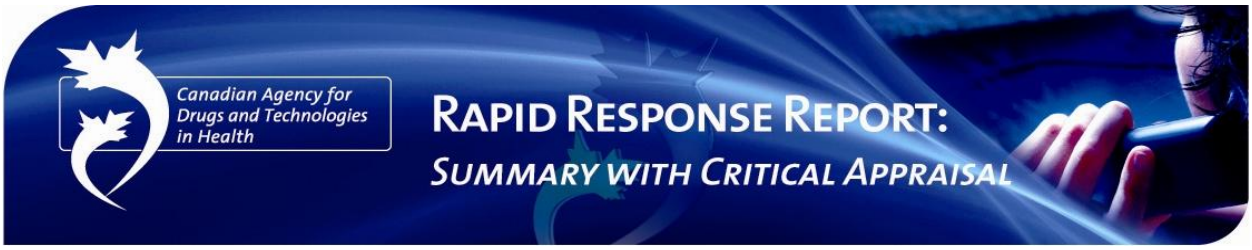

TITLE: Tricyclic Antidepressants, Clonidine, Venlafaxine, and Modafinil for the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: A Review of the Clinical Evidence

DATE: 21 March 2013

CONTEXT AND POLICY ISSUES

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder with inappropriate levels of inattention, hyperactivity, and impulsivity manifesting in childhood and continuing into adulthood, resulting in functional impairment in academic, family and social settings.[1] The prevalence of ADHD in the general population is approximately 3% to 4%.[2,3] while it affects approximately 4.4 percent of American adults.[4]

Stimulants such as methylphenidate and amphetamine are first line agents and a major component of pharmacotherapy in children and adults with ADHD, but the addictive character of stimulants and the chronic nature of ADHD can lead to abuse potential and side effects in many organs including the cardiovascular system.[5,6] Approximately 10 to 30% of patients do not respond optimally to stimulant therapy due to adverse events, lack of efficacy or non-adherence to treatment.[7] Non-stimulant therapy with atomoxetine, tricyclic antidepressants (TCAs), clonidine, and venlafaxine has been used as an alternative approach in the treatment of ADHD.[8-11] A novel non-traditional stimulant, wakefulness-promoting compound modafinil, has also been used in the treatment of ADHD with low-abuse potential.[12,13]

This report aims to review to clinical effectiveness of non-stimulants (TCA, clonidine, venlafaxine) and modafinil for the treatment of adults with ADHD.

RESEARCH QUESTIONS

1. What is the clinical efficacy of tricyclic antidepressants (TCAs) for the treatment of adults with ADHD?

2. What is the clinical efficacy of clonidine for the treatment of adults with ADHD?

3. What is the clinical efficacy of venlafaxine for the treatment of adults with ADHD?

4. What is the clinical efficacy of modafinil for the treatment of adults with ADHD?

KEY MESSAGE

Findings from available evidence showed a reduction in ADHD symptoms from baseline values for patients receiving either venlafaxine or placebo but the difference between the two groups was not statistically significant, despite a larger number of patients on venlafaxine who met treatment response criteria. The efficacy of modafinil in reducing ADHD symptoms is not significantly different than d-amphetamine, and the superiority of modafinil over placebo is not consistent across trials. There was no evidence on the clinical effectiveness of TCAs and clonidine in the treatment of adults with ADHD. Limited and short-term evidence caution the interpretation of the findings. Randomized controlled studies with extended follow-up periods are needed to confirm the lasting beneficial effects of non-stimulants in the long term and to guide treatment decisions.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, Ovid PsychINFO, The Cochrane Library (2013, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1998 and February 21, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults with ADHD
Intervention	TCAs Clonidine Venlafaxine Modafinil
Comparator	Usual care Other ADHD medications Placebo
Outcomes	Clinical effectiveness: symptom reduction, quality of life, adverse events, abuse potential
Study Designs	Health technology assessments, systematic reviews, meta-analyses and randomized controlled trials (RCTs)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 1998, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included randomized studies was assessed using the Downs and Black checklist.[14]

Numeric scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 99 citations. One additional study was identified by searching the grey literature. After screening of abstracts, 23 potentially relevant studies were selected for full-text review.

Three studies[15-17] were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 2.

Study design

This report included three randomized, placebo-controlled studies that examined the clinical efficacy of venlafaxine[15] and modafinil.[16,17] One study on modafinil was a three-phase cross-

over study with 2-week drug treatments separated by 4-day washout periods.[17] Length of follow-up was 6 weeks in one study,[15] and 9 weeks in one study.[16]

Population

The study on venlafaxine included 42 adults with ADHD.[15] The studies on modafinil included 22 and 330 adults with ADHD, respectively.[16,17] All patients met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria for adult ADHD.

Interventions and comparators

The study on venlaxafine compared its efficacy to placebo,[15] and the studies on modafinil compared its efficacy to placebo,[16] or to both placebo and dextroamphetamine.[17]

Outcomes

The three included studies measured the improvements in ADHD symptoms and the tolerability of the drugs, using different scales such as the Conners Adult ADHD Rating Scale (CAARS),[15] the Adult ADHD Investigator Symptom Rating Scale (AISRS),[16] or the Diagnostic and Statistical Manual of Mental Disorder Behavior Checklist for Adults (DSM-IV ADHD).[17]

Summary of Critical Appraisal

In general, the included studies were randomized, double-blind, placebo-controlled trials, with their inherent strengths such as reduced potential for selection bias and increased internal validity. The studies had hypotheses, main interventions and outcomes clearly described. None of the studies included a power calculation to determine whether the study size was large enough to detect clinically important effects. The scales used to measure the efficacy of the treatment options were different between trials, varying from CAARS[15] to AISRS[16] and DSM-IV ADHD Checklist, making the comparisons between trials uncertain. The small size of the included trials limits the generalizability of the findings. Finally, the study periods were from 6 weeks[15,17] to 9 weeks,[16] which may be too short to see a lasting effect of the treatment on a chronic disorder such as ADHD.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. <u>What is the clinical efficacy of tricyclic antidepressants for the treatment of adults with ADHD?</u>

The literature search did not identify any study comparing the clinical efficacy of tricyclic antidepressants for the treatment of adults with ADHD.

2. <u>What is the clinical efficacy of clonidine for the treatment of adults with ADHD?</u>

The literature search did not identify any study comparing the clinical efficacy of clonidine for the treatment of adults with ADHD

3. What is the clinical efficacy of venlafaxine for the treatment of adults with ADHD?

One randomized, double-blind, placebo-controlled trial examined the efficacy and tolerability of venlafaxine (titrated to a maximum of 225mg/day) for the treatment of adults with ADHD.[15] Changes in ADHD symptoms compared to baseline values, using the Conners Adult ADHD Rating Scale (CAARS), treatment responses (defined as a 25% drop in ADHD index), and adverse event rates were measured after 6 weeks of treatment. Findings showed the efficacy of the non-stimulant drug venlafaxine to reduce ADHD symptoms but failed to demonstrate its superiority over placebo.

Data found there was a statistically significant decrease in ADHD symptoms such as inattentive symptoms and hyperactive/impulsive symptoms in both the venlafaxine group and the placebo group compared to baseline values after 6 weeks of treatment. However, the differences between the two groups were not statistically significant. A greater number of patients achieved a treatment response after 6 weeks with venlafaxine (75%) compared with placebo (19%). This difference was statistically significant. There were no serious adverse events reported in both groups during the trial, and there were no statistically significant differences in weight or blood pressure in both groups compared to baseline values, while sexual dysfunction occurred in 2 patients with venlafaxine and in none with placebo.

4. What is the clinical effectiveness of modafinil for the treatment of adults with ADHD?

Two randomized, double-blind, placebo-controlled trials studied the efficacy and safety of modafinil for the treatment of adults with ADHD.[16,17] One study measured the changes in ADHD symptoms compared to baseline values using the Adult ADHD Investigator Symptom Rating Scale (AISRS) and the Adult ADHD Self-Report Scale (ASRS) and adverse event rates after 9 weeks of treatment with different doses of modafinil (from 255mg/day to 510mg/day) or placebo.[16] One study measured the changes in ADHD symptoms compared to baseline values using the Diagnostic and Statistical Manual of Mental Disorders ADHD (DSM-IV ADHD) Checklist and adverse event rates after 6 weeks of treatment with modafinil (titrated to a maximum of 400mg/day), d-amphetamine (titrated to a maximum of 40mg/day), or placebo.[17] In general, the efficacy of modafinil in reducing ADHD symptoms is not statistically significant different than d-amphetamine, and the superiority of modafinil over placebo is not consistent across trials.

Findings from the first trial[16] showed there were no statistically significant differences in ADHD symptoms (determined by both AISRS and ASRS scores) between the modafinil groups at any dose or the placebo group compared to the baseline values after 9 weeks of treatment. The differences between the treatment groups and the placebo group were also not statistically significant. Patients receiving modafinil at any dose experienced more adverse events such as headache, insomnia and nervousness than those with placebo, which led to a withdrawal rate of 27% of patients in the modafinil group and 8% of patients in the placebo group, though overall a similar number of patients in each group experienced at least one adverse event. The statistical significance of differences in adverse event rates was not reported. Findings from the second trial[17] showed that both modafinil and d-amphetamine provided a statistically significant reduction in ADHD symptoms (determined by DSM-IV ADHD Checklist) as compared to

placebo after 6 weeks of treatment. Compared to patients with d-amphetamine, those with modafinil experienced less hyperactivity and inattention symptoms, but the differences were not statistically significant. There were no statistically significant differences between modafinil, d-amphetamine or placebo groups in adverse event rates such as insomnia, irritability and muscle tension.

Limitations

The limited number of studies included in the review cautions the interpretation of the findings, and limits the generalizability. The included trials had 6 to 9 weeks of follow up, therefore it is not certain if the effects of non-stimulants and modafinil can be maintained with long-term administration. There were no studies on clinical effectiveness of TCAs and clonidine in the treatment of adults with ADHD.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited evidence showed the efficacy of non-stimulant drug venlafaxine to reduce ADHD symptoms but failed to demonstrate its superiority over placebo, despite a larger number of patients on venlafaxine meeting treatment response criteria. The efficacy of modafinil in reducing ADHD symptoms is not significantly different than d-amphetamine, and the superiority of modafinil over placebo is not consistent across trials. There was no evidence on clinical effectiveness of TCAs and clonidine in the treatment of adults with ADHD. Limited and short-term evidence caution the interpretation of the findings. A systematic review and meta-analysis performed by CADTH in 2011 on pharmacological and non-pharmacological therapies for adults with ADHD also failed to identify studies on comparative effectiveness of TCAs.[18]

Despite the fact that non-stimulants were expected to reduce the side effects caused by stimulants leading to improvement in ADHD treatment effectiveness, a systematic review and indirect comparison meta-analysis based on placebo-controlled RCTs found that neither the non-stimulants atomoxetine and bupropion or long-acting stimulants reduced adverse events compared to short-acting stimulants in adults with ADHD.[19] The improvements in effectiveness or adverse event profiles of non-stimulants (in which TCAs, venlafaxine and clonidine belong) and long-acting stimulants over short-acting stimulants were not evident in this study.

Based on our review findings and the available evidence, current best evidence supports the use of stimulants as first-line treatment for most adults with ADHD, as mentioned in the NICE clinical guideline issued in 2008.[20] The guideline stated on page 31:

1.7.1.5 Following a decision to start drug treatment in adults with ADHD, methylphenidate should normally be tried first.

1.7.1.6 Atomoxetine or dexamfetamine should be considered in adults unresponsive or intolerant to an adequate trial of methylphenidate (this should usually be about 6 weeks)[11]. Caution should be exercised when prescribing dexamfetamine to those likely to be at risk of stimulant misuse or diversion.

Randomized controlled studies with extended follow-up periods are needed to confirm the lasting beneficial effects of non-stimulants in the long term. Studies of different pharmacological treatment options on different ADHD subgroup populations based on ADHD subtypes or comorbidities will also help in tailoring therapeutic modalities and guide treatment decisions.

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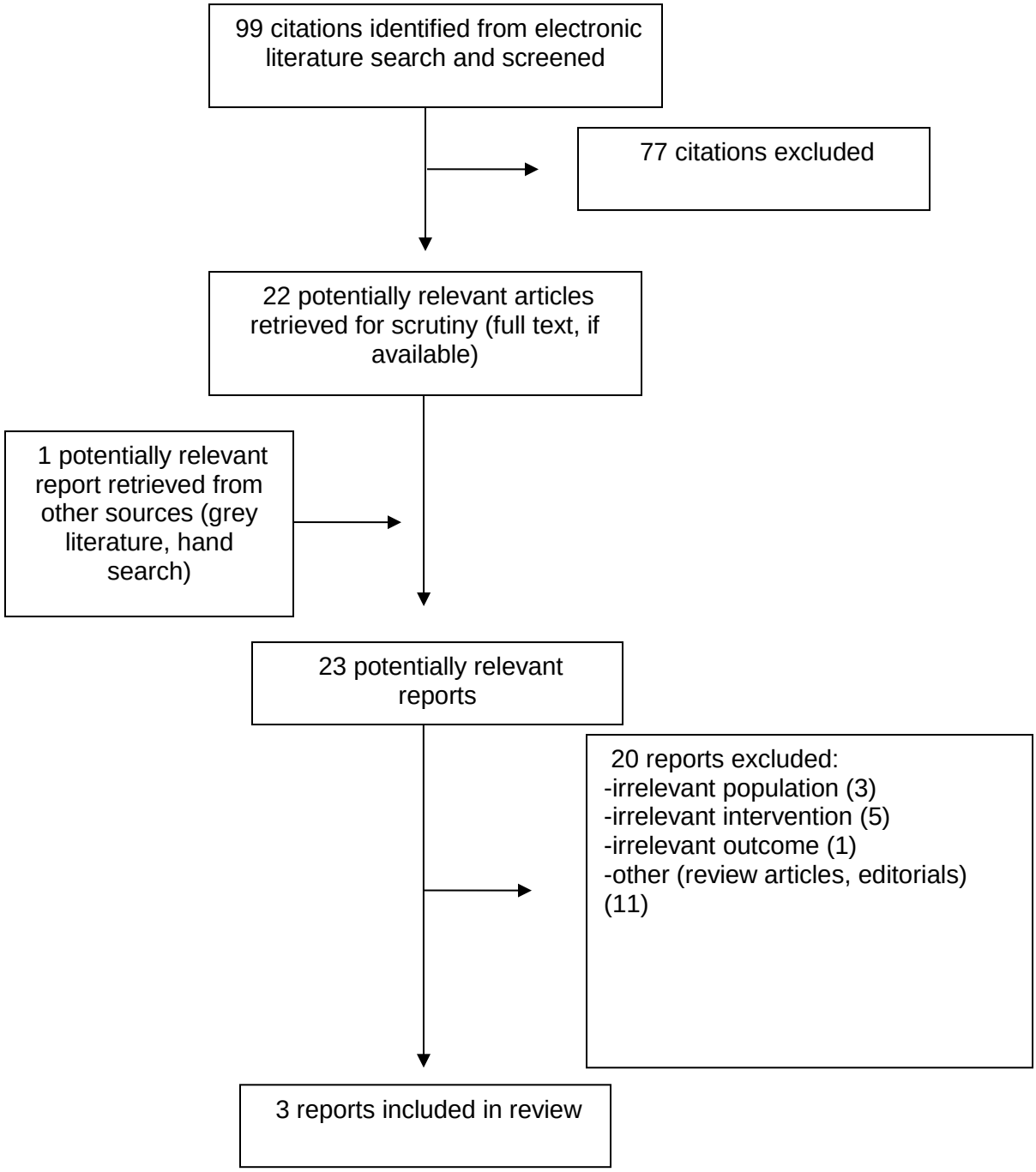
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included studies

First Author, Year, Country,	Study objectives,	Intervention Comparator(s)	Included patients Study types Length of follow-up	Main clinical outcomes reported
Amiri,[15] 2012 Iran	"*The purpose of this study was to evaluate the possible therapeutic effect of venlafaxine in adults with ADHD*" (p 76)	Venlafaxine Placebo	44 adults with ADHD (mean age 30.5) (22 patients in each group) Randomized, double-blind, placebo-controlled study 6 weeks	Improvement in ADHD symptoms measured by the Conners Adult ADHD Rating Scale (CAARS) (inattentive symptoms, hyperactive/impulsive symptoms, total ADHD symptom score, ADHD index) Safety (adverse effects)
Arnold,[16] 2012 US	"*This study evaluated the efficacy and tolerability of modafinil at a range of doses, versus placebo, in alleviating symptoms of ADHD in adults*" (p 1)	Modafinil Placebo	338 adults with ADHD (mean age 39.3) (264 patients in modafinil groups, 74 patients in placebo group) Randomized, double-blind, placebo-controlled study 9 weeks	Improvement in ADHD symptoms measured by the Adult ADHD Investigator Symptom Rating Scale (AISRS), the Adult ADHD Self-Report Scale (ASRS) Safety (adverse effects)
Taylor,[17] 2000 US	"*Our objective was to compare the efficacy of the new wake-promoting drug modafinil to that of dextroamphetamine for the treatment of attention deficit hyperactivity disorder (ADHD) in adults*" (p 311)	Modafinil Dextroamphetamine Placebo	22 adults with ADHD (median age 43) (cross-over study) Randomized, double-blind, placebo-controlled, cross-over study 6 weeks	Improvement in ADHD symptoms measured by the DSM-IV ADHD Behavior Checklist for Adults, the Controlled Oral Word Association Test (COWAT), Stroop and Digit Span Safety (adverse effects)

ADHD: attention-deficit/hyperactivity disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th edition)

Appendix 3: Summary of Critical Appraisal of Included Studies

Table A2: Summary of Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Amiri, [15]2012	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • patients randomized • randomization assignment was concealed • estimates of random variability and actual probability values provided • losses to follow-up described • study subjects and investigators were blinded to the intervention that they received	• uncertain whether study had sufficient power to detect a clinically important effect
Arnold,[16] 2012	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • patients randomized • estimates of random variability and actual probability values provided • losses to follow-up described • study subjects and investigators were blinded to the intervention that they received	• uncertain whether randomization assignment was concealed • uncertain whether study had sufficient power to detect a clinically important effect
Taylor,[17] 2000	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • patients randomized • estimates of random variability and actual probability values provided • losses to follow-up described • study subjects and investigators were blinded to the intervention that they received	• uncertain whether randomization assignment was concealed • uncertain whether study had sufficient power to detect a clinically important effect

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness of tricyclic antidepressants)		
There were no studies identified for this research question		
Research question 2 (clinical effectiveness of clonidine)		
There were no studies identified for this research question		
Research question 3 (clinical effectiveness of venlafaxine)		
Amiri,[15] 2012	**Change in ADHD symptoms from baseline after 6 weeks** (CAARS) (mean, SD) Venlaxafine (maximum 225mg/day) Inattentive symptoms: 25.35 (1.95) Hyperactive/impulsive symptoms: 26.60 (10.78) ADHD symptoms total: 28.80 (12.21) ADHD index: 25.35 (12.47) Placebo Inattentive symptoms: 14.65 (12.72) Hyperactive/impulsive symptoms: 11.35 (11.87) ADHD symptoms total: 13.55 (12.83) ADHD index: 12.05 (6.01) The change in symptoms score from baseline in both fenlaxafine and placebo groups are statistically significant (*P*< 0.001) The changes between the 2 groups are not statistically significant (*P* >0.05) **Treatment response after 6 weeks** (25% drop in ADHD index) Venlafaxine (maximum 225mg/day) 75% of patients Placebo 19% of patients The differences between the 2 groups are statistically significant (*P* < 0.001) **Tolerability after 6 weeks** (adverse effects) No serious adverse events reported in both groups. No statistically significant changes in weight, systolic and diastolic blood pressure in both groups Dry mouth: in 50% of the venlafaxine group and 30% of the placebo group (difference between the 2 groups not statistically significant) Sexual dysfunction: reported in 2 patients receiving venlafaxine and none in the placebo group	"*In this double-blind trial, the symptoms of adult ADHD decreased after a 6-week trial of either venlafaxine or a placebo with no significant difference. However, a significant treatment response defined as a 25% drop in ADHD index (measured by a self-report scale) was achieved by venlafaxine"* (p 76) "*No serious adverse effects were reported during the trial*" (p 80)

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
Research question 4 (clinical effectiveness of modafinil)		
Arnold,[16] 2012	**Change in ADHD symptoms from baseline after 9 weeks** (AISRS, ASRS) Changes in the AISRS total score (mean) Modafinil 255mg/day: -10.8 Modafinil 340mg/day: -13.8 Modafinil 425mg/day: -11.2 Modafinil 510mg/day: -10.1 Placebo: -12.0 No statistically significant differences between modafinil and placebo groups Changes in the ASRS total score (mean, SD) Modafinil 255mg/day: -10.7 (14,59) Modafinil 340mg/day: -14.1 (14.89) Modafinil 425mg/day: -11.6 (13.64) Modafinil 510mg/day: -10.6 (13.76) Placebo: -13.1 (15.03) No statistically significant differences between modafinil and placebo groups **Tolerability after 9 weeks** (adverse effects) 86% of all modafinil patients and 85% of the placebo patients experienced at least 1 adverse event Headache All modafinil: 30% of patients Placebo: 21% of patients Insomnia All modafinil: 28% of patients Placebo: 11% of patients Nervousness All modafinil: 21% of patients Placebo: 10% of patients Statistical significance not reported for differences in adverse event rates	"*Modafinil was reasonably tolerated but did not demonstrate a benefit on ADHD symptoms in adults"* (p 1)
Taylor,[17] 2000	**ADHD symptoms from baseline after 6 weeks** (using scales) Modafinil (maximum 400mg/day) DSM-IV ADHD Checklist - total (mean, SD) 18.3 (11.2) DSM-IV ADHD Checklist - hyperactivity subscore (mean, SD) 7.3 (6.4) DSM-IV ADHD Checklist - inattention subscore (mean, SD) 10.5 (5.3) d-amphetamine (maximum 40mg/day)	"*Scores on the DSM-IV ADHD Checklist ($p < 0.001$) were significantly improved over the placebo condition following treatment with both active medications. Performance on the COWAT ($p < 0.05$) reached trend levels of significance. Both medications were generally well tolerated. This preliminary study*

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
	DSM-IV ADHD Checklist - total (mean, SD) 20.0 (11.3) DSM-IV ADHD Checklist - hyperactivity subscore (mean, SD) 9.0 (5.4) DSM-IV ADHD Checklist - inattention subscore (mean, SD) 11.0 (6.7) Placebo DSM-IV ADHD Checklist - total (mean, SD) 28.8 (10.0) DSM-IV ADHD Checklist - hyperactivity subscore (mean, SD) 12.2 (6.8) DSM-IV ADHD Checklist - inattention subscore (mean, SD) 16.6 (4.3) Modafinil vs d-amphetamine (DSM-IV ADHD Checklist – total) ANOVA F score: 0.36 ($P > 0.05$) Placebo vs modafinil (DSM-IV ADHD Checklist – total) ANOVA F score: 18.43 ($P < 0.001$) Placebo vs d-amphetamine (DSM-IV ADHD Checklist – total) ANOVA F score: 16.79 ($P < 0.001$) **ADHD symptoms from baseline after 6 weeks** (using cognitive tests) Modafinil (maximum 400mg/day) COWAT Test (mean, SD) 87.7 (9.3) Digit Span (forward) (mean, SD) 10.3 (2.3) Digit Span (backwardward) (mean, SD) 7.5 (2.5) Stroop-Color-Word (mean, SD) (51.6 (9.9) d-amphetamine (maximum 40mg/day) COWAT Test (mean, SD) 86.5 (10.6) Digit Span (forward) (mean, SD) 10.3 (2.3) Digit Span (backwardward) (mean, SD) 7.6 (2.3) Stroop-Color-Word (mean, SD) 52.0 (8.0) Placebo COWAT Test (mean, SD) 75.4 (25.0) Digit Span (forward) (mean, SD) 10.0 (2.7) Digit Span (backwardward) (mean, SD) 7.0 (2.0) Stroop-Color-Word (mean, SD) 48.1(8.6) Modafinil vs d-amphetamine (COWAT Test) ANOVA F score: 0.19 ($P > 0.05$) Placebo vs modafinil (COWAT TEST) ANOVA F score: 5.00 ($P < 0.05$) Placebo vs d-amphetamine (COWAT TEST) ANOVA F score: 6.28 ($P < 0.05$) **Tolerability after 6 weeks** (adverse effects) Insomnia (number of patients, percent) Modafinil: 4 (19%)	*suggests that modafinil may be a viable alternative to conventional stimulants for the treatment of adults with ADHD*" (p 311)

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
	d-amphetamine: 8 (38%) Placebo 4 (19%) Irritability (number of patients, percent) Modafinil: 4 (19%) d-amphetamine: 3 (14%) Placebo 2 (10%) Muscle tension (number of patients, percent) Modafinil: 4 (19%) d-amphetamine: 5 (24%) Placebo 1 (5%) No statistically significant differences between placebo and modafinil or d-amphetamine	

ADHD: attention-deficit/hyperactivity disorder; AISRS: Adult ADHD Investigator Symptom Rating Scale; ANOVA: analyses of variance; ASRS: Adult ADHD Self-Report Scale; CAARS: the Conners Adult ADHD Rating Scale; COWAT: the Controlled Oral Word Association Test; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th edition); SD: standard deviation; SD: standard deviation