despite extensive efforts regarding recruitment only a small sample size was achieved. Moreover, the findings for the present trial are inconclusive. However, in view of the existing use of herbs as remedies for ADHD and its associated sleep problems, the noted dearth of scientific studies in this area, and the concerns over the use of the standard ADHD medical drugs and the lack of alternative pharmacological treatment options, it is vital that this work continues.
REFERENCES


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APPENDIX A

The application for ethics approval (minus attachments)
RMIT HUMAN RESEARCH ETHICS COMMITTEE

APPLICATION FOR APPROVAL OF PROJECT INVOLVING HUMAN SUBJECTS

Section A: Approvals and Declarations

**Project Title:** Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

**Protocol Number:** FDAF001

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<th>1. Complete this column if you are undertaking Research for a Degree Awarded by RMIT or another university. (Bachelor/Masters/PhD).</th>
<th>1. Complete this column if your Research is Not for Any Degree.</th>
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<tr>
<td><strong>Investigator</strong>&lt;br&gt;Name: Ms Fiona Dey&lt;br&gt;Student No: 8210843E&lt;br&gt;Qualifications: BBSc DipAppSc (Nursing)&lt;br&gt;DipAppSc (Naturopathy) MNHAA&lt;br&gt;Department: Psychology and ID Studies&lt;br&gt;Address: PO Box 71 Bundoora Vic 3083&lt;br&gt;Phone: (H) 9859-4346 (M) 0408 511 437&lt;br&gt;Email: <a href="mailto:s8210843@student.rmit.edu.au">s8210843@student.rmit.edu.au</a></td>
<td><strong>Principal Investigator</strong>&lt;br&gt;Name: &lt;br&gt;Qualifications: &lt;br&gt;Department: &lt;br&gt;Campus: &lt;br&gt;Phone: &lt;br&gt;Email:</td>
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<td><strong>Supervisor:</strong>&lt;br&gt;Name: Dr Andrew Francis&lt;br&gt;Qualifications: BBSc (Hons) PhD&lt;br&gt;Department: Psychology and ID Studies&lt;br&gt;Campus: Bundoora&lt;br&gt;Phone: 9925-7782</td>
<td><strong>Other Investigator/s:</strong>&lt;br&gt;Name/s: &lt;br&gt;Qualifications: &lt;br&gt;Department: &lt;br&gt;Campus: &lt;br&gt;Phone:</td>
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Section A2

Project Title: Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

Name/s of other persons associated with the conduct of the work described in this proposal (you may increase space to include all those involved):

Name: Mr Jacques Duff Qualifications: BA (Psychology) GradDipPsychology MAPS MAAAPB Role: Second Supervisor

Name: Mr Kerry Bone Qualifications: BSc (Hons) DipPhytotherapy FNIMH FNHAA MCPP Role: Consultant

Declaration by the investigator(s):

I have read the current NH&MRC Statement on Human Experimentation and the relevant Supplementary Notes to the Statement, and accept responsibility for the conduct of the procedures detailed below in accordance with the principles contained in the statement and any other condition laid down by the University's Human Research Ethics Committee.

Signed: ........................................... Date: ...........................................
Signature of Principal Investigator

Signed: ........................................... Date: ...........................................
Signature(s) of other investigator(s)

Signed: ........................................... Date: ...........................................
Signature of Supervisor
(if applicable)
Section A3

Project Title: Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

Declaration by the Head of Department

Statement on the adequacy of the project's experimental design:

Ethical Issues that are to be addressed by the Human Ethics Committee:

The project set out in the attached application, including the adequacy of its experimental design and compliance with recognised ethical standards, has the approval of the Department/Faculty.

Signed: ........................................... Date: ........................................

Signature of Head of Department

Department: ........................................ Extn: ........................................

Faculty: ........................................ Campus: ........................................

Should substantive amendments to the proposal be sought by the HREC or its Faculty Sub-Committee, these are to be endorsed below:

Amendments made at the date indicated:

Signed: ........................................... Date: ........................................

Signature of Head of Department
Section A4

Faculty Human Research Sub-Committee Use Only

Date application received: .................................. Faculty HRE Sub-Committee.
Register No.: ..................

Recommended project classification: AR  MR  NR  (circle one)

Approved by Faculty Sub-Committee: Date: ............................................

Period of Approval - From: .............. To: ..........................

OR

Referred to RMIT HREC: Date: ............................................

Comments/Provisos:

Signature: .................................................. Date: ..........................
Faculty HRE Sub-Committee Chair

Date PI notified/sent to RMIT HREC: ............................................

Section A5

University Human Research Ethics Committee Use Only

(b)  AR Project  RMIT HREC Register No: ........................

Period of approval: From: .............. To: ..........................

Comments/Provisos:

Signature: .................................................. Date: ..........................
(HREC Chair)

Date PI notified/returned to HREC Sub-Committee: ............................................
SECTION B: PROJECT PARTICULARS

1. Title of Project

Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

2. Project description: for HREC assessment of ethical issues

Attention Deficit Hyperactivity Disorder (ADHD) is typically diagnosed in young children and is estimated to affect millions of children throughout the world. It is generally considered to affect between 2% and 9.5% of children (Barkley, 1998a), an incidence that is also described as "approximately one child in every classroom" (Rapport, 1995, p.353). Children with ADHD have chronic difficulties in the areas of inattention, impulsivity and overactivity. In addition they frequently have sleep problems (Barkley, 1998b). Approximately 80% of children diagnosed with ADHD in childhood continue to meet ADHD diagnostic criteria, and to display symptoms, as adolescents (Rapport, 1995). Between 25% and 70% of ADHD children will continue to have symptoms as adults (Barkley and Murphy 1998; Silver, 1992).

Various theories have been proposed regarding the cause of ADHD. Research has included brain imaging studies and genetic studies, investigating factors such as cerebral blood flow and neurotransmitter levels (Gordon, 1999; Levy, Barr and Sunohara, 1998). Pharmacological treatment is the most commonly used form of treatment with 80% to 90% of ADHD children receiving medication (Australian Psychological Society, 1997; Sheridan and Sanders, 1996). The main drugs used are the psychostimulants. Other relevant classes of drugs are the tricyclic antidepressants and the alpha adrenergic agonists. The newer antidepressants and major tranquillisers may also be used, depending on the child (Jarman, 1996).

Stimulant drugs are widely prescribed in Australia, and the number of prescriptions has significantly increased in recent years (Valentine, Zubrick and Sly, 1996). The relevant drugs are methylphenidate and dexamphetamine. They are considered to be highly effective as about 75% of ADHD children display dramatic improvements in cognitive processing, behaviour and academic performance (Jarman, 1996). However, approximately 20% to 35% of ADHD children do not respond to these medications (National Health and Medical Research Council, 1996; Wilens and Biederman, 1992). There are many side effects of stimulants. They include insomnia, diminished appetite, weight loss, growth retardation, abdominal pain, headaches, impaired alertness, psychosis, nervousness, irritability, sadness and increased crying (Cyr and Brown, 1998; Greenhill, 1992; MIMS, 1999). They can also cause behavioural "rebound" at the end of the day, adverse cardiovascular and liver effects, and tics. In addition dexamphetamine is considered to have a high potential for drug abuse. The long term safety and efficacy of stimulants in children has not been extensively studied and little is known about their use in adolescence (Bennett, Brown, Craver and Anderson, 1999). Most studies on the stimulants have been short term despite the fact that long term treatment is considered to be indicated (National Institutes of Health, 2000).

Imipramine and desipramine are the most commonly used tricyclics. They are considered to be less effective than stimulants but of value for children who have anxiety or depression. Imipramine is preferred over desipramine because of a lower incidence of cardiovascular side effects (Greenhill, 1992; Jarman, 1996). There have been cases of sudden death in children taking desipramine (Cyr and Brown, 1998). Side effects of imipramine include impaired alertness, dry mouth, decreased appetite, nausea, insomnia, increased anxiety and adverse cardiovascular effects (MIMS, 1999).

Clonidine is an antihypertensive drug that is used in the treatment of ADHD, either alone or in combination with stimulants. It is an alpha adrenergic agonist considered useful for the control of aggressive behaviour, and for counteracting some stimulant side effects such as sleep disturbance and lack of appetite (Jarman, 1996). Side effects of clonidine include drowsiness, dry mouth, nausea, vomiting, depression and adverse cardiovascular effects (MIMS, 1999). Of particular concern is the increase in the number of cases of clonidine overdose in children, a serious condition which requires treatment in an intensive care unit. The increased incidence of such overdose has been related to the increased use of this drug in children for treating ADHD (Kappagoda, Schell, Hanson and Hutchins, 1998).
Aims and Significance

At present there is no alternative pharmacological treatment for those children who do not respond to these drugs, or cannot tolerate them due to side effects. The aim of this project is to ascertain whether certain phytomedicines (herbal medicines) may provide an alternative pharmacological treatment for ADHD children. The proposed study is significant as it will be the first major study of its type. The main reason for deciding to investigate herbal medicines is that their use is associated with a lower incidence of side effects when compared to the use of orthodox medical drugs.

Project Methodology

The research protocol that has been developed is a randomised placebo-controlled double-blind parallel clinical trial of three months duration.

Eight herbs have been selected for this study. They are all herbs that are commonly used in the practice of herbal medicine in Australia and are not restricted regarding their use or supply. It is proposed that two herbal combinations be trialled in the treatment group, with each combination consisting of four herbs. One combination will be given in the morning and the other at night. They will be prepared as tablets by MediHerb Pty Ltd, who will also prepare the placebo product. MediHerb Pty Ltd provides full indemnity for all products. A letter regarding this is being prepared and will be forwarded as soon as possible. As details of the herbs chosen and the dosages to be administered are of a patentable nature this information is confidential and has been supplied separately. Products will be supplied in sterile plastic containers supplied by MediHerb. These will be labelled with the subject’s name, date, dosage details, time of administration, institution name (RMIT), clinical trial identification and storage instructions.

Screening of subjects for the trial will take place in the following way. Parents/caregivers who express interest in having their child participate in the study will be screened by telephone when they contact the investigator. Basic information about their child will be sought at this time. If their child meets the trial inclusion criteria (please refer to Section C: Details of Subjects) they will be sent an information sheet (the plain language statement) regarding the trial. If their child has not been diagnosed as per the inclusion criterion for ADHD diagnosis referral will be made to one of the clinic supervisors at the RMIT Psychology Clinic for assessment. Parents/caregivers will then be contacted several days later to see if they require any further information. If they wish for their child to take part in the trial they will be asked to attend a face to face interview.

Prior to this interview they will be asked to complete an initial interview consent form. The aims of the interview will be to obtain information regarding the child’s behaviour and to ensure that the child meets the trial inclusion and exclusion criteria. Evidence of ADHD diagnosis and completion of the medical practitioner clearance form (as per inclusion criteria) will also be discussed at this time. Also information about possible adverse effects or side effects of trial herbs will be discussed, and an information sheet supplied. Please refer to attached forms. If the parents/caregivers wish for their child to participate and the trial criteria are met informed consent will be obtained. Following the completion of informed consent the subjects will be randomly allocated to either the placebo group or the treatment group. Random assignment of subjects to placebo or treatment group will be achieved through using random number tables. Only Dr Francis will know the randomisation codes and thus which groups the subjects have been allocated to. The primary investigator will therefore remain blind as to which groups the subjects are in.

Trial Phases

Baseline: 2 weeks
Treatment: 3 months
Post-treatment: 2 weeks after completion of treatment
Follow-up: 3 months after completion of post-treatment

Measures

The following tests or measures will be used in order to determine the effects of the herbal combinations on daytime behaviour and sleep. Copies of all relevant items are attached. Please also find attached the case report/record form.
The test of variables of attention (TOVA) is a computer-based continuous performance test that is used to objectively monitor treatment over time. It is used in the assessment of children with ADHD to measure errors of omission (a measure of inattention or vigilance) and errors of commission (a measure of impulsivity and/or disinhibition). The child is required to sit at a computer and pay attention to the screen whilst holding a push-button control switch. They are instructed to press the button when a target appears, and not to press it when a non-target appears. A short practice run, lasting 5 minutes, is undertaken before the test begins. The duration of the actual test is 24 minutes. The data generated is printed out in the form of a graph. The TOVA will be administered at baseline and post-treatment. Time: 30 minutes.

Quantitative electroencephalography (QEEG) will be used to objectively monitor treatment. This is a computer-based method used to measure brain-wave activity. A fitted electrode cap with leads placed according to the International 10/20 System is applied to achieve a standardised 16 channel Mindset EEG recording. A small quantity of conductive gel is applied to each lead in the cap using a blunt syringe. The child's earlobes are wiped before applying leads to them. The child is seated in a chair and a series of standardised tests, each lasting approximately 3 minutes, are administered. They are instructed to 1) sit quietly with eyes closed 2) sit with eyes open, focussing on a point in the distance 3) read for comprehension from a book suitable for their age group and 4) perform a visuo-spatial test. The visuo-spatial test consists of playing a simple computer game on a laptop computer. A video camera, trained on their face, is in operation during the testing to record movements, for example eye-blinking, that affect the QEEG recording. The QEEG will be administered as per the TOVA. Time: 1 hour.

The Child Behavior Checklist (Achenbach and Edelbrock) is used to assess social competence and behaviour problems. According to Barkley (1990) it is the most well-developed and empirically-derived rating scale, and is useful for the initial assessment of ADHD children. It will be completed by the parents/caregivers at baseline, end of treatment phase and at follow-up. Time: 15-20 minutes.

The Conners Rating Scales-Revised will be used for both parents/caregivers and teachers to obtain information regarding the child's behaviour. They are available in both long and short forms, and have been used extensively in medication trials. The long forms will be administered at the baseline and follow-up phases, and the short forms will be used during the treatment phase and at post-treatment. At baseline the Conners scales will be administered twice in accordance with the usual protocol recommended in the literature (Barkley, Fischer, Newby and Breen, 1988; Conners, 1997; Conners, 1998). Time: long forms up to 20 minutes, short forms up to 10 minutes.

A daily sleep diary will be completed by the parents/caregivers. Time: 5 minutes.

A side effects scale will be completed by the parents/caregivers on a weekly basis in order to assess the incidence of side effects (if any) from the tablets used. Time: 5 minutes.

The Child Attention Problems (Edelbrock) scale, for teachers, was developed primarily for assessing stimulant drug effects (Barkley, 1990). It will be completed on a weekly basis. Time: <5 minutes.

**Primary and secondary efficacy variables**

Primary efficacy variables will be the Conners scales.

Secondary efficacy variables will be the TOVA, QEEG and sleep diary.
<table>
<thead>
<tr>
<th>TEST OR MEASURE</th>
<th>BASELINE</th>
<th>TREATMENT PHASE</th>
<th>POST TREATMENT</th>
<th>FOLLOW UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. TOVA</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>2. QEEG</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>3. Child Behaviour Checklist</td>
<td>✓</td>
<td>✓ end of phase</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4. Conners Rating Scale- Revised (Parents)</td>
<td>✓</td>
<td>✓ monthly</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5. Conners Rating Scale- Revised (Teachers)</td>
<td>✓</td>
<td>✓ monthly</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6. sleep diary</td>
<td>✓ daily</td>
<td>✓ daily</td>
<td>✓ daily</td>
<td>✓ daily for a two week period only</td>
</tr>
<tr>
<td>7. side effects</td>
<td>✓ weekly</td>
<td>✓ weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Child Attention Problems</td>
<td>✓</td>
<td>✓ weekly</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Proposed statistical analysis

Multivariate analyses will be performed with post hoc tests where appropriate. Regarding sleep data the analysis will be primarily on a case by case basis, as each child is expected to have differing sleep complaints, and thus differing sleep variables that will be of specific interest. Data from the sleep diaries will be used to construct actograms, which is the conventional method for analysing shifts in sleep-wake cycles. The actograms will be visually analysed for phase shifts, alterations in sleep latencies, nocturnal awakenings and total sleep time. Graphs will also be constructed for other variables of interest and visually analysed for changes from baseline to other trial phases. If data is sufficient group analyses will be conducted using analysis of variance procedures.

Procedures for monitoring subject compliance

Weekly telephone contact will be maintained with parents/caregivers. There is a question on the sleep diary regarding missed tablets. If necessary counting of remaining trial tablets will take place.

Follow-up of subjects after completion of data collection

The parents/caregivers will be contacted by the investigator by telephone three months after the final data collection is completed. This will be as a courtesy to ascertain their child's wellbeing and behaviour at that time, and to see if any issues have arisen for them following their involvement in the study.
Documents used in protocol preparation

The following documents have been read by the investigator and followed in the preparation of the study protocol.


National Health and Medical Research Council (NHMRC). (1992). *National Statement on Ethical Conduct in Research Involving Humans.*


Therapeutic Goods Administration (TGA). (1991). *Clinical Trials of Drugs in Australia: Clinical Trial Notification (CTN) scheme and the Clinical Trial Exemption (CTX) scheme.*


3. Proposed commencement of project

As MediHerb Pty Ltd require three months notice for the manufacture of product it is envisaged that the trial will commence 1st February 2001.

4. Proposed duration of project: proposed commencement/finish dates

The study will last for a total of seven months from commencement for each subject. Preliminary data analysis will commence as soon as possible.

Commence: 1st February 2001

Finish: 1st February 2002

5. Source of funding

The Department of Psychology and Disability Studies RMIT (internal) and MediHerb Pty Ltd (external) are jointly funding the project. In addition MediHerb Pty Ltd will donate all active and placebo products. Please refer to attached letter.

SECTION C: DETAILS OF SUBJECTS

1. Number, type, age range and any special characteristics of subjects

An a priori power analysis for a two-tailed two-group treatment/placebo design was carried out to estimate a desired sample size using the G Power computer package. An estimated effect size of \( d = 0.65 \) for each outcome variable was selected, based on an examination of previous related research, using similar designs and dependent measures.

Given \( \alpha = 0.05 \) and a desired power of .8, a total sample size of sixty subjects was calculated. Given that some matching will take place in the design to control for the error associated with certain individual difference variables, this number may be a slight over-estimate of the necessary sample size.

Sixty children (males and females) who meet the following criteria will be recruited.

Inclusion Criteria

To be included a child must be aged between 8 to 16 years and diagnosed with ADHD based on DSM-IV criteria (American Psychiatric Association, 1994) by a paediatrician, psychiatrist, or psychologist. Evidence of the diagnosis will be required in writing in the form of a letter from the health professional concerned.
In addition the child must experience disturbance to their sleep that causes significant distress to the parents/caregivers or child, or interferes significantly with the child's functioning or well being. The sleep disturbance may consist of difficulties settling to sleep, night time waking or early morning waking.

The child must receive a medical clearance to participate in the study from a registered medical practitioner. Please refer to attached form.

**Exclusion Criteria**

Children who are taking any of the following medications will be excluded due to the possibility of an interaction with St John's Wort. Please refer to the confidential Project Herbs document.

- HIV protease inhibitors (idenavir, nelfinavir, ritonavir, saquinavir)
- Immunosuppressants (cyclosporin, tacrolimus)
- HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, delavirdine)
- Warfarin
- Anticonvulsants (carbamazepine, phenobarbitone, phenytoin)
- Digoxin
- SSRIs and related antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, nefazodone)
- Triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan)
- Oral contraceptives
- Theophylline

Children who are taking the following will be excluded due to the caution concerning concurrent use of ginkgo. Please refer to the confidential Project Herbs document.

- Aspirin (except for occasional use)

Children who are currently taking any of the following medical drugs and/or alternative treatments for ADHD will be excluded to avoid confounding the study results.

- Methylphenidate
- Dexamphetamine
- Imipramine
- Desipramine
- Clonidine
- Zinc supplements
- Magnesium supplements
- Homoeopathic remedies
- Phosphatidylserine
- Efalex and other essential fatty acids supplements
- Pycnogenol and/or grapeseed products
- AD-FX (a product that contains ginkgo)
- Any product containing one or more of the trial herbs

Should the child cease taking these for a period of one month they will be considered for inclusion.

**2. Source of subjects**

Children in the community. As teachers will be asked to fill out two rating scales permission will be sought from the appropriate authorities. Please see attached details.

**3. Means by which subjects are to be recruited**

Subjects will be recruited by the investigator. Advertisements will be placed in newspapers, on community noticeboards and at health practitioners' clinics. In addition advertisements will be placed in the practitioner publications of the National Herbalists Association of Australia and the Victorian
Herbalists Association. Advertising will also take place through ADHD support groups, and information about the project will be placed on the Department of Psychology and Disability Studies website. Please see copies attached.

4. Are any of the subjects "vulnerable" or in a dependent relationship with any of the investigators?

The subjects are vulnerable as they are 1. children and 2. have ADHD. None will be in a dependent relationship with the experimenters.

SECTION D: PROJECT CLASSIFICATION AND ESTIMATION OF POTENTIAL RISK TO SUBJECTS

1. Project classification based on risk to subjects

This project is classified as an at risk (AR) project as it involves the clinical trialling of herbal medicines in children.

2. Classed as AR so identify all risks to subjects and explain how intend to protect against or minimise risks

1. Risks regarding use of herbal and placebo products. There is a risk of side effects or adverse drug reactions occurring. This is discussed under contingency planning.
2. Risks relating to exposure to electrical equipment for the TOVA and QEEG testing. The clinic operated by Mr Duff has safety switches and power-conditioning equipment in place. Mr Duff has agreed to provide training regarding the use of the equipment concerned.

3. How potential benefits to the subject or contributions to the general body of knowledge outweigh the risks

ADHD is a chronic lifetime disorder which has been linked with substance abuse, and adverse effects on academic performance, vocational success and social and emotional development (National Health and Medical Research Council, 1996; National Institutes of Health, 2000). As such there is an enormous cost to the community. Yet at present there is no alternative pharmacological treatment to the orthodox medical drugs discussed previously. This leaves children who do not respond to the drugs or cannot tolerate them due to side effects with no other pharmacological treatment option. The parents/caregivers of ADHD children are extremely stressed due to the difficulties in caring for such children. These difficulties involve dealing with both daytime behavioural problems and nighttime sleep problems. It is hoped that the trial will provide benefits to the subjects in the form of a suitable treatment for ADHD symptomatology that does not have the side effects of the medical drugs used. As this is to be the first major study of its type it stands to contribute information to the general body of knowledge regarding the treatment of this condition and associated sleep problems. If the treatments trialled are of benefit then they will be of help to the many ADHD children who at present are left with no pharmacological treatment option.

4. Contingency planning: first aid/debriefing

Participation of any child will be discontinued if an adverse reaction to any trial product occurs.

An adverse reaction may consist of an adverse drug reaction (ADR), adverse event (AE), serious adverse event (SAE) or serious adverse drug reaction (serious ADR) (International Committee on Harmonisation, 1997). The following definitions have been taken from the International Committee on Harmonisation guidelines (1997).

An adverse drug reaction (ADR) occurs when there is a noxious and unintended response to a medicinal product, and a causal relationship between the product and the event is at least a reasonable possibility and cannot be ruled out.
An adverse event (AE) is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product" (p.2).

A serious adverse event (SAE) or serious adverse drug reaction (serious ADR) is defined as "any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect" (pp.7-8).

Under the guidelines of the Therapeutic Goods Administration the reporting times for such reactions are:

serious adverse events: as soon as possible, but at least within 72 hours of being informed

other adverse events: within 15 days of being informed

Any such reaction or event will be handled in the following way:

Parents/caregivers will be advised to stop administering the tablets immediately and to contact Dr Francis to obtain information regarding which preparation their child is receiving (placebo or active herbal product) and the investigator. They will then be advised to consult with their child's medical practitioner or the nearest hospital emergency department, if they have not already done so. Any such reactions or events will be reported immediately to both the RMIT HREC and the Therapeutic Goods Administration.

A more detailed written report will then follow, including the following information:
- subject code number
- details of time and date at which the reaction or event occurred
- full details of the reaction or event
- interval between the last administration of any trial product and the onset of the reaction or event
- any concomitant treatment/s received in the preceding 48 hours by the subject and/0r details of any change/s in their normal routine in the preceding 48 hours
- duration, frequency and severity of the reaction or event
- the nature of any follow-up medical treatment required

Please refer to the attached adverse events report form.

Daily followup contact with the parents/caregivers will be maintained until the issue is resolved to their satisfaction and the satisfaction of the RMIT HREC.

Parents/caregivers will be advised at the commencement of the study that if they observe anything that they believe to be an adverse reaction to the trial products they should cease administering the products immediately, and contact the investigator and their child's medical practitioner as soon as possible. Parents/caregivers will be provided with the investigator's telephone number and the senior supervisor's telephone number. Both have answering facilities in place so that they can be contacted twenty four hours a day and seven days a week, should the need arise. Side effects scale will be completed by the parents/caregivers on a weekly basis. In addition during meetings with them they will be questioned regarding the general health and well being of their child. If the child has been ill in any way specific questions will be asked by the investigator to ascertain whether the child may have experienced an adverse reaction related to trial product. Particular attention will be paid to signs and symptoms such as stomach aches, nausea, vomiting, diarrhoea, lack of appetite, dizziness, headaches, excessive daytime sleepiness, fever, or skin rash. Any such problems, as well as any other reported signs and symptoms, will be recorded, and reporting procedures undertaken as outlined above.

The randomisation code will be readily accessible should an AE or SAE occur. A hard copy will be located in Dr Francis's office. This hard copy will be able to be accessed by another staff member.
from the Department of Psychology and Disability Studies if necessary. In addition the code will be located on several secure computers to which Dr Francis has access.

A child's participation in the trial will be terminated if such an event occurs. In addition if the parents/caregivers wish to withdraw their child at any time, for whatever reason, then their child's participation will be terminated. If a subject withdraws voluntarily for whatever reason follow-up telephone calls will be made on a weekly basis for at least four weeks unless the parents/caregivers indicate that this is not necessary.

5. Checklist for ethical issues

(c) video of face during QEEG testing - The child and the accompanying adult/s will be informed that the video camera is in operation during the QEEG testing solely for the purpose of recording any movements that may affect the QEEG recordings.

(d) exposure to electrical supply for both TOVA and QEEG testing - Please refer to Section D Part 2.

(h) herbal or placebo tablets to be taken internally (orally) - As advised in the confidential herbal document the tablets may be crushed if necessary to facilitate administration.

(i) there is a risk of an adverse reaction occurring - Please refer to Section D Parts 2 and 4, and the confidential herbal document.

(l) placebo control condition to be used - This will be explained to the parents/caregivers at the outset.

SECTION E: INFORMED CONSENT

1. Attach to application

(a) plain language statement - attached

(b) consent form - attached

2. Dissemination of results

Results may appear in professional publications and conference presentations. Parents/caregivers will be informed that this may occur at a later date and that confidentiality will be maintained. Any such publication or presentation will not contain any identifying information.

SECTION F: CONFIDENTIALITY OF RECORDS

1. Procedures to ensure confidentiality

All data and information related to this project will be stored in a locked filing cabinet at all times. Data that is transcribed to electronic media will be stored on a database that is password protected.

2. Who is responsible for security of confidential data?

The investigator will be responsible for the security of the data.

3. How long will data be held?

Data will be held for the period of time required by RMIT, that is 15 years.

4. Who will have access to data and for what purpose?

Only the investigator and the project supervisors (Dr Francis and Mr Duff) will have access to the data strictly for purposes related to this project.
SECTION G: OTHER ISSUES

1. Payment of subjects?

There will not be any payment made to subjects.

2. Where will the project be conducted?

The project will be conducted in the subject's normal home environment. The initial interview, and meetings with parents/caregivers to discuss progress and supply further materials and tablets, may be conducted in the home environment, in the RMIT Psychology Clinic, in the investigator's office at RMIT, or at Mr Duff's clinic in East Doncaster. The TOVA and QEEG testing will be conducted at Mr Duff's clinic. Teachers will be supplied with the teacher rating scales to complete at the child's school.

3. Submission to other ethics committees

The project is not being submitted to another ethics committee and has not previously been submitted to another ethics committee.
1. references list - main section
2. letter - second supervisor
3. letter - project consultant
4. CV - investigator
5. CV - senior supervisor
6. CV - second supervisor
7. CV - project consultant
8. initial interview consent form
9. initial interview form
10. medical practitioner clearance form
11. informed consent form
12. QEEG mindset equipment information
13. Child Behaviour Checklist
14. Conners Rating Scale - Revised (Parent) long form
15. Conners Rating Scale - Revised (Parent) short form
16. Conners Rating Scale - Revised (Teacher) long form
17. Conners Rating Scale - Revised (Teacher) short form
18. sleep diary
19. side effects rating scale
20. Child Attention Problems scale
21. application for Department of Education, Employment and Training
22. application for Catholic Education Commission
23. advertisement - public
24. advertisement - health professionals
25. advertisement - Department of Psychology and Disability Studies website
26. ethical issues checklist
   extra documents developed - to add here -
   27. telephone screening form (for investigator)
   28. ADHD evidence of diagnosis form
29. case report record form
30. adverse events report form
COVERSHEET FOR HERBAL MEDICINES SECTION

ETHICS APPLICATION

Ms Fiona Dey

Department of Psychology and Disability Studies

RMIT University

Please note that this section of the application contains information of a patentable nature. As such it is requested that all information contained in it be kept confidential.

Thank you.
PROJECT HERBS: DETAILED INFORMATION

Please note that this document is confidential. It contains detailed information regarding the project herbs, their dosages and how they are to be administered. It should be noted that five of the herbs have "approved" status in the Commission E monographs (Blumenthal, Busse, Goldberg, Gruenwald, Hall, Klein, Riggins and Rister, 1998). Commission E is the expert interdisciplinary committee for herbal drugs established by the German government. Their monographs are now available in English (Blumenthal et al., 1998) and "approved" herbs are those which received positive evaluations by the Commission.

HERBS

ginkgo Ginkgo biloba

part used:
the leaves

traditional use:
Ginkgo was not used in traditional herbal medicine.

therapeutic effects:
Standardised extracts of ginkgo leaves are widely used in Europe for circulation. The effects of ginkgo include increased cerebral blood flow, tissue oxygenation and nutrition, and enhanced memory and cognitive function. Information on the use of ginkgo leaves comes from clinical trials on the standardised extract conducted in the past three decades (Mills and Bone, 2000). Ginkgo acts as an antioxidant, tissue perfusion enhancer, circulatory stimulant and nootropic. Based on clinical trials this herb is indicated in the treatment of disorders and symptoms due to restricted cerebral blood flow, including memory and/or cognitive impairment. In a recent review paper nine randomised placebo-controlled double-blind trials were assessed and were found to collectively suggest that ginkgo is more effective than placebo for treating dementia (Ernst and Pittler, 1999).

contraindications and drug interactions:
Mills and Bone (2000) state that "There is very low risk associated with the administration of Ginkgo" (p.405) and that there are no contraindications for use. It is recommended that caution be exercised in patients on anticoagulant or antiplatelet medication. According to Blumenthal et al. (1998) and Schulz, Hänsel and Tyler (1998) the only known contraindication for the use of ginkgo is hypersensitivity to ginkgo preparations. There are no known interactions with other drugs.

adverse effects:
There is no restriction on the long-term use of ginkgo and it is advisable to give the herb to patients for at least six weeks before assessing clinical benefit (Mills and Bone, 2000). According to Weiss (1988) ginkgo is well tolerated and no toxic side effects have been reported. Willard (1991) reports that despite extensive toxicity studies on this herb virtually none was found. Side effects are very rare, consisting of mild gastric upset, headache, or allergic skin reactions (Blumenthal et al., 1998; Schulz et al., 1998).

bacopa Bacopa monnieri (also known as Bacopa monniera)

part used:
the whole plant

traditional use:
Bacopa is the foremost nerve tonic of Ayurveda (a form of traditional Indian medicine). It is used to improve memory and mental capacities (Bone, 1996).

therapeutic effects:
The actions of bacopa are nervine tonic, nootropic, sedative and anxiolytic. It is used as a brain tonic to aid concentration and learning. Placebo-controlled clinical studies have been conducted on the nootropic effects of bacopa in children, both on its own and in formulations, and have shown a beneficial effect (Bindra, Joglekar, Pandit, Rane, Moghe, Desai, Dhavale, Melgiri and Kamble, 1998; Sharma, Chaturvedi and Tewari, 1987). Morgan and Bone (1999) suggest that it is indicated to assist learning and intellectual development in children.

contraindications and drug interactions:
No information has been found.

adverse effects:
Adverse reactions are not expected for therapeutic doses of bacopa (Morgan and Bone, 1999). The chemical constituents contained in bacopa, the bacosides, were found to be well-tolerated by healthy human volunteers in a double-blind placebo-controlled trial (Singh and Dhawan, 1997).
paenony *Paeonia lactiflora* (also known as *Paeonia albilflora*)

**part used:**
the root

**traditional use:**
Paenony has been used for thousands of years in Chinese medicine (Foster and Chongxi, 1992). It has been used in traditional systems of medicine to treat dementia (World Health Organization, 1999).

**therapeutic effects:**
Paenonyflorin, a constituent of paenony, has been studied in animal research as a cognition enhancer (Ohta, Ni, Matsumoto, Watanabe and Shimizu, 1993). Bone (1996) lists the actions of paenony as including cognition enhancer and states that one of the herb's uses is to assist memory. It is also used to treat epilepsy in Japan and China in combination with other herbs.

**contraindications and drug interactions:**
No information has been found.

**adverse effects:**
No information is available regarding adverse reactions to paenony (World Health Organization, 1999).

*St John's Wort* (hypericum) *Hypericum perforatum*

**part used:**
the aerial parts

**traditional use:**
In traditional herbal medicine St John's Wort was used for the treatment of nervous system complaints, particularly for conditions such as excitability.

**therapeutic effects:**
St John's Wort has a mild antidepressant effect. Indications for use that are supported by clinical trials include the treatment of mild to moderate depression and the treatment of anxiety (Kim, Strelitzer and Goebert, 1999; Schulz et al., 1998). St John's Wort is used in Europe in the treatment of bed wetting and night terrors in children (Weiss, 1988).

**contraindications and drug interactions:**
According to Blumenthal *et al.* (1998) there are no known contraindications for St John's Wort and no known drug interactions. Some recent papers (Ernst, 1999) have suggested that St John's Wort may interact with certain medical drugs, affecting their activity. It is known that several commonly available foods and drinks affect the same enzyme systems and thus may also affect the rate at which these drugs are metabolised (Jobst, McIntyre, St George and Whitelegg, 2000; Rasmussen, 2000). In addition for the drugs involved it has been stated that there are "varying degrees of evidence of a possible interaction with St John's Wort" and that for some of the drugs concerned "there is at present no more than a theoretical possibility of interaction" (Medsafe Editorial Team, 2000, p.1). To avoid any possibility of interaction these drugs are listed in the subject exclusion criteria although most of them are not relevant to ADHD treatment.

**adverse effects:**
Adverse effects are rare from the use of St John's Wort at normal dosages (Mills and Bone, 2000). This herb is considered to be well tolerated, with an incidence of adverse reactions in the literature that is similar to that of placebo (Ernst, Rand, Barnes and Stevinson, 1998). Those listed as the most common are gastrointestinal symptoms, dizziness, confusion and tiredness. Photosensitivity has been cited as a possible adverse reaction, especially in individuals with fair skin (Blumenthal *et al.*, 1998). This is due to it resulting from the consumption of large amounts of St John's Wort by light skinned grazing animals. In humans it is considered to be extremely rare (Ernst *et al.*, 1998). One researcher has stated that photosensitivity has not been observed after therapeutic doses of St John's Wort for depression (Reuter, 1995). St John's Wort is considered to be therapeutically equivalent to the drug imipramine for treating mild to moderate depression and better tolerated by patients (Woelk, 2000).

*valerian* *Valeriana officinalis*

**part used:**
the root and rhizome

**traditional use:**
Valerian was traditionally used to promote sleep and as an anxiolytic for nervous unrest.

**therapeutic effects:**
Valerian improves sleep latency and sleep quality, lowers periods of wakefulness and reduces anxiety. It acts as a mild sedative. From clinical trials there is support for indications of insomnia, restlessness and nervous tension. Schulz *et al.* (1998) review ten controlled clinical studies of
valerian preparations. Valerian may also be used in the treatment of depression or anxiety. Clinical trials of a valerian proprietary product have been conducted in children (Schilcher, 1997).

**contraindications and drug interactions:**
There are no known contraindications or drug interactions (Blumenthal *et al.*, 1998; Bradley, 1992).

**adverse effects:**
There are no known side effects for valerian (Blumenthal *et al.*, 1998; Schulz *et al.*, 1998; Scientific Committee of European Scientific Cooperative On Phytotherapy, 1997). Regarding safety this herb may be used long term and no adverse effects from ingestion of valerian are expected when consumed within the recommended dosage (Mills and Bone, 2000). The authors of a recent clinical trial paper commented on the extremely low number of adverse events during the valerian treatment periods (Donath, Quispe, Diefenbach, Maurer, Fietze and Roots, 2000). The adverse events consisted of one attack of previously known migraine, one episode of gastrointestinal complaints, and one complaint relating to the use of polysomnography equipment. The authors of a recent review paper assessing randomised placebo-controlled double-blind trials found that reports of adverse events due to valerian use were scarce, and that those reported were mild and similar to those experienced with placebo (Stevinson and Ernst, 2000).

**skullcap Scutellaria lateriflora**

**part used:**
the herb

**traditional use:**
The actions and indications for skullcap in the literature are taken from its traditional use in herbal medicine. Willard (1991) reports that this herb has a calming effect. He lists its traditional uses as including insomnia, excitability and restlessness.

**therapeutic effects:**
Mills and Bone (2000) discuss skullcap as being sedative, relaxant and nerve tonic. Based on traditional use skullcap is used to treat nervous exhaustion, tension, anxiety, insomnia and restless sleep (Fisher and Painter, 1996).

**contraindications and drug interactions:**
No information has been found.

**adverse effects:**
No information has been found regarding adverse effects of skullcap. There have been four overseas case reports of skullcap being associated with hepatotoxicity (MacGregor, Abernethy, Dahabra, Cobden and Hayes, 1989) however these were later considered to be caused by another plant being substituted for skullcap. There are no known cases of hepatotoxicity occurring as a result of the use of authenticated *Scutellaria lateriflora* (Bone, 2000).

**passionflower Passiflora incarnata**

**part used:**
the aerial parts

**traditional use:**
Passionflower has traditionally been used to promote sleep (Schulz *et al.*, 1998).

**therapeutic effects:**
Schulz *et al.* (1998) list the indications for passionflower as states of nervous unrest. Weiss (1988) says that the herb has mild sedative and sleep inducing properties and is a very useful supportive plant in herbal preparations. Based on traditional use passionflower is indicated in the treatment of insomnia, restlessness and anxiety (Fisher and Painter, 1996). Passionflower as a tea has been recommended for use in children for nervous restlessness (Schilcher, 1997).

**contraindications and drug interactions:**
There are no known contraindications or drug interactions (Blumenthal *et al.*, 1998).

**adverse effects:**
There are no known side effects for passionflower (Blumenthal *et al.*, 1998).

**chamomile (German) Matricaria recutita** *(also known as Chamomilla recutita)*

**part used:**
the flowers

**traditional use:**
Chamomile has traditionally been used to treat restlessness and anxiety. The traditional use of this herb includes the treatment of children (Mills and Bone, 2000).
therapeutic effects:
Chamomile is a mild sedative and relaxant. According to the World Health Organization (1999) the use of chamomile as a tea for the treatment of restlessness, and mild insomnia due to nervous disorders, is supported by clinical data.

contraindications and drug interactions:
There are no known contraindications or drug interactions (Blumenthal et al., 1998). Chamomile used as a topical preparation may cause allergic skin reactions in persons who are sensitive to plants in the Compositae or daisy plant family (Mills and Bone, 2000).

adverse effects:
Regarding internal use of chamomile there have been a few reported cases of anaphylactic or allergic reactions; however, they all involved the use of the herb as a tea. It has been stated that given the widespread consumption of this herb such reactions are extremely rare (Fisher and Painter, 1996; Mills and Bone, 2000). According to Blumenthal et al. (1998) there are no known side effects for chamomile.

INFORMATION REGARDING DOSAGE AND ADMINISTRATION

The following dosages in dried herb equivalents have been formulated by Mr Kerry Bone, Director of Research and Development, MediHerb Pty Ltd and project consultant. Mr Bone has advised that wherever possible a standardized, phytochemically-profiled extract will be used.

Morning:
- Ginkgo: 1.5g
- Bacopa: 700mg
- Paeony: 500mg
- St John’s Wort: 900mg

Night:
- Valerian: 300mg
- Skullcap: 250mg
- Passionflower: 200mg
- Chamomile: 250mg

Please find attached sample tablets to illustrate tablet size. The dosage will be 1 tablet per 10 kg body weight in both instances. Mr Bone has advised that the tablets may be crushed, if necessary, in order for the child to take them.

Regarding timing of administration the morning tablets will be given at breakfast time, within the time range of 5 a.m. to 9 a.m. The night tablets will be given an hour before bedtime, within the time range of 5 p.m. to 9 p.m.
1. references list - herbs section
2. plain language statement
3. tablets sample - to illustrate size of trial tablets
APPENDIX B

HREC letter granting approval for the trial
3rd July 2001

Ms Fiona Dey
C/o Psychology and Disability Studies
RMIT Bundoora

Dear Ms Dey,

Project No 1/01Dey: Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

At its meeting held on 27th June 2001, the RMIT Human Research Ethics Committee considered your final amendments to this project. Following is the relevant extract from the minutes:

"The Committee noted that this project was approved subject to conditions at meeting 4/01 held 30th May 2001.

The Committee approved final amendments to the plain language statement and other documents.

Members also considered the memorandum from Dr Andrew Francis and Ms Fiona Dey dated 12 June 2001. The Committee stated its position on medical clearances as follows:

Where a special consultation was needed to obtain clearance to participate in a study, the cost should be met from the research budget. However, the Committee saw no problem if parents obtained the clearance from the medical consultant who regularly monitored the child's condition either during a routine consultation at which a range of matters were discussed, or by submitting the clearance form for completion."

I have forwarded the signed CTN Form to Professor Neil Furlong for signature after which it will be sent to Dr Francis. I look forward to your confirming that indemnity arrangements between Mediherb and RMIT have been satisfactorily finalised.

Please note the following information which pertains to all HREC approved projects:

Projects are normally approved for a period of three years from the date of this advice, but this is conditional on the receipt of annual reports. If your work is completed within twelve months a final report, only, is required. The relevant forms are available from the web site:


If, as you proceed with your investigation, you find reason to amend your research method, you should advise the RMIT Human Research Ethics Committee and seek approval of the
proposed changes. If you decide to discontinue your research before its planned completion you must also advise the Committee of the circumstances.

Please note that you should immediately report to the Committee in the event of any adverse effects on subjects, or unforeseen events, which may affect the ethical acceptability of your project.

Also we were recently advised that any confidential research data which is in electronic form should be stored on CD, Zip Disk or diskette. It should not be stored on a computer that is connected to the web or to a network.

We wish you well with this investigation.

Yours Sincerely,

Adrienne Patterson
Secretary
RMIT Human Research Ethics Committee

CC  Dr Andrew Francis, Psychology and Disability Studies
    Dr John Reece, Psychology and Disability Studies
APPENDIX C

CEO letter granting ethics approval for teachers to be involved
Ms F Dey  
Masters Student  
C/- Dr A Francis  
Department of Psychology and Disability Studies  
RMIT University  
PO Box 71  
BUNDOORA VIC 3083

Dear Ms Dey,

I am writing with regard to your letter received on 24 September 2001 in which you referred to your forthcoming research project into the use of herbal medicines for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). I understand that this research is part of your studies for a Masters degree at RMIT University. You have asked approval to approach Catholic schools in the Archdiocese of Melbourne as you wish to survey teachers of students involved in the study.

I am pleased to advise that your research proposal is approved in principle subject to the following standard conditions.

1. The decision as to whether or not research can proceed in a school rests with the School Principal. So you will need to obtain approval directly from the Principal of each school that you wish to involve.

2. You should provide each Principal with an outline of your research proposal and indicate what will be asked of the school. A copy of this letter of approval, and a copy of notification of approval from the University's Ethics Committee, should also be included.

3. You should provide the names of schools which agree to participate in the research project to the Information Services Unit of this Office.

...2
4. Any substantial modifications to the research proposal, or additional research involving use of the data collected, will require a further research approval submission to this Office.

5. Data relating to individuals or schools are to remain confidential.

6. Since participating schools have an interest in the research findings, you should discuss with each Principal ways in which the results of the study could be made available for the benefit of the school community.

7. At the conclusion of the study, a copy or summary of the research findings should be forwarded to the Information Services Unit of the Catholic Education Office.

I wish you well with your research study. If you have any queries concerning this matter, please contact Mr Mark McCarthy of this Office.

With every best wish,

Yours sincerely,

[Signature]

(Rev. T. M. Doyle)
DIRECTOR OF CATHOLIC EDUCATION
APPENDIX D

DEET letter granting ethics approval for teachers to be involved
SOS001979

19 December 2001

Ms Fiona Dey
Department of Psychology & Disability Studies
RMIT University
P.O. Box 71
Bundoora 3083

Dear Ms Dey

Thank you for your application of 19 September 2001 in which you request permission to conduct a research study in government schools titled: *Phytomedicines as pharmacological alternatives in the treatment of ADHD in children.*

I am pleased to advise that on the basis of the information you have provided your research proposal is approved in principle subject to the conditions detailed below.

1. Should your institution’s ethics committee require changes or you decide to make changes, these changes must be submitted to the Department of Education, Employment and Training for its consideration before you proceed.

2. You obtain approval for the research to be conducted in each school directly from the principal. Details of your research, copies of this letter of approval and the letter of approval from the relevant ethics committee are to be provided to the principal. The final decision as to whether or not your research can proceed in a school rests with the principal.

3. No student is to participate in this research study unless they are willing to do so and parental permission is received. Sufficient information must be provided to enable parents to make an informed decision and their consent must be obtained in writing.
4. As a matter of courtesy, you should advise the relevant Regional Director of the schools you intend to approach. An outline of your research and a copy of this letter should be provided to the Regional Director.

5. Any extensions or variations to the research proposal, additional research involving use of the data collected, or publication of the data beyond that normally associated with academic studies will require a further research approval submission.

6. At the conclusion of your study, a copy or summary of the research findings should be forwarded to me at the above address.

I wish you well with your research study. Should you have further enquiries on this matter, please contact Craig Irvin, Project Manager, School and Community Development Division, on 9637 2358.

Yours sincerely

[Signature]

Karen Moore
Acting Manager
School Community Links & Networks

encl.
Herbal medicines for the treatment of ADHD

Phytomedicines as pharmacological alternatives
in the treatment of Attention Deficit Hyperactivity
Disorder (ADHD) in children.

This document is the plain language statement or subject
information sheet for this project.

BACKGROUND

This research project is being conducted to see whether certain herbal medicines (or phytomedicines)
are of benefit in the treatment of ADHD. Although many children take orthodox medical drugs for
ADHD, and related sleep problems, not all children respond to them. Also some children cannot
tolerate the drugs due to side effects. In this project herbs will be given to treat both daytime
behaviour problems and sleep problems in ADHD children. Children aged between 8 to 16 years are
required for the study. They must have received a diagnosis of ADHD from a paediatrician,
psychiatrist or psychologist. Evidence of this will be required in writing. They must also have a
written clearance to participate in the research from a medical practitioner. Forms will be supplied for
you to take to the relevant practitioners.

This project is being undertaken in the Department of Psychology and Disability Studies by Ms Fiona
Dey, a Masters degree student who has a background in psychology, nursing and naturopathy/herbal
medicine. The senior supervisor for the project is Dr Andrew Francis of RMIT. The project also
involves Mr Jacques Duff, a clinical psychologist in private practice, and Mr Kerry Bone of
MediHerb Pty Ltd. All products used in the study will be donated by MediHerb Pty Ltd, a major
manufacturer of herbal medicines. Funding for the project is being supplied by both RMIT and
MediHerb. RMIT and MediHerb have in place public and products liability insurance covering legal
liability to pay damages or compensation to others for loss and/or injury as a result of an occurrence
in connection with this proposed clinical trial.

WHAT WILL WE HAVE TO DO?

If it is thought that your child is able to be included an initial face to face interview will take place.
Your written permission will be sought for this. The main aim of the interview will be to obtain
information about your child’s behaviour. You will also be asked about their general health, if they
have any allergies, and for details of any medications or supplements that they are taking. If they are
taking certain medications or supplements they will have to cease taking them for one month in order
to be eligible to be included in the study. In addition you will be asked if they have ever experienced
any adverse reaction/s to herbal medicines.

The interview will clarify whether or not your child is eligible to be included. If you wish for your
child to participate, and your child is eligible, you will be asked to retain a copy of this information
sheet and to sign a consent form. You will be given a copy of the consent form to keep in a safe
place.

Your child will then be randomly put into one of two groups: the placebo group or the treatment
group. They will be required to take tablets twice a day, morning and night, for three months. The
tables may be crushed if taking them is a problem. The dosage for the tablets will be calculated based
on body weight. As this is a scientific study the tablets will be coded, and only Dr Francis will know
whether your child is taking the placebo (inactive) tablets or the herbal tablets. To see what effects the
tables have the following tests will be used:

- Test of Variables of Attention (TOVA): a computer-based test which is like a computer game.
  This test will be done twice and it takes 30 minutes.
Quantitative Electroencephalography (QEEG): testing to record your child’s brain waves. Your child’s face will be videotaped during this test to record any movements, for example eye-blinking, that show up on the QEEG. This test will also be done twice and it takes 1 hour.

- checklists that you and your child’s teacher will need to complete on a regular basis. The main ones take about 5 to 10 minutes to complete. There are others that take up to 20 minutes to do but they will only be completed three times during the project.

- a sleep diary that you will be asked to fill out each day. This takes about 5 minutes.

- a side effects checklist that you will be asked to complete weekly. This takes about 5 minutes.

As we wish to obtain information about your child’s behaviour at school we will be asking for your permission for us to contact your child’s teacher. The TOVA and QEEG testing will be conducted at Mr Duff’s clinic in East Doncaster. As these tests involve exposure to electrical equipment safety switches and power-conditioning equipment are in place at the clinic. The interview may take place at RMIT in Bundoora. Regular meetings will be arranged to organise testing, checklists and tablets, and regular telephone contact will be maintained.

There will be a two week baseline period to obtain information before the three month trial commences. The trial will be followed by a posttreatment evaluation after a further two weeks and then a followup assessment after another three months. This will be the final data collection point. Thus you would be involved in the project for a total time of about seven months. You will then be contacted by telephone a further three months later as a courtesy to ascertain your child’s wellbeing and behaviour at that time, and to see if any issues have arisen from your involvement in the study.

CONFIDENTIALITY

Your privacy will be respected. Only Ms Dey, Dr Francis and Mr Duff will have access to confidential information and any results that are published will not include any personal or identifying information.

WHAT HERBS ARE BEING USED?

The herbs which will be used in this study are ginkgo, bacopa, paeony, St John’s Wort, valerian, skullcap, passionflower and chamomile. A patent application has been lodged regarding the use of these herbs.

ARE THERE ANY SIDE EFFECTS OR INTERACTIONS?

Special care has been taken in the selection of these herbs. They are all regularly prescribed by naturopaths and herbalists to treat certain conditions, either on their own or in combination. However this will be the first clinical trial of its type. And regarding their specific use in this trial there is currently no data on their side effects in combination, or with other medications.

In reviewing the literature the following information regarding side effects and interactions has been found for these herbs.

**ginkgo Ginkgo biloba**

Ginkgo is considered to be well-tolerated and no toxic side effects have been reported. The side effects that have been documented are very rare and consist of mild gastric upset, headache, or allergic skin reactions. According to the literature there are no known interactions with other drugs, however caution is recommended if someone is taking an anticoagulant medication.

**bacopa Bacopa monniera**

No information has been found regarding reported or known side effects or drug interactions for bacopa.
paeony *Paeonia lactiflora*

No information has been found regarding reported or known side effects or drug interactions for paeony.

St John's Wort *Hypericum perforatum*

Side effects are considered to be rare for St John's Wort. Those reported in the literature are gastrointestinal symptoms, dizziness, confusion and tiredness. Sensitivity of the skin to sunlight has been listed as a possible side effect for individuals with fair skin but it is considered to be extremely rare. According to recent reports St John's Wort is thought to interact with a variety of medical drugs, and if a child is taking any of the drugs concerned they will not be able to be included in the trial.

valerian *Valeriana officinalis*

No information has been found regarding reported or known side effects or drug interactions for valerian. In one study one person had an attack of migraine, which they had experienced previously, and one episode of gastrointestinal complaints was reported.

skullcap *Scutellaria lateriflora*

No information has been found regarding reported or known side effects or drug interactions for skullcap.

passionflower *Passiflora incarnata*

No information has been found regarding reported or known side effects or drug interactions for passionflower.

chamomile *Matricaria recutita*

No information has been found regarding reported or known side effects or drug interactions for chamomile. There have been a few reported cases of allergic reaction to chamomile, however they involved its use as a tea, or as an external preparation.

**WHAT IF AN ADVERSE REACTION OCCURS?**

As with any kind of medication there is always the risk of a side effect or adverse reaction. If such a reaction occurs you will be advised to stop the tablets immediately and to contact Dr Francis, Ms Dey, and your child's doctor or the nearest hospital emergency department.

Ms Dey and Dr Francis will then immediately undertake full reporting procedures to report all details to both the RMIT University Human Research Ethics Committee (RMIT HREC) and the Commonwealth Government's Therapeutic Goods Administration.

**OUTCOMES**

We cannot promise any beneficial effects to your child regarding their daytime behaviour or sleep as a result of being involved in this research. The information gained from this project will contribute to the body of knowledge about ADHD, and will hopefully assist the development of alternative treatment products for this condition and related sleep problems. Expressing an interest in our work in no way obliges you to participate, and if you do agree to participate you may withdraw your child from the project at any time.

**TERMINATION OF PARTICIPATION**

Your child's involvement in the trial will be terminated if an adverse reaction occurs. In addition, as stated above, you may withdraw your child from the project at any time.
Thank you for taking the time to read this information. If you require further details please contact:

Ms Fiona Dey  
BBSc DipAppSc (Nursing) DipAppSc (Naturopathy) MNHAA  
Investigator  
Telephone: (03) 9925-7376  
Facsimile: (03) 9925-7303  
email: s8210843@student.rmit.edu.au

Dr Andrew Francis  
BBSc (Hons) PhD  
Senior Supervisor  
Telephone: (03) 9925-7782  
Facsimile: (03) 9925-7303  
email: andrew.francis@rmit.edu.au

Any complaints about your participation in this project may be directed to the Secretary, RMIT Human Research Ethics Committee, University Secretariat, RMIT, GPO Box 2476V, Melbourne Vic 3001. The telephone number is (03) 9925-1745.
APPENDIX F

MediHerb Pty Ltd report regarding the post-trial tests conducted on the herbs
HPLC assessment of various components in the ADHD tablets.  
R02006 - R02007.

Prepared by: Anita Matthias

The main component of each herb present in both the day and night ADHD tablets were assessed using the methods given in the appropriate TMM. They were able to be identified and quantitated as given in Tables 1 and 2. Due to the possibility of misidentification due to interfering peaks from other herbs, the chromophore for each compound has been given below (Figures 1-7) comparing both the standards (either pure or from a sample of the herb itself; the chromophore on the left) and the peaks obtained in the tablets themselves (the chromophore on the right).

<table>
<thead>
<tr>
<th>Herb</th>
<th>TMM</th>
<th>Compound</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingko biloba</td>
<td>TMM 656</td>
<td>Quercetin</td>
<td>17.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kaempferol</td>
<td>2.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IsoRhamnetin</td>
<td>0.25</td>
</tr>
<tr>
<td>Paeonia lactiflora</td>
<td>TMM 662</td>
<td>Paeoniflorin</td>
<td>6.67</td>
</tr>
<tr>
<td>Hypericum perforatum</td>
<td>TMM 678</td>
<td>Rutin</td>
<td>5.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperoside</td>
<td>6.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isoquercitrin</td>
<td>2.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quercitrin</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quercetin</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperforin</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Table 1: ADHD Daytime Tablets (average of duplicate assays)

<table>
<thead>
<tr>
<th>Herb</th>
<th>TMM</th>
<th>Compound</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valeriana officinalis</td>
<td>TMM 618</td>
<td>Valerenic acid</td>
<td>0.26</td>
</tr>
<tr>
<td>Passiflora incarnata</td>
<td>TMM 658</td>
<td>Vitexin</td>
<td>4.15</td>
</tr>
<tr>
<td>Scutellaria lateriflora</td>
<td>TMM 659</td>
<td>Baicalin</td>
<td>4.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oroxylin A -7-O glucoside</td>
<td>1.36</td>
</tr>
<tr>
<td>Matricaria recutita</td>
<td>TMM 701</td>
<td>Apigenin</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>UH</td>
<td>Apigenin-7-glucoside</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>UH</td>
<td>Luteolin-7-glicoside</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 2: ADHD Nighttime Tablets
Figure 1: Gingko chromophores. Quercetin and Kaempferol were identified by both chromophore and retention time. Isorhamnetin was identified using only retention time as the chromophore is not conclusive.

Figure 2: Paeonia chromophores. Paeoniflorin was identified by both chromophore and retention time.
Figure 3A: St John's Wort chromophores. Rutin, hyperoside, isoquercitrin and quercitrin were identified by both chromophore and retention time.
Figure 3B: St John’s Wort chromophores. Quercetin and hyperforin were identified by both chromophore and retention time.

Figure 4: Valerian chromophores. Valerenic acid was identified by both chromophore and retention time.
Figure 5: Passionflower chromophores. Vitexin at the same retention time was not found. Seven peaks with similar chromophores were identified and summed to obtain the total vitexin derivative amount given in Table 2. The chromophore on the right is for one of these derivative peaks.

Figure 6: Skullcap chromophores. Baicalin was identified by both chromophore and retention time. Oroxylin-7-glucoside was identified from the chromophore given in TMM659 and its retention time relative to baicalin.
Figure 7: Chamomile chromophores. Apigenin, apigenin-7-glucoside and luteolin-7-glucoside were identified by both chromophore and retention time.
APPENDIX G

Information sheet for participants regarding the TOVA and QEEG
TOVA AND QEEG BRAINMAPPING
INFORMATION SHEET FOR RMIT ADHD HERBAL CLINICAL TRIAL

These tests are being conducted at the following address:

**Behavioural Neurotherapy Clinic**
2/314 Manningham Road Doncaster Vic 3108
(at south east corner of Manningham Road and High Street)

<table>
<thead>
<tr>
<th>Clinic telephone for making appointment (03) 9848-9100</th>
</tr>
</thead>
<tbody>
<tr>
<td>When making appointment you must state that this is for the Herbal Clinical Trial</td>
</tr>
</tbody>
</table>

Please allow two hours for your first visit. This should allow time for the TOVA and the QEEG.

**TOVA (visual Test of Variables of Attention)**
This is a computer-administered continuous performance task. The TOVA is being used in this clinical trial to give an objective measure of treatment efficacy.

During the 24 minute test protocol the child will be presented with a series of visual targets and non-targets on the computer screen. They will be instructed to press a microswitch as quickly as possible after seeing a target, and not to press the microswitch when a non-target appears. A practice session, lasting 5 minutes, is given before the test is commenced.

**QEEG BRAINMAPPING**
The QEEG is also being used in this trial to objectively monitor treatment. The QEEG is a computer-based method of recording brain-wave activity. A fitted electrode cap is applied to the child’s head to allow for the recording to be taken. The attached photo shows a child wearing a cap at the clinic.

The child's earlobes are wiped with a cleansing paste and a small quantity of conductive paste applied. Conductive gel is then applied to each sensor in the cap using a syringe with a blunt needle. In order to obtain a low impedance level, which allows for a good recording to be taken, each sensor is checked following the application of the gel. If necessary the blunt needle is gently "wiggled" in the electrode to part the hair, and more gel may be applied to ensure a good contact.

The child is seated in a chair, and once the preparation is completed an eye mask is put on so that a 6-10 minutes of eyes-closed recording can be taken.

**PREPARATION FOR QEEG BRAINMAPPING**
The child’s hair must be washed and dried thoroughly on the day, but no hair-conditioner used.

Fiona Dey
Department of Psychology and Disability Studies
RMIT University
telephone (03) 9925-7376 [mobile 0408 511 437]
faxsimile (03) 9925-7303
email s8210843@student.rmit.edu.au
APPENDIX H

Sleep Diary section
Sleep Diary

Child’s Name: ____________________________

Diary Number: _______

Date this diary commenced: ____________________________

Department of Psychology and Disability Studies
RMIT University

Investigator:
Ms Fiona Dey
Telephone: 9925-7376 (mobile 0408 511 437)
Email: s8210843@student.rmit.edu.au

Supervisor:
Dr Andrew Francis
Telephone: 9925-7782
Email: andrew.francis@rmit.edu.au

Subject Code Number: FDAF001-__________
EVENING QUESTIONS
To be completed before going to bed.

Child Sleep Information.

1. Was your child sleepy during the day? (Please circle a number)
   Not sleepy at all 0 1 2 3 4 5 Very sleepy

2. Did your child have a nap today? Yes ☐ No ☐ Don't know ☐
   If Yes: Time nap started _______ Time nap ended _______ Location _______

3. If your child is taking medication, did they have their medication today?
   Yes ☐ No ☐ If no, why was dose missed? ______________________

4. What time did you leave your child for sleep tonight? _______ p.m.

5. How sleepy did your child seem at this time? (Please circle a number)
   Not sleepy at all 0 1 2 3 4 5 Very sleepy

6. Did your child call out or get up before going to sleep? Yes ☐ No ☐
   If yes, please complete the following:

<table>
<thead>
<tr>
<th>Time</th>
<th>Call out</th>
<th>Get up</th>
<th>Other</th>
<th>Reason</th>
<th>What did you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. What time do you think your child fell asleep? _______ p.m.

8. Where did your child fall asleep? ______________________

9. Did your child take the trial tablets today? Yes ☐ No ☐
   If no, why? Refused to take ☐ Forgot ☐ Other Reason ______________________

10. Do you have any other comments to make?
    ______________________

Please complete questions opposite

Behavior and well being questions about your child.

1. How irritable was your child today? (Please circle a number)
   Not irritable at all 0 1 2 3 4 5 Very irritable

2. Overall, how would you rate your child's behavior today? (Please circle a number)
   Very difficult 0 1 2 3 4 5 Very well behaved

3. Do you have any other comments to make regarding your child's behavior or well being? E.g. my child was feeling sick
    ______________________
    ______________________
    ______________________
    ______________________
    ______________________

Behavior and well being questions about yourself.

4. How are you feeling at the moment? (Please circle a number)
   Stressed 0 1 2 3 4 5 Calm
   Tired 0 1 2 3 4 5 Active

5. Do you have any other comments to make regarding your own well being?
    ______________________
    ______________________
    ______________________
    ______________________
    ______________________

Who completed the evening questions today?

Date: ______________________
MORNING QUESTIONS
To be completed when you wake up.

Child Sleep Information.

1. What time did your child wake up? __________: a.m.
2. Did your child wake during the night? Yes ☐ No ☐ Don’t know ☐
   If yes, complete the following:

<table>
<thead>
<tr>
<th>Time of waking</th>
<th>Possible reason for waking (Eg: had a nightmare)</th>
<th>How long child was awake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Where did your child sleep last night?

4. Did you sleep in your child’s room last night? Yes ☐ No ☐ For part of the night ☐

5. How difficult was it to wake your child this morning? (Please circle a number)
   Easy (child woke self) 0 1 2 3 4 5 Very difficult

6. Was there any disruption to normal routine which may have disturbed your child’s sleep last night?
   Yes ☐ No ☐ If yes, what was the disruption?

7. How would you rate your child’s sleep last night? (Please circle a number)
   Not restless at all 0 1 2 3 4 5 Very restless

8. Do you have any other comments to make regarding your child’s sleep last night.

__________________________________________________________
__________________________________________________________

Behaviour and well being questions about your child.

1. How irritable was your child this morning within the first hour after waking?
   (Please circle a number)
   Not irritable at all 0 1 2 3 4 5 Very irritable

2. How sleepy/drowsy did your child seem this morning within the first hour of waking? (Please circle a number)
   Not drowsy at all 0 1 2 3 4 5 Very drowsy

3. How difficult was your child’s behaviour this morning within the first hour of waking? (Please circle a number)
   Not at all difficult 0 1 2 3 4 5 Very difficult

4. Do you have any other comments to make regarding your child’s behaviour or well being? Eg: my child was feeling sick

__________________________________________________________
__________________________________________________________

Behaviour and well being questions about yourself.

5. How would you rate your own sleep last night? (Please circle a number)
   Very poor 0 1 2 3 4 5 Very good

6. How long do you estimate you slept for last night _____ hrs _____ mins

7. How are you feeling this morning? (Please circle a number)
   Not tired at all 0 1 2 3 4 5 Very tired

   Not stressed at all 0 1 2 3 4 5 Very stressed

8. Do you have any other comments to make regarding your own well being?

__________________________________________________________
__________________________________________________________

Who completed the morning questions today? ____________________
Date: ____________________
APPENDIX I

Side Effects Rating Scale
SIDE EFFECTS RATING SCALE

Child's Name: ________________________________

Date: ________________________________

Name of Person Completing this form: ________________________________

Instructions:

This scale is to be completed weekly. Please rate each behaviour from 1 (Not at All) to 5 (Frequent) by circling the appropriate number beside the item concerned. Please circle only one number beside each item.

<table>
<thead>
<tr>
<th>Number</th>
<th>Item Description</th>
<th>Not at All</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stomachaches</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Nausea</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Vomiting</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Diarrhoea</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Lack of appetite</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Headaches</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sleepy in daytime</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Feverish</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Skin rash</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Did your child have any health problems during the past week? If yes, please give brief details here.

Should you have any questions please contact Fiona Dey on telephone (03) 9925-7376 or 9925-7727 (mobile number 0408 511 437) or by email at <s8210843@student.rmit.edu.au>. Thank you.
APPENDIX J
CAP
CHILD ATTENTION PROBLEMS

CHILD’S NAME: ___________________________ AGE: __________

CHILD’S SEX (please circle):  male  female

NAME OF PERSON COMPLETING THIS FORM: ___________________________

DATE: _______________________

Directions: Below is a list of items that describe pupils. For each item that describes the pupil now or within the past week please circle the relevant number (0, 1, 2) to indicate your answer. Please answer all items as well as you can, even if some do not seem to apply to this pupil.

<table>
<thead>
<tr>
<th></th>
<th>Not True</th>
<th>Somewhat or Sometimes True</th>
<th>Very or Often True</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fails to finish things he/she starts</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Can’t concentrate, can’t pay attention for long</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Can’t sit still, restless, or hyperactive</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. Fidgets</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. Daydreams or gets lost in his/her thoughts</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6. Impulsive or acts without thinking</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. Difficulty following directions</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8. Talks out of turn</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>9. Messy work</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10. Inattentive, easily distracted</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11. Talks too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12. Fails to carry out assigned tasks</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Please feel free to write any comments about the pupil’s work or behaviour in the last week on the reverse side of this page. Adapted from Barkley (1990)
APPENDIX K

Consent form for the initial face-to-face interview
INITIAL INTERVIEW CONSENT FORM

Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

Names of Investigators:
Ms Fiona Dey (Investigator)
Telephone: (03) 9925-7376
e-mail: s8210843@student.rmit.edu.au

Dr Andrew Francis (Senior Supervisor)
Telephone: (03) 9925-7782
e-mail: andrew.francis@rmit.edu.au

I agree to take part in the initial interview for the above project.

I understand that I will be asked to provide personal information regarding my child. I am aware that this interview is for the purpose of establishing whether or not my child is eligible to participate in the above study, and that my child may not be invited to participate.

I have been informed that all information I provide during this interview will be kept confidential and anonymous, and will be identifiable via identity code only.

I am aware that I may withdraw from this interview at any time.

Signature: __________________________________________

Date: __________________________

Witness: __________________________________________
APPENDIX L

Investigator’s form for the initial face-to-face interview
INITIAL INTERVIEW FORM (for completion by investigator)

Date: ________________________________

Child's Name: ________________________________________________________________

Date of Birth: _____________________ Current Age: ______________________

Names of Parent/s or Caregiver/s: ______________________________________________

Address: _____________________________________________________________________

___________________________________________________________________________

postcode ____________________________

Telephone: (H) ______________________ (W) ________________________________

School Grade/Year: ____________ School: ______________________________________

Address: _____________________________________________________________________

___________________________________________________________________________

postcode ____________________________

Telephone Number: ______________________________

Teacher's Name: ______________________________________________________________

Who gave the diagnosis of ADHD? ____________________________________________

Date: ____________ Profession: _________________________________________________ Form received: yes no

Medical Clearance Form completed: yes no

Medications: current __________________________________________________________

___________________________________________________________________________

___________________________________________________________________________

___________________________________________________________________________
supplements

Any other health problems?

Any allergies?

Any adverse reaction/s to any previously taken herbs?

Details of daytime behaviour problems:

Details of sleep problems:

Weight:
APPENDIX M

Sample letter to school principal
Dear *principal's name

I am a higher degree by research student in the Department of Psychology and Disability Studies at RMIT University. The major component of my research project is a clinical trial investigating the use of herbal medicines for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children. Please refer to the enclosed plain language statement for details.

I am writing to you in order to obtain your permission for a teacher at your school, *insert name, to participate in my research. *His/her participation would require the completion of the following teacher rating scales for *insert child's name, *insert child's name *insert as appropriate parent/s or caregiver/s *has/have given permission for *him/her to participate in this research.

The Conners Rating Scales-Revised (Teachers) will be used to obtain information regarding the child's behaviour. They are available in both long and short forms, and have been used extensively in medication trials. The long forms will be administered at the baseline (twice) and follow-up phases (once), and the short forms will be used during the treatment phase (monthly) and at post-treatment (once). At baseline the Conners scales will be administered twice in accordance with the usual protocol recommended in the literature. Time: long forms up to 20 minutes, short forms up to 10 minutes.

The Child Attention Problems (Edelbrock) scale, for teachers, was developed primarily for assessing stimulant drug effects. It will be completed on a weekly basis. Time: <5 minutes.

The timeline for the research is as follows:

Trial phases:
Baseline: 2 weeks
Treatment: 3 months
Post-treatment: 2 weeks after completion of treatment
Follow-up: 3 months after completion of post-treatment

An application regarding this project has been submitted to *insert the relevant education authority name. In addition the project has been approved by the RMIT University Human Research Ethics Committee.

Should you require any further information please do not hesitate to contact me.

Yours sincerely

Ms Fiona Dey
Telephone: (03) 9925-7376
Facsimile: (03) 9925-7303
email: s8210843@student.rmit.edu.au
APPENDIX N

Evidence of ADHD diagnosis form
ADHD DIAGNOSIS FORM

Project Title: Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

Names of Investigators:

Ms Fiona Dey
BBSc DipAppSc (Nursing) DipAppSc (Naturopathy) MNHAA
Investigator
Telephone: (03) 9925-7376
Facsimile: (03) 9925-7303
email: s8210843@student.rmit.edu.au

Dr Andrew Francis
BBSc (Hons) PhD
Senior Supervisor
Telephone: (03) 9925-7782
Facsimile: (03) 9925-7303
email: andrew.francis@rmit.edu.au

This form is to be completed by a paediatrician, psychiatrist, or psychologist.

I ____________________________ (name of practitioner) have

diagnosed ____________________________ (name of participant) as having

Attention Deficit Hyperactivity Disorder (ADHD) according to DSM-IV criteria.

Practitioner's Signature: ____________________________

Qualifications: ________________________________________________

______________________________________________

Address: ________________________________________________

Telephone: ____________________________

Date: ____________________________
APPENDIX O

Medical practitioner clearance form
MEDICAL PRACTITIONER CLEARANCE FORM

Project Title: Phytomedicines as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

Names of Investigators:
Ms Fiona Dey
BBSc DipAppSc (Nursing) DipAppSc (Naturopathy) MNHAA
Investigator
Telephone: (03) 9925-7376
Facsimile: (03) 9925-7303
email: s8210843@student.rmit.edu.au

Dr Andrew Francis
BBSc (Hons) PhD
Senior Supervisor
Telephone: (03) 9925-7782
Facsimile: (03) 9925-7303
email: andrew.francis@rmit.edu.au

I ____________________________ (name of medical practitioner) have examined ____________________________ (name of participant).

I have also read a description of the proposed research study and understand that participants may be given herbal medicine preparations.

In my opinion there is no medical problem present, or current medications being taken, that suggest that this child should not participate.

Medical Practitioner's Signature: ____________________________

Qualifications: ____________________________

______________________________

Address: ____________________________

Telephone: ____________________________

Date: ____________________________
APPENDIX P

Informed consent form
Prescribed Consent Form For Persons Participating In Research Projects Involving Tests and/or Procedures

RMIT UNIVERSITY Faculty of Applied Science Department of Psychology and Disability Studies

Project Title: Phytotherapeutics as pharmacological alternatives in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children.

Names of Investigators:
Ms Fiona Dey (Investigator)
Telephone: (03) 9925-7376 or 9925-7727 (mobile 0408 511 437)
email: s8210843@student.rmit.edu.au

Dr Andrew Francis (Senior Supervisor)
Telephone: (03) 9925-7782
e-mail: andrew.francis@rmit.edu.au

Name of Child Participant: ________________________________

Names of Parents or Guardians: ________________________________

1. I have received a statement explaining the tests or procedures involved in this project. This statement names the herbs to be used and includes information about their possible side effects and interactions.

2. I consent to participate in the above project, the particulars of which - including details of tests or procedures, and herbs - have been explained to me.

3. I authorise the investigator or his or her assistant to use with me the tests or procedures referred to in 1. above. I also give permission for my child's teacher to be contacted and to complete the checklists referred to in 1.

4. I acknowledge that:
   (a) The possible effects of the tests or procedures, and herbs, have been explained to me to my satisfaction.
   (b) I have been informed that I am free to withdraw my child from the project at any time.
   (c) The project is for the purpose of research and/or teaching. It may not be of direct benefit to me.
   (d) The confidentiality of the information I provide will be safeguarded. However should information of a confidential nature need to be disclosed for moral, clinical or legal reasons, I will be given an opportunity to negotiate the terms of this disclosure.
   (e) The security of the research data is assured during and after completion of the study. The data collected during the study may be published, and a report of the project outcomes will be provided to MediHerb Pty Ltd. Any information which will identify me will not be used.

Where participant is under 18 years of age:

I consent to the participation of ________________________________ in the above project.

Signature: ___________________________________ Date: __________________

Signature: ___________________________________ Date: __________________
(Signatures of parents or guardians)

Signature: ___________________________________ Date: __________________
(Witness to signature)

Participants should be given a photocopy of this consent form after it has been signed.

Any complaints about your participation in this project may be directed to the Secretary, RMIT Human Research Ethics Committee, University Secretariat, RMIT, GPO Box 2476V, Melbourne Vic 3001. The telephone number is (03) 9925-1745.
APPENDIX Q

Case report/record form
CASE REPORT/RECORD FORM

Subject's Name ________________________________

Evidence of ADHD Diagnosis received ________________________

Medical Clearance Form received ________________________

Informed Consent obtained ________________________

Data Collection Points (measures and dates)

BASELINE: TWO WEEKS

commence ____________________ conclude ________________________

1. TOVA ____________________
2. QEEG ______________________
3. CBCL ______________________
4. Conners Parents long (twice) first ____________________ second ____________________
5. Conners Teachers long (twice) first ____________________ second ____________________
6. sleep diary daily 14 days

8. CAP ______________________

TREATMENT: THREE MONTHS

commence ____________________ conclude ________________________

3. CBCL end of phase only ______________________
4. Conners Parents short monthly first ____________________ second ____________________

third ______________________
5. Conners Teachers short monthly first ____________________ second ____________________

third ______________________
6. sleep diary daily 90 days

7. side effects scale weekly 12 weeks

8. CAP weekly 12 weeks
POSTTREATMENT: TWO WEEKS AFTER TREATMENT

commence ____________________  conclude ____________________

1. TOVA ____________________
2. QEEG ____________________
3. Conners Parents short ______________
4. Conners Teacher short _____________
5. sleep diary daily 14 days

7. side effects scale weekly 2 weeks first ____________________ second _____________
8. CAP ____________________

FOLLOWUP: THREE MONTHS AFTER POSTTREATMENT

commence ____________________  conclude ____________________

3. CBCL ____________________
4. Conners Parents long _____________
5. Conners Teacher long ______________
6. sleep diary daily 14 days

8. CAP ____________________

COURTESY TELEPHONE CALL: THREE MONTHS AFTER FOLLOWUP
(three months after all data collection completed)

date ____________________________
who spoke to _______________________________
comments __________________________________________

________________________________________________________________________

________________________________________________________________________
APPENDIX R
Definitions of the criteria used for the independent rating of the line graphs
Substantial change (SC): Data showing that for the behaviour there was a significant and consistent change across the phases of the trial. That is, the graph shows that the behaviour increased or decreased significantly, and that the direction of change was maintained.

Moderate change (MC): Data showing that for the behaviour there was a consistent change across the phases of the trial, and that the direction of change was maintained. However, the magnitude of change is not great enough for it to be considered substantial.

No change (NC): Data showing that there was no change in the behaviour across the phases of the trial.

Variability (V): Data showing fluctuation, or fluctuations, in the behaviour across the phases of the trial. That is, the behaviour changes, but the direction of the change is not consistent.

Cannot decide (CD): Cannot classify the behaviour according to one of the above criteria.

In addition, the independent rater devised the criterion Not enough data points (NED), which they used as a rating, and/or as a comment. Due to the lack of data points on some graphs they expressed their concern about being unable to reliably assess change. They also expressed concern about the graphs that had scales that did not commence at zero. Therefore, they only gave ratings for seven sets of line graphs (that is, for seven measures) out of 64: CBCL Problems Scales Externalising, CAP, and the five prime sleep variables.
APPENDIX S
Withdrawal report for participant 6
ADHD HERBAL TRIAL: REPORT TO RMIT HREC CONCERNING WITHDRAWAL OF PARTICIPANT SIX

Code Number: FDAF001-006
ADHD medication status: On medication – 10 mg Ritalin three times a day
Details: Male, 8 years of age
Date of starting trial: Commenced trial baseline phase on Sunday 10 October 2004 and commenced trial treatment phase (i.e. trial tablets) on Sunday 24 October 2004 at a dose of two tablets for each *product (i.e. two tablets morning and night) based on bodyweight as per protocol
*the trial was designed to test two herbal combinations, one given in the morning, the other at night

Date of withdrawal: I received a voicemail on my mobile from the mother on Monday 20 December 2004 (she left the message the day before) to say that she had ceased the tablets as they “seemed to be making his behaviour a lot worse”; I rang her, and left a message that I would call her the following day from RMIT as I would be able to talk to her at length, and would have his file

Code broken: On Tuesday 21 December 2004, after speaking to the mother (she had stopped the tablets on 16 December), I emailed Dr Andrew Francis to ask him to break the code for this child, and he replied that this child was on the placebo tablets; in the meantime I emailed Ms Adrienne Patterson to inform the HREC, and I also sent an email to Dr Reg Lehmann of MediHerb Pty Ltd (cc Drs Andrew Francis and John Reece) to inform him of the situation

Followup: I contacted the mother again by telephone later on Tuesday 21 December 2004 and informed her of the above, and reiterated that we should meet in January; I also contacted Dr Lehmann again to see if the tablets contained a preservative, as the mother said the child reacts to preservatives; he replied that the tablets contain no preservatives but that there is a brown colouring agent in them, and he later supplied me with the details of that - it is “brown chocolate as synthetic dyestuff Food Additive No. 155”; I tried a few times to call the mother in January; we met at RMIT on Tuesday 8 February 2005 and her son was present; at that meeting she returned all trial forms
(completed and uncompleted) and all remaining trial tablets; she said on Tuesday 21 December 2004 that his behaviour was a “little bit better” and at the RMIT meeting she commented that it was probably a few weeks before he settled down, and that he had been a “lot better” and was back on his previous supplements; she also commented that when she gave him the trial tablets around 15 to 30 minutes later he would be worse and would stay a “lot more hyperactive” and that it was like the reaction that he has to certain breads and other foods

Important points to note:

It appears that this child reacted to the placebo tablets, however there are confounding issues:

1. he went off certain supplements to go into the trial (in accordance with the trial exclusion criteria and the one month washout period), and both parents, his school teacher and the teacher’s aides, noticed a change in his behaviour at that stage
2. daylight saving affects his routine (his parents had said it always affects him), and it was the start of the Summer holidays, and almost Christmas when the tablets were stopped
3. his mother had been crushing the tablets and mixing them with Milo (this had been checked with project consultant Mr Kerry Bone of MediHerb Pty Ltd) and she wondered if it had been a case of “too much chocolate at once” as although he regularly has Milo he rarely has chocolate as such, because it affects his behaviour
4. the mother had health issues of her own at around the same time and was “sleep deprived”

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APPENDIX T

Detailed tables derived from the investigator's ratings of the line graphs, and the ratings given by the independent rater where applicable.
The criteria that were used in the rating of the line graphs were presented in Chapter 2, subsection 2.5.1, and Appendix R, and they are abbreviated as follows:

- **Substantial change** SC
- **Moderate change** MC
- **No change** NC
- **Variability** V
- **Cannot decide** CD
- **Not enough data points** NED

*Note.* The criterion *Not enough data points* was devised by the independent rater.

**CBCL**

The following tables present the results for the CBCL Competence Scales.

**Table T.1 CBCL Competence Scale - Activities**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour deteriorated initially, then improved. His follow-up score was better than his baseline score.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated, but not to the level of the baseline score.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The trend was towards deterioration, however the treatment phase data point was missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His score for the treatment phase remained the same as his baseline score, but then improved at the follow-up point.</td>
</tr>
</tbody>
</table>
### Table T.2 CBCL Competence Scale - Social

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved between baseline and treatment. His score at follow-up was the same as at treatment.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>NC</td>
<td>His score remained the same.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour deteriorated between baseline and treatment. It improved between treatment and follow-up, with the score at follow-up being better than at baseline.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated, however the treatment phase data point was missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>NC</td>
<td>His score remained the same.</td>
</tr>
</tbody>
</table>

### Table T.3 CBCL Competence Scale - School

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>NC</td>
<td>His behaviour remained the same.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved but then deteriorated to a level below baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>NC</td>
<td>His behaviour remained the same.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated between baseline and treatment, and then remained stable.</td>
</tr>
</tbody>
</table>
Table T.4 CBCL Competence Scale - Total Competence Score: the sum of the scores for Activities, Social, and School

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His score improved between baseline and treatment. His score at follow-up was the same as at baseline.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His score deteriorated between baseline and treatment, and improved at follow-up so as to be above baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated between baseline and treatment, but then improved. His follow-up score was almost the same as at baseline.</td>
</tr>
</tbody>
</table>

The following tables present the results for the CBCL Problem Scales.

Table T.5 CBCL Problem Scale I - Withdrawn

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved and then deteriorated, but not to the same level as at baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour improved and then deteriorated, but not to the same level as at baseline.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The trend was one of deterioration, however the treatment phase data point is missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated before improving. His follow-up score was better than his baseline score.</td>
</tr>
</tbody>
</table>
Table T.6 CBCL Problem Scale II - Somatic Complaints

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>His score improved between baseline and treatment, however the follow-up data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His score improved between baseline and treatment, and then remained stable.</td>
</tr>
<tr>
<td>3. Active</td>
<td>CD</td>
<td>His score improved between baseline and treatment, however the follow-up data point is missing.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The trend was one of deterioration however there are no data for the treatment phase.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

Table T.7 CBCL Problem Scale III - Anxious/Depressed

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved. His follow-up score was better than his baseline score.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated, although not to the same level as baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated to a level beyond that of baseline.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The baseline and follow-up scores were the same, however the treatment phase score is missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved. The score at follow-up was better than the score at baseline.</td>
</tr>
</tbody>
</table>
### Table T.8 CBCL Problem Scale IV - Social Problems

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved, although not to the same level as at baseline.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His treatment phase score was the same as his baseline score, and then his behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His baseline and follow-up scores were the same, and his behaviour deteriorated at the treatment phase.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour at follow-up was worse than at baseline, however the treatment phase data point is missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated between baseline and treatment, and then improved. The follow-up score was better than the baseline score.</td>
</tr>
</tbody>
</table>

### Table T.9 CBCL Problem Scale V - Thought Problems

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated, but not to the same level as baseline.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His treatment score was the same as his baseline score, however his behaviour improved at follow-up.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His behaviour at follow-up was worse than at baseline.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved. The follow-up score was the same as the baseline score.</td>
</tr>
</tbody>
</table>
Table T.10 CBCL Problem Scale VI - Attention Problems

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour deteriorated between baseline and treatment, and then remained stable.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>NC</td>
<td>His score stayed the same.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His score at follow-up was worse than his score at baseline.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved. His follow-up score was better than his baseline score.</td>
</tr>
</tbody>
</table>

Table T.11 CBCL Problem Scale VII - Delinquent Behaviour

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His score improved, and then deteriorated. His score at follow-up was worse than his score at baseline.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved. His score at follow-up was better than his score at baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His score at follow-up was worse than his score at baseline.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His score at treatment was the same as at baseline, however his behaviour improved at follow-up.</td>
</tr>
</tbody>
</table>
### Table T.12 CBCL Problem Scale VIII - Aggressive Behaviour

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved. The score at follow-up was the same as the treatment score.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated. His follow-up score was worse than his baseline score.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His follow-up score was better than his baseline score.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved. His follow-up score was better than his baseline score.</td>
</tr>
</tbody>
</table>

The following tables present the results of scores that are derived from more than one CBCL Problem Scale.

### Table T.13 CBCL Problem Scale - Internalising: the sum of the scales for Withdrawn, Somatic Complaints, and Anxious/Depressed, minus one duplicated item

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated, but not to the same level as at baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated, but not to the same level as at baseline.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His score at follow-up was worse than his baseline score.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated, but then improved to a point beyond baseline.</td>
</tr>
</tbody>
</table>
The following tables present the results for the CBCL Problem Scale - Externalising for both the investigator, and the independent rater.

**Table T.14a CBCL Problem Scale - Externalising: the sum of the scales for Delinquent Behaviour, and Aggressive Behaviour - Investigator**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour improved and then deteriorated, but not to the level of baseline.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved and then deteriorated, but not to the level of baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated to a level beyond that of baseline.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His behaviour at follow-up was better than his behaviour at baseline.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved to a level beyond that of baseline.</td>
</tr>
</tbody>
</table>

**Table T.14b CBCL Problem Scale - Externalising: the sum of the scales for Delinquent Behaviour, and Aggressive Behaviour - Independent Rater**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>NED</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>NED</td>
</tr>
<tr>
<td>3. Active</td>
<td>CD</td>
<td>NED</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>NED</td>
</tr>
<tr>
<td>5. Active</td>
<td>CD</td>
<td>NED</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No rating given</td>
<td>No comment made.</td>
</tr>
</tbody>
</table>
Table T.15 CBCL Problem Scale - Total Score: the sum of all Problem Scale items

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His score improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His score improved, but then deteriorated to approximately the same level as baseline.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His score improved, but then deteriorated to approximately the same level as baseline.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The treatment phase data point is missing. His score at follow-up was worse than his score at baseline.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His score deteriorated, but then improved to a level beyond that of baseline.</td>
</tr>
</tbody>
</table>

**CPRS-R**

The following tables present the results for the CPRS-R:L.

Table T.16 CPRS-R:L Subscale A. Oppositional

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
Table T.17 CPRS-R:L Subscale B. Cognitive Problems/Inattention

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>

Table T.18 CPRS-R:L Subscale C. Hyperactivity

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
Table T.19 CPRS-R:L Subscale D. Anxious-Shy

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

Table T.20 CPRS-R:L Subscale E. Perfectionism

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
### Table T.21 CPRS-R:L Subscale F. Social Problems

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

### Table T.22 CPRS-R:L Subscale G. Psychosomatic

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

### Table T.23 CPRS-R: L Subscale H. Conners’ ADHD Index

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>

### Table T.24 CPRS-R: L Subscale I. Conners’ Global Index: Restless-Impulsive

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
Table T.25 CPRS-R:L Subscale J. Conners' Global Index: Emotional Lability

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

Table T.26 CPRS-R:L Subscale K. Conners' Global Index: Total

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
### Table T.27 CPRS-R:L Subscale L. DSM-IV: Inattentive

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>

### Table T.28 CPRS-R:L Subscale M. DSM-IV: Hyperactive-Impulsive

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
### Table T.29 CPRS-R:L Subscale N. DSM-IV: Total

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>

The following tables present the results for the CPRS-R:S.

### Table T.30 CPRS-R:S Subscale A. Oppositional

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated, although not to the level of month one.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated. However, the overall trend was one of improvement.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated, however the overall trend was one of deterioration.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
### Table T.31 CPRS-R:S Subscale B. Cognitive Problems/Inattention

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated, however the overall trend was one of deterioration.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated to a level beyond that of month one.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated, and the overall trend was one of deterioration.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of deterioration, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>

### Table T.32 CPRS-R:S Subscale C. Hyperactivity

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated, however the overall trend was one of improvement.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour deteriorated, and then improved, although not to the level of month one.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour deteriorated in month three.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of deterioration, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
### Table T.33 CPRS-R:S Subscale D. Conners' ADHD Index

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of deterioration, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>

The following tables present the results of the T-scores for the CPRS-R across the entire trial.

### Table T.34 CPRS-R:T-scores Subscale A. Oppositional

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved and then deteriorated, although not to the level of baseline. The follow-up data point is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated, however the overall trend was one of improvement.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour improved initially, and then deteriorated. The remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
Table T.35 CPRS-R: T-scores Subscale B. Cognitive Problems/Inattention

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>His behaviour improved initially, and then deteriorated. The follow-up data point is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, and then improved, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour improved initially, and then deteriorated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>

Table T.36 CPRS-R: T-scores Subscale C. Hyperactivity

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and the follow-up data point is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour was stable, and then it improved. The remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
Table T.37 CPRS-R: T-scores Subscales H. (long form) & D. (short form) Conners’ ADHD Index

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>Most data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated initially, and the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>

**CTRS-R**

The following tables present the results for the CTRS-R:L.

Table T.38 CTRS-R:L Subscale A. Oppositional

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>Participant number and treatment</td>
<td>Rating</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>1. Active</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
<tr>
<td>3. Active</td>
<td>SC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
### Table T.41 CTRS-R:L Subscale D. Anxious-Shy

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
</tbody>
</table>

### Table T.42 CTRS-R:L Subscale E. Perfectionism

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>
### Table T.43 CTRS-R:L Subscale F. Social Problems

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

### Table T.44 CTRS-R:L Subscale H. Conners’ ADHD Index

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
### Table T.45 CTRS-R:L Subscale I. Conners’ Global Index: Restless-Impulsive

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

### Table T.46 CTRS-R:L Subscale J. Conners’ Global Index: Emotional Lability

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>SC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>3. Active</td>
<td>SC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
### Table T.47 CTRS-R:L Subscale K. Conners’ Global Index: Total

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

### Table T.48 CTRS-R:L Subscale L. DSM-IV: Inattentive

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
</tbody>
</table>
Table T.49 CTRS-R:L Subscale M. DSM-IV: Hyperactive-Impulsive

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>NC</td>
<td>There was no change.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>

Table T.50 CTRS-R:L Subscale N. DSM-IV: Total

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>MC</td>
<td>His behaviour deteriorated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved.</td>
</tr>
</tbody>
</table>
The following tables present the results for the CTRS-R:S.

Table T.51 CTRS-R:S Subscale A. Oppositional

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>The trend was one of improvement, however the post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>The data point for the month three is missing, otherwise there was no change.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>The data point for the month one is missing. The remaining data shows deterioration in behaviour, followed by some improvement.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>The overall trend was one of improvement.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of deterioration, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>

Table T.52 CTRS-R:S Subscale B. Cognitive Problems/Inattention

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>The trend was one of improvement, however the post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>Blank</td>
<td>No graph.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour improved, and the improvement was maintained.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>Blank</td>
<td>No graph as he withdrew.</td>
</tr>
<tr>
<td>Participant number and treatment</td>
<td>Rating</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated, and the post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>The trend was one of improvement, however the data point for month three is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>The initial trend was one of deterioration, however this was followed by improvement.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour was unchanged initially, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>The trend was one of improvement, followed by some deterioration at post-treatment.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing as he withdrew.</td>
</tr>
<tr>
<td>Participant number and treatment</td>
<td>Rating</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated. The post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated. The month three data point is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>CD</td>
<td>His behaviour deteriorated, and then appears to have remained unchanged, however the month three data point is missing.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour deteriorated initially, and then remained stable.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however the remaining data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
The following tables present the results of the $T$-scores for the CTRS-R across the entire trial.

**Table T.55 CTRS-R: $T$-scores Subscale A. Oppositional**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated, and the post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>The month three data point is missing. His other scores were stable.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>There was initial deterioration, followed by improvement, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>His behaviour was unchanged until it improved between post-treatment and follow-up.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>Most of the data points are missing due to his withdrawal.</td>
</tr>
</tbody>
</table>

**Table T.56 CTRS-R: $T$-scores Subscale B. Cognitive Problems/Inattention**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour improved, and then deteriorated. The post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however half of the data points are missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however half of the data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>The overall trend was one of deterioration.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>There was an initial improvement in his behaviour, however half of the data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
### Table T.57 CTRS-R: T-scores Subscale C. Hyperactivity

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>His behaviour improved initially, and then fluctuated. The post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and the month three data point is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>The initial trend was one of deterioration. Half of the data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>MC</td>
<td>The overall trend was one of improvement.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>His behaviour improved initially, however half of the data points are missing due to his withdrawal.</td>
</tr>
</tbody>
</table>

### Table T.58 CTRS-R: T-scores Subscales H. (long form) & D. (short form) Conners’ ADHD Index

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>His behaviour improved, and then deteriorated. The post-treatment data point is missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>His behaviour fluctuated, and the month three data point is missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>CD</td>
<td>The overall trend was one of deterioration, however the month three data point is missing.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>CD</td>
<td>His behaviour deteriorated, and then improved, however the remaining data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>The initial trend was one of improvement, however half of the data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
**CAP**

The following tables present the results for the CAP for both the investigator, and the independent rater.

**Table T.59a CAP - Investigator**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>V</td>
<td>Several of the data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
### Table T.59b CAP - Independent Rater

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>overall=V</td>
<td>baseline vs treatment=MC, baseline vs post-treatment=NC, baseline vs follow-up=NC</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>overall=NC</td>
<td>important to start from 0 on Y axis, baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up=NC</td>
</tr>
<tr>
<td>3. Active</td>
<td>overall=MC</td>
<td>baseline vs treatment=MC, baseline vs post-treatment=MC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>overall=MC</td>
<td>baseline vs treatment=MC</td>
</tr>
<tr>
<td>5. Active</td>
<td>NC</td>
<td>on a scale beginning with 0 this would look very different</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=MC</td>
</tr>
</tbody>
</table>

### Sleep Diary

The following tables present the results for the five prime sleep variables derived from the Sleep Diary for both the investigator, and the independent rater.

### Table T.60a Sleep Latency - Investigator

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing as he withdrew.</td>
</tr>
</tbody>
</table>
**Table T.60b Sleep Latency - Independent Rater**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>overall=NC</td>
<td>if this is the same measure, would be best to have the same scale for all, baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up=NC</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>overall=SC</td>
<td>baseline vs treatment=SC, baseline vs post-treatment=SC, baseline vs follow-up=SC</td>
</tr>
<tr>
<td>3. Active</td>
<td>overall=V?</td>
<td>baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up=SC</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>overall=MC</td>
<td>baseline vs treatment=SC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>5. Active</td>
<td>overall=MC</td>
<td>baseline vs treatment=MC, baseline vs post-treatment=MC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC</td>
</tr>
</tbody>
</table>

**Table T.61a Number of Times Awake - Investigator**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>Some awakenings occurred during baseline and treatment.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>Some awakenings occurred in the treatment phase.</td>
</tr>
<tr>
<td>3. Active</td>
<td>CD</td>
<td>Some awakenings occurred in the baseline phase.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>NC</td>
<td>The graph is blank, and some data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>Numerous awakenings were noted, however his behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>Some awakenings were recorded initially, however he later withdrew from the trial.</td>
</tr>
<tr>
<td>Participant number and treatment</td>
<td>Rating</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>1. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NED</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NED</td>
</tr>
<tr>
<td>3. Active</td>
<td>NED</td>
<td>No comment made.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>NED</td>
<td>No comment made.</td>
</tr>
<tr>
<td>5. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC</td>
</tr>
</tbody>
</table>
### Table T.62a Total Time Awake - Investigator

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>CD</td>
<td>Some of his awakenings lasted for 10 minutes.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>CD</td>
<td>Some of his awakenings lasted for 10 minutes.</td>
</tr>
<tr>
<td>3. Active</td>
<td>CD</td>
<td>The longest time he was awake for was 5 minutes, and this occurred during the baseline phase.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>NC</td>
<td>The graph is blank, and some data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>CD</td>
<td>There were many awakenings, and the longest time he was awake for was 120 minutes.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>There were some initial awakenings, and the longest time he was awake for was 5 minutes. He later withdrew from the trial.</td>
</tr>
</tbody>
</table>

### Table T.62b Total Time Awake - Independent Rater

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>NED</td>
<td>no baseline</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>NED</td>
<td>No comment made.</td>
</tr>
<tr>
<td>3. Active</td>
<td>NED</td>
<td>No comment made.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>NED</td>
<td>No comment made.</td>
</tr>
<tr>
<td>5. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=SC, baseline vs post-treatment=MC</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC</td>
</tr>
</tbody>
</table>
**Table T.63a Total Sleep Time - Investigator**

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing as he withdrew.</td>
</tr>
<tr>
<td>Participant number and treatment</td>
<td>Rating</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1. Active</td>
<td>No overall rating given</td>
<td>axes need to start at 0, baseline vs treatment= MC, baseline vs post-treatment=NC, baseline vs follow-up=NC</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up = NC</td>
</tr>
<tr>
<td>3. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, baseline vs post-treatment = NC, baseline vs follow-up=NC</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=SC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>5. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, V</td>
</tr>
</tbody>
</table>

*Table T.63b Total Sleep Time - Independent Rater*
Total T.64a Overall Sleep Quality - *Investigator*

<table>
<thead>
<tr>
<th>Participant number and treatment</th>
<th>Rating</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>3. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>V</td>
<td>His behaviour fluctuated, and some of the data points are missing.</td>
</tr>
<tr>
<td>5. Active</td>
<td>V</td>
<td>His behaviour fluctuated.</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>CD</td>
<td>There was some initial fluctuation, and he later withdrew from the trial.</td>
</tr>
<tr>
<td>Participant number and treatment</td>
<td>Rating</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>1. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, treatment vs post-treatment=MC, treatment vs follow-up=MC</td>
</tr>
<tr>
<td>2. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=MC, treatment vs post-treatment=MC, treatment vs follow-up=MC</td>
</tr>
<tr>
<td>3. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>4. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=MC, baseline vs post-treatment=NED, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>5. Active</td>
<td>No overall rating given</td>
<td>baseline vs treatment=NC, baseline vs post-treatment=NC, baseline vs follow-up=MC</td>
</tr>
<tr>
<td>6. Placebo</td>
<td>No overall rating given</td>
<td>baseline vs treatment=MC</td>
</tr>
</tbody>
</table>