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Drug treatment of ADHD (Attention-Deficit/Hyperactivity Disorder) in adults in Germany

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Drug treatment of ADHD (Attention Deficit/Hyperactivity Disorder) in Adults in Germany

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Index of abbreviations

AAQoL	Adult ADHD Quality of Life Scale
ADD	Attention deficit disorder
ADHD	Attention deficit/hyperactivity disorder
ADHD-RS	ADHD rating scale
ADSA	Attention deficit scale for adults
AE	Adverse event
AISRS	Adult ADHD Investigator Symptom Rating Scale
AMED	Allied and Complementary Medicine Database
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APA	American Psychiatric Association
ASRS v.1.1	Adult ADHD Self-report Scale v.1.1
ATX	Atomoxetine
BAADS	Brown ADD Scale
BIOSIS	Biosciences Information Service
BMBF	Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung)
BMI	Body Mass Index
Bp	Bupropion
BROWN-AS	Brown Adult Scale
BtMG	Narcotics Law (Betäubungsmittelgesetz)
CAARS	Conners Adult ADHD Rating Scale
CAARS-Inv	Conners Adult ADHD Rating Scale/Investigator-rated
CAARS-O	Conners Adult ADHD Rating Scale/Observer-rated
CAARS-S	Conners Adult ADHD Rating Scale/Self-rated
CAARS:Inv:SV	Conners Adult ADHD Rating Scale: Investigator-rated: Screening Version
CBA	Cost/benefit analysis
CC	Complete Condition
CCMed	Current Contents Medicine (database)
CDR	Cognitive Drug Research
CEA	Cost effectiveness analysis
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression/Improvement
CGI-I-ADHD	Clinical Global Impression Improvement Scale ADHD
CGI-O-S	Clinical Global Impression/Overall Severity
CGI-S	Clinical Global Impression/Severity of Illness subscale
CI	Confidence interval
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRD	Centre for Reviews and Dissemination
CUA	Cost/utility analysis

Index of abbreviations – continued

d	Strength of effect
DAHTA	German Agency for Health Technology Assessment (Deutsche Agentur für Health Technology Assessment)
DARE	Database of Abstracts of Review of Effects
DERP	Drug Effectiveness Review Project
DES	Discrete event simulation
DEX	Dextroamphetamine
Df	Degrees of freedom
DGPPN	German Society for Psychiatry, Psychotherapy and Nervous Diseases (Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde)
DIMDI	German Institute for Medical Documentation and Information (Deutsches Institut für Medizinische Dokumentation und Information)
DIQ	Documentation and Information System Quality Assurance (database) (Dokumentations- und Informationssystem Qualitätssicherung)
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM III	Diagnostic and Statistical Manual of Mental Disorders, Version 3
DSM III-R	Diagnostic and Statistical Manual of Mental Disorders, Revision 3
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, Version 4
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorder, Text Revision 4
EED	Economic Evaluation Database
ECG	Electrocardiogram
EMBASE	Excerpta Medica Database
ERIC	Education Resources Information Center (database)
ETHMED	Ethics in Medicine (database)
F	F-statistics
File No.:	File number
fMRI	Functional magnetic resonance imaging
GAF	Global assessment of functioning
German Scientific Working Group	German Scientific Working Group Technology Assessment for Health Care
GLM	Generalized linear model
gms	German Medical Science (database)
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
HAWIE-R	Hamburg-Wechsler intelligence test for adults
Heclinet	Health Care Literature Information Network (database)
HMO	Health maintenance organisation
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, 9th version
ICD-10	International Classification of Diseases, 10th version
ICER	Incremental cost effectiveness ratio
IPA	International Pharmaceutical Abstracts (database)
IQ	Intelligence quotient
IQWiG	Institute for Quality and Efficiency in Healthcare

Index of abbreviations – continued

ISSHP	Index to Social Sciences & Humanities Proceedings (database)
ISTP	Index to Scientific and Technical Proceedings (database)
ISTPB	Index to Scientific and Technical Proceedings and Books (database)
ITT	Intention-to-treat
LIFE	Longitudinal Interval Follow-up Evaluation
LIT	Lithium
LOCF	Last observation carried forward
LOE	Loss of efficacy
LSAS	Liebowitz social anxiety scale
MAS-XR	Mixed amphetamine salts extended-release
Med	Medication
MEDLINE	Medical Literature Analysis and Retrieval System On-line (database)
MeSH	Medical Subject Headings
MPH	Methylphenidate
N	Number
N. i.	No information
N. R.	Not relevant
NHS	National Health Service
NHS-CRD-DARE	National Health Service Centre for Reviews and Dissemination Database of Abstracts of Review of Effects
NHS-CRD-HTA	National Health Service Centre for Reviews and Dissemination Health Technology Assessment Database
NHS-EED	National Health Service Centre for Reviews and Dissemination Economic Evaluation Database
NS	NS2359
OLG	Higher Regional Court (Oberlandesgericht)
OR	Odds Ratio
OROS	Osmotic release oral system
OROS-MPH	Osmotic release oral system/methylphenidate extended release
p	p-value
PAR	Paroxetine
PAR/DEX	Paroxetine in combination with dextroamphetamine
PET	Positron-emission tomography
PI	Placebo
POS	Point of service
PPA	Per protocol analysis
PPO	Preferred Provider Organisation
PreMedline	(database)
PrePrint	Preliminary database of the Thieme Publisher's database
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSS	Patient Satisfaction Survey
PsycINFO	(database)
PTSD	Post-traumatic stress disorder
PubMed	(Search interface for MEDLINE)
Q-LES-Q	Quality of life enjoyment and satisfaction questionnaire
QALY	Quality-adjusted life year

Index of abbreviations – continued

RCT	Randomised controlled trial
RR	Relative risk
RRR	Relative risk reduction
SA	Sensitivity analysis
SAS	Social adjustment scale
SC	Sample size calculation
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SciSearch	Science Search (database)
SD	Standard deviation
SDS	Sheehan Disability Scale
SMD	Standardized mean difference
SOMED	Social medicine (database)
SPECT	Single-photon emission computed tomography
STAI	State-Trait Anxiety Inventory
StGB	Criminal Code
T	Day
TAEA	Treatment-emergent adverse event
USA	United States of America
WHO	World Health Organization
Wk	Week
WRAADS	Wender Reimherr ADHD Scale
WURS	Wender Utah Rating Scale
WURS-k	Wender Utah Rating Scale short form

Glossary

Adverse event (AE)	Event in which the patient unexpectedly is harmed.
Affective disorder	Psychological disorder in which affectivity (feelings, emotions and moods) of a person is changed over long periods of time.
Agoraphobia	Fear in certain places, such as public streets and places or in crowds.
Baseline	Values or findings before the treatment.
Baseline phase	Phase at the start of medical studies for collecting the initial data but without intervention.
Bipolar disorders	Psychological disorder that is characterised by a course with depressive and manic episodes.
Blinding	Deliberate lack of knowledge of the study participants and/or the study staff over assignment to the study groups
Body Mass Index (BMI)	Measurement unit for definition of overweight and obesity. It is calculated as the quotient of body weight and the square of height.
Borderline	Emotionally unstable personality disorder in which the symptoms of a neurosis and a psychosis occur alternately.

Glossary – continued

Carry-over effect	Transfer of the effect of one therapy to another.
Case number	The number of participants in a study.
Caudate nucleus	Brain area that is partially responsible for body movement and coordination.
Comorbidity	Occurrence of all additional diseases which are associated with the underlying disease.
Comparison preparation	Preparation (including the placebo) that is used for comparison with the study preparation.
Complete condition (CC)	Patients who complete the study.
Compliance	Keeping the therapy instructions of the doctor or examiner by the patients (e.g. regarding medication intake).
Concealment	Hidden allocation to the respective study arms.
Confidence interval (CI)	Describes the value range around a parameter to be estimated, in which the true value lies within a certain probability (usually 95%).
Control group, control arm	Group of study participants that receives the placebo or another drug.
Dialectical behaviour therapy	Ability training in groups that is intended to supplement individual therapy.
Disease concordance	The degree of probability that a mono- or dizygotic twin will become ill if its sibling suffers from the disease.
Disposition	Susceptibility for the development of a disease.
Dizygotic twins	Non-identical twins
Dopa-decarboxylase	Enzyme that synthesises dopamine.
Dopamine	Messenger substance of the nervous system, important for physical and mental activity.
Drop-outs	Patients who do not complete the study.
Dual noradrenergic/ dopaminergic antidepressant	Antidepressant with impact on noradrenaline and dopamine.
Dysregulation	Regulation disorder.
Dysthymia	Chronic depressive mood.
Decision-analytical modelling	Decision models are a quantitative, systematic approach for decision-finding in uncertainty, in which both the probabilities for the occurrence of an event and the resulting consequences are taken into account.
Executive function	Involves different and complex cognitive processes that ensure the internal behaviour planning and control, that is, the self-regulation of a person.
Exculpation	Freeing a person of guilt.
Functional magnetic resonance imaging	Imaging method that examines functions of the human brain triggered by means of motor, visual, auditory or other stimuli by means of electromagnetic waves.
Glucose metabolism	Metabolisation of glucose as an energy carrier.
Heritability	Measure of the degree of inheritance.
Incremental cost effectiveness ratio (ICER)	Relationship of the additional effects occurring due to an intervention and the resulting costs.

Glossary – continued

Insomnia	The term insomnia combines disorders of falling and staying asleep.
Intention-to-treat (ITT)	Inclusion of all patients according to their original group allocation in the analysis of the results, regardless whether they have completed the allocated treatment or dropped out of the study prematurely.
Intention-to-treat analysis (ITT analysis)	Inclusion of all randomised patients in the analysis.
Major depression	Severe depression with associated symptoms such as low spirits, lack of appetite, sleep disorders, lack of drive and suicidal fantasies.
Mania	Psychiatric disorder that is expressed as a pathologically elevated mood.
Meta-analysis	Systematic summary of study results and their statistical analysis.
Monozygote	Term for twins or higher degree multiple siblings that have arisen from a single fertilised ovum.
Neurotransmitter	Biochemical substances that transmit stimuli from one nerve cell to another.
Noradrenaline	Messenger substance of the central nervous system.
Off-label prescription	Prescription of a drug outside the approved indication.
Occipital lobes	Posterior part of the cerebrum.
Per protocol analysis (PPA)	Inclusion of all patients in the analysis who have performed the study according to the protocol.
Persistence	Continuation of a symptom or a disease.
Placebo	Preparation without active ingredient.
Positron emission tomography (PET)	Imaging procedure that makes metabolic processes visible in the human body.
Post-traumatic stress disorder (PTSD)	Subsequent reaction to extreme stress and traumatic events.
Prefrontal cortex	Part of the frontal lobe of the cerebral cortex, substrate of various cognitive functions and higher psychological performance in the sense of initiation and planning, social behaviour, certain memory functions (working memory) and emotionality.
Prevalence	Frequency of a disease in a population at a particular point in time.
Primary end points	Parameters that enable a clinically relevant assessment.
Psychoeducation	Intervention that informs the patient and his/her family members about the disease and its treatment and promotes conscious handling of the disease.
Psychostimulants	Substances for treatment of psychological illnesses that have a stimulating effect on the organism.
Quality-adjusted life years (QALY)	Index measure for the assessment of a year in life in relation to the state of health.
Rebound effect	Intensified recurrence of the illness symptoms after lowering of the effective level of a medication.
Reliability	Measure of the precision and reliability of a scientific study. Along with validity and objectivity, it constitutes one of the three most important quality criteria in the performance of scientific studies.
Resorption	Substance uptake in biological systems, e.g. the uptake of certain medicinal active ingredients in the human body.
Responder	A patient who responds to an intervention.

Glossary – continued

Secondary end points	Target variables of second rank that are especially used when the primary end points show no clear statistical significance.
Serotonin	Messenger substance of the central nervous system, acts to elevate the mood.
Significance	The probability that the differences to be examined did not arise by chance
Single-photon emission computed tomography (SPECT)	Computer-supported sectional imaging technique for recording the spatial distribution of radiopharmaceuticals in organs.
Stimulants	Substances that have a stimulating effect on the organism.
Striatum	Part of the basal stem ganglia of the brain.
Study centre	Place at which the study is performed.
Synapse	Contact point between nerve cells and other cells or between nerve cells.
Synaptic gap	Space between two neurons.
Titration	Determination of the optimal dose of a medication.
Treatment group, arm	Group of persons, who were treated with the study preparation.
Validity	The quality criterion of the validity of a measurement method that makes statements on the measurement precision of a test with regard to a criterion.
Wash-out phase	Phase for phasing out medications.

Abstract

Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is a mental disorder. Symptoms include hyperactivity, disturbance of attention, and impulsivity. This disorder always begins in childhood, but can remain through adulthood. ADHD affects all areas of life and limits the quality of life due to its symptoms and the high rate of associated disorders that can develop.

An established form of therapy is using stimulant medications, most commonly, containing methylphenidate as the active ingredient. However, in Germany this ingredient is not approved for adults suffering from ADHD. Therefore, many adults cannot obtain appropriate medication to treat this disorder.

Objective

The following report (Health Technology Assessment [HTA]) examines the efficacy and cost effectiveness of the medical treatment of ADHD in adults as well as the ethical, social and legal aspects thereof.

Methods

In August 2009, a systematic literature search is performed in all relevant scientific databases. The selected citations fulfill predetermined inclusion criteria. The data in the publications is then systematically extracted, reviewed and assessed. A manual search of citations is conducted as well.

Results

Nineteen studies fulfill the inclusion criteria: nine randomised controlled trials (RCTs), five meta-analyses, three economic studies and two studies relevant to the legal aspects of the HTA.

All RCTs reveal that adult patients who receive medication containing a stimulant (methylphenidate or amphetamine) or atomoxetine, see a reduction of ADHD symptoms compared to the placebo-treated patients. The drug response rate among the control group ranges from 7 to 42 %; in the treatment group from 17 to 59.6 %. The meta-analyses confirm the findings of the RCTs.

In light of the control group, it can be ascertained that there are higher annual costs (both direct and indirect) for patients with ADHD. The average annual medical expenses for an adult with ADHD were 1,262 US-dollar in 1998 and 1,673 US-dollar in 2001 (the converted and inflation-adjusted rate for 2009: between 1,270 and 1,619 Euro).

The use of stimulants may impair the patient's ability to drive, travel or do sports. No relevant studies can be identified concerning the ethical, social and/or legal aspects of stimulant medication for ADHD patients.

Discussion/Conclusion

Medical treatment, particularly including methylphenidate and atomoxetine, proves to have a positive effect. In order to attain an optimal drug response, dosing must be determined on an individual basis.

There is a need of high-quality studies that directly compare various agents – an aspect which is relevant to the efficacy of a therapy. No definite statement can be made about the cost effectiveness of the medical treatment of ADHD in adults. More health economic studies are therefore required.

Apart from the unquestionable mental indication, it is already recommended by health economic reasons to establish the conditions for an adequate treatment with these drugs also for adults.

Summary

Health policy background

Attention-Deficit/Hyperactivity Disorder (ADHD) is a mental disorder which is characterized by attentional problems, impulsiveness and hyperactivity. It affects all areas of life and limits the quality of life due to its symptoms and high rate of associated disorders, such as depression and anxiety. The development of associated disorders is multifaceted.

ADHD begins in childhood but can continue through adulthood. The incidence of ADHD among adults is between 2 and 5 %. ADHD appears more frequently among men than women.

There are several medications available for treating ADHD however, in Germany these medications are currently only approved for children. Furthermore, statutory health insurance only reimburses this medication when prescribed to children.

Scientific background

For many years, ADHD was falsely classified as a psychiatric disorder among children and teens. Now it is known that ADHD can persist into adulthood. The persistence rate found in studies varies considerably, ranging from 4 to 66 %. Although, the rate is consistently higher for men compared to women.

ADHD affects many areas of life such as school, work and leisure time. The symptoms of ADHD change as the child reaches adulthood. For the most part, adults show reduced hyperactivity.

Motor skills or activities generally decrease with age and adults find ways of concealing this. Yet, just as in children, symptoms such as attention deficit, hyperactivity, impulsiveness, lack of organization, emotional disorders as well as difficulty in handling stress appear in adults.

The diagnosis of ADHD is based on the international classification system of mental disorders. A central aspect of the diagnosis is a precise anamnesis. Since the core ADHD symptoms are already apparent in childhood, adults must have shown these symptoms before the age of seven in order to be diagnosed with ADHD. Further validation of the diagnosis can be performed using various methods such as self-evaluation or third party assessment.

The diagnosis of ADHD does not automatically mean that treatment is necessary. Treatment is based upon the degree of the disorder as well as the associated mental and social limitations.

If treatment of ADHD is deemed necessary, various methods can be used (psychotherapy, training, pharmacotherapy). In pharmacotherapy, stimulants (methylphenidate [MPH], amphetaminesulfate), norepinephrine uptake inhibitor (atomoxetine [ATX]) and other anti-depressants (bupropion, venlafaxine) can be used. According to the guidelines for adult ADHD, the German Society for Psychiatry, Psychotherapy and Nervous Diseases recommends stimulant medications containing MPH as the preferred treatment. Stimulants have a central excitatory effect on an organism. ATX regulates the neurotransmitters in the brain without causing stimulation.

Due to its excitatory effect, stimulants are subject to particular prescription requirements (German Narcotics Law, Appendix 3). Currently, adult patients in Germany can only receive treatment through off-label prescriptions containing stimulants, since pharmaceutical products for ADHD have been solely approved for children and youth. Therapies containing ATX are approved for adults and can be reimbursed by health insurances if the individual received treatment for ADHD during his/her childhood or youth.

ADHD is associated with other mental diseases. Numerous studies show a strong correlation between ADHD and drug abuse as well as anxiety disorders, affective disorders and personality disorders.

Research questions

The efficacy and cost effectiveness of the medical treatment of ADHD, in adults, in Germany, will be evaluated by a systematic assessment of all available evidence. In addition to medical and economic aspects, the ethical, social and legal aspects will be considered.

Study questions regarding the efficacy of medical treatment of ADHD in adults are as follows:

1. What is the efficacy of drug treatment compared to no treatment at all?
2. Are there variations in the efficacy of different drug treatments?
3. What is the efficacy of behavioural therapy in combination with drug treatment compared to no treatment at all?
4. What is the efficacy of behavioural therapy in combination with drug treatment compared to only drug treatment?

Study questions regarding an economic evaluation are as follows:

1. What are the annual costs incurred for the drug treatment of adult ADHD patients, either in combination with behavioural therapy or as a stand-alone or monotherapy?
2. What can be said about the cost effectiveness of the drug treatment of adult ADHD patients, either in combination with behavioural therapy or as a monotherapy?

Further research questions include:

1. Which ethical, social and legal aspects should be taken into account in respect to the drugtreatment of ADHD?
2. How do these aspects influence an evaluation of the health economics of this therapy?
3. Is there a willingness to treat from the side of the patients/general public?
4. Is there a willingness to treat from the side of the providers and what consequences might this have for patients and providers?
5. Is there a willingness to treat from the side of those bearing the costs and what consequences might this have for patients and providers?

Methods

In August 2009, a systematic literature search iwas performed in all relevant scientific databases. A manual search of citations is conducted as well. The identified citations are selected by two people independently from each other of the research according to predetermined inclusion criteria. Only literature from 2000 or later is included and the publication language is not considered a limitation. The data in the publications are then systematically extracted, reviewed and assessed in regard to quality.

Results

Nineteen studies fulfill the inclusion criteria: nine randomised controlled trials (RCTs), five meta-analyses, three economic studies and two studies relevant to the legal aspects of the HTA.

RCTs

In all RCTs, the treatment group receives drug treatment of ADHD and the control group receives a placebo. The active ingredients and the dosing vary considerably in the treatment groups. Four out of nine publications use the active ingredient MPH for the treatment and a placebo for the control. The remaining studies explore other agents such as ATX, bupropion, paroxetine, dextroamphetamine and a substance labeled as NS2359.

There is no standardized method for measuring the reduction of symptoms across all studies. In the majority of the studies, the Attention Deficit Hyperactivity Rating Scale (ADHD-RS) as well as the Conners' self-reporting or third party reporting scales, are used.

The inclusion criteria of the studies are formulated differently, some more concrete than others. While some authors require the absence of further mental illnesses, others are more precise in their specifications and explicitly exclude participants with schizophrenia and/or affective disorders. Three of the studies exclude patients who are non-responsive to the ingredient under investigation. None of the studies allow persons with current drug or alcohol abuse to participate, nor do they allow pregnant or nursing women to be in the study.

All studies show a reduction of ADHD symptoms in the treatment groups, according to the given scale (ADHD-RS, Conners Scale, Clinical Global Impressions Scale). Overall, the group differences in the MPH studies are subject to a broader range of deviation than those in the ATX studies.

Dextroamphetamine, as a monotherapy, as well as in combination with paroxetine, significantly reduces the ADHD symptoms ($p < 0.012$). Both bupropion and NS2359 show a statistically-proven, positive therapeutic effect compared to the placebo. However, since only one adult ADHD study is available for each of the aforementioned agents, this does not make a strong case for evidence.

The response rates of the studies lie between 7 and 42 % in the control group and between 17 and 59.6 % in the treatment group. Neither ATX study provides a response rate in percent.

One study emphasizes that the response can be dependent upon the ADHD subtype. A subtype is a further classification of ADHD e. g. a predominantly hyperactive, a predominantly inattentive and a combined ADHD subtype. In this study, patients with combined ADHD subtypes (subtypes classified according to the criteria of the Diagnostic and Statistical Manual for Mental Disorders) had a higher response to the placebo (42 %) than to NS2359 (30 %). However, patients with a predominantly inattentive ADHD subtype show a significantly higher response rate ($p < 0.001$) in the treatment group (7 % vs. 41 %).

Systematic reviews with meta-analyses

The systematic literature search in relevant databases identified five relevant systematic reviews with meta-analyses. The predefined reasons for inclusion and exclusion are reported in each study. In two of the systematic reviews with meta-analyses, the process of data extraction and the quality of the underlying studies are described. Only one meta-analysis specifies the inclusion and exclusion criteria concerning patients with co-morbid mental disorders.

The quality of the systematic reviews varies considerably. All of the meta-analyses have pronounced shortcomings, some more than others. Among the shortcomings, are the lack of sub-group analyses according to individual active ingredients or underlying study design.

The results of all systematic reviews with meta-analyses reveal that the active ingredient under investigation (MPH, ATX) is more effective for treating ADHD symptoms than placebo.

Economic studies

Three publications related to the economic aspects of ADHD in adulthood can be identified.

In light of the control group, it can be ascertained that there are higher direct (e. g. medications) and indirect (e. g. loss of earnings) annual costs for patients with ADHD. The average costs of medication for adults with ADHD range between 1,270 and 1,619 Euro (converted and inflation-adjusted). It should however be noted that since the calculation is based on different years of reference, the basis of comparison is somewhat limited. In summary, ADHD in adulthood results in higher direct and indirect costs – the latter of which far exceed the direct costs.

Results of the ethical and social review

No relevant studies can be identified – either through the systematic literature research in databases or manually – concerning the ethical and/or social aspects of stimulant medication for ADHD patients. Therefore, it is not possible to provide an evaluation based on scientific publications.

Results of the legal review

Two publications are identified which address the legal aspects of ADHD in adults and the treatment thereof. These publications are non-systematic studies, for example, which examine legal aspects that might influence the quality of life.

The legal issues related to ADHD, generally, revolve around the use of stimulant medication, since stimulants fall under the category of narcotics. Particularly the legal aspects of stimulant use in regards to driving, traveling, performing military service and doing competitive sports must be considered.

Results pertaining to society and care

No relevant sources of literature can be identified – either through the systematic literature review or manually – pertaining to society and/or care.

Nevertheless, the lack of available drug therapies for adults with ADHS does not only affect social and legal aspects. Due to the fear of law suits, doctors prescribe medication less often for adult ADHD-patients who then go without necessary treatment.

Discussion

The social drawbacks and high costs for the public make ADHD a highly relevant topic in terms of health and economics. ADHD can lead to substantial mental and social difficulties which affect many areas of daily life. Additionally, ADHD is connected with a high risk of associated mental illnesses. Adequate drug treatment can reduce the signs of illness for ADHD patients so that symptoms such as lack of concentration can be improved.

The RCTs used for the evaluation fulfill a minimum standard of qualitative methods; there are various shortcomings in the design, implementation and reporting of some studies. In studies with high drop-out rates, results must be interpreted carefully. The drop-out rates, although relatively inconsistent, generally exceed 20 %.

Another major problem is the inconsistent measurement of the responses to the medication. Currently, no uniform or standardized method such as the Hamilton Depression Scale used to measure depressive illnesses, exists for measuring the reduction of ADHD symptoms. The quantitative assessment of ADHD symptoms is based upon self-evaluation and third-party evaluation scales – both are subjective, situational and can greatly differ from one another.

The results of the identified studies must be tested for their applicability to the German health care system. For example, one way in which the study results may not transfer one-to-one to Germany is the difference in patient characteristics such as lower or higher body mass indexes (BMI).

Clearly the costs do not apply to the German health care system since reimbursement plans and prices of medication (fixed and discount contracts in Germany) vary in different health systems. It is not possible to state how these diverse factors impact the costs.

Conclusions/Recommendations

Early medical treatment of ADHD is highly relevant for health policy and for economics due to:

- the social drawbacks that impact many areas of daily life
- the high risk of developing further mental illnesses and
- the costs to society.

Apart from the unquestionable mental clinical picture, it is already recommended by health economic reasons to establish the conditions for an adequate treatment with these medicaments also for adults.

Based on the literature, evidence shows that active ingredients MPH, Dextroamphetamine and ATX have a positive effect in treating ADHD in adults. Furthermore, there are indications of a dose-effect relationship. In order to attain an optimal drug response, dosing must be determined on an individual basis.

The conclusions are based upon nine RCTs, five meta-analyses and three economic studies, as described in this report.

Generally, the study duration is a few weeks, which is too short to determine any long term effects. Therefore, negative long term effects of drug treatment cannot be excluded. Further research in this field is necessary.

Moreover, active ingredients are only tested against placebos. There is a need of high-quality studies that directly compare various agents – an aspect which is relevant to the efficacy of a therapy.

In order to determine the cost effectiveness of the drug treatment of adult ADHD, further economic studies are necessary. These studies should be applicable to the German health care system.

Main document

1 Health policy background

Attention deficit/hyperactivity disorder (ADHD) is a neurobiological function disorder that is characterised in adults as well as in children and adolescents by attention deficits, disorders of the impulse and affect control, and hyperactivity. ADHD always starts in childhood (with the diagnosis often not being made when hyperactivity is lacking) and can persist into adulthood, where the clinical symptoms change with age. Longitudinal studies[12, 54, 84, 85, 86, 97] have revealed a persistence rate of the ADHD symptoms into adulthood of up to 66 %. The prevalence of ADHD in adulthood amounts to between 2 and 5 %[38]. The prevalence is greater in men than in women.

A diagnosed ADHD does not itself result in a need for treatment[43]. Whether therapy is required depends on the degree of expression of the ADHD as well as the psychological and social impairment. If treatment of the ADHD is considered necessary, it can involve several elements (psychotherapy, pharmacotherapy, psychoeducation) that are employed depending on the individual set of ADHD symptoms in the affected person. A drug therapy is indicated when pronounced symptoms are present that lead to significant impairment, such as problems in school and training and threatening loss of employment.

ADHD in adulthood constitutes an increased risk for numerous other psychological disorders, such as depression, anxiety disorders, personality disorders and substance abuse. The reasons for the development of one of these comorbidities are strongly varied and depend, for example, on the similarity with neurobiological processing mechanisms of various disease profiles[124].

Effective medications for the treatment of ADHD are available (e. g. methylphenidate [MPH], atomoxetine [ATX]), but these are currently only approved for children and adolescents in Germany. Therefore, the health insurance providers usually do not bear the costs for the treatment of adults under current circumstances and the affected persons must themselves pay for the costs of the therapy.

The illness itself, as well as the increased morbidity of patients with ADHD, is associated with high costs for the healthcare system. Apart from the direct medical costs, it must be assumed that ADHD in adulthood will be associated with further economic losses due to problems in training and employment. For example, employees with a diagnosed ADHD lose more time at the workplace[115]. Current study data confirms that the direct medical costs are far surpassed by the indirect economic effects of ADHD. Furthermore, it must be assumed that comorbidities play a significant role in generating the costs of ADHD[112].

In particular, the persistence of ADHD, the high rate of comorbidities and the associated direct and indirect costs make ADHD a relevant illness in terms of social and healthcare policy. The effects of ADHD appear in almost all areas of life of the affected persons and their quality of life is often markedly limited by the symptoms of ADHD and the high rate of comorbidities. ADHD also means multiple stresses for persons of reference and relatives, as a result of which they stand an increased risk of suffering psychological illnesses themselves. The current lack of approval for various substances for the treatment of ADHD in adulthood constitutes a major problem and results in many affected persons not receiving the appropriate medication or not being able to afford it.

Therefore, the question of the efficacy of the drug treatment of ADHD in adulthood is of great relevance. Apart from efficacy, the assessment should also include the cost effectiveness and ethical, social and legal aspects.

2 Scientific background

2.1 Definition and classification of ADHD

Attention is the orientation of perception, imagination and thought toward certain current or anticipated contents of experience[10] It is closely linked to concentration and perception, memorizing ability and memory.

ADHD becomes apparent in various fields of life (family, school, job, leisure time), where the symptoms are present in an age-characteristic manifestation[76, 146]. ADHD is often wrongly considered an illness that only afflicts children and adolescents. The course of ADHD from childhood to adulthood is determined by a change in symptoms[1]. Adults usually exhibit a reduced hypermotor activity, since motor activity generally declines with age and adults have often learned to hide it better. Attentional problems and inefficient organisation structures are characteristic of ADHD in adulthood[66, 123].

Two systems are available to classify ADHD: the classification scheme according to the International Statistical Classification of Diseases and Related Health Problems[145] (ICD) of the World Health Organisation (WHO) and the classification scheme according to the Diagnostic and Statistical Manual (DSM) of Mental Disorders DSM-IV[9] of the American Psychiatric Association (APA).

The DSM-IV defines the ADHD according to criteria in the areas of inattentiveness, hyperactivity and impulsiveness (Table 1: Comparison of the diagnoses in DSM-IV and ICD-10). Not all persons show concurrent abnormalities in all three areas. A subdivision according to the following subtypes can be performed based on the DSM-IV classification:

- In the primarily inattentive type, the characteristics of inattentiveness are fulfilled, while hyperactivity/impulsiveness are not or not as strongly pronounced.
- By contrast, the primarily hyperactive/impulsive type predominantly exhibits the characteristics of motor unrest and impulsiveness. By contrast, an attention deficit is not or not sufficiently strongly pronounced.
- In the mixed type, characteristics both of inattentiveness and of hyperactivity and impulsiveness are present.

Table 1: Comparison of the diagnoses in DSM-IV and ICD-10

DSM-IV	ICD-10
Attention deficit/hyperactivity disorder, primarily of the inattentive type (314.00)	Attention disorder without hyperactivity (F 98.8)
Attention deficit/hyperactivity disorder, mixed type (314.01)	Simple activity and attention disorder (F 90.0)
Attention deficit/hyperactivity disorders, predominantly hyperactive/impulsive type (314.01)	Hyperkinetic disorder of social behaviour (F 90.1)

DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ICD-10 = International Classification of Diseases, 10th revision.

Source: Author's design.

The criteria of ICD-10 differ only to a minor degree from those of DSM-IV, but there is no further division according to subtypes, unlike the DSM-IV.

2.2 Epidemiology

ADHD usually starts in early childhood or adolescence. ADHD is often documented in children of preschool age, but in Germany the diagnosis is usually made during school age[33]. In the Bremen Adolescence Study [Bremer Adoleszenzstudie][46], the average age of establishing the diagnosis lies at 10.2 years.

First occurrences of the disease in adulthood have not been described in the literature and are considered improbable[43, 96] Therefore, the frequency of ADHD can be estimated from the number of children and adolescents in whom the symptoms persist beyond puberty. Longitudinal studies in part describe very different persistence rates. The rate fluctuates as a function of definition and sample

characteristics[12, 54, 84, 85, 86, 97]. Table 2: Persistence rates of ADHD in longitudinal studies shows a comparison of persistence rates of ADHD in longitudinal studies.

Table 2: Persistence rates of ADHD in longitudinal studies

Authors	Number of subjects included (N)	Mean age at the start of the study (years)	Mean age at follow-up (years)	Persistence of ADHD symptoms (%)
Gittelmann et al. 1985	101	6 to 12	16 to 23	31
Mannuzza et al. 1991	94	7	18	43
Mannuzza et al. 1993	91	9	26	11
Mannuzza et al. 1998	85	7	24	4
Rasmussen/Gillberg 2000	50	7	22	56
Barkley et al. 2002	147	4 to 12	21	66

ADHD = attention deficit/hyperactivity disorder. N = number.

Source: Modified according to Krause/Krause[69].

The prevalence rates for ADHD in children, adolescents and adults have been examined in numerous studies[111]. Since several classification systems are available for ADHD (ICD-10, DSM-IV and the predecessor version DSM-III), deviations in the prevalence rates are possible depending on the underlying classification.

The prevalence of ADHD of children and adolescents at the age of three to 17 years was determined by the Robert Koch Institute in the context of child and adolescent health surveys from May 2003 to May 2006[111]. For this purpose, data on 7,569 boys and 7,267 girls from 167 representative towns and communities in the Federal Republic of Germany was used. Participants were classified as ADHD cases if their parents reported a diagnosis established by a doctor or a psychologist. Overall, a prevalence rate of 4.8 % is stated, but boys show a significantly higher prevalence than girls (boys: 7.9 %; girls: 1.8 %)[111] In another 4.9 % of participants, there is a suspicion of ADHD. During the course of ageing, there is a marked increase in prevalence from 1.5 % during preschool age (three to six years) to 5.3 % during elementary school age (seven to ten years) and 7.1 % during the age of eleven to thirteen years. ADHD is also more frequently diagnosed in participants of lower socioeconomic status than in those with high status.

The prevalence of ADHD in employed adults of the ages from 18 to 44 years was examined in a multinational study by the WHO[38]. According to the results of a survey of a random sample of 7,075 participants in ten countries (Belgium, Columbia, France, Germany, Italy, Lebanon, Mexico, the Netherlands, Spain, the United States of America), 3.5 % of all employed persons meet the DSM-IV criteria for the illness[38]. In all countries, the prevalence differs significantly with respect to sex and occupation but not with respect to age, education or family status. Women are clearly less afflicted by ADHD at 2.5 % than men at 4.2 %. With respect to age, there is no statistically significant difference between the age group of 18 to 29 years with a prevalence of 3.8 % and the age group of 30 to 44 years with a prevalence of 3.2 %[38].

In an American study (number of cases: 3,199; age range: 18 to 44 years), a prevalence of 4.4 % was determined according to the criteria of the DSM-IV[63], as determined by means of a telephone survey. The share is 3.2 % in women and 5.4 % in men. There is no decrease of the prevalence with increasing age. The frequency in the age group from 18 to 24 years lies at 4.5 %, in the age group from 25 to 34 years at 3.8 % and in the age group from 35 to 44 years at 4.6 %.

We refer here to Section 2.6 (ADHD and psychiatric comorbidities) with regard to the prevalence of comorbidities.

2.3 Aetiology and pathogenesis

ADHD is a disease in which neuroanatomic, neurochemical, genetic and psychosocial factors play a role.

2.3.1 Neuroanatomic and neurochemical foundations

ADHD is a neurobiological disorder. Generally, it must be assumed that a complex dysregulation of neurotransmitters, especially dopamine and noradrenaline, underlies this disease[44].

In numerous structural imaging methods, neurochemical and functional abnormalities have been demonstrated in ADHD patients. Functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET) provide insights into disorders of the brain perfusion and the brain metabolism.

Using PET examinations, the frontal cortex shows a reduced glucose metabolism[155] and a reduced activity of dopa-decarboxylase in the pre-frontal cortex[45] in ADHD patients compared with healthy persons. Krause et al.[72] using SPECT examinations of ADHD patients, observed an increased dopamine transporter availability in the striatum, which normalised during treatment with stimulants. Furthermore, a reduced perfusion of the frontal brain and the striatum as well as increased perfusion in the occipital lobes were found using SPECT examinations[82, 83]. Functional magnetic resonance imaging examinations in persons afflicted with ADHD showed a lower activation in right-side prefrontal systems and in the left caudatum compared with control subjects without ADHD[106].

2.3.2 Genetic disposition

The interplay of genetic and non-genetic factors as the cause of ADHD can be shown in studies of twins, adoptions and families.

In studies of twins, the disease concordance is determined, in order to find the heritability, i. e., the degree of probability for one twin to develop ADHD when the other twin has ADHD. A disease concordance of 100 % in monozygotic twins would speak exclusively for genetic factors. By contrast, an identical concordance for mono- and dizygotic pairs exclusively indicates environmental factors[122]. A survey by Smidt et al.[122] in 2003 resulted in a heritability estimate for ADHD of 60 % to 80 % based on 23 studies of twins. In all included studies, a higher concordance rate for ADHD was found for monozygotic pairs of twins than for dizygotic pairs[122] In monozygotic pairs, the rates ranged from 50 to 80 %, in dizygotic pairs they were on average 35 %[53, 91, 122].

To identify family clusters and peculiarities, Smidt et al.[122] used twelve family studies in which the focus was not just on the afflicted person but also included the parents and siblings. The results showed that the parents and siblings of the afflicted exhibit ADHD problems five times more frequently than comparable relatives in a control population without ADHD[122].

An adoption study also assumes a significant genetic influence of ADHD; biological parents of children with ADHD are clearly more frequently affected by ADHD than adoptive parents [27, 122].

2.3.3 Psychosocial factors

Apart from the purely medical-biological causes, psychosocial factors can affect the development of ADHD-typical symptoms and the course of the behavioural factors.

An increased risk for the genesis of behavioural problems particularly exists with a controlling, authoritarian and inconsistent parenting style that can result in adjustment disorders[76]. Additional factors that can be associated with the development of ADHD are a low social status, lacking experience of success, mostly critical social feedback, frequent punishment and lack of rewards for the ADHD-affected person due to his/her behaviour[76, 100].

Another possible cause for ADHD is a negative or disturbed parent/child interaction. This can be an unfavourable family situation, such as intrafamiliar tensions up to a dysfunctional home and familial violence, in which the child experiences a lack of limits, safety or rules[19, 22, 100]. Compared with control families, family conflicts and a reduced family cohesion are more frequently found in families with an ADHD-affected person[19, 22].

2.4 Clinical profile

The symptoms of ADHD always start in childhood but the clinical profile of ADHD changes with increasing age[73]. Analogous to the set of symptoms in childhood, attention deficits, hyperactivity, impulsiveness and disorganisation, emotional disorders and stress intolerance can occur.

The attention deficit signifies the problem that the affected person cannot concentrate for a longer period on an activity or task that does not appear to interest him/her. ADHD-affected persons tend to become bored even after a few minutes of the same activity, and this can be noticed negatively, especially in school or at work[1, 69]. Even the most minute noises disrupt focussing on the work process due to susceptibility to stimuli, as a result of which the work often cannot be completed in the time available. Impairment of attention can also result in problems in the family and social environment when, for example, the affected person is incapable of following a conversation for an extended period of time[69]. Hyperactivity in adults manifests itself in persistent movements, for example, in continuously repeating foot movements with a high frequency and silent finger drumming[73].

Another typical symptom of ADHD is impulsive behaviour. In children, lacking self-control is an expression of impulsiveness and this manifests itself in continuous disruption at school[73]. The children appear very impatient and have great difficulty in waiting. Even before a question has been completed, they already give their answer and often interrupt others. Adult ADHD-affected persons tend in part towards unconsidered decisions, spending of money and verbal statements without thinking of the long-term consequences[66, 123]. Teamwork aptitude and social competence can be limited by impulsiveness.

Also characteristic of ADHD are disorderliness and chaotic self-organisation at work and in the private sphere. Here it can often be observed how a messy room in childhood and adolescence becomes a disorderly home in adulthood[73]. The disorganised behaviour of many of the affected persons also shows in the difficulty of organising time (schedules and appointments are not adhered to) and in house-keeping. Furthermore, problems can occur at work.

Apart from the negative symptoms, ADHD patients also exhibit positive illness symptoms. Among the frequent strengths are a good assessment of the personality qualities of others, a willingness to take risks, flexibility and sensitivity. ADHD-affected persons usually are very capable of enthusiasm that is expressed in curiosity and openness toward novelty. In addition, they also often have a pronounced artistic creativity.

2.5 Diagnostics

Establishing the diagnosis of ADHD is guided by the international classification systems for psychiatric disorders – DSM-IV and ICD-10. As a precondition for a diagnosis of ADHD according to ICD-10 criteria, the respective symptoms must have been present in secured form for a period of at least six months. To establish the diagnosis, the two cardinal symptoms of inattentiveness and hyperactivity are required[43]. Another requirement is that the set of symptoms develops before the seventh year of age. In DSM-IV, the categories hyperactivity and impulsiveness are summarised into one complex. ADHD is present if six or more symptoms of inattentiveness are found and/or six or more symptoms of hyperactivity and impulsiveness are sufficiently formed[43].

The diagnosis of ADHD should only be formulated by qualified doctors with appropriate psychiatric experience and special expertise in the diagnostics of ADHD[92] As shown in Table 3: Example of a diagnosis formulation using special diagnostic instruments, the diagnostic process should consist of an interview with the affected person, a retrospective recording of the ADHD symptoms, a recording of the current complaints of the affected person and – if possible – a third-party medical history, which will be considered in detail in the following sections. Self- and third-party rating scales are by no means sufficient to formulate the diagnosis, they can only serve as a starting point for recognising signs and symptoms of ADHD in adults.

A retrospective formulation of the ADHD diagnosis in adulthood is generally difficult due to several factors. Usually, the main persons of reference for the affected person are parents and teachers, where assessment of the symptoms in childhood is concerned. In the majority of cases, the affected

person is the only source of information available. This poses the question of how accurately affected persons can assess their own behaviour and present it.

An evaluation of report cards, especially from elementary school, provides valuable objective information on learning behaviour, concentration and social behaviour during school age.

Table 3: Example of a diagnosis formulation using special diagnostic instruments

Interview with the affected person
Use of self-assessment scales *Retrospective recording of the ADHD symptoms* • WURS *Recording of current symptoms* • CAARS • ADSA • BAADS • ASRS v.1.1
Third-party medical history *Retrospective recording of the ADHD symptoms* • Parents rating scale *Recording of current symptoms* • CAARS
Psychological testing

ADD = Attention deficit disorder. ADHD = Attention deficit/hyperactivity disorder. ADSA = Attention deficit scale for adults. ASRS v.1.1 = Adult ADHD Self-Report Scale version 1.1. BAADS = Brown ADD Scale. CAARS = Conners Adult ADHD Rating Scale. WURS = Wender Utah Rating Scale.

Source: Author's design.

2.5.1 Interview with the affected person

A structured interview with the affected person on his/her current life situation is the critical diagnostic step. According to the Guidelines of the German Association for Psychiatry, Psychotherapy and Nervous Diseases (DGPPN) for ADHD in adulthood, the interview should include a complete psychiatric examination to rule out the presence of other psychiatric disorders[43] In addition, the interview should contain important aspects of the developmental and family history regarding an ADHD.

2.5.2 Use of self-assessment scales

When using the self-rating scales, the patient's information is decisive. Here, two scales are differentiated: one to indicate possible symptoms in childhood, and self-rating scales and forms for recording the current symptoms in adulthood.

The Wender Utah Rating Scale (WURS) is available for retrospective examination of ADHD in childhood[142]. WURS is a self-rating procedure in which, by means of 25 items, the degree of expression of childhood characteristics, character and types of behaviour are assessed

Table 4: Wender Utah Rating Scale (WURS))[142]. Adults indicate on a 5-point scale from 0 to 4 how strong the symptoms were during the ages six to ten. If a total score of 36 or more is achieved, there is suspicion of the presence of ADHD in childhood. WURS is recommended by the DGPPN guidelines as a standardised examination instrument for the diagnostics of ADHD[43]. A German abridged version of WURS (known as WURS-k), which was introduced by Retz-Junginger[101], includes 21 similar heterogeneous items and, in this way, is only insignificantly different from the familiar 25-item version.

Table 4: Wender Utah Rating Scale (WURS)

	As a child I was (or had)	Not at all or very slightly	Mildly	Moderately	Quite a bit	Very much
1.	Concentration problems, easily distracted	0	1	2	3	4
2.	Anxious, worrying	0	1	2	3	4
3.	Nervous, fidgety	0	1	2	3	4
4.	Inattentive, daydreaming	0	1	2	3	4
5.	Hot-or short-tempered, low boiling point	0	1	2	3	4
6.	Temper outbursts, tantrums	0	1	2	3	4
7.	Trouble with stick-to-it-tiveness	0	1	2	3	4
8.	Stubborn, strong-willed	0	1	2	3	4
9.	Sad or blue, depressed, unhappy	0	1	2	3	4
10.	Disobedient, rebellious, sassy	0	1	2	3	4
11.	Low opinion of myself	0	1	2	3	4
12.	Irritable	0	1	2	3	4
13.	Moody, ups and downs	0	1	2	3	4
14.	Angry	0	1	2	3	4
15.	Trouble seeing things from someone else's point of view	0	1	2	3	4
16.	Acting without thinking, impulsive	0	1	2	3	4
17.	Tendency to be immature	0	1	2	3	4
18.	Guilty feelings, regretful	0	1	2	3	4
19.	Losing control of myself	0	1	2	3	4
20.	Tendency to be or act irrational	0	1	2	3	4
21.	Unpopular with other children	0	1	2	3	4
22.	Trouble with authorities, trouble with school, visits to principal's office	0	1	2	3	4
23.	Overall a poor student, slow learner	0	1	2	3	4
24.	Trouble with mathematics or numbers	0	1	2	3	4
25.	Not achieving up to potential	0	1	2	3	4

WURS = Wender Utah Rating Scale.

Source: Ward et al.[142].

For an assessment of the symptoms in adulthood present at the time of recording, various self-rating forms are available. Two instruments shall be named as examples.

A helpful, standardised examination instrument for assessing the current symptoms is the Conners Adult ADHD Rating Scale (CAARS). The 66-item version for adult patients is available as a self- and third-party rating form[32]. In addition, there is a short version with 26 items and a screening version with 30 questions. The analysis is separated according to sex and age. In the long test, the 66 questions are answered in four stages (0 = not at all, never; 1 = a little, sometimes; 2 = strong, frequently; 3 = very strong, very frequent), as a result of which the participants or interviewers are intended to assess to what extent the queried behaviour modes apply to them.

The Adult ADHD Self-Report Scale v.1.1 (ASRS v.1.1) is a screening test developed by the WHO with a self-rating scale for persons over 18 years and serves to record ADHD symptoms in adulthood. The test consists of 18 questions and is freely accessible on the Internet[136]. The official German version is available as a short screening test, composed of the six most relevant questions of the English-language version[145]. The questions are answered in five stages (never, rarely, sometimes, often, very often).

2.5.3 Third-party medical history

Third-party medical history information from parents and teachers is important for the diagnosis of an ADHD, but is often not available for adults[142]. Similar to the use of self-rating scales, it is possible here to differentiate between a retrospective recording of ADHD symptoms and a diagnosis based on current complaints.

The Parents' Rating Scale, which is presented to the mother or another relative of the affected person, can provide evidence regarding the retrospective diagnosis of an ADHD, (see Table 5: Parents' Rating Scale[69, 142]. The Parents' Rating Scale includes ten questions that refer to childhood and in which the symptoms are assessed on a scale from zero to three according to their degree of severity. An ADHD is considered probable when a score of twelve or more has been achieved[73].

Table 5: Parents' Rating Scale

		Not at all	Just a little	Pretty much	Very much
1.	Restless (overactive)	0	1	2	3
2.	Excitable, impulsive	0	1	2	3
3.	Disturb other children	0	1	2	3
4.	Fails to finish things started (short attention span)	0	1	2	3
5.	Fidgets	0	1	2	3
6.	Inattentive, distractible	0	1	2	3
7.	Demands must be met immediately; gets frustrated	0	1	2	3
8.	Cries	0	1	2	3
9.	Mood changes quickly	0	1	2	3
10.	Temper outbursts (explosive unpredictable behaviour)	0	1	2	3

ADHD probable with a total score of 12; to be filled in by the mother.

ADHD = Attention deficit/hyperactivity disorder.

Source: Ward et al.[142].

An instrument for recording ADHD that was already presented in Section 2.5.2 (Use of self-assessment scales) is the CAARS. A special advantage of this instrument is that equivalent recording forms are also available for a third-party evaluation[69]. The German language guideline for ADHD in adulthood of the DGPPN recommends the CAARS as a standardised assessment scale[43].

2.5.4 Psychological testing

It is possible to perform psychological testing in the context of the diagnostic process to examine to what extent functions are impaired.

The German guidelines of the DGPPN propose the following psychological tests[43]:

- Intelligence quotient measurement (e. g. Hamburg-Wechsler intelligence test for adults [HAWIE-R])
- Neuropsychological tests on attention and executive functions (e. g. test battery on attention testing, Wisconsin Card Sorting Test, Category Test, Continuous Performance Task)
- Possibly, tests for special talents and tests for partial performance disorders

Standardised and normed psychological test procedures neither secure the diagnosis of an ADHD beyond doubt nor can they completely rule out the presence of the disorder. Psychological testing merely serves as a supporting measure and can contribute to securing the diagnosis.

2.6 ADHD and psychiatric comorbidities

ADHD is often associated with other phychiatric diseases. Many studies show a strong link especially to substance abuse and affective anxiety and personality disorders. The reasons for the development of one of these comorbidities are strongly varied and relate, for example, to the similarity of the neurobiological processing mechanisms of various disease profiles[124].

Table 6: Comorbidity rate of psychiatric disorders in adult ADHD patients in comparison to healthy persons (N = 3,199) shows the result of a large epidemiological study in the United States of America (USA)[63]. In this study, the authors assess questionnaire data of 3,199 18 to 44-year olds with respect to DSM-IV disorders and compare the frequency of psychiatric diseases in 154 persons affected by

ADHD with the frequency in the remaining sample. The ADHD sample exhibits higher values for drug dependency, depressive and bipolar disorders, agoraphobia and social phobia, anxiety disorders, post-traumatic stress disorders, panic disorders and impulse control disorders than the remaining questioned persons.

Table 6: Comorbidity rate of psychiatric disorders in adult ADHD patients in comparison to healthy persons (N = 3,199)

Comorbidity	Prevalence of disorders in %	
	ADHD sample	Healthy subjects
Affective disorders		
Major depression	18.6	7.8
Dysthymia	12.8	1.9
Bipolar disorders	19.4	3.1
Other disorders	38.3	11.1
Anxiety disorders		
Generalised anxiety disorder	8.0	2.6
PTSD	11.9	3.3
Panic disorder	8.9	3.1
Agoraphobia	4.0	0.7
Specific phobias	22.7	9.5
Social phobia	29.3	7.8
Obsessive-compulsive disorder	2.7	1.3
Other anxiety disorders	47.1	19.5
Substance abuse		
Alcohol abuse	5.9	2.4
Alcohol dependency	5.8	2.0
Drug abuse	2.4	1.4
Drug dependence	4.4	0.6
Other forms of substance abuse	15.2	5.6
Impulse control disorder	19.6	6.1

ADHD = attention deficit/hyperactivity disorder. PTSD = Post-traumatic stress disorder.

Source: Kessler et al.[63].

Other prevalences of comorbidities in ADHD patients compared with a control group of patients without an ADHD are shown in Table 7: Prevalence of comorbidities. Compared with the control group, persons with a diagnosed ADHD are significantly more often affected by psychiatric illnesses, such as anxiety disorders (13.77 % vs. 3.46 %), bipolar disorders (4.48 % vs. 0.58 %) and depressions (17.10 % vs. 2.93 %)[115].

Table 7: Prevalence of comorbidities

Comorbidity	Prevalence of disorders in %		p-value
	In the presence of ADHD (N = 2,252)	In the control group (N = 2,252)	
Anxiety disorders	13.77	3.46	<0.01
Bipolar disorders	4.48	0.58	<0.01
Depression	17.10	2.93	<0.01
Drug or alcohol abuse	5.11	1.87	<0.01
Social phobia	0.04	0	0.32
Enuresis	0.18	0.13	0.71

ADHD = attention deficit/hyperactivity disorder. N = number.

Source: Secnik et al.[115].

When individual comorbidities are considered, numerous studies indicate increased substance abuse in ADHD (see also Table 6: Comorbidity rate of psychiatric disorders in adult ADHD patients in comparison to healthy persons (N = 3,199) and Table 7: Prevalence of comorbidities)[39, 63, 115] There is a complex link between an ADHD and the development of addiction diseases that has not yet been clarified. Factors that play a role in this regard could be the increased impulsiveness in the context of the underlying disease, social problems due to dropping out of school and difficulties at the work place as well as family problems. Furthermore, it must be assumed that substance abuse often is conducted as self-medication and self-therapy[124].

Adolescents with ADHD also stand a markedly greater risk of nicotine abuse compared with control persons. The increased smoking by ADHD patients is in part explained by the direct effect of nicotine on the dopamine and serotonin balance and its attention- and performance-enhancing effect[39].

An increased occurrence of alcohol abuse can be found in the context of ADHD illness. In Biederman et al.[21], the numbers for alcohol abuse or dependence in adult ADHD lie at 44 % (N = 239). By contrast, only 24 % of the 268 control persons without ADHD showed an alcohol problem [21]. Downey et al.[41] describe, in a study of adults with ADHD, a frequency of 33.3 % for alcohol abuse or dependency.

The development of affective disorders such as depression and bipolar disorders (cf. Table 6: Comorbidity rate of psychiatric disorders in adult ADHD patients in comparison to healthy persons (N = 3,199) and Table 7: Prevalence of comorbidities) is frequently described as a consequence of ADHD[63, 115]. Affective disorders include a group of disorders and diagnoses that extend from mania and bipolar disorders to depression. The review by Sobanski[124] of 2006 shows that there is a causal connection between ADHD and the development of depression. In adult patients with ADHD, the prevalence of a depressive disorder lies at 35 to 50 %, whereas in the general population the life-time prevalence of depressive disorders is stated to be 18 %[124].

The diagnosis of comorbid depressive disorders in ADHD is often made difficult by the fact that an overlap of symptoms in the disease profiles often occurs according to the criteria of DSM-IV. Most of the core symptoms of depression, such as reduced interest, appetite deficiency, sleep or concentration disorders can also be observed in ADHD.

2.7 Aspects of economics

2.7.1 General principles of the evaluation in healthcare economics

The healthcare economics evaluation of a medical intervention relates the effects achieved with the intervention and the costs caused or saved by the deployment in relation to each other and compares them with the cost of at least one alternative intervention[42]. The additional effects occurring due to the intervention and contingent costs then define the incremental cost effectiveness ratio (ICER).

Effects are measured in a healthcare economics evaluation either as clinical parameters, user benefit or in monetary units and, in this way, also determine the study type of the economic evaluation. As a rule, the following study forms are differentiated: Cost minimisation analysis, cost benefit analysis [CBA]), cost utility analysis [CUA]) and (cost effectiveness analysis [CEA])[42]. While clinical parameters represent measurable variables, e. g. the number of avoided deaths, benefit values are more complex parameters. Quality-adjusted life years (QALY) are often used as benefit values. For a QALY, the quality of life in a particular state of health and the period that the patient spends in this state of health are both included in the calculation. The advantage of the QALY is the simultaneous accounting for the gains in years lived and the patient's quality of life.

The determination of costs is a central element of an economic evaluation. Costs constitute resource consumption (quantities), evaluated in prices, that arise while performing a diagnostic or therapeutic intervention in a disease, or that accrue as its consequence (e. g. secondary illness)[74]. The accruing costs are differentiated into different categories: direct medical, direct non-medical and indirect[93].

The direct costs include the resource consumption that is directly associated with the medical diagnostics or therapy of an illness or the follow-up treatment. These include the costs incurred on an outpatient through the use of doctor's, laboratory and hospital services, pharmaceutical, medicinal and auxiliary means as well as emergency doctor deployment. Direct non-medical costs constitute resource consumption that is not associated with medical care but caused by the illness. Examples are

transport, household and time costs[78]. Indirect costs specify the loss in value creation potential by illness, invalidity or premature death. Therefore, they are also called macroeconomic productivity losses incurred by the affected persons or their relatives due to an illness[74].

In cases of complex decision problems, especially when long-term as well as short-term effects and costs are to be taken into account, decision-analytical modelling is used. Decision analysis is a systematic approach for finding a decision in conditions of uncertainty[118]. For simpler decision problems with a short time line, for example, the decision tree method is available for the analysis, whilst, in more complex problems with a longer time line, for example, Markov or discrete event simulation (DES) models can be used[16].

The objective of the decision analysis consists in supporting the selection of the action strategy while taking into account the medical benefit, the risk and the costs of various action alternatives[119].

2.7.2 Relevance of ADHD to economics

Secnik et al. report direct medical costs that are caused by ADHD in adulthood [115]. Apart from the costs, the study also shows the resource consumption underlying the costs for the ADHD group (N = 2,252) and the control group (N = 2,252). Differences between groups regarding the resource consumption are especially found in the medical contacts. While 27.53 % of patients with ADHD visit a psychiatrist and 16.03 % a psychologist, in the control group merely 2.22 % of patients contact a psychiatrist and 1.83 % a psychologist[115]. Therefore, in 2001, the basis year, patients with a diagnosed ADHD had higher costs compared with the control group in the outpatient sector (3,009 US-dollars vs. 1,492 US-dollars; $p < 0.01$), in the hospital sector (1,259 US-dollars vs. 514 US-dollars; $p < 0.01$) and for prescribed drugs (2,771 US-dollars vs. 1,673 US-dollars; $p < 0.01$)[115].

In a further cost analysis by Swensen and co-workers[133], average costs of 3,786 US-dollars were determined by means of data on adults with ADHD for 1998 as compared with 1,131 US-dollars for persons not afflicted by ADHD[133].

Apart from the direct medical costs, it must be assumed that ADHD in adulthood is associated with further economic losses due to work-related problems. For example, employees with diagnosed ADHD lose more time at the workplace (43.03 days vs. 29.34 days; $p = 0.03$)[133]. The total annual indirect costs amount for employees who suffer from ADHD to 11,861 US-dollars compared with 8,024 US-dollars in the control group. The annual indirect costs according to Swensen et al. amount to 5,043 US-dollars in adult ADHD patients and 1,656 US-dollars in the control group[133].

In another study of employees of a large company in the USA, the costs caused by ADHD affected persons exclusively due to the disease (caused by poorer work performance, more frequent lost times, increased work accidents) were calculated at 4,336 US-dollars per person per year[64].

Generally, it is assumed that the study data so far confirm that the direct medical costs are by far surpassed by the indirect costs of ADHD.

The costs of psychological comorbidities (depression, addiction) are not explicitly listed in the above studies. However, it must be assumed that comorbidities play a significant role in the costs of ADHD and that all additional costs in comparison with the control group can be attributed to the causative ADHD[112].

2.8 Social aspects in the context of ADHD

2.8.1 Ethical and social aspects

Depending on the degree of expression, ADHD can be associated with a marked impairment of social life. The social consequences of ADHD can affect numerous areas of life such as work, family and circle of friends[112]. Apart from the stress on ADHD patients due to the illness-related symptoms per se, affected persons are exposed to an increased risk of comorbidities, such as depression, anxiety disorders and substance abuse. Furthermore, ADHD-affected persons often have an unhealthy lifestyle with pronounced risk behaviour (e. g. in practising extreme sports), which also markedly increases the illness risk for comorbidities.

Affected persons have difficulties in maintaining their attention focus long enough and to direct it with sufficient endurance to a single task.

They are characterised by an eagerness to know and an obsession for detail. Remarkably, hyperfocussing, i. e. the ability to be able to dedicate oneself to particularly interesting problems extremely intensively and persistently, is frequently observed. Successful adults with ADHD can develop good endurance in researching a matter that interests them, so that they become specialists in a short time[69]. However, ADHD-specific hyperfocussing is also associated with the risk of never finding an end in a matter, which can lead to considerable problems among friends and family as well as in the work environment.

Adults with an ADHD often have problems structuring their daily routine due to their disorganisation. They tend toward leaving behind objects such as car keys and wallets or to forget locking doors and closing windows[69, 71].

In the personal and social area, those affected by ADHD also show limitations. Tensions occur due to the strong and unpredictable mood fluctuations and impulsive behaviour. Fluctuating partner relationships, frequent divorces, dissatisfaction in the partnership due to unclear agreements, and unstable friendships, through to social isolation, can occur[69]. In young adults, the number of undesired pregnancies and the risk of contracting a sexually-transmitted disease are increased[112]. Frequent excessive behaviour in eating, drinking, sexuality, sports and leisure time can be observed[69].

Krause and Krause describe in their book their experiences over many years of handling adult ADHD sufferers on a daily basis. Persons with ADHD suffer from significant self-doubt and a lack of confidence because they feel inferior and, as a result, fear disappointing their friends and family[69]. Most affected persons have experienced much stress in their development. These experiences can prevent the development of a stable sense of self-value. This negative self-assessment can result in withdrawal, even isolation, depression and suicide attempts[69].

Furthermore, the risk of causing severe traffic accidents is increased. Criminality and convictions are also increased. Rösler et al.[103] have found, in a study performed in Germany on the prevalence of ADHD, a frequency of 45 % among 129 incarcerated male adolescents and youths according to DSM-IV and a frequency of 21.7 % according to ICD-10 criteria (see Table 8: ADHD prevalence rates among 129 male incarcerated adolescents)[103]. Often, poorer opportunities for learning or exercising an occupation and the associated costs are the consequence.

Table 8: ADHD prevalence rates among 129 male incarcerated adolescents and youths

ICD-10			DSM-IV			
F.90.0 Simple activity and attention disorder	F.90.1 Hyperkinetic disorder	Total	314.01 ADHD mixed type	314.01 ADHD prevalently hyperactive impulsive type	314.00 ADHD predominantly inattentive type	Total
5.4 %	16.3 %	21.7 %	21.7 %	21.7 %	1.6 %	45 %

ADHD = attention deficit/hyperactivity disorder. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ICD-10 = International Classification of Diseases, 10th revision.

Source: Author's design.

The problems at the occupational level become evident in persons with ADHD changing their work more frequently and being terminated more often than persons without ADHD. In comparisons, their work performances tend to be more poorly evaluated. In general, it is observed that persons with ADHD often have difficulties achieving a position appropriate to them[112]. Failures and personal defeats result more frequently from this than in comparison populations.

Therefore, persons with ADHD more frequently have occupational problems because they cannot structure and have a motivation problem with strictly carrying through on tasks once begun and, due to disorganised behaviour, with satisfactorily completing tasks given to them.

2.8.2 Legal aspects

In a consideration of the legal aspects, implications resulted on one hand from the core symptoms of ADHD, while on the other hand, legal peculiarities arise when taking into account treatment with stimulants that fall under the Narcotics Law (BtMG).

2.8.2.1 General legal aspects relating to ADHD

Effects of ADHD in road traffic:

Inattention can have fatal consequences in road traffic. ADHD is not included in the catalogue that lists illnesses and disorders that rule out the ability to drive, so that in persons affected by ADHD with or without pharmacotherapy, it is the assessment of the fitness of an individual to drive, and thus his overall capability before and during a journey that counts[51 55].

ADHD and culpability:

Persons with psychological illnesses can be considered to not be culpable or be culpable to a reduced degree according to Paragraphs 20 or 21 of the Criminal Code (StGB). According to § 20 StGB, those act without culpability, *"who when committing the deed are incapable of seeing the wrongness of the act or of acting according to this insight due to a pathological psychological disorder, due to a deep-seated disorder of consciousness or due to a feeble mind or due to another psychological abnormality."* A reduced culpability exists according to § 21 StGB when *"the ability of the perpetrator to recognize the wrongness or to act according to this insight for the reasons listed in § 20 is significantly reduced"*[116]. In this case, the penalty can be reduced according to § 49 paragraph 1.

ADHD without the presence of a comorbid disorder is usually not a sufficient reason for de- or exculpation according to §§ 20, 21 StGB, i.e. it is rather improbable that the capacity for insight into the wrongness of an act could be impaired by ADHD alone[55].

On the other hand, the Higher Regional Court (OLG) in Hamm determined in a revision decision of 05/11/2007 (3 Ss 461/07) that an untreated ADHD can be considered a serious psychiatric abnormality within the meaning of §§ 20, 21 StGB, that consequently affects the capacity to control one's actions when committing a crime in a legally relevant manner and, therefore, can result in a reduced culpability[61].

2.8.2.2 Legal aspects taking into account the applied treatment

Since stimulants fall under the BtMG, a series of legal peculiarities must be noted in the treatment of ADHD with MPH.

Effects of ADHD in road traffic:

When assessing the driving ability of an ADHD patient, it must always be estimated whether an impairment due to treatment with a narcotic is present. By taking stimulants, there is the potential for impairment of driving ability due to the medication itself. This may have consequences not only in criminal law (§ 316 StGB), but also in civil law, e. g. in association with claims for compensation of damages.

Since stimulants improve attentiveness, they can affect driving behaviour positively. In subjects with ADHD who are taking MPH, a study performed in a driving simulator and on the open road showed that a significant improvement of driving behaviour was found under administration of MPH[34].

Fundamentally, ADHD patients should undergo a critical examination for driving ability before every drive during the adjustment and conversion phase with a psychopharmaceutical[55].

Cost bearing for pharmacological therapies:

According to the DGPPN guidelines, MPH is the means of first choice in the drug treatment of an ADHD. So far, pharmaceuticals for the treatment of ADHD in Germany are only approved for children and adolescents. For adult patients (over 18), there is only the option of an off-label prescription (Joint

Federal Committee), which means that approved pharmaceuticals can under special conditions also be used for indications for which they are not approved according to the Pharmaceuticals Law.

It is a precondition for prescription that the patient shows clear symptoms, that there is no alternative treatment option, and that studies on the efficacy of the respective medication are available. The health insurance companies will not accept the costs in most cases since the Federal Social Security Court decided in a judgement of 30/06/2009 that adult medications with the active ingredient MPH cannot be claimed for from the statutory health insurance funds (File number: B 1 KR 5/09 R)[26]. The court arrived at the conclusion that so far no knowledge has been published that permits statements on the quality and effectiveness of the medication in adult ADHD patients.

2.9 Therapy

A diagnosis of ADHD does not imply a necessity for treatment[43]. Whether therapy is required depends on the degree of expression of the ADHD as well as the psychological and social impairment.

When treatment of the ADHD is considered necessary, it can involve several elements (psychotherapy, pharmacotherapy, psychoeducation) that are employed depending on the individual set of ADHD symptoms of the affected person. Detailed information on the disease profile and instruction of the patient (psychoeducation) usually constitute the first measure. In cases of more strongly pronounced symptoms, drug treatment is usually required. The German guideline of the DGPPN recommends for treatment of the ADHD in adults a multimodal therapy that includes a combination of pharmacotherapy with psychotherapy (see Figure 1: Therapy algorithm)[43]. If comorbidities, such as depression or addiction diseases are in the foreground, they should receive priority in treatment with a specific therapy (e. g. antidepressant medication). The objective of the treatment is to reduce the disease symptoms of ADHD[43].

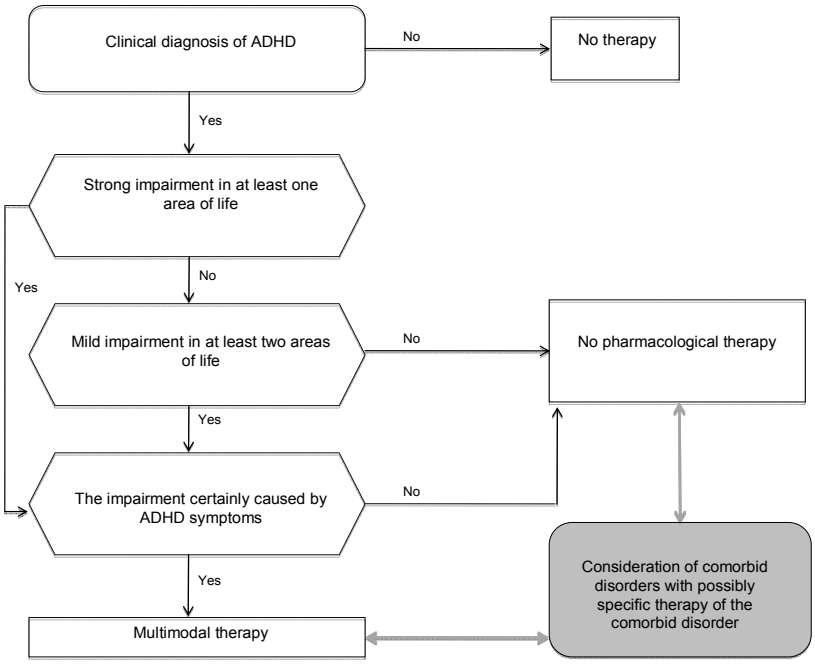

Figure 1: Therapy algorithm

ADHD = Attention deficit/hyperactivity disorder.
Source: Modified from Ebert et al.[43].

2.9.1 Pharmacotherapeutic interventions

The treatment concept for ADHD includes therapy with active ingredients from the group of psychostimulants and other substances. The following pharmacotherapies are available for treating ADHD[43]:

- Stimulant treatment, e. g. MPH, amphetamine sulphate,
- Treatment with noradrenaline reuptake inhibitors (e. g. ATX),
- Treatment with other antidepressants (e. g. bupropion and venlafaxine),
- Treatment with other pharmaceuticals (e. g. nicotine receptor agonists, phenylalanine, lithium).

According to the German guideline of the DGPPN, stimulant treatment with MPH is recommended as the therapy of first choice[43].

So far, pharmaceuticals for the treatment of ADHD are only approved for children and adolescents in Germany. Therefore, adult patients can only be treated in the context of off-label prescriptions.

2.9.1.1 Treatment with stimulants

Stimulants possess a stimulating effect on certain sections of the central nervous system that depends on different mechanisms according to the substance. Due to their stimulating effect, these active ingredients are subject to a special prescription requirement according to Appendix 3 of the BtMG Narcotics Law[18].

Before the initiation of a drug therapy, especially with stimulants, a detailed discussion with the patient is required. Furthermore, physical examinations (liver function parameters, blood count, determination of body size and weight, thyroid gland values) are required. Stimulant treatment with MPH is currently the therapy of first choice[43].

The pharmacological effect primarily consists of reversible blocking of the dopamine transporter, which results in an increase of the dopamine concentration at the synapse[123]. The ability to concentrate and the willingness to perform and make decisions improve, and irritability is reduced in affected persons with ADHD. MPH increases perception and attention, so that information is better converted in the working memory and can be recalled more quickly.

The active ingredient MPH is marketed by several pharmaceutical manufacturers in Germany (Ritalin®, Concerta®, Equasym®, Equasym retard®, Medikinet®, Medikinet retard®, Methylphenidat-1 A Pharma®, Methylphenidat HEXAL®, Methylpheni TAD®, Ritalin LA®), some having different active ingredient release rates[105]. The therapy for children and adolescents is started according to the specifications with a low daily dosage (5 mg). With good tolerability, an individual dose increase in weekly intervals by 5 to 10 mg daily can be performed (titration method) until the optimal dose has been reached[47]. The maximum dose is 60 mg daily and should not be exceeded, with the total daily dose being distributed across several individual doses.

The therapeutic effect occurs about 30 minutes after the administration and generally lasts about four hours, so that in many patients several daily intakes are required. This can result in problems with compliance and, as a consequence, make it impossible to achieve a stable daily dose. In recent years, slow-release preparations/preparations with delayed active agent release (e. g., Ritalin-LA®, Concerta®, Medikinet retard®) but with longer effectiveness (six to eight hours) have been introduced for the treatment of ADHD[143]. In the case of Concerta®, the duration of effectiveness can be up to 12 hours due to a special process (osmotic-controlled release delivery system [OROS])[143]. MPH-OROS is a special capsule development that releases MPH via an osmotic principle of action[143]. If no positive effect can be observed after the start of MPH and sufficient dosing, then diagnosis, dosing and compliance must be checked. If the therapy with MPH proves to be insufficient, a change of the medication, for example to an amphetamine, is recommended.

Loss of appetite, sleep disorders, tearfulness, headaches and dizziness have been named as side effects[70]. Contraindications for a therapy with MPH include, for example, pregnancy and nursing, untreated arterial hypertension, heart racing, coronary heart disease, cardiomyopathies and schizophrenia[96]. If MPH is suddenly discontinued after a longer period of use, the originally treated symptoms such as concentration and/or mood problems can recur, which may in the short term be more intense than they were without medication. This increased revitalisation is described as the rebound effect.

An increased potential for abuse and dependency under intake of stimulants does not exist for ADHD[51]. Studies on adolescents with ADHD show a decrease of the risk of later developing a dependency on drugs if treatment with MPH is started early[23, 62].

In cases of non-responsiveness to MPH with a secured diagnosis, an administration of amphetamines may result in an improvement of symptoms. In contrast to the USA, where ready-to-use preparations are available (Adderall®, Benzedrine®), amphetamines are only available as the raw substance in Germany and, therefore, must be formulated as a juice or a capsule[68].

2.9.1.2 Treatment with non-stimulating active ingredients

Apart from the stimulants, the noradrenaline reuptake inhibitor ATX has become established in the treatment of ADHD. ATX acts via the regulation of the neurotransmitter in the brain. The substance selectively inhibits the presynaptic noradrenaline transporter and, as a result, increases the concentration of noradrenaline in the synaptic gap, but also of dopamine which is simultaneously taken up in the prefrontal cortex via the noradrenaline transporter[15, 17, 77]. This is supposed to dampen the typical ADHD symptoms[121]. ATX has no direct effect on other messenger substances such as serotonin. After oral application, ATX is quickly and almost completely resorbed[17]. The average maximum plasma concentration is only achieved after one to two hours[15, 37]. In contrast to MPH, ATX does not have a stimulating effect and is not subject to the provisions of the BtMG.

The tolerability of ATX is good according to the available studies. The spectrum of the side effects is largely comparable with that of the stimulants (e. g. MPH). Among the therapeutically adverse effects, a reduced appetite, stomach aches, nausea, vomiting and loss of weight must be emphasized[48].

The administration occurs according to the information in the specifications either as a one-time dose in the morning or in two parts, i. e. in the morning and the evening. ATX is available under the trade name Strattera® in the form of capsules in strengths of 10, 18, 25, 40, 60 and 80 mg. The recommended target dose is 80 mg ATX daily in children and adolescents over 70 kg body weight and in adults[48]. It can take four weeks from the beginning of therapy until ATX starts to take effect, during which time ATX must be taken regularly. This requires good compliance by the patient, which is not always given in the disease profile of ADHD.

ATX is only approved in Germany for the treatment of ADHD in children over the age of six and in adolescents. The specifications for Strattera® explicitly note that starting a treatment with Strattera® in adulthood is inappropriate[48]. However, a treatment started in childhood or adolescence can be continued into adulthood. Therefore, therapy with Strattera® is approved in adults if this therapy was already started in childhood or adolescence.

Buproprion is a dual noradrenergic and dopaminergic antidepressant that has demonstrated good efficacy in controlled studies on more than 200 adults, including those with ADHD[149, 152]. In Germany, bupropion is approved under the trade name Elontril® exclusively for depression and with the trade name Zyban® for withdrawing nicotine-dependent patients.

Another treatment option that so far has only been successfully tested in children and adolescents could be the active ingredient carbamazepine[120]. Carbamazepine is an agent against seizure disorders and is preferably used with epilepsies. There are no studies on adults with ADHD for this substance.

2.9.2 Psychotherapeutic interventions

A psychotherapy is indispensable in many ADHD-affected adults due to comorbid disorders (e. g. depressive moods, anxiety disorders) and the psychosocial consequences such as loss of employment or disruptions of relationships. Additional reasons that speak for a psychotherapeutic treatment are:

- Psychosocial consequences of ADHD cannot be sufficiently influenced by drug treatment.
- The affected persons do not respond sufficiently to drug treatment.
- The affected persons do not wish to receive drug treatment.
- A drug treatment possibly does not improve all symptoms.
- The psychological development is characterised by a life-long traumatisation due to ADHD symptoms.

Psychotherapy is understood as a general umbrella term for various methods that can be used as individual and group therapy in states of psychological and physical ailments and problems.

The behavioural therapy is characterised by a time-limited cooperation between the therapist and the patient that attempt to effect a permanent modification of patient behaviour through processes such as learning, re-learning and unlearning. The behavioural therapy should ideally be adjusted for every patient directly to the individual circumstances[99]. Characteristic for behavioural therapy is the concentration on current instead of previous behavioural modes.

A behavioural therapy for ADHD should act toward a reduction of the ADHD symptoms and aim toward giving the patient improved abilities for handling the ADHD symptoms[37]. The affected patient will be helped to implement sensible organisational structures in ordinary life at home and at work and to learn self-control techniques.

In previous years, various therapy concepts have been created and evaluated for ADHD in adults. A cognitive behavioural therapy developed by Safren et al. in the form of individual sessions consists of the three modules (1) organisation and planning, (2) deflectability and (3) cognitive therapy[109, 110]. The participants pass through all three modules and can then repeat them or optionally select an additional module (e. g. handling anger, stress reduction, self-assertiveness training, communication skills).

In the German-speaking countries, the Freiburger Concept of ADHD treatment by Hesslinger et al. is made available[56]. This is a behaviour-therapeutic group programme (seven to nine participants) that is based on a therapy for the treatment of borderline patients (dialectical behaviour therapy, i.e. a skills training in groups that is intended to supplement individual therapy, according to Linehan)[56]. The therapy consists of 13 weekly two-hour sessions with varying content, such as impulse control, chaos and control, and stress management[56]. An important component of the therapy is also homework that must be completed by the participants. The Freiburger concept is currently being evaluated in comparison with the administration of stimulants over three years in a randomised, blinded, multicentre study that is sponsored by the Federal Ministry for Education and Research (BMBF).

Further studies on group therapies are available from Wilens et al., Stevenson et al., Rostain et Ramsay and Weiss et Hechtman and regarding individual therapy by Wiggins et al., Stevenson et al., Bramham et al., Solanto et al., Virta et al. and Zylowska et al.[25, 104, 125, 141, 147, 151, 155].

Depth-psychological approaches, such as the psychoanalytic-interactional method are indicated in deep self-value problems and structural ego disorders.

Studies that show the effect and long-term effect of depth-psychological methods in adults with ADHD are still lacking.

3 Research questions

The efficacy and cost effectiveness of drug treatment of ADHD in adulthood in Germany will be evaluated by systematically working through all available evidence. Apart from medical and economic aspects, ethical, social and legal aspects will also be used for assessment.

Quality of life and overall well-being, the reduction of symptoms, driving ability (road traffic), frequency of adverse events/ tolerability (e. g. measured by means of laboratory parameters), functional level (see Section 4.3 [Inclusion and exclusion criteria]) as well as work and occupational incapacity have been determined as the patient-relevant end points.

The following questions arise in the examination of the medical efficacy of drug therapy in adult ADHD patients:

1. How does the efficacy of drug therapy compare with no treatment?
2. How does the efficacy of various drug therapies appear?
3. How does the efficacy of a drug treatment as a supplementary therapy with a behaviour-therapeutic treatment compare with no treatment?
4. How does the efficacy of a drug treatment as a supplementary therapy to a behavioural-therapeutic treatment compare with a purely drug therapy?

The following is intended to be answered in the economic assessment:

1. What costs arise from a drug therapy in adults with ADHD as a monotherapy and/or a supplementary therapy compared with a behavioural-therapeutic treatment (annually)?
2. How should the cost effectiveness of the drug therapy in adult patients with ADHD as monotherapy and/or supplementary therapy be evaluated compared with a behavioural-therapeutic intervention?

Furthermore, additional questions arise:

1. What ethical, social and legal aspects must be considered in the use of drug therapy?
2. How do these aspects affect the assessment of the therapy in terms of economics/healthcare policy?
3. What is the estimation/acceptance of the need for care by the affected persons/the public?
4. What is the assessment/acceptance of the need for care by the service providers and what are the consequences for the affected person and the service provider?
5. What is the assessment/acceptance of the need for care by the cost bearer and what consequence does this have for the affected party and the service provider?

The studies identified in the literature search will be examined, with regard to their design, their methodological transparency and their quality, as to what extent they satisfy the requirements for answering these questions. Furthermore, it must be asked whether the relevant international studies on economics and legal aspects are transferable to the German healthcare system.

4 Methods

4.1 Search strategies

The literature searches were performed based on search terms and a research strategy by Art & Data Communications in cooperation with the authors and on behalf of the German Institute for Medical Documentation and Information (DIMDI) on 18/08/2009. The research was performed by means of a free text search with keywords and the interlinkage with AND/OR operators as well as in combination with the respective key-wording (e. g. Medical Subject Headings) of the respective database. A complete listing of the search terms is found in 9.1). To limit the number of documents and to exclusively identify the most current publications, the searches referred to the literature from 2000. There is no limitation with regard to the language of publication. When necessary, foreign language publications were translated.

The following 35 databases, exclusively, were searched for literature: NHS-CRD-HTA, DAHTA-Datenbank, NHS-EED, NHS-CRD-DARE, Cochrane Library – CDRD, MEDLINE, EMBASE, AMED, BIOSIS Previews, MEDIKAT, Cochrane Library – Central, gms, SOMED, CAB Abstracts, ISTPB + ISTP/ISSHP, ETHMED, GLOBAL Health, Deutsches Ärzteblatt, EMBASE Alert, SciScearch, CCMed, Social SciSearch, Karger-Verlagsdatenbank, Kluwer-Verlagsdatenbank, Springer-Verlagsdatenbank, Springer-Verlagsdatenbank PrePrint, Thieme-Verlagsdatenbank, Derwent Drug File, IPA, gms Meetings, DIQ-Literatur, Heclinet, Hogrefe-Verlagsdatenbank und Volltexte, Thieme-Verlagsdatenbank PrePrint, Krause & Pachernegg Verlagsdatenbank. The selection of the relevant databases was performed in consultation with Art & Data Communication, which was commissioned by DIMDI.

In addition to the systematic literature search by DIMDI, the authors performed a manual search in the reference lists of the identified studies, on the Internet and in the tables of content of relevant journals.

4.2 Selection of literature citations (first selection)

The literature citations identified by the search in the bibliographic databases were imported into the literature administration programme Reference Manager Version 11 and, in a first selection step, preselected according to their relevance independently of each other by two reviewers familiar with the approach of evidence-based medicine by means of their titles and abstracts according to the inclusion and exclusion criteria. Literature that both reviewers considered potentially relevant was ordered as a full text. A consensus was established in discussions with respect to publications about which there was no unanimity. To ensure the significance of the content, an expert with psychopharmacological and neuroscientific qualifications in the field of ADHD in adulthood was involved in the process.

The result of the first selection included all literature quotations that suggested fulfilment of the inclusion and exclusion criteria. A final assessment was performed in a second selection once the full texts had been made available. Furthermore, the references of the literature citations were examined for relevant articles possibly not included.

Also, publications on the scientific background were collected in a special file and ordered.

4.3 Inclusion and exclusion criteria

According to the criteria listed in Table 9: Inclusion criteria for literature citations on the assessment of efficacy, the following study types are included: systematic overview tables, metaanalyses, Health Technology Assessment (HTA) reports, guidelines and primary studies on the effectiveness of the drug treatment of ADHD in adulthood.

Table 9: Inclusion criteria for literature citations on the assessment of efficacy

Study population Patients from 18 years with a diagnosis of ADHD
Intervention Drug therapy Behaviour therapeutic/drug therapy
Comparison intervention in controlled studies Placebo Direct comparison studies for drug therapy (head-to-head) Behaviour therapeutic/drug therapy
Patient-relevant end points Quality of life and overall well-being Reduction of the symptoms Driving ability (road traffic) Frequency of adverse events/tolerability Functional level Work and occupational disability
Study type Randomised, controlled clinical trials Non-randomised, controlled intervention studies Systematic reviews Meta-analyses HTA reports Evidence-based guidelines

ADHD = attention deficit/hyperactivity disorder. HTA = Health Technology Assessment.

Study population

The study population includes according to the question all adult patients (from 18 years) with diagnosed ADHD. Since ADHD in childhood and adolescence exhibits different symptoms that are measured using age-specific tests, the minimum age of the study participants was fixed at 18.

Since an ADHD rarely occurs in isolation but often is associated with comorbidities (e. g., depression, anxiety disorders and substance-dependent addiction illnesses), the study population also includes ADHD patients with accompanying illnesses.

Intervention and comparative intervention in the control groups

The intervention to be examined in this HTA includes all drug therapies of the ADHD with or without an accompanying behavioural therapy.

The therapies listed in Table 9: Inclusion criteria for literature citations on the assessment of are considered comparison therapies, with drug therapies taking priority. Studies, in which the comparison intervention does not include a drug therapy, that is, for example, a pure behavioural therapy, are excluded from the assessment.

To ensure comparability of the study results, the intervention and control groups must be treated and recorded in the same manner, except for the treatment.

Patient-relevant end points

Quality of life and overall well-being, the reduction of symptoms, driving ability (road traffic), frequency of adverse events/tolerability, functional level are included as patient-relevant end points. Furthermore, work and occupational incapacity are included.

The changes in ADHD symptoms can be measured by means of various scales (e. g. CAARS, Brown Attention Deficit Disorder Scale [BAADS]). A restriction to particular scales did not occur.

Adults with ADHD have a higher accident risk in road traffic[13]. Studies assess to what extent driving ability is altered in ADHD patients after taking medication for the treatment of ADHD.

Another patient-relevant end point is the functional level. The functional level is a collective term for cognitive capabilities[60].

An untreated ADHD must be considered a risk factor for developing an addiction and for developing psychological comorbidities. A successful treatment of an underlying ADHD can also include comorbid psychiatric disorders, such as depression and anxiety disorders. However, these parameters do not enter the assessment at a primary level.

Study type

To answer the question, the study types listed in Table 9: Inclusion criteria for literature citations on the assessment of efficacy are used. Apart from primary studies, additional secondary literature was considered in the analysis.

4.4 Selection by means of full texts (second selection)

The literature citations found in the first selection by means of the titles and abstracts were selected in an additional search step on the basis of full texts. The aspects listed and described in Section 4.3 (Inclusion and exclusion criteria) served as the basis of the selection.

4.5 Criteria for assessment of the literature remaining after the second selection

The data of the included literature citations were evaluated and assessed by means of their methodology and study quality.

4.5.1 Assessment and extraction of the publications on efficacy

To assess the methodological quality of the studies, check-lists of the German Scientific Working Group Technology Assessment for Health Care[52] (German Scientific Working Group) were used. Of these, the check-lists for systematic reviews and meta-analyses and the publications that contain information syntheses and the check-list for the primary studies were used. The essential points that were queried by means of the check-lists were the selection of the study participants, the statistical analysis, classification of the intervention, valid and reliable recording of the intervention, and the comparability of intervention and patient characteristics.

Furthermore, the most important parameters of the studies were extracted in tabular form for the assessment of the identified primary studies for medical efficacy (Table 10: Extracted parameters of the included studies). The analysis of the data was performed by means of standardised extraction forms[52].

Table 10: Extracted parameters of the included studies

Parameter	Description
Study objective and target criteria	Characteristics of the intervention and control group, target sizes
Study design	Country of implementation, number of centres, setting, type of randomisation, number of randomised patients, number of patients with analysed results, case number calculation
Study characteristics	Inclusion and exclusion criteria, study duration, number of groups and patients, drop-outs, compliance
Characteristics of the study population	Age, sex, duration of the illness, comorbidities, symptoms of the ADHD
Results	Changes in symptoms, driving behaviour, functional level, quality of life

ADHD = Attention deficit/hyperactivity disorder.

The evidence classification of the medical studies is performed based on the evidence classification of the DGPPN guidelines according to the plan in Table 11: Classification of the strength of evidence [43]:

Table 11: Classification of the strength of evidence

Strength of evidence	Description
Evidence Ia	Evidence based on metaanalyses of randomised, controlled studies
Evidence Ib	Evidence based on at least one or more randomised, controlled study
Evidence IIa	Evidence based on at least one very well designed, controlled study without randomisation
Evidence III	Evidence based on well designed, non-experimental descriptive studies
Evidence IV	Evidence based on reports/opinions from groups of experts, consensus conferences and/or clinical experience of recognised authorities

Source: Ebert et al.[43].

Corresponding to the classification of the strength of evidence, there is a classification of the strength of recommendation[43]:

- Level A evidence: Data derived directly from the evidence of Category I.
- Level B evidence: Data directly derived from the evidence of Category II or extrapolated from the evidence of Category I.
- Level C evidence: Data derived directly from the evidence of Category III or extrapolated from the evidence of Categories I or II.
- Level D evidence: Data directly derived from the evidence of Category IV or extrapolated from the evidence of Categories I, II or III.

The relevant parameters of the considered studies were systematically summarised and juxtaposed in tabular form for comparison. For this purpose the result parameters reported in the studies are described comparatively.

To the extent that the result parameters of the studies are comparable, metaanalyses were performed. For this purpose, a statistical analysis for heterogeneity must initially be performed. Subsequently, a suitable model of the meta-analysis for estimating the effect of the end points was determined and the effect estimator was pooled.

4.5.2 Assessment, extraction and synthesis of the information in the included studies for assessment of economic aspects of effectiveness

The documentation of the methodological quality of the economic studies is performed while considering the check-list for assessing the methodological quality of economics methods by the German Scientific Working Group[117]. The catalogue of criteria includes questions on the study question, the evaluation framework, the analytical methods, the modelling, the health effects and the costs. For this purpose, the aspect is examined by means of the catalogue of criteria on study quality whether the respective criterion was treated, indicated and fulfilled in the publication.

The qualitative characteristics of the included studies were extracted. The extraction of the data was performed by means of a standardised questionnaire[117].

The studies included in the information synthesis were summarised in short descriptions. The study was described based on the “Documentation structure for the standardised reporting of economic primary studies and syntheses of primary studies”[117] (Table 12: Documentation structure for standardised reporting of economic primary studies and syntheses of primary studies (developed by the German Scientific Working Group Technology Assessment for Health Care)).

Table 12: Documentation structure for standardised reporting of economic primary studies and syntheses of primary studies (developed by the German Scientific Working Group Technology Assessment for Health Care)

1 Questioning and evaluation framework 1.1 Technology 1.2 Questioning 1.3 Perspective 1.4 Time line 1.5 Type of economic evaluation
2 Study design and study or target population 2.1 Study type 2.2 Dating of the underlying data 2.3 Study population/target population 2.4 Setting 2.5 Specification of the technology
3 Health effects
(1) Primary study 3.1 Examined target variables 3.2 Inclusion/exclusion criteria 3.3 Recruiting mode 3.4 Participation rate 3.5 Reproducibility of the study results 3.6 Analysis of the study 3.7 Drop-outs 3.8 Results of the study 3.9 Effect measure for the economic analysis *(2) Synthesis of primary studies* 3.1 Clinical parameters examined in the synthesis 3.2 Assumptions 3.3 Consideration of primary studies: Study designs and inclusion/exclusion criteria 3.4 Sources and search strategies in the literature search 3.5 Validity and quality criteria in the assessment of primary studies 3.6 Methods of assessment of the relevance and validity or quality of primary studies 3.7 Methods of the extraction of data from primary studies 3.8 Number of included primary studies 3.9 Method of the synthesis of the health-related parameters 3.10 Examination of the heterogeneity of the health-related parameters 3.11 Results of the synthesis 3.12 Effect measures for economic analysis
4 Costs 4.1 Included resource changes 4.2 Description of the quantity structure 4.3 Monetary assessment of the quantity structure 4.4 Currency
5 Discounting
6 Results 6.1 Determined health effects 6.2 Determined costs 6.3 Synthesis of costs and effects
7 Treatment of uncertainties
8. Discussion and conclusions of the authors 8.1 Comments regarding the restrictions/weaknesses/bias of the analysis 8.2 Comments regarding the ability to generalise the results (external validity) 8.3 Conclusions
9 Commentary
10 Similar publications/original publications/technical reports (if available)

Source: Siebert et al.[117].

To be better able to compare the costs and to make statements regarding the costs, they must be adjusted for currency and inflation. The currency conversion, i. e. the conversion into euros was performed via the country lists according to the gross domestic product (purchasing power parities) of the respective year.[94] The gross domestic product signifies the total value of goods that were produced within a year by a national economy and serve end consumption. The inflation correction was performed so that total costs are comparable with reference to 2009. This was accomplished using the general consumer price index determined and published by the Federal Statistical Agency[131]. The obtained currency-converted and inflation-adjusted values were rounded.

5 Results

5.1 Results of the first selection

The literature search yielded 1,846 hits for the assessment of efficacy and cost effectiveness as well as for ethical, social and legal aspects of the drug treatment of ADHD in adulthood. After looking through the search results according to the described inclusion and exclusion criteria, 1,561 citations were excluded. Subsequently, 285 articles were ordered as full texts for assessment.

Another 45 citations were included to describe the medical and healthcare policy background.

5.2 Results of a second selection

A total of 238 citations were excluded from the assessment. More detailed information on the reasons for exclusion are presented in Appendix 8.4 (after viewing the literature excluded in full text with reason for exclusion).

The remaining 47 publications (35 publications on randomised, controlled studies [RCTs], seven meta-analyses, of which five entered the assessment, three economic studies and two studies on legal aspects) were included in the information assessment and, potentially, the synthesis. A list of the included literature citations after viewing the full text is found in Appendix 9.3 (List of literature included after viewing the full text). The two metaanalyses were excluded, since they also included children and adolescents.

Figure 2: Flow shows the selection of the citations from the electronic databases in a flow diagram. The representation conforms to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[81].

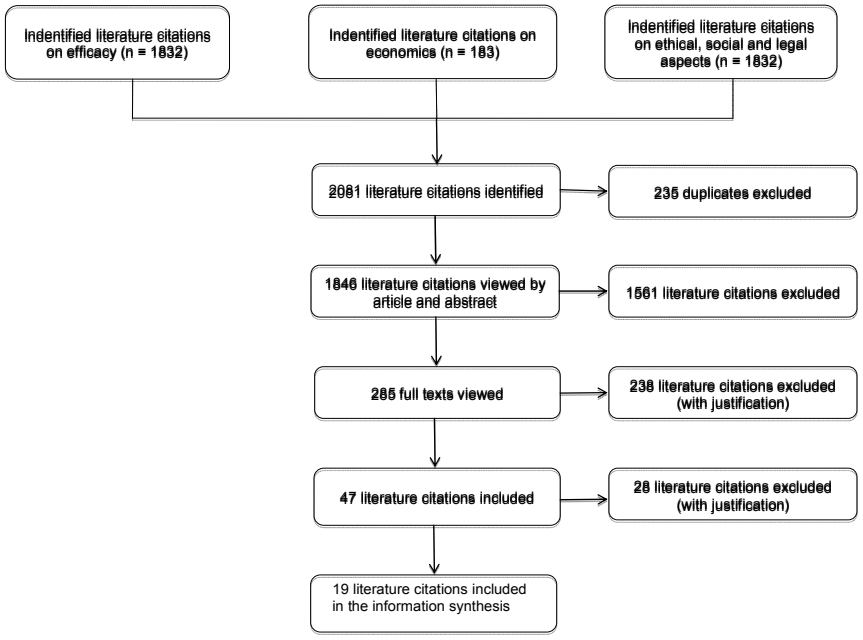

Figure 2: Flowchart

No additional literature citations were identified by means of the manual search.

5.3 Results of the third selection

The check-lists of the 35 RCTs are to be found in Appendix 9.5 (Check-lists of the included studies) and 9.7 (Check-lists of the excluded studies). 26 RCTs were excluded from the qualitative and quantitative assessment of the studies due to methodological deficiencies. According to Table 13: Overview

over the randomised controlled studies only studies that do not meet at least two of the required criteria (missing description of the sample size calculation and randomisation, high drop-out rate) are ruled out.

Decisive for ruling out studies was the overall quality of the study and the number of qualitative deficiencies. This includes aspects of statistics, study duration, dosing and the external validity of the study.

The studies excluded in Table 13: Overview over the randomised controlled studies were not used to answer the research questions.

Table 13: Overview over the randomised controlled studies

Source	Description of the sample size calculation	Description of the randomisation	Sufficiently high responder rate (drop-outs ≤ 30 %)	Reason for exclusion/comment
Adler et al. 2008a	–	–	X	• No description of the sample size calculation • No description of the randomisation • No ITT analysis • Fixed dose titration • Short study duration Study is excluded from further assessment
Adler et al. 2008b	–	–	–	• No description of the sample size calculation • No description of the randomisation • High drop-out rate (ATX = 61.6 %; PI = 51.1 %) Study is excluded from further assessment
Adler et al. 2009a	X	X	X	• Patients with known unresponsiveness were excluded Study was included for further assessment
Adler et al. 2009b	X	X	–	• High drop-out rate (ATX = 66.4 %; PI = 55.4 %) • Patients with known unresponsiveness were excluded Study is excluded from further assessment
Adler et al. 2009c	X	X	–	Study was included for further assessment
Barkley et al. 2007	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size: In total, 18 patient data analysed • Pilot study • Short intervention period Study is excluded from further assessment
Biederman et al. 2006	–	–	X	• No description of the sample size calculation • No description of the randomisation Study is excluded from further assessment
Carpentier et al. 2005	–	X	X	• No description of the sample size calculation • Small sample size: In total, 19 patient data analysed • Fixed dosing Study is excluded from further assessment
Chamberlain et al. 2007	–	–	n.i.	• No description of the sample size calculation • No description of the randomisation • Small sample size: In total, 20 patient data analysed • Fixed dosing Study is excluded from further assessment
Dorrego et al. 2002	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size Study is excluded from further assessment

Table 13: Overview of the randomised controlled studies – continued

Source	Description of the sample size calculation	Description of the randomisation	Sufficiently high responder rate (drop-outs ≤ 30 %)	Reason for exclusion/comment
Jain et al. 2007	X	–	X	• Patients with known unresponsiveness were excluded • No description of the randomisation Study was included for further assessment
Kooij et al. 2001	–	X	X	Study was included for further assessment
Kuperman et al. 2001	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size Study is excluded from further assessment
Levin et al. 2006	–	X	–	• No description of the sample size calculation • Intervention not uniform • High drop-out rate (depending on group between 24 % and 34 %) Study is excluded from further assessment
Levin et al. 2007	–	–	–	• No description of the sample size calculation • No description of the randomisation • High drop-out rate (MPH = 57 %; PI = 55 %) Study is excluded from further assessment
Medori et al. 2008	X	X	X	• Patients with known unresponsiveness were excluded Study was included for further assessment
Michelson et al. 2003	–	X	Study 1: X Study 2: –	Study 1 was included for further assessment. Study 2 was excluded from further assessment.
Reimherr et al. 2007	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size • Short therapy phases • Fixed dosing Study is excluded from further assessment
Rösler et al. 2009	–	–	–	• No description of the sample size calculation • No description of the randomisation • High drop-out rate (MPH = 24 %, PI = 43 %) Study is excluded from further assessment
Schubiner et al. 2002	X	X	–	• No definition of the primary end point • High drop-out rate (MPH = 55 %, PI = 42 %) • Small sample size Study was excluded from further assessment, since a primary end point was not defined
Spencer et al. 2001	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size • Short therapy phase Study is excluded from further assessment
Spencer et al. 2007	–	–	X	• No description of the sample size calculation • No description of the randomisation • Fixed dosing • No proper ITT analysis Study is excluded from further assessment
Spencer et al. 2008a	–	X	X	Study was included for further assessment
Spencer et al. 2008b	–	–	–	• No description of the sample size calculation • No description of the randomisation • High drop-out rate • Patients with known unresponsiveness were excluded Study is excluded from further assessment
Spencer et al. 2005	–	–	X	• No description of the sample size calculation • No description of the randomisation • Patients with known unresponsiveness were excluded Study is excluded from further assessment

Table 13: Overview of the randomised controlled studies – continued

Source	Description of the sample size calculation	Description of the randomisation	Sufficiently high responder rate (drop-outs ≤ 30 %)	Reason for exclusion/comment
Taylor et al. 2001	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size • Short therapy phases Study was excluded from further assessment
Tenenbaum et al. 2002	–	–	n.i.	• No description of the sample size calculation • No description of the randomisation • Small sample size • Short therapy phases Study is excluded from further assessment
Turner et al. 2004	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size • Fixed dosing • No information on therapy duration Study is excluded from further assessment
Turner et al. 2005	–	–	X	• No description of the sample size calculation • No description of the randomisation • Small sample size • Fixed dosing • No information on therapy duration Study is excluded from further assessment

ATX = Atomoxetine. ITT = Intention-to-treat. n. i. = no information. MPH = Methylphenidate. Pl = Placebo.

The sample size calculation and randomisation are central elements in the study planning of an RCT. The sample size calculation in clinical studies aims to demonstrate (statistically significant) differences of a defined effect in a comparison with different interventions or in comparison with a placebo. To this applies that the higher the sample sizes, the more likely a difference can be identified even if it is small. With a given number of patients, a difference is more likely to be shown if it is stronger.

The objective of randomising patients in therapy groups is to minimise the risk of distortion of the results by selection, i. e. by conscious and unconscious systematic allocation of patients with a particularly good or bad prognosis to individual treatments. There are several methods for performing the randomisation that allocate the patient to a treatment.

A customised dose adjustment constitutes an important aspect of an effective ADHD treatment. In contrast to medication in childhood, adjustment to a customised dose in adulthood is more problematic, because the metabolisation is subject to stronger influences. Low dosing quantities relative to body weight often show better therapeutic effects[69]. By contrast, high doses often harbour the risk of side effects and in some patients even result in a worsening of the clinical profile. An optimal titration should not just be determined by body weight but also by therapeutic response.

Furthermore, high drop-out rates constitute a limiting factor in study quality. Missing data are usually replaced by the “Last observation carried forward” (LOCF) method. In the LOCF method, the last measured value is continued for drop-outs. Preconditions are the results of the first and another examination, so that, e.g. a patient who discontinues the interventional treatment due to side effects, despite an improvement, contributes to the apparent beneficial effect of the medication. If the results of drop-outs are continued with the last recorded value, possible ADHD improvements of the study participants remain unrecorded. If the patient leaves the study early, a possible later benefit after customized adjustment of the study medication to the patient is not recorded in the analysis.

The Institute for Quality and Economics in Healthcare (IQWiG) has set a threshold value of 30 % for the entire study population[57]. This determination is an arbitrary decision but it can be considered adequate. By contrast, Schulz et al.[114] consider drop-out rates of more than 20 % as no longer being meaningful.

The last restriction of the study quality that could lead to the exclusion of the study during the third selection is the exclusion of patients from the study without prior demonstrable response to the therapy. With limitation to patients that have demonstrably already responded to the study medication, one can anticipate an error that results in overestimating the actual efficacy.

5.4 Results of the primary studies on efficacy

The included nine RCTs with a total of 1,712 randomised patients are presented comparatively with regard to their methods and results. The following tables provide an overview of the examination and the control interventions, the defined primary and secondary patient-relevant endpoints, the study design and the underlying study populations. As well, methodological peculiarities of the studies that affect the study results are described in detail. The basis of assessment are the extraction tables, which are found in Appendix 9.6 (Extraction forms of the assessed studies (included after the third selection)).

5.4.1 Overview of the study objective and the patient-relevant end points

Table 14: Overview of the intervention and control groups as well as the primary and secondary end points) describes the content of the examined interventions as well as the primary and secondary patient-relevant end points.

Table 14: Overview of the intervention and control groups as well as the primary and secondary end points

Source	Intervention	Control	Primary end points	Secondary end points
Adler et al. 2009a	OROS-MPH (MPH) • Start with 36 mg; dose titration of 18 mg every 7 d until custom dosing has been achieved • Custom dosing is achieved when the AISRS drops by 30 % since the baseline examination and the CGI-I rating is 1 (very strong improvement) or 2 (strong improvement) or the maximum dose titration of 108 mg has been achieved • In cases of intolerability, the dose can be reduced once to 18 mg • Compliance with the therapy instructions is recorded in a journal	Placebo • Start with 36 mg placebo; dose titration of 18 mg every 7 d until custom dosing would have been achieved • Custom dosing is achieved when the AISRS v.1.1 drops by 30 % since the baseline examination and the CGI-I rating is 1 (very strong improvement) or 2 (strong improvement) or the maximum dose titration of 108 mg has been achieved • In cases of intolerability, the dose can be reduced once to 18 mg • Compliance with the therapy instructions is recorded in a journal	AISRS-v.1.1 change (baseline to study end)	• CGI-I • Vital signs • Weight • ECG • Blood pressure, heart rate • Adverse events
Adler et al. 2009c	ATX • Twice daily, in the morning and afternoon/evening • 2-week initiation phase without medications • Dosing: at least 7 d 40 mg daily, then at least 7 d 80 mg daily. Patients with remaining significant symptoms at week 10 or later will receive a dose of maximally 100 mg daily • Dose reductions are possible, but not below 40 mg daily • Wash-out phase of stimulants: 24 hours • Evaluation after 2, 4, 8, 10, 12, 14 weeks after active intake of the medications	Placebo	• CAARS:Inv:SV Total ADHD Symptom Score change (baseline to study end) • Change of the CAARS:Inv:SV subscales inattentiveness, hyperactivity impulsiveness, ADHD index (baseline to study end)	• LSAS • CGI-O-S • STAI • AAQoL • TEAE, vital signs
Jain et al. 2007	MPH • Wash-out: 1 week • Oral administration once daily (10-, 15-, 20-, 30-, 40-, 50-, 60- or 80-mg capsules) • Weekly dose titration to optimal adjustment during the first 3 weeks 2 weeks of constant dosing, then change of the treatment group • The necessity and the time of a dose titration is estimated by means of the CGI scale	Placebo • Wash-out: 1 week • Oral administration once daily	• CGI during constant dose • CAARS	• Other CAARS scales (self- and third-party assessment) • PSS • HAM-A, HAM-D • LIFE

Table 14: Overview on the intervention and control groups and the primary and secondary end points – continued

Source	Intervention	Control	Primary end points	Secondary end points
Kooij et al. 2001	MPH • Start with 0.5 mg/kg daily in the 1st week • Titration to 0.75 mg/kg daily in the 2nd week • Titration to 1 mg/kg daily in the 3rd week	Placebo	• DSM-IV ADHD-RS modified • CGI-I-ADHD	• HAM-D • HAM-A • SDS • GAF • Effect Rating Scale of Barkley modified
Medori et al. 2008	MPH • MPH_18 mg: Oral administration of once daily 18 mg MPH over 5 weeks • MPH_36 mg: Oral administration of once daily 36 mg MPH over 5 weeks • MPH_72 mg: Dose titration; D 1-4: 36 mg/d, then 54 mg/d for 3 days, subsequently 72 mg/d for 4 weeks • Wash-out phase of 4 weeks before administration of the 1st study medication	Placebo • Once daily one placebo tablet over 5 weeks • Wash-out phase of 4 weeks before administration of the 1st study medication	Change of the total score of the third-party rating scale CAARS-O with 18 items between the start and end of the study, or the last collected value	Change of the CAARS-O total score and subscale in weeks 1, 3 and 5. Changes from the start to the end of the study in: • Total score and subscale of the self-evaluation scale CAARS-S (short version with 26 items) • CGI-S • SDS Assessment of safety
Michelson et al. 2003 (Study I)	ATX • Administration in the morning and evening • Start with 60 mg daily • If necessary, titration to 90 mg daily after 2 weeks • If necessary, titration to 120 mg daily after 4 weeks	Placebo	Third-party assessment after CAARS sum score for inattentiveness and hyperactivity/impulsiveness	• CGI severity • WRAADDS • HAM-A, HAM-D • Sheehan Disability

Table 14: Overview on the intervention and control groups and the primary and secondary end points – continued

Source	Intervention	Control	Primary end points	Secondary end points
Weiss et al. 2006	• Wash-out phase of 1 week before the start of study • Weekly dose titration over a period of 4 weeks (defined according to CGI-I) • During the titration phase: Follow-up every 2 weeks (6 sessions) PAR: • Oral administration of 20 mg daily; dose titration by 10 mg to a maximum of 40 mg/daily DEX: • Oral administration of 5 mg daily; dose titration by 5 mg to a maximum of 20 mg daily PAR/DEX: • Simultaneous administration of both active ingredients; no information on precise dosing • 9 sessions of a problem-oriented psychotherapy (developed by the authors)	Placebo/PAR Placebo/DEX • No information on dosing and duration of intake • 9 sessions of a problem-oriented psychotherapy (developed by the authors)	• Changes of the ADHD-RS (investigator-rated) • HAM-D • HAM-A	• Changes of the CGI-I from start to end of the study or to the last recorded value • Measurements at study end: CGI-I-ADHD, CGI-I, GAF, proportion of SCID mood and anxiety disorder • Weight, blood pressure, pulse, adverse events, simultaneously taken medication
Wilens et al. 2001	Bupropion • Oral administration of 100 mg bupropion in the morning • Dose titration of 100 mg weekly • Maximum dose: 200 mg twice daily.	Placebo Placebo administration identical to that of bupropion	• CGI scale • ADHD-RS	• HAM-D • Beck Depression Inventory • HAM-A
Wilens et al. 2008b	NS2359 Oral administration of 0.5 mg in the morning for 8 weeks	Placebo	• ADHD-RS (investigator-rated)	• ADHD rating scale (self-rating scale) • CGI • CAARS

AAQoL = Adult ADHD Quality of Life Scale. ADHD = Attention deficit/hyperactivity disorder ADHD-RS = ADHD Rating Scale.. AISRS-v.1.1 = Adult ADHD Investigator Symptom Rating Scale, Version 1.1. ATX = Atomoxetine. CAARS = Conners Adult ADHD Rating Scale. CAARS:Inv:SV = Conners Adult ADHD Rating Scale: Investigator-rated: Screening Version. CAARS-O = Conners Adult ADHD Rating Scale/Observer-rated. CAARS-S = Conners Adult ADHD Rating Scale/Self-rated. CGI = Clinical Global Impression. CGI-I-ADHD = Clinical Global Impression Improvement Scale ADHD. CGI-I = Clinical Global Impression Improvement. CGI-O-S = Clinical Global Impression Overall Severity. CGI-S = Clinical Global Impression/Severity of Illness Subscale. DEX = Dextroamphetamine. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ECG = Electrocardiogram. GAF = Global assessment of functioning. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. n. i. = no information. LIFE = Longitudinal Interval Follow-up Evaluation LSAS = Liebowitz social anxiety scale MPH = Methylphenidate. OROS = Osmotic-controlled release delivery system. OROS-MPH = Osmotic-controlled release delivery system Methylphenidate extended release. PAR = Paroxetine. PAR/DEX = Paroxetine in combination with dextroamphetamine PSS = Patient Satisfaction Survey. SAS = Social adjustment scale. SCID = Structured Clinical Interview for DSM-IV Axis I Disorders. SDS = Sheehan Disability Scale. STAI = State-Trait Anxiety Inventory. d = day. TAEA = Treatment-emergent adverse event. Wk = Week. WRAADS = Wender Reimherr ADHD Scale.

All presented studies exhibit as the intervention group a drug treatment of ADHD and as the control group a treatment with a placebo, where the intervention groups differ markedly especially because of the administered active ingredients and their dosing. Of the nine identified publications, four[7, 59, 67, 88] were conducted with the active ingredient MPH in the intervention arm and a placebo as the control arm. The other studies examined other active ingredients such as ATX[4, 90], bupropion[152], paroxetine and dextroamphetamine[144] as well as NS2359[148].

A customized dose titration measured against the severity of the ADHD occurred in two studies[7, 59]. In Adler et al.[7], the treatment starts with 36 mg OROS-MPH daily. The weekly titration of 18 mg depends on the improvement of the Adult ADHD Investigator Symptom Rating Scale (AISRS) and the Clinical Global Impression (CGI). The maximum daily dose is 108 mg. The study by Jain et al.[59] also comprises a customized weekly titration, measured as the CGI success.

Kooij et al.[67] describe a dose titration over a period of three weeks that is not guided by the individual treatment success, but successively increased to 1 mg/kg body weight.

The study by Medori et al.[88] is the only one with a three-armed study design and different fixed dosages per intervention arm. There was no customized titration.

A uniform measurement of the relief of symptoms was not found across the different studies. Most studies used the ADHD-RS[144, 148, 152] and the third-party and self-rating scales of Conners[4, 59, 88, 90]. Essentially, the CAARS should be the preferred scale, since validity and reliability are confirmed in the examinations[2]. Furthermore, in one study the third-party rating scale AISRS is used, which in principle provides for a similar assessment method as the ADHD-RS, only that the assessment is performed by a clinical investigator and not the patient[7]. Also, three studies[59, 67, 152] document the overall well-being of the subjects using the CGI.

5.4.2 Study design

As is evident in Table 15: Study design of included studies regarding below, both studies with parallel as well as with a crossover study design are being performed. Crossover design means that the patients change from a first to a second assessment phase, with a conversion to placebo or intervention.

Table 15: Study design of included studies regarding efficacy

Source	Design	Number of centres	Setting
Adler et al. 2009a	RCT, multicentre, parallel, double-blind	27 (USA)	n. i.
Adler et al. 2009c	RCT, multicentre, parallel, double-blind	30 (no detailed information)	Outpatient
Jain et al. 2007	RCT, multicentre, crossover, double-blind	n. i.	Outpatient
Kooij et al. 2004	RCT, crossover, double-blind	n. i.	Outpatient
Medori et al. 2008	RCT, multicentre, parallel, double-blind	51 (13 European countries)	n. i.
Michelson et al. 2003 (Study I)	RCT, multicentre, parallel, double-blind	17 (all in North America)	Outpatient
Weiss et al. 2006	RCT, multicentre, parallel, double-blind	5 2 in the USA 3 in Canada	Outpatient
Wilens et al. 2001	RCT, parallel, double-blind	n. i.	Outpatient
Wilens et al. 2008b	RCT, multicentre, parallel, double-blind	3 (USA)	Outpatient

n. i. = no information. RCT = Randomised controlled trial. USA = United States of America.

Seven[4, 7, 59, 88, 90, 144, 148] of the nine studies are multicentre studies, where no information is provided on central or different methods at the individual centres.

The randomisation (Table 16: Randomisation, case number calculation, blinding and applied statistical methods of the included studies) for group formation is not described in three studies[59, 148, 152].

Therefore, it cannot be assumed without doubt that these studies were actually randomised. Nevertheless, these studies are included in the following assessment due to the further good methodological description and approach. Apart from the randomisation itself, the concealment of the randomisation, that is, that the treatment allocation cannot be predicted, is of critical significance. Only three studies[7, 144, 148] make a statement in this regard.

In all included studies, patients and investigators are blinded.

Table 16: Randomisation, case number calculation, blinding and applied statistical methods of the included studies

Source	Type of randomisation	SC	Statistical analysis methods	Blinding
Adler et al. 2009a	• 1: 1 Randomisation • Stratified block randomisation	Yes	• ANCOVA • Cochran-Mantel-Haenszel Test • ITT analysis • LOCF estimate	Doubled up (patient, investigators)
Adler et al. 2009c	• 1: 1 Randomisation ATX or Pl • Blinded, computer-generated randomisation	Yes	• ANCOVA • Maximum likelihood-based mixed model repeated measure • Akaikes information criterion • Kenward-Rogers Method • ITT analysis • LOCF estimate • Fisher's Exact Test	Doubled up (patient, investigators)
Jain et al. 2007	n. i.	Yes	• ITT analysis and PPA • LOCF estimate • Wilcoxon Rank sum test • McNemar Test	Doubled up (patient, investigators)
Kooij et al. 2004	Computer-generated randomisation to determine the therapeutic series	n. i.	• McNemar Test • T-test • Subgroup analysis: Chi-square test/ Fisher's Exact Test	Doubled up (patient, investigators)
Medori et al. 2008	• Computer-generated, permuted block randomisation • Stratification according to study centre	Yes	• ANCOVA • LOCF estimate • Least squares method • Dunnett method • Cochran-Mantel-Haenszel Test	Doubled up (patient, investigators)
Michelson et al. 2003 (Study I)	Computer-generated randomisation	n. i.	• ITT analysis • LOCF estimate • Repeated measures mixed model with mixed procedure • ANOVA • Fisher's Exact Test	Doubled up (patient, investigators)
Weiss et al. 2006	Block randomisation	Yes	• 2 x 2 factor model • ITT analysis • LOCF estimate • Secondary end points Chi-square test/Fisher's Exact Test	Doubled up (patient, investigators)
Wilens et al. 2001	n. i.	Yes	• ITT analysis • LOCF estimate • Fisher's Exact Test • Wilcoxon signed rank test • Wilcoxon rank sum test • Generalized Estimation Equation	Doubled up (patient, investigators)
Wilens et al. 2008b	n.i.	Yes	• ANOVA • Spatial Correlation Model • Main component analysis	Doubled up (patients, investigators)

ANCOVA = Covariance analysis. ANOVA = Variance analysis. ATX = Atomoxetine. ITT = Intention-to-treat. n. i. = no information. LOCF = Last observation carried forward. MPH = Methylphenidate. Pl = Placebo. PPA = Per protocol analysis. SC = sample size calculation.

5.4.3 Study characteristics

Included were patients over 18 with the diagnosis of adult ADHD according to DSM. In addition, other diagnostic scales were used of which most are based on DSM criteria. In Adler et al.[4] states of social anxiety are inclusion criteria along with ADHD.

The exclusion criteria are formulated with varying specificity. Thus, some authors[59, 148] demand the absence of other illnesses that could explain symptoms and of unstable psychiatric illnesses, while others[4, 7, 88] specify with more precision and exclude schizophrenia and affective disorders. Also, in three studies[7, 59, 88], patients with known non-responsiveness to the examined active ingredient were excluded. None of the studies included subjects with current drug or alcohol abuse or pregnant and nursing women.

A comprehensive overview of the inclusion and exclusion criteria is provided in Table 17: Inclusion and exclusion criteria of the included studies on efficacy..

Table 17: Inclusion and exclusion criteria of the included studies on efficacy.

Source	Inclusion criteria	Exclusion criteria
Adler et al. 2009a	• Age between 18 and 65 years • Presence of ADHD according to DSM-IV criteria • Body weight of at least 45.4 kg • Persistence of the ADHD symptoms into adulthood • AISRS score of at least 24 • GAF score must lie between 41 and 60	• Persons with signs of states of anxiety and tension, restlessness, HAM-A score ≥ 21, signs of depression (HAM-D ≥ 17), paroxysmal illnesses, thyroid gland hyperfunction • Persons with a depression diagnosed according to DSM-IV or states of anxiety • Persons with known non-responsiveness to MPH, allergies to MPH • Presence of certain medical requirements • Persons, who take medications that can interfere with the effect of MPH • Known or suspected heart abnormalities • Diagnosis or family history of Tourette's syndrome, or motor or verbal ticks • Patients with a comorbid psychiatric diagnosis according to DSM-IV criteria • Persons who were in a state of drug or alcohol dependence in the last 6 months or had suicidal intents during recent years or showed suicidal behaviour • Persons who had an eating disorder in the last 3 years • Persons who are taking antipsychotic medication
Adler et al. 2009c	• Age: 18 to 65 years • Diagnosis: ADHD and social anxiety states according to DSM-IV-TR • Diagnostic criteria of ADHD: CAARS • Diagnostic criteria of the social anxiety states: Structured clinical interview according to DSM-IV-TR Axis I Disorders/Research Version • LSAS ≥50 (Examination 1) • LSAS improvement of ≤ 30 % (Examination 2) • CGI-O-S Score ≥4 (Examination 1 and 2)	• Major depression diagnosis is not more than 6 months old (Examination 1) • Acute or chronic compulsive-obsessive illnesses, bipolar disorders, psychoses, artificial disorders, somatoform disorders and/or acute panic disorders, post-traumatic stress disorders, eating disorders within a year (Examination 1) • Alcohol or drug abuse • Abuse of prescription medications

Table 17: Inclusion and exclusion criteria of the included studies on efficacy – continued

Source	Inclusion criteria	Exclusion criteria
Jain et al. 2007	• Age: 18 to 60 years • Diagnosis of ADHD according to DSM-IV criteria • Presence of an ADHD since childhood • Weight: 50 to 90 kg • IQ: at least 80 according to the Wechsler adult intelligence scale-III in Examination 1 or in the last 5 years • CAARS-S or CAARS-O ≥ 65	• Allergies to MPH or amphetamines • Known severe side effects from MPH or known responsiveness to MPH • Severe illnesses • Severe high blood pressure (values over 100 mm Hg diastolic and 170 mm Hg systolic) • Anxiety disorders according to HAM-A • Depression according to HAM-D • Drug or alcohol abuse in the past • Illnesses of the sensory organs • Autism • Psychoses or other volatile psychological states that require a treatment • Patients that are treated with the following medications: Guanethidine, blood pressure-enhancing medications, monoaminoxidase inhibitors, coumarin anticoagulants, etc.
Kooij et al. 2004	• Diagnosis of ADHD according to DSM-IV criteria • Comorbid psychiatric diseases	• Contraindication for MPH • Clinically significant internal and unstable psychological diseases • Abnormal laboratory values • Tick disorders • IQ < 75 • Psychotropic use • Former use of MPH/amphetamines • Pregnant/nursing
Medori et al. 2008	• Confirmed diagnosis according to DSM-IV and according to the Conners Adult ADHD Diagnostic Interview • Age: 16 to 65 years • Chronic course of the ADHD with presence of some ADHD symptoms before the 7th year of life • CAARS score ≥ 24 during screening	• Minor response or intolerability for MPH • Presence of acute unstable psychiatric diseases (e.g. acute mood disorders, bipolar diseases, acute compulsive-obsessive neuroses) • Substance-dependent addiction diseases (abuse/dependency) according to DSM-IV criteria within the last 6 months • Schizophrenia or affective psychoses in the family • Severe illnesses (e.g. liver or renal insufficiency or cardiac, gastrointestinal, psychiatric or metabolic disorders), hyperthyroidism, myocardial infarction or stroke in the last 6 months before the screening • Paroxysmal diseases, glaucoma or unadjusted hypertension in the medical history
Michelson et al. 2003 (Study I)	• Adult patients • Diagnosis: ADHD according to DSM-IV criteria and CAARS • At least a moderate degree of severity of ADHD • Confirmation of the diagnosis by a 2nd appraiser	• Comorbid major depression, anxiety disorders, bipolar/psychotic disorders • Patients with severe illnesses • Patients with alcohol dependency • Current drug abuse
Weiss et al. 2006	• Age: 18 to 65 years • Diagnosis of ADHD according to DSM-IV criteria	• Persons with eating disorders, substance abuse, brain organic psychosyndrome, neurological disorders, psychoses, acute risk of suicide • Other comorbid disorders
Wilens et al. 2001	• Age: 20 to 59 years • Recruiting: Advertising and transfer • Diagnosis: ADHD according to DSM-III-R or DSM-IV	• Severe chronic diseases • Heart rhythm disorders or paroxysmal illnesses in the past • IQ < 75 • Organic brain syndrome • Unstable psychological constitution • Bipolar disorders • Alcohol or drug abuse or dependencies 6 months before the start of the study • Current intake of psychopharmaceuticals

Table 17: Inclusion and exclusion criteria of the included studies on efficacy – continued

Source	Inclusion criteria	Exclusion criteria
Wilens et al. 2008b	• Age: 18 to 55 years • Diagnosis: ADHD according to DSM-IV criteria • CGI-O-S Score ≥ 4	• Current health problems • Pathological baseline lab values • Developmental delays • Psychotic disorders • Bipolar disorders • HAM-D > 15 • Eating disorders • Organic brain disorders with non-febrile paroxysmal diseases • Drug abuse, alcohol abuse, positive urine drug test (cocaine, heroine, marijuana) in the last 6 months. • Taking of stimulants 1 week before randomisation; benzodiazepine, antiepileptics 2 weeks before randomisation, antidepressants 4 weeks before the randomisation, antipsychotics and monoaminoxidase inhibitors 8 weeks before randomisation.

ADHD = attention deficit/hyperactivity disorder. AISRS = Adult ADHD Investigator Symptom Rating Scale. CAARS = Conners Adult ADHD Rating Scale. CAARS-O = Conners Adult ADHD Rating Scale/Observer-rated. CAARS-S = Conners Adult ADHD Rating Scale/Self-rated. CGI = Clinical Global Impression Scale. CGI-O-S = Clinical Global Impression Overall Severity. DSM-III-R = Diagnostic and Statistical Manual of Psychological Disorders, 3rd revision. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. DSM-IV-TR = Diagnostic and Statistical Manual of Psychological Disorders, 4th text revision. GAF = Global assessment of functioning. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. MPH = Methylphenidate. IQ = Intelligence quotient ITT = Intention-to-treat. LSAS = Liebowitz social anxiety scale LOCF = Last observation carried forward.

The duration of intervention in the studies varies between two weeks and five months. It is essentially determined by the active ingredient to be examined. Since the onset of the effect can take up to four weeks with ATX, a longer intervention period is allowed for in the ATX studies.

The calculated sample sizes fluctuate, as do the study durations. The number of subjects per study ranges from 40[152] to 442[4], since different assumptions underlie the sample size calculation in different studies.

Information on the number of drop-outs is found in all studies, but they are reported in varying detail. The descriptions of the drop-outs in the studies of Adler et al.[4, 7] and Michelson et al.[90] are presented so as to be sufficiently transparent. These publications state the number of the prematurely exiting patients per treatment group and the reasons for their exit.

The studies of Jain et al.[59] and Wilens et al.[152] do not list the prematurely exiting participants separately according to intervention and control group, so that differences between the groups are not evident. Medori et al.[88] lists drop-outs by treatment group but without stating the reasons. The studies of Weiss et al.[144] and Wilens et al.[148] report the drop-outs in detail separately for the intervention and the control group, but the reasons for exiting are only stated for the two groups together. The study of Kooij et al.[67] does not have any drop-outs.

Only three studies[4, 144, 148] provide information on compliance.

Table 18: Study duration, patient number, drop-outs and compliance in the included studies on studies on efficacy summarises the study characteristics.

Table 18: Study duration, patient number, drop-outs and compliance in the included studies on efficacy

Source	Study duration	Number of groups/ number of patients	Drop-outs in %	Compliance
Adler et al. 2009a	7 weeks	Number of randomised patients: N = 229 N(MPH) = 113; N(Pl) = 116 Number of analysed patients: N = 226 N(MPH) = 110; N(Pl) = 116	MPH = 27.2 Pl = 22.4	Return of the packages
Adler et al. 2009c	16 weeks	Number of randomised and analysed patients: N = 442 N(ATX) = 224; N(Pl) = 218	ATX = 43.3 Pl = 37.2	n. i.
Jain et al. 2007	5 to 11 weeks	Number of randomised patients: N = 50 Number of analysed patients (ITT): N = 48 Number of analysed patients (PPA): N = 39 No information on the distribution of patients in the comparison arms.	Total = 12	Return of the packages and questioning of the patients
Kooij et al. 2004	2 x 3 weeks, 1 week wash-out	Number of randomised and analysed patients: N = 45 N(MPH/Pl) = 25; N(Pl/MPH) = 20	No drop-outs	Electronic monitoring (no detailed information)
Medori et al. 2008	5 weeks	Number of randomised patients: N = 402 Number of analysed patients (primary end point): N = 394 N(MPH 18 mg) = 99; N(MPH 36 mg) = 101; N(MPH 72 mg) = 99; N(Pl) = 95	Total = 9 MPH 18 mg = 5.9 MPH 36 mg = 9.8 MPH 72 mg = 13.7 Pl = 6.2	Return of the packages
Michelson et al. 2003 (Study I)	10 weeks	Number of randomised patients: N = 280 N(ATX) = 141; N(Pl) = 139 Number of analysed patients: N(ATX) = 133; N(Pl) = 134	ATX = 28 Pl = 23	Return of the packages
Weiss et al. 2006	5 months	Number of randomised and analysed patients: N = 98 No information on the distribution of the patients.	Total = 35 Intervention = 38 Pl = 23	Return of the packages
Wilens et al. 2001	6 weeks	Number of randomised and analysed patients: N = 40 N(Bp) = 21; N(Pl) = 19	Total = 0.05	Return of the packages
Wilens et al. 2008b	8 weeks	Number of randomised and analysed patients: N = 126 N(NS) = 63; N(Pl) = 63	NS = 19 Pl = 30	n. i.

ATX = Atomoxetine. Bp = Bupropion. ITT = Intention-to-treat. n. i. = no information. MPH = Methylphenidate. N = Number. NS = NS2359. Pl = Placebo. PPA = Per protocol analysis.

5.4.4 Characteristics of the study population

An overview of the included patient sample is provided in Table 19: Characteristics of the study population.

Table 19: Characteristics of the study population

Source	Distribution of sex in % (proportion of men)	Average age (in years)	Dose/day (average)	Expression of the ADHD in %	Average primary end point value baseline
Adler et al. 2009a	MPH = 57.3 Pl = 55.2	MPH = 39.9 (SD = 12.27) Pl = 38.2 (SD = 11.40)	MPH = 67.7 mg (SD = 27.9) Pl = 86.9 mg (SD = 27.81) Dose titration	Combined subtype: MPH = 29.1; Pl = 81	AISRS score: MPH = 38.6 (SD = 6.85) Pl = 38.1 (SD = 7.31)
Adler et al. 2009c	Total = 53.6	Total = 38	Last ATX dosing = 82.9 mg Dose titration	Combined subtype: Total = 57.2	CAARS-Inv Total Score: ATX = 29.6 (SD = 10.4) Pl = 31.2 (SD = 9.4) CAARS-Inv index subscale: ATX = 19.8 (SD = 6.8) Pl = 20.5 (SD = 5.8) CAARS-Inv hyperactivity/impulsiveness: ATX = 12.7 (SD = 5.9) Pl = 12.7 (SD = 5.6) CAARS-Inv inattentiveness: ATX = 17.0 (SD = 6.0) Pl = 18.5 (SD = 21.3)
Jain et al. 2007	According to ITT: Total = 62.5 According to PPA: Total = 59	According to ITT: Total = 37.2 According to PPA: Total = 37.9	MPH = 57.8 mg (SD = 20.1) Pl = 64.9 mg (SD = 17.5) Dose titration	n. i.	CAARS-S scale ITT: Total = 72.8 (SD = 8.4) CAARS-S scale PPA: Total = 72.3 (SD = 8.2) CAARS-O scale ITT: Total = 73.5 (SD = 7) CAARS-O scale PPA: Total = 73.4 (SD = 6.8)
Kooij et al. 2004	Total = 53.3	Total = 39.1	End of Week 3: MPH/Pl = 0.91 mg/kg Pl/MPH = 0.98 mg/kg	Combined subtype: Total = 43	n. i.
Medori et al. 2008	MPH_18 mg = 57.4 MPH_36 mg = 45.1 MPH_72 mg = 53.9 Pl = 61.5	MPH_18 mg = 34.2 MPH_36 mg = 33.8 MPH_72mg = 33.6 Pl = 24.5	Fixed dosing with 18 mg, 36 mg, 72 mg	Combined subtype: MPH_18 mg = 63.4 MPH_36 mg = 74.5 MPH_72 mg = 75.5 Pl = 69.8	CAARS:O-SV Total Score: MPH_18 mg = 35.6 MPH_36 mg = 37.3 MPH_72 mg = 36.6 Pl = 37.2

Table 19: Characteristics of the study population – continued

Source	Distribution of sex in % (proportion of men)	Average age (in years)	Dose/day (average)	Expression of the ADHD in %	Average primary end point value baseline
Michelson et al. 2003 (Study I)	ATX = 64.5 Pl = 62.6	ATX = 40.2 (SD = 11.7) Pl = 40.3 (SD = 11.6)	Most frequent dosing Study I: 90 mg: 40.4% 120 mg: 39.7% 60 mg: 19.9% Dose titration	Combined subtype: ATX = 71.6 Pl = 71.9	Average CAARS-Inv score Total ADHD Symptom Score ATX = 33.6 (SD = 7.2) Pl = 33.2 (SD = 7.8) Inattentiveness ATX = 18.4 (SD = 4.2) Pl = 18.6 (SD = 4.4) Hyperactivity/impulsiveness ATX = 15.2 (SD = 5.0) Pl = 14.5 (SD = 5.4)
Weiss et al. 2006	Total = 64	Total = 37.5 (SD = 10.75)	Maximum dosing of PAR 40 mg/d and DEX 40 mg/d: 52.6% Maximum dosing in Pl: 68%	Combined subtype: Total = 60	Average ADHD-RS-IV-Inv total: 32.20 (SD = 7.55)
Wilens et al. 2001	Total = 55 Bp = 57 Pl = 53	Total = 38.3 (SD = 11.1) Bp = 37.0 (SD = 11.8) Pl = 39.6 (SD = 10.4)	Distribution of the daily Bp dosing: 400 mg: 76% 300 mg: 10% 200 mg: 14%	Combined subtype: Total = 35 Inattentive subtype: Total = 58	n. i.
Wilens et al. 2008b	NS = 74.6 Pl = 66.7	NS = 35.0 Pl = 35.2	n. i.	Combined subtype: NS = 60.3; Pl = 50.8 Inattentive subtype: NS = 27 Pl = 46	n. i.

ADHD = Attention deficit/hyperactivity disorder. AISRS = Adult ADHD Investigator Rating Scale. ATX = Atomoxetine. Bp = Bupropion. CAARS-Inv = Conners Adult ADHD Rating Scale/Observation-rated. CAARS-S = Conners Adult ADHD Rating Scale/Investigator-rated. CAARS-S = Conners Adult ADHD Rating Scale/Self-rated. DEX = Dextroamphetamine. ITT = Intention-to-treat. n. i. = no information. MPH = Methylphenidate. NS = NS2359. PAR = Paroxetine. Pl = Placebo. PPA = Per protocol analysis. SD = Standard deviation.

The study population includes in all studies adult men and women with ADHD who have a minimum age of 18 years. The proportion of men ranges from 45.1 % to 74.6 %. A greater proportion of men is found almost throughout all studies, which could be due to the greater prevalence rate in men. The age of the participants is stated as being on average in the range from 33 to 40 years.

Strong deviations appear in the studies with respect to the average daily dosing. MPH is administered orally in various doses. It should be noted in the MPH studies with dose titration that the intervention group was dosed lower throughout compared with the placebo group but without being able to determine statistically significant differences[7, 59, 67].

ATX was also administered orally and in varying doses. In Adler et al.[4], the average last daily ATX dosage was 82.9 mg. By contrast, Michelson et al.[90] state the percent proportion of various dosages, which was 39.7 % for 120 mg, 40.4 % for 90 mg and 19.9 % for 60 mg. The dosages in the other studies are shown in Table 19: Characteristics of the study population. None of the studies exhibited a significant difference between the patient groups with respect to the demographic parameters.

5.4.5 Results for primary end points

The change of the primary end points in the group comparison is shown in Table 20: Changes of the primary end points between the start and end of the study. All studies listed in Table 20 were used to answer the research question. The biggest difference in the changes between the baseline and the end of the study in the group comparison was revealed in the high-dosage MPH group of the study by Medori et al.[88]. All studies showed an improvement in the ADHD symptoms measured on various scales in the intervention groups. Overall, the group differences in the MPH studies are subject to a greater fluctuation range than the ATX studies (ATX: -1.6 to -3.1; MPH: -0.19 to -6.1), which may be a consequence of the different scales.

The level of significance in six studies[4, 7, 67, 90, 148, 152] was determined at 0.05 and in one study[88] at 0.016. Jain et al.[59] give for the test variable of the sample a p-value of < 0.05 and Weiss et al.[144] a p-value of 0.05.

On this basis, the authors of seven studies[4, 59, 67, 88, 90, 148, 152] have evaluated the change as statistically significant. Therefore, a tendency in favour of the examined active ingredients compared with the placebo must be assumed. The observed therapy duration and the ADHD measurement scale used have remained without influence on the result, since both in longer and in shorter studies with varying measurement scales the deviations have been assessed as equally significant or not-significant. With regard to individual active ingredients, evidence for ATX is recognizable. The study by Adler et al.[4] shows significant results across all scales, as does the study by Michelson et al.[90] on the comprehensive scale according to CAARS. For MPH, Medori et al.[88] recorded statistically significant results for all dosages. Jain et al.[59] and Kooij et al.[67] only reported significant results in the self-rating scale according to CAARS and the CGI.

Overall, both for ATX and for MPH, evidence of effectiveness is recognizable in favour of the examined active ingredient.

A marked reduction of the ADHD symptoms can be demonstrated for dextroamphetamine as monotherapy and in combination with paroxetine ($p < 0.012$)[144]. Bupropion and NS2359 show positive therapy effects compared with the placebo that are statistically secured. However, only one study relating to ADHD in adulthood is available for these active ingredients to be able to assume a high degree of evidence[148, 152].

Table 20: Changes of the primary end points between the start and end of the study

Source	Active ingredient	Scale	Intervention group		Control group		Difference[1)]	p-value and CI
			N	Change (SD)	N	Change (SD)		
Adler et al. 2009a	MPH	AISRS	110	-10.6 (1.09)	116	-6.8 (1.06)	-3.8[2)]	0.12
Adler et al. 2009c	ATX	CAARS-Inv Total Score CAARS-Inv index subscale	224	-8.7 (10.0) -5.7 (7.3)	218	-5.6 (10.2) -3.2 (6.7)	-3.1[2)] -2.5[2)]	< 0.001; 95 % CI [-6.0;-2.2] [3)] < 0.001; 95 % CI [-6.0;-2.2] [3)]
Jain et al. 2007	MPH	CAARS-S CAARS-Inv CGI-I	Both arms: 48 (crossover)	n. i.	Both arms: 48 (crossover)	n. i.	n. i.	0.0033[3)] 0.0967 0.0005[3)]
Kooij et al. 2004	MPH	ADHD-RS CGI	20/25	n. i.	25/20	n. i.	-0.19 -0.72	0.064 0.026[3)]
Medori et al. 2008	MPH_18 mg MPH_36 mg MPH_72 mg	CAARS-Inv	99 101 99	-10.6 (10.34) -11.5 (9.97) -13.7 (11.11)	95	-7.6 (9.93)	-3.0[2)] -3.9[2)] -6.1[2)]	0.015; 95 % CI [-12.7;-8.55] [3)] 0.013; 95 % CI [-13.4; -9.5][3)] < 0.001; 95% CI [-15.9; -11.5][3)]
Michelson et al. 2003	ATX	CAARS-Inv sum score: CAARS-Inv Inattentive CAARS-Inv Hyperact	133	-9.5 (10.1) -5.0 (5.7) -4.5 (5.1)	134	-6.0 (9.3) -3.1 (5.8) -2.9 (4.9)	-3.5[2)] -1.9[2)] -1.6[2)]	0.005; 95 % CI [-5.61;-0.99][3)] 0.17; 95 % CI [-3.21;-0.45] 0.17; 95 % CI [-2.67;-0.27]
Weiss et al. 2006	PAR DEX PAR/DEX	ADHD-RS, HAM-A, HAM-D	24 23 25	n. i.	26	n. i.	n. i.	DEX and PAR/DEX vs. PAR and PI: 0.012
Wilens et al. 2001	Bp	ADHD-RS CGI	21	Improvement by 42 % n. i.	19	Improvement by 24 % n. i.	18 percent n. i.	0.05[3)] n. i.
Wilens et al. 2008b	NS2359	ADHD-RS-Inv	63	-7.8 (1.3)	63	-6.4 (1.3)	-1.4[2)]	< 0.45[3)]

ADHD-RS = ADHD Rating scale. AISRS = Adult ADHD Investigator Symptom Rating Scale. ATX = Atomoxetine. Bp = Bupropion. CAARS-Inv = Conners Adult ADHD Rating Scale/Investigator-rated. CAARS-S = Conners Adult ADHD Rating Scale/Self-rated. CGI = Clinical Global Impression Scale DEX = Dextroamphetamine. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. n. i. = no information. CI = Confidence interval. MPH = Methylphenidate. PAR = Paroxetine. PI = Placebo. SD = Standard deviation.

[1)] The difference constitutes the respective change between the baseline and the follow-up in the group comparison.

[2)] Own calculations.

[3)] Values statistically significant.

A uniform measurement and evaluation of the therapeutic effect was not found across the different studies. Overall, ten different scales were used for measurement. The majority of these is ADHD-specific.

In the studies, response rates from 7 % to 42 % were found in the control group and from 17 % to 59.6 % in the intervention group (Table 21: Representation of the response rate in the intervention and control groups of the included studies on efficacy). The two ATX studies provide no information on the percent response rate.

The study by Wilens et al.[148] shows that the response rate can be dependent on the ADHD subtype. In this study, patients with ADHD of the combined subtype according to the DSM-IV criteria responded more strongly to the placebo (42 %) than to NS2359 (30 %). By contrast, patients of the primarily inattentive subtype according to the DSM-IV criteria showed a significantly higher response ($p < 0.001$) in the intervention group (41 % vs. 7 %).

In three studies[7, 59, 88], patients with known non-responsiveness to MPH were excluded. A difference regarding the response rate is not evident compared with the other studies, but should be included in the interpretation of the results as a possible error. The inclusion of the patients with known non-responsiveness to MPH is closer to reality and could have resulted under circumstances in a lower response rate.

When the response rates of the studies are related to the used doses, a tendency towards increase of the response with increased daily dose can be recognized.

Table 21: Representation of the response rate in the intervention and control groups of the included studies on efficacy

Source	Active ingredient	End point	Responders active ingredient in %	Responders control in %	p-value***	Dosage
Adler et al. 2009a	MPH	AISRS	36.9*	20.9*	0.009*	MPH = 67.7 mg Pl = 86.9 mg Dose titration
Adler et al. 2009c	ATX	CAARS-Inv	n. i.	n. i.	n. i.	N. R.
Jain et al. 2007	MPH	CAARS, CGI	48.7**	23.1**	0.0158**	MPH = 57.8 mg Pl = 64.9 mg Dose titration
Kooij et al. 2004	MPH	ADHD-RS, CGI	ADHD-RS + CGI: 38* Only ADHD-RS: 42* Only CGI: 51*	ADHD-RS + CGI: 7* Only ADHD-RS: 13* Only CGI: 18*	ADHD-RS + CGI: 0.003* Only ADHD-RS: 0.011* Only CGI: 0.011*	End of Week 3: MPH/Pl = 0.91 mg/kg Pl/MPH = 0.98 mg/kg
Medori et al. 2008	MPH	CAARS-Inv	18 mg = 50.5* 36 mg = 48.5* 72 mg = 59.6*	27.4*	<0.001*	Fixed dosage
Michelson et al. 2003	ATX	CAARS sum score (third-party assessment)	n. i.	n. i.	n. i.	N. R.
Weiss et al. 2006	PAR, DEX	ADHD-RS, HAM-D, HAM-A	DEX = 85.7** PAR/DEX = 66.7** PAR = 20**	21.1**	0.001 for DEX	Maximum dosage of PAR 40 mg/d and DEX 40 mg/d: 52.6 % Maximum dosage in Pl: 68%
Wilens et al. 2001	Bp	CGI, ADHD-RS	CGI: 52* ADHD-RS: 76*	CGI: 11* ADHD-RS: 37*	CGI: 0.007* ADHD-RS: 0.02*	Distribution of the daily dosage: 400 mg: 76 % 300 mg: 10 % 200 mg: 14 %
Wilens et al. 2008b	NS2359	ADHD-RS	Total: 33* Inattentive subtype: 41* Combined subtype: 30*	Total: 33* Inattentive subtype: 7* Combined subtype: 42*	Total: 0.55* Inattentive subtype: < 0.001* Combined subtype: 0.23*	n. i.

ATX = Atomoxetine. ADHD-RS = ADHD Rating Scale. AISRS = Adult ADHD Investigator Rating Scale. Bp = Bupropion. CAARS = Conners Adult ADHD Rating Scale. CAARS-S = Conners Adult ADHD Rating Scale/Investigator-rated. CGI = Clinical Global Impression. DEX = Dextroamphetamine. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, 4th version 4. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. MPH = Methylphenidate. n. i. = no information. N. R. = Not relevant. PAR = Paroxetine. Pl = Placebo.

* A responder is defined as an improvement of at least 30 % with respect to the primary end points.

** A responder is defined as a large improvement or a very large improvement of the CGI.

*** The p-value indicates the statistical significance of the responder between the active ingredient and the control groups.

In the study by Kooij et al.[67], the authors performed a subgroup analysis with the objective of uncovering possible associations between MPH response and age, sex and comorbidity. However, the response rates of MPH are not affected by sex, age, comorbidity, degree of severity of anxiety disorders, depression or intelligence.

Table 22: Association between study design and response rates

Study design	Responders to the active ingredient in %
Crossover	48.7, 38-51
Parallel	36.9, 48.5-59.6, 17-65, 52, 76, 30-41

The influence of the duration of the respective active medicated arm and the applied study designs on the response rates is not recognizable. As is evident in Table 22: Association between study design and response rates and Table 23: Association between study duration and response rates, both parallel studies and the examinations in the crossover design arrive at very different results.

Table 23: Association between study duration and response rates

Duration (weeks)	Responder to the active ingredient in % (only MPH)
To 3	38-51 (Kooij et al.[67])
5	48.5-59.6 (Medori et al.[90])
5-11	48.7 (Jain et al.[59])
7	36.9 (Adler et al.[7])

MPH = Methylphenidate.

Furthermore, in some studies strength of effects were calculated to make a statement on the efficacy of the medication. Strength of effects indicate the difference between medication and placebo independently of the measurement scales, which permits a comparison of the various studies with different scales. The strength of effect is a general measure that describes differences in averages between the effect in the intervention group compared with the comparison group in relation to the standard deviation. The following applies: The larger the difference between the placebo and the active ingredient, the larger the strength of effect.

Cohen's d-value indicates a small effect from 0.2, a medium effect from 0.5 and a large effect from 0.8[14, 108]. However, the determination of a relevance limit such as $d \geq 0.2$ is subjective. Figure 3: Formula for calculating the strength of effect according to Cohen's d shows the formula for calculating the strength of effect according to Cohen's d.

$$d = (m_t - m_c)/s$$

$$s = (((n_t - 1)\, s_t^2 + (n_c - 1)s_c^2)/(N - 2))^{½}$$

s = Pooled variance

m_t = Average of the treated group

m_c = Average of the control group

s_t = Standard deviation of the treated group

s_c = Standard deviation of the control group

n_t = Number in the treatment group

n_c = Number in the control group

$N = n_t + n_c$ = Number in total

Figure 3: Formula for calculating the strength of effect according to Cohen's d

Source: Sachs/Hedderich[108].

Table 24: Sizes of effect in the included studies on efficacy There are already significant fluctuations within the MPH studies[88]. As can be seen, the strength of effect essentially depends on the dosage: The greater the dosage, the greater the effect. Furthermore, the sequence of the treatment in cross-over studies (placebo/active or active/placebo) can make a difference, as is evident in Kooij et al.[67].

Table 24: Sizes of effect in the included studies on efficacy

Source	Active ingredient	End point	Strength of effect
Adler et al. 2009a	MPH	AISRS	n.i.
Adler et al. 2009c	ATX	CAARS-Inv	0.47
Jain et al. 2007	MPH	CAARS, CGI	CAARS: 0.53 CGI: 0.90
Kooij et al. 2004	MPH	ADHD-RS, CGI	CGI: End of 3rd week: 0.30* CGI: End of 7th week: 0.63* ADHD-RS: End of 3rd week: 0.30* ADHD-RS: End of 7th week: 0.32*
Medori et al. 2008	MPH	CAARS-Inv	MPH_18 mg = 0.38 MPH_36 mg = 0.43 MPH_72 mg = 0.62
Michelson et al. 2003	ATX	CAARS sum score (third-party assessment)	0.35
Weiss et al. 2006	PAR, DEX	ADHD-RS, HAM-D, HAM-A	n. i.
Wilens et al. 2001	Bp	CGI, ADHD-RS	n. i.
Wilens et al. 2008b	NS2359	ADHD-RS	n. i.

ADHD-RS = ADHD Rating scale. AISRS = Adult ADHD Investigator Symptom Rating Scale. ATX = Atomoxetine. Bp = Bupropion. CAARS = Conners Adult ADHD Rating Scale. CAARS-S = Conners Adult ADHD Rating Scale/Investigator-rated. CGI = Clinical Global Impression. DEX = Dextroamphetamine. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. MPH = Methylphenidate. n. i. = no information. PAR = Paroxetine.

* Own calculation according to Cohen's d.

A significant variation of the strength of effect according to Cohen's d can also be found in the ATX studies. Both strengths of effect move in the medium range (0.35 and 0.47).

If the strengths of effect for MPH and ATX are compared, it becomes clear that the greater strengths of effect and greater ranges of strength of effect (0.30 to 0.90) are present in the MPH studies, but this may be due to the greater number of studies and the partially larger study populations.

A more advanced meta-analysis was not conducted due to qualitative deficiencies in the studies and the different study populations and characteristics.

5.4.6 Results for the secondary end points

Secondary patient-relevant end points are additional indicators of the efficacy of a treatment. However, they only have a limited meaning since they are not adjusted to a statistical method or a sample size calculation.

In the included studies, secondary end points include laboratory parameters and aspects of the quality of life such as scales (CGI, CAARS) that are used in other studies to measure primary end points. The following discussions comprise the results of the most relevant secondary end points. The extraction forms are available in Appendix 9.6 (Extraction forms of the assessed studies (included after the third selection)) for detailed information.

Depression and anxiety disorders

Results regarding the effects of medication on depression and anxiety disorders are reported by four studies[59, 67, 90, 152]. The Ham-A, HAM-D, Beck Depression, State-Trait Anxiety Inventory (STAI) and LSAS scales were used to quantify the disorders.

In the study by Kooij et al.[67], MPH is associated with statistically significantly ($p = 0.002$) stronger illness phenomena regarding depression and anxiety disorders as compared with the placebo. By

contrast, the studies by Jain et al.[59], Michelson et al.[90] and Wilens et al.[152] could not determine a link between treatment and change in the depression or anxiety disorders.

Vital signs

Vital signs were considered another end point. The term vital signs include life signs such as pulse, blood pressure and heart rate. In the study by Adler et al.[7], a reduction of the systolic blood pressure and an elevation of the diastolic blood pressure were observed in both groups, as well as a faster pulse in the MPH group and a slower pulse in the placebo group. Adler et al.[4] and Weiss et al.[144] also report an increase of the diastolic blood pressure. Medori et al.[88] note a statistically significant ($p < 0.001$) reduction of the blood pressure up to the third week in the intervention group with 36 mg as compared with the placebo group.

In summary, a uniform statement on possible changes and especially the clinical relevance cannot be made with regard to vital signs.

Function level and quality of life

The quality of life and the function level are determined by means of diverse instruments (Adult ADHD Quality of life Scale [AAQoL], Patient Satisfaction Survey [PSS], Sheehan Disability Scale [SDS]).

The general functional level was recorded in the study by Kooij et al.[67] using the Global Assessment of Functioning (GAF) scale. The GAF scale can particularly serve to make comprehensive statements on the clinical progress of patients by means of a single measure. The functional level of the affected persons improved during the course of the studies. The authors grade this result as not statistically significant ($p = 0.104$) [67].

Three studies provide information on SDS [67, 88, 90]. All studies arrive at the conclusion that in the intervention group in comparison with the placebo on average lower SDS values and, therefore, a stronger functional improvement can be determined. A statistically significant result ($p = 0.004$) is manifest in the study of Medori et al.[88], especially in the high-dosed MPH group.

The data obtained on AAQoL and PSS show that the treatment of ADHD with ATX or MPH is superior to the placebo[4, 59].

5.4.7 Results regarding the side effects

Since the spectrum and the frequency of possible side effects depend on the administered active ingredient and its dosing, the side effects are considered in the following, separated according to MPH, ATX, bupropion, NS2359 and dextroamphetamine/paroxetine.

The range of the side effects of MPH extends from relatively harmless accompanying phenomena (e. g. fatigue) to severe adverse events. Adler et al.[7] report a large number of side effects in the MPH group (84.5 %) and the placebo group (63.8 %), where no severe side effects occurred. A discontinuation of the study due to side effects occurred in 38 % of cases with MPH and 23 % with the placebo. The dose can at any time be reduced if side effects occur. In all patients, reduced appetite, headaches, dry mouth and anxiety are observed most commonly.

In the study by Jain et al.[59], especially insomnia and nervousness are reported with MPH. Severe side effects were not observed.

In Kooij et al.[67], especially reduced appetite (in 22 % of the patients) and dry mouth (in 24 % of patients) were particularly evident among therapeutically adverse effects with MPH. The proportion of all side effects is greater with MPH at 82% than with the placebo at 69 %, but not to a statistically significant extent ($p = 0.11$). Due to side effects, eight patients reduced the MPH dosage.

In the study by Medori et al.[88], the side effects consisted especially of loss of appetite (25 % with MPH, 7 % with placebo), headaches (21 % with MPH, 18 % with placebo) and weight loss ($p < 0.001$). The proportion of side effects increases with the dosage. Therefore, side effects in the intervention group with 18 mg MPH daily amounted to 75.2 % as compared with 82.4 % with 72 mg daily. Similarly, the proportion of drop-outs due to adverse therapeutic effects is larger in the high-dose group. Severe side effects occurred in equal proportions in the group with 18 mg (2 %) and 72 mg (2 %).

The spectrum of the side effects of ATX is largely comparable with that of MPH. The most commonly reported adverse therapeutic effects are headaches, sleep disorders, nausea and dryness of the mouth ($p < 0.001$)[4].

Bupropion shows good tolerability during application and no statistically significant differences ($p < 0.05$) regarding side effects as compared with the placebo[152]. Likewise, no differences can be found in NS2359 treatment[148].

The number of reported severe adverse effects as well as faster pulses and weight loss is statistically significantly increased with paroxetine in combination with dextroamphetamine ($p < 0,001$). Patients[144] who receive paroxetine treatment alone, however, gain weight on average.

In summary, there is no proof of harm caused by administering a medication.

5.4.8 Summary of the results regarding medical efficacy

For most examined active ingredients, a positive effect can be demonstrated with regard to restlessness, attention deficit, impulsiveness and depressive mood disorders, without a tolerance developing. A statistically significant change was reported in eight studies[4, 59, 67, 88, 90, 144, 148, 152]. Overall, studies with ATX exhibit the greatest improvement of ADHD symptoms measured by means of various scales in the intervention groups.

The responder rates in the studies fluctuate from 7 % to 42 % in the control group and from 17 % to 59.6 % in the intervention group, where the responder rates are partially differently defined. Neither of the two ATX studies state the response rate in percent.

5.4.9 Critical assessment of study quality

In the following, the study quality of the individual studies is presented. The presentation is guided by the most important points in the check-lists for the randomised studies: sample size calculation, randomisation, statistics, study duration, number of drop-outs, validity of the results. In addition, studies are assessed according to the quantity of the dosing and the applied measurement scales.

Adler LA et al. Efficacy and safety of OROS Methylphenidate in adults with attention-deficit-hyperactivity disorder. A randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. Journal of Clinical Psychopharmacology 2009a; 29: 239-247[7].

It is assessed positively in this study that the methodology (sample size calculation, randomisation, statistics) is transparently described and adequate statistical tests are used. To achieve a balance of the factors of influence, a computer-generated, stratified block randomisation according to centres was performed. However, no information is found on the recruiting of patients.

As another strength of the study, customised dosing that is guided by the improvement of the ADHD measurement scale AISRS should be emphasized. In cases of repeatedly missed intakes, the clinical investigator must re-evaluate the suitability of the person regarding the study requirements.

In this study, it is negative that through exclusion of patients with a known non-response to MPH, the ability to generalise the exposed population is limited and a significant overestimate of the results can occur. Furthermore, patients with comorbid psychiatric disorders such as depression and states of anxiety are excluded. On one hand, ADHD is not negatively affected by comorbid illnesses as a result. On the other hand, these comorbidities are very commonly found in patients with ADHD and can be due to an underlying ADHD illness (cf. Chapter 2.7 Aspects of economics). The external validity, i. e. the transferability of the composition of the study population and of the results to ordinary conditions is not always given in RCTs through subject selection and the study design.

The high number of drop-outs is also considered problematic. A drop-out rate of 20 % was included in the sample size calculation, but the actual rate exceeded this by far. At the end of the study, the data is not available to the planned and required extent and the analyses are based in the intervention group on only 62.8 % of the initially included patients. The values for the other patients were continued according to the LOCF method. Therefore, the probability is low that an actually present difference in effectiveness of moderate dimensions will be discovered.

Adler et al. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. Depression and Anxiety 2009c; 26: 212-221[4].

This publication by Adler et al.[4] is positively assessed with regard to the description of the statistical analysis. Furthermore, a study duration of 16 weeks can be classified as suitable, since ATX does not act immediately after intake but must be taken over a period of at least six weeks.

The gaps in presenting the methodology must be considered a weakness of the publication. There is no description of the recruiting of the patients and recording of compliance and concealment.

As already shown in another publication by Adler et al.[7], this study, too, has a very high rate of drop-outs which limits the meaningfulness of the study to a high degree. Of the 442 randomised patients, only 264 patients completed the study. Sample size calculation was performed but without taking into account an assumed number of drop-outs.

The randomisation of the patients is described as a blinded, computer-generated randomisation, but a detailed description of the randomisation (e. g. decentralised or centralised) is not provided, although it would have been important due to the multicentre study design.

In addition, the fixed dose titration that does not relate to the improvement of the ADHD symptoms or body weight should be seen as a weakness of the study. However, especially ATX requires a customised dosing due to the varied metabolisation of the medication.

Apart from the limitations explained, it should be noted that the study is restricted to a limited patient sample, since only patients with ADHD and states of anxiety according to DSM-IV-TR criteria were included.

Jain et al. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled cross-over study. J Clin Psychiatry 2007; 68: 268-277[59].

In this study, the customised dose titration, measured with the CGI, the definition of compliance and the blinding of patients and investigators should be positively emphasized in this study. The description of the statistical analyses is transparent and the current methods are used. The inclusion and exclusion criteria of the study are clearly defined. Patients with known non-responsiveness to MPH and patients with psychological disorders such as depression and anxiety disorders were excluded. Therefore, its transferability to the general population is limited.

A weakness of the study is using the crossover design rather than the more high-quality parallel design. It should be noted that this study design is only considered for few medical questions. Precondition for this study design is that healing of the illness is impossible and that the patient's condition in Period 2 is comparable with Period 1. To allow adverse time or interaction effects (carry-over effects) to subside, a wash-out period can be interposed in which neither of the two treatments is administered. The value of crossover studies is improved because subjects are less likely to drop-out, if they can rest assured that they will be given the active ingredient in one of the two crossover study phases.

Furthermore, the publication contains no information on the number of centres, concealment and randomisation. Also, the patient characteristics are only provided for their entirety and not by groups.

According to the CAARS scales, the patients have very pronounced ADHD symptoms at the start of the study. The initial level is relevant for the improvement, since patients with strong symptoms can improve more than patients with milder symptoms. In weakly affected patients, an objective result is more difficult to reach.

Kooij et al. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. Psychological Medicine 2004; 34(6): 973-982[67].

Overall, this is a double-blind, monocentre crossover study with a low sample size, but of sufficient methodical quality. The explicit inclusion of comorbid psychiatric illnesses should be assessed as positive for its external validity. Patients with prior use of MPH or amphetamines were excluded. However, a distortion of the study results or limitations regarding transferability to the general population is not anticipated from this exclusion of patients.

A wash-out phase of one week is sufficient with the active ingredient MPH since the substance is completely eliminated after maximally four days. An effect on a subsequent placebo therapy cannot be expected from prior administration of MPH.

The statistical methodology is sufficiently described and suitable statistical tests were performed. Another clear advantage of the study is performing a subgroup analysis that analyses the link between MPH response, age, sex and comorbidities. Furthermore, it can be seen as positive that all patients completed the study.

However, the publication gives no details on duration of the study, concealment and sample size calculation. Furthermore, the inclusion criteria are not clearly defined since no age limits are stated and, therefore, children and adolescents should be included. In fact, only adults with ADHD were included.

The low compliance of the study participants is also considered problematic, as a result of which a distortion potential arises in the study. The proportion of patients who do not follow therapy instructions (take at least 80 % of the medications, electronic monitoring) is 29 %. Poor compliance can result in a reduced effectiveness of MPH since the determined dosing is not achieved and, therefore, can affect the response rate negatively. Kooij et al.[67] do not explain the causes of the poor compliance but these can be multilayered, e. g. due to the occurrence of adverse events.

Furthermore, the baseline characteristics are only described for the entire study sample, but not for the individual groups separately, so that none of the initial group differences become evident. The medication is titrated after one and two weeks and is administered in doses related to body weight .

Medori et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS Methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2008; 63: 981-989[88].

Positive aspects are the multicentre study design, securing the compliance and the transparent presentation of applied statistical methods (covariance analysis, Cochran-Mantel-Haenszel test, Dunett method). Randomisation was performed as a computer-generated, permuted block randomisation with stratification according to study centre that appears adequate in view of the multicentre study design. Also, a sufficiently high sample size and a sufficiently high number of patients who completed the study are described.

The study is also largely transparently documented. The description of the inclusion criteria constitutes the exception. It is noted that patients with acute unstable psychiatric illnesses (e. g. acute mood disorders, bipolar diseases, acute compulsive-obsessive neuroses) were excluded, but it is not evident to what extent patients with acute or prior depressions or anxiety disorders were included. Furthermore, the external validity of the study is weakened by the fact that patients with a low response rate to MPH were excluded and all patients received a fixed dose.

In summary, it can be note that this study is not particularly meaningful for individual patients. An optimal effectiveness of MPH can only occur with a dose adjustment and not with a fixed dosage. Therefore, it is possible, for example, that the dose of patients in the 18-mg and 36-mg groups is too high and an optimal result was not achieved. In cases of an excessive dose, MPH can result in a worsening of the ADHD symptoms.

Michelson et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biological Psychiatry 2003; 53: 112-120[90].

The publication by Michelson et al.[90] describes two multicentre RCTs. The study's advantage is its multicentre design. However, due to qualitative weaknesses, only one study will be included in the analysis.

Points of criticism are the exclusion of comorbid disorders, the fixed dosing, the short intervention period and the lacking description of the sample size calculation. The statistics and the randomisation are presented in detail. The statistics and the randomisation of the two studies were not described separately, but this is not considered necessary.

The method of analysis in the study by Michelson et al.[90] is indicated for an intention-to-treat (ITT) population , but in fact only 265 of the 289 randomised patients are analysed.

Weiss et al. A randomized double-blind trial of Paroxetine and/or Dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. J Clin Psychiatry 2006: 67: 611-619[144].

The objective of the study by Weiss et al.[144] is the assessment of efficacy and safety of paroxetine and dextroamphetamine in monotherapy and combination therapy in adults with ADHD. Also, all patients received a problem-oriented psychotherapy that was developed by the authors. For this purpose, a multicentre study design with five centres in Canada and the USA was selected. The patients were recruited through psychiatric clinics and outpatient clinics. A positive aspect of the study is the individual weekly dose titrations over a period of four weeks, as defined according to the Clinical Global Impression Improvement Scale (CGI-I). Furthermore, the concealment, compliance and sample size calculation are described transparently. The randomisation is designated a block randomisation. A stratified randomisation would have been better in this case to ensure a distribution equality in all centres.

As a point of criticism, the high drop-out rate of, on average, 35 % across all groups should be noted. The occurrence of adverse events was the most common reason for dropping out. Drop-outs are included in the sample size calculation, but only as a proportion of 20 %. The high drop-out rate constitutes a limiting factor in the study quality, because for 35 % of the patients missing values must be replaced, as a result of which a distortion of the study results can arise. It cannot be assessed which distortions will arise from this.

The statistical analysis of the primary patient-relevant end points were implemented with a 2 x 2 factor model, that is, dextroamphetamine (DEX and PAR/DEX) vs. no dextroamphetamine (PAR and placebo) x paroxetine (PAR and PAR/DEX) vs. no paroxetine (DEX and placebo).

Wilens et al. A controlled clinical trial of Bupropion for attention deficit hyperactivity disorder in adults. Am Journal of Psychiatry 2001; 158: 282-288[152].

In the study by Wilens et al.[152], a transparent presentation of the analytical methods and the use of conventional statistical methods such as Fisher's Exact Test and the Wilcoxon rank sum test are positive points.

However, the study shows some methodical weaknesses. A description of the randomisation was not provided. The sample size calculation was presented but its logic is difficult to understand since it is based on an assumption of 20 patients per comparison group and no drop-outs were planned in.

It is evident in the baseline characteristics that an equal distribution of the randomisation did not succeed: The bupropion group has a clearly higher proportion of patients with current depression and depression in the past. The information on the baseline values of the primary end-point ADHD-RS are entirely lacking, so that the degree of severity of the illness at the start of the study is not recognisable. Therefore, it cannot be assessed whether intervention and control groups were initially comparable.

Furthermore, the generalisability is restricted, since no comorbid disorders were considered and the majority of the included subjects comes from a higher social group. Furthermore, the low sample size is a clear weakness of the study that presumably does not permit valid statistical statements.

Wilens et al. A randomised controlled trial of a novel mixed monoamine re-uptake inhibitor in adults with ADHD. Behavioral and Brain Functions 2008b; 4: 24-34[148].

The relatively short therapy duration of the study and the homogeneity of the study population that is presented as a limitation of the study even by the authors restrict the ability to generalise the results. Furthermore, the study only includes a low dosage of the active ingredient NS2359 that may be insufficient for the treatment of ADHD patients. Methodical weaknesses can be found in the missing description of the randomisation and the concealment. The recruiting used advertising and the local media.

The number of drop-outs is high at 30 %, but they are included in the sample size calculation (at 20 %).

Summary assessment of study quality

All studies are RCTs with a high level of evidence (Ib). Almost all of the assessed studies were commissioned by the industry and were of a relatively short therapeutic duration (treatment period under a year), so that no long-term effects can be derived from the results.

The quality and the transparency of the studies differed significantly both in the report quality as well as in the design and implementation. The results of the primary studies partially relate to a small patient sample. The defective description of the randomisation and the sample size calculation as well as the absence of recommendations for clinical action must be faulted. Despite an adequate implementation of superordinate study aspects (e. g. adequate randomisation and hiding of allocation), the result is possibly already falsified due to the exclusion of known non-responders to MPH from some studies. Further reasons for a high distortion potential are the large numbers of drop-outs and an inadequate implementation of the ITT principle.

The statistical analyses are assessed as adequate. In all studies both the patients and the examiners were blinded.

Table 25: Assessment of study quality and external validity of the included studies on efficacy presents a concluding overview of study quality and external validity.

Table 25: Assessment of study quality and external validity of the included studies on efficacy

Quality item	Adler et al. 2009a	Adler et al. 2009c	Jain et al. 2001	Kooij et al. 2007	Medori et al. 2008	Michelson et al. 2003	Weiss et al. 2006	Wilens et al. 2001	Wilens et al. 2008b
Inclusion criteria defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diagnostic criteria described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patients with known non-responsiveness included?	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Randomisation described?	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Sample size calculation described?	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Double-blind?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Response rate ≥ 70 % in both study arms?	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Reasons for participants dropping out described?	Yes	Yes	Yes	N. R.	No	Yes	No	Yes	No
Patient-proximate, relevant end points?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

N. R. = Not relevant.

5.5 Results of the systematic reviews with meta-analyses

In the systematic literature search, five systematic reviews with meta-analyses were found. The extraction forms and check-lists are deposited in Appendices 9.5 (Check-lists of the included studies) and 9.6 (Extraction forms of the assessed studies (included after the third selection)).

5.5.1 Study objective and end points

In all systematic reviews with meta-analyses, the efficacy of the medication is examined in adult patients with ADHD in comparison with the placebo. The active ingredients considered in the analyses differ in the meta-analyses. The patient-relevant end point is the expression of the ADHD symptoms measured by means of conventional ADHD scales such as CAARS.

5.5.2 Methods

All present systematic reviews with meta-analyses describe a systematic literature search in the relevant databases. Furthermore, the inclusion and exclusion criteria that were specified in advance regarding the study design are reported and two systematic reviews with meta-analyses describe the approach to data extraction and the quality of the underlying studies[95, 139]. An additional definition of inclusion and exclusion criteria in patients with accompanying psychological disorders is only provided in one meta-analysis[65].

Table 26: Presentation of the methodology of the included systematic reviews with meta-analyses provides an overview of the methodology of the systematic reviews with metaanalyses and the number of included studies.

Table 26: Presentation of the methodology of the included systematic reviews with meta-analyses

Source	Number of included studies	Active ingredient	Included databases (information from the authors)
Faraone et al. 2004	6	MPH	PubMed*, Ovid**, ERIC, Cinahl, MEDLINE, PreMEDLINE, Cochrane, E-Psyche, Social Science Abstracts
Kösters et al. 2008	18	MPH	MEDLINE, Cochrane Clinical Trials Register, PsycInfo Supplementation by manual search
Meszaros et al. 2009	11	Without restriction	PubMed*, MEDLINE Consideration of literature
Peterson et al. 2008	22	Without restriction	Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE; EMBASE, PsycINFO
Veerbeck et al. 2009	8	Antidepressants and lithium	Cochrane Library (Central), PubMed*, PsycINFO Supplementation of the search with a manual search

EMBASE = Experta Medica Database. ERIC = Education Resources Information Center. MEDLINE = Medical Literature Analysis and Retrieval System Online. MPH = Methylphenidate. RCT = Randomised controlled trial.

* PubMed is not a database but a search interface.

** Ovid is not a database but a database provider.

The meta-analysis was conducted by Faraone et al.[50] using a random effects model. The heterogeneity of the studies was not mathematically examined.

The study by Kösters et al.[65] attempts to update the meta-analysis of Faraone et al.[50] and to examine to what extent methodological aspects could have falsified the result of the meta-analysis. The calculation of the MPH strengths of effect was conducted using the averages of the intervention and control group and the pooled standard deviations of the intervention and control group. The strengths of effect were only calculated for end points that assess ADHD symptoms. If different measurement scales are used in the process, their average strength of effect is calculated and pooled in a random effects model. The heterogeneity of the studies was examined using the I^2 statistic [65].

In Peterson et al.[95], the data of the placebo-controlled studies are pooled separately for all end points (measurement scales that assess ADHD symptoms, such as ADHD-RS) by active ingredient to calculate the relative risk with a 95 % confidence interval. The meta-analysis was performed using a random effects model and the heterogeneity of the studies was examined using Cochran's Q-test[95].

The strengths of effect were calculated according to Cohen by Meszaros et al.[89]. Subsequently, the strengths of effects were combined in a random effects model into a shared, pooled effect estimator (placebo vs. intervention) and the results were presented separately according to stimulants and non-stimulants. The study did not make any statements on a heterogeneity test[89].

In the analysis performed by Veerbeck et al.[139], individual RCTs are also pooled in a random effects model, if possible. A heterogeneity examination was not performed.

5.5.3 Results of the studies

The average strength of effect of the ADHD symptoms (measurement scale: CGI and ADHD-RS) is statistically significant in favour of MPH at 0.9 in Faraone et al.[50] ($p < 0.001$). The strength of effect for

MPH is even higher when the therapy result is assessed by the treating doctors and not by the patients in a self-rating. Furthermore, better therapeutic effects (strength of effect: 1.3) result with higher doses of 70 mg/d (1.05 mg/kg) compared to lower doses, defined in this study as a feed of 44 mg/d (0.63 mg/kg). Time of the study, sex ratio and length of therapy (all p-values > 0.05) have no influence on the study result. Similarly, there is no evidence of a publication bias.

With a pooled strength of effect (ADHD symptoms) of 0.42, MPH is also more effective in the study by Kösters et al.[65] than the placebo ($p < 0.001$), but the absolute effect is clearly lower than reported in Faraone et al.[50]. In the subgroup of the ADHD patients with existing substance abuse, MPH was not effective (strength of effect: 0.36; 95 % CI [-0.17; -0.88]. In the heterogeneous subgroup of the six studies with parallel group design, MPH does not show a significant superiority compared with the placebo (strength of effect: 0.36; 95 % CI [0.27; 0.50]). Only the ten studies with crossover design that are less heterogeneous show a superiority of MPH (strength of effect: 0.44; 95 % KI [0.27; 0.60]). A link between the average daily MPH dose and the strength of effect cannot be confirmed.

In a comparison of twelve studies in which a total of 1,191 adult ADHD patients were treated, Meszaros et al.[89] conclude that the pharmacotherapy is effective with a strength of effect of 0.65 (95 % CI [0.48; 0.81]). The strengths of effect are greater for stimulants, as already presented in the study by Faraone et al.[50], when higher dosages are prescribed (strength of effect: 0.69; 95 % CI [0.36; 0.97]; $p < 0.001$). The pooled strength of effect of non-stimulants is 0.59 (95 % CI [0.37; 0.81]; ($p < 0.001$)).

In the study by Peterson et al.[95], the relative risk of a clinical response to ADHD medications compared with the placebo is greater across all medication groups, with a relative risk of 4.32 with fast-acting stimulants, 95 % CI [3.03; 6.16] and of 1.35 with slow-acting stimulants (95 % CI [1.0; 1.84]). The indirect comparison of the relative risks in the medicated groups shows significant differences ($p = 0.0001$), where the fast-acting stimulants are superior to the other medication groups.

In Verbeeck et al.[139], only treatment with bupropion shows an average strength of effect, but it is still lower than for stimulants. In this meta-analysis, the pooled odds ratio is stated. It comes to the conclusion that patients with a bupropion treatment are 2.4-times more likely to achieve an improvement of the clinical end points as compared with patients in a placebo treatment.

The results of the meta-analyses are presented comparatively in Table 27: Presentation of the results from the systematic reviews with meta-analyses (drug therapy vs. placebo).

Table 27: Presentation of the results from the systematic reviews with meta-analyses (drug therapy vs. placebo)

Source	Number of patients in all studies (N)	Primary end points	Pooled strengths of effect
Faraone et al. 2004	N = 235 N(MPH) = 140 N(Pl) = 113	ADHD symptoms (CGI and ADHD-RS)	0.9, $p < 0.001$
Kösters et al. 2009	N = 683	All measurement scales that relate to ADHD symptoms	0.42; 95 % CI [0.20;0.63] $p < 0.001$
Meszaros et al. 2009	N = 1191 N(med) = 1297 N(Pl) = 694	ADHD-RS, CGI, CAARS, AISRS	Total: 0.65; 95 % CI [0.48; 0.81] Stimulants: 0.67; 95 % CI [0.36-0.97]; $p < 0.001$ Non-stimulants: 0.59; 95 % CI [0.37;0.81] $p < 0.001$
Peterson et al. 2008	N = 2203	ADHD-RS, AISRS, WRAADDS	n. i. RR Bp =1.87; 95 % CI [1.36; 2.58] RR fast-acting stimulants = 4.32; 95 % CI [3.03;6.16] RR slow-acting stimulants = 1.35; 95 % CI [1.00; 1.84]
Verbeeck et al 2009	N = 617	ADHD-RS, CGI, WRAADS	n. i. Odds ratio = 2.42; 95 % CI [1.09;5.36]

ADHD = attention deficit/hyperactivity disorder. ADHD-RS = ADHD Rating Scale. AISRS = Adult ADHD Investigator Symptom Rating Scale. Bp = Bupropion. CAARS = Conners Adult ADHD Rating Scale. CGI = Clinical Global Impression Improvement Scale. n. i. = no information. CI = Confidence interval. Med = Medication. MPH = Methylphenidate. N = Number. Pl = Placebo. RR = Relative risk. WRAADDS = Wender Reimherr ADHD Scale.

5.5.4 Study quality

The quality of the included systematic reviews with meta-analyses is quite varied. However, all publications exhibit more or less pronounced weaknesses. These include, for example, lacking subgroup analysis according to individual active ingredients and the underlying study design. In a subgroup analysis, the primary studies are subdivided according to identical or similar characteristics, whereupon a meta-analysis is performed separately for every subgroup. Furthermore, sensitivity analyses (e. g. the examination of the meta-analysis with only high-qualitative studies) were entirely lacking. In the sensitivity analysis, possible factors are examined that may affect the meta-analysis. These factors of influence can be of a methodical (e. g. blinding of the study) or content nature (e. g. type of the scale used for measurement of the ADHD symptoms). Especially for heterogeneity, it becomes necessary to perform sensitivity analyses to clarify the cause of heterogeneity.

The weaknesses of the meta-analyses of Faraone et al.[50], Meszaros et al.[89] and Kösters et al.[65] are particularly evident in the lacking qualitative assessment of the individual studies and the lacking information on data extraction. An examination of the methodological quality of the studies is required to identify the various types of bias. The inclusion of studies of low quality in a meta-analysis can devalue its conclusions and, therefore, should be taken into account in the interpretation of the results.

The study by Verbeeck et al.[139] only performs a very minimal methodological description of the meta-analysis, which by contrast is performed in detail in the study by Peterson et al.[95].

The meta-analysis by Meszaros et al.[89] only conducted the literature search in one literature database. Therefore, there is a probability that relevant publications were not identified.

Validity criteria and an assessment of the evidence in the studies are not presented in any of the meta-analyses, nor is the included literature listed. Also, information on reasons for exclusion is missing.

Another major point of criticism is the lacking examination of the heterogeneity of the studies in the publications by Verbeeck et al.[139] and Meszaros et al.[89]. In meta-analyses, the heterogeneity describes to what extent the effects found in the included studies are similar (homogeneous) or different (heterogeneous). The statistical heterogeneity test can determine whether the differences between the studies are larger than would be expected by chance. As the cause of the heterogeneity, differences in patient characteristics, intervention or patient-relevant end points between studies are possible, which must be assessed from a clinical perspective. Performing a meta-analysis of heterogeneous studies is considered to be problematic in principle, since it can be assumed that the studies do not represent the same therapy effect and, therefore, are not comparable.

The only meta-analysis with an examination of the heterogeneity of the studies using the I^2 statistic was produced by Kösters et al.[65]. The I^2 value conforms to the share in total variance between studies due to heterogeneity. An I^2 value up to 25 % shows only a minor study heterogeneity. The I^2 value of the meta-analysis by Kösters et al.[65] lies in the high range at 61 %. However, the data is pooled in a random-effects model despite the heterogeneity. The meta-analysis by Peterson et al.[95] examines the heterogeneity of the studies by means of Cochran's Q-test. In fast-acting stimulants the Q-test value is 6.83 ($p = 0.45$), in slow-acting stimulants it is 16.62 ($p = 0.005$) and in bupropion, it is 1.07 ($p = 0.59$).

The meaningfulness of the meta-analyses is limited due to these methodical weaknesses, but the interpretations of the results by the authors and their conclusions appear plausible.

Fundamentally, it must be noted that four publications combine the results of the parallel and the crossover group in their meta-analysis. However, Curtin et al.[35, 36] note in two publications that the studies should not be combined in a meta-analysis with different study designs due to possible carry-over effects. Thus, the result of the treatment can be affected in the second phase and the comparison distorted.

Although statistical evidence of publication bias is not found in any of the meta-analyses, it cannot be safely ruled out. Due to the low number of studies included in the meta-analysis, the strength of effect determined in the meta-analysis could already be affected by a few unpublished studies.

5.6 Results of economic studies

By means of the systematic literature search, three full texts[87, 115, 154] can be identified that appear to have relevant content for the assessment of economic aspects.

The studies will be presented individually in the following. The presentation is based on the documentation structure for the standardised reporting of economic primary studies and syntheses of primary studies[117].

The extraction forms and check-lists are deposited in Appendices 9.5 (Check-lists of the included studies) and 9.6 (Extraction forms of the assessed studies (included after the third selection)).

5.6.1 Presentation of the studies

Secnik et al. Comorbidities and costs of adult patients diagnosed with attention-deficit disorder. Pharmacoeconomics 2005; 23(1): 93-102[115].

Study objective and design

The objective of this retrospective case control study is to determine the macroeconomic consequences of ADHD in adulthood. Direct and indirect costs are differentiated. The direct costs are defined as outpatient and inpatient costs and prescription-requiring medication. Indirect costs are defined as costs arising due to disease-related absences (determined using company-specific absence rates, sick pay and work compensation payments). Apart from the costs, the study also presents the resource consumption underlying the costs by the ADHD (N = 2,252) and the control group (N = 2,252). The base year of cost recording was 2001. The study was performed in the USA.

The examination of the homogeneity of the ADHD studies with the control group regarding comorbidities and use of medical services is performed by means of the chi-square test and the T-statistic. The differences between the two groups regarding absences from work were examined by means of the covariance analysis (ANCOVA).

Results for the costs

Differences between groups regarding the resource consumption are especially found in physician contacts. While 27.53 % of patients with ADHD visited a psychiatrist and 16.03 % a psychologist, in the control group merely 2.22 % of the patients contacted a psychiatrist and 1.83 % a psychologist. The comparison of direct costs in medical treatment is significant in all areas ($p < 0.01$). Thus, the costs for outpatient treatment of ADHD patients amount to 3,009 US dollars (as opposed to 1,492 US dollars for the control group) and the costs due to inpatient treatment to 1,259 US-dollars (compared with 514 US-dollars for the control group). The costs of prescribing medication amount to 1,673 US-dollars (as compared with 1,008 US-dollars for the control group). The total proportion of the direct costs for the ADHD group is 5,651 US-dollars (as compared with 2,771 US-dollars).

No significant difference showed for absences but employees with ADHD are more frequently absent from work unexcused (4.33 days vs. 1.13 days; $p < 0.01$). Overall, it was found that employees with ADHD are absent more frequently from work than employees in the control group (43.03 days vs. 29.34 days; $p = 0.03$).

The total annual costs for employees with ADHD are significantly higher compared with the control group (11,816 US-dollars vs. 8,024 US-dollars; $p < 0.01$).

Study quality

According to the authors, this study underestimates the macroeconomic significance of ADHD since the number of undiagnosed sufferers is high. Also, according to the inclusion criteria only participants are included who have had a year of continuous insurance coverage and steady employment. However, frequent loss and change of work are characteristics of persons with ADHD. Therefore, underestimating the costs is possible. For example, persons who were already terminated due to repeated absences in the first months were not included. As well, it should be recorded whether large companies with a different termination policy or small companies were involved. Large companies

react more strongly to crises than small companies and, especially in poor economic times, lay off more employees. Small companies tend to hold on to their staff longer since they are more dependent on their skilled employees. Therefore, the study results can only be generalised to a limited extent.

It should also be critically noted that characteristics of the study population such as ethnicity, alcohol or tobacco consumption are not evident in the data.

Matza et al. A review of the economic burden of ADHD. Cost Effectiveness and Resource Allocation 2005; 3: 5-13[87].

Study objective and design

The study by Matza et al.[87] is an assessment and summary of the literature regarding the costs of ADHD in children, adolescents and adults. However, the following only discusses the aspects relating to adults.

To identify relevant studies, a literature search was performed in the MEDLINE database. No information was presented on the methodology of data extraction and quality assessment. The literature search yielded the following three studies on economic aspects of ADHD in adulthood that all relate to the US population: Swensen et al.[133], Birnbaum et al.[24] and Secnik et al.[115].

Results of the cost comparison

In a further cost analysis by Swensen and co-workers[133], average costs of 3,786 US-dollars were determined by means of data on adults with ADHD for 1998 as compared with 1,131 US-dollars for persons not afflicted by ADHD.

Apart from the direct medical costs, it must be assumed that ADHD in adulthood is associated with further economic losses due to work-related problems. For example, employees with diagnosed ADHD lose more time at the workplace (43.03 days vs. 29.34 days; p = 0.03). The total annual indirect costs amount for employees who suffer from ADHD to 5,043 US-dollars as compared with 1,656 US-dollars in the control group.

Birnbaum et al.[24] examined the additional costs due to ADHD in patients from ages seven to 44 years (N = 1,219) and their family members under age 65 (N = 3,692). The results show average annual direct costs for ADHD treatment of 412 US-dollars for women and 529 US-dollars for men. Overall, the additional costs amount to 130 million US-dollars for women and 400 million US-dollars for men. The other average additional costs amount to 2,609 US-dollars annually for women and 3,022 US-dollars for men.

The study and results of Secnik et al.[115] have already been discussed and presented in this chapter.

Wu et al. Health care costs of adults treated for attention-deficit/hyperactivity disorder who received alternative drug therapies. J Manag Care Pharm 2007; 13 (7): 561-569[154].

Study objective and design

The study objective is the comparison of the pharmaceutical and total costs from the perspective of companies managing personal insurance for adults with ADHD who are starting a therapy with OROS-MPH, amphetamines (mixed amphetamine salts extended-release [MAS-XR]) or ATX. The basis for the data set are five million insurees of large employer insurance companies in the years 1999 to 2004 in the USA. Included were privately insured employees, pensioners and co-insured relatives from the age of 18 to 64 years with a diagnosis of ADHD according to the ICD-9 criteria and at least one prescription for OROS-MPH, MAS-XR or ATX over a defined time period. The data of 4,569 insurees were included.

All costs were recorded over a period of six months and corrected for inflation using the consumer price index for medical treatment for 2004. The determination of the medical costs is based on the payment of the employer to the service provider for inpatient and outpatient care in hospitals, physicians' services, visits to emergency rooms and other services.

The data analysed is based on an ITT analysis. To compare the direct medical costs between OROS-MPH and those of other therapies multivariate regression models were adjusted for patient character-

istics at the start of the study. Comparisons of use by shares of patients were analysed using the chi-square test and a descriptive analysis of the costs using t-tests.

Study population

The patients included in the study were on average 32 years old. The cohort consists of 43 % women and 3 % reported drug abuse in the preceding six months. 26 % of patients suffered from depression and anxiety disorders in the previous six months. Regarding demographic data, significant differences were demonstrated between the three examined intervention arms.

Results for the costs

The following Table 28: Presentation of the direct costs shows the direct costs of the study.

Table 28: Presentation of the direct costs

	OROS-MPH (US-dollars)	MAS-XR (US-dollars)	ATX (US-dollars)
Absolute costs (6 months)	2,008	2,169	2,540
Drug costs (6 months)	282	322	392

ATX = Atomoxetine. MAS-XR = Mixed amphetamine salts extended release. OROS-MPH = Osmotic-controlled release delivery system/methylphenidate extended release.

The absolute costs for the therapy with ATX are significantly higher compared with the two comparison interventions (p = 0.023). The proportion of the pharmaceutical costs in the total costs for OROS-MPH and ATX is 38 %, for MAS-XR 34 %. The largest proportion of the total costs with 53 % is caused by outpatient costs. The costs for inpatient treatment range from 7 % to 13 %.

In the multivariate regression analysis, 156 US-dollars less in direct costs were determined for patients treated with OROS-MPH over a period of six months after the start of therapy than for patients who were treated with MAS-XR and 226 US-dollars less than for patients with ATX. The stated differences are statistically significant (p = 0.001).

Study quality

A limitation of the study can be seen in the fact that the total costs for the three intervention arms were analysed for the observation period and not the costs due to ADHD alone. In this regard, the data must be interpreted with care since no comparison group alone was examined and statements on costs ascribable to ADHD are not possible.

The authors also state that the results cannot be transferred to the general population in the USA because insurees with low income were not included and, furthermore, possible self- and supplementary payments were not considered.

5.6.2 Summary of the results

The number of performed studies on the economic aspects of ADHD in adulthood is low.

In summary, high direct and indirect costs can be determined for the disease profile of ADHD in adulthood, where the indirect costs exceed the direct costs by a multiple.

Table 29: Comparative presentation of the annual direct costs for an ADHD group and a control group contrasts the annual direct costs of the study by Secnik et al.[115] and Swensen et al.[133].

Overall, the study by Secnik et al.[115] shows higher total costs than that of Swensen et al.[133]. However, it should be noted that the reference years of the calculation are different and, therefore, only a limited base of comparison can be created. So that costs are more comparable, they must be adjusted for inflation. Also, the basis of the cost calculation differs in the two studies.

Table 29: Comparative presentation of the annual direct costs for an ADHD group and a control group

	ADHD (US-dollars)	Control (US-dollars)
Secnik et al. 2005 (reference year 2001)		
Outpatient costs	3.009	1.492
Inpatient costs	1.259	514
Costs of medication	1.673	1.008
Total	5,941	3,014
Swensen et al. 2004 (reference year 1998)		
Provider´s office	522	211
Hospital inpatient	591	95
Hospital outpatient	1.302	400
Pharmacy	1.262	375
Other costs	110	49
Total	3,787	1,130

ADHD = Attention deficit/hyperactivity disorder.

The following Table 30: Comparative presentation of the annual direct costs for an ADHD group and a control group: currency-converted and inflation-adjusted shows the costs currency-converted and inflation-adjusted.

Table 30: Comparative presentation of the annual direct costs for an ADHD group and a control group: currency-converted and inflation-adjusted

	ADHD (Euros)	Control (Euros)
Secnik et al. 2005		
Outpatient costs	2,912	1,444
Inpatient costs	1,218	497
Costs of medication	1,619	975
Total	5,749	2,917
Swensen et al. 2004		
Provider´s office	525	212
Hospital inpatient	595	96
Hospital outpatient	1,310	402
Pharmacy	1,270	377
Other costs	111	49
Total	3,810	1,137

ADHD = Attention deficit/hyperactivity disorder.

In the light of increasing expenditures for the treatment of persons suffering from ADHD, the aspect of cost effectiveness is increasingly gaining in importance for a rational selection of therapeutic strategies. The cost effectiveness of the drug therapy options of ADHD in adults cannot be assessed.

The results of the identified economic studies must be examined for transferability to the situation in the German care system.

A limitation that restricts the transferability of the study results to the German context are possible differences of the patient characteristics, such as a higher/lower body mass index (BMI) and weight. For example, a low weight can go hand-in-hand with reduced resource consumption and, therefore, lower costs.

No differences are to be expected regarding the prevalence. As well, the quantitative situation determined for contacts with physicians determined in the study by Secnik et al.[115] appears transferable to Germany.

As far as the costs are concerned, non-comparability must be assumed in the assessment of the resource consumption, since the remuneration in the various healthcare systems (mandatory insurance of all persons in Germany) and also the prices for medication (fixed amounts and discount agreements in Germany) are different. It cannot be assessed how the different framework conditions affect the level of costs.

5.7 Results of the ethic and social assessment

No relevant citations were found in the literature regarding the assessment of the ethical and social aspects of a drug treatment of adults with ADHD. Consequently, an assessment is not possible.

5.8 The results of the legal assessment

By means of the systematic literature search, two publications[31, 55] were identified that discuss legal aspects of ADHD in adulthood and in the treatment of ADHD. However, these publications are not studies in which, for example, the influence of legal aspects on the quality of life are presented but unsystematic studies. Unfortunately, both studies regarding this question were methodologically weak. Nevertheless, their insights shall be taken up.

No relevant hits resulted from the manual search that could be used for a legal assessment.

Legal issues with regard to ADHD result primarily in the context of medication with stimulating substances, since they are subject to the Narcotics Law. When using these active ingredients, especially legal peculiarities in the areas of road traffic, travel, military service and high performance sports must be taken into account.

However, due to the limiting study quality, the results could only be used conditionally to answer the research question.

5.9 Results regarding aspects of society and care

No relevant sources were identified in the literature using the systematic and manual searches to answer the question regarding aspects of society and care.

6 Discussion and answer to the research questions

The objective of this study is a systematic investigation of the available evidence on clinical effectiveness and cost effectiveness of drug treatment of ADHD in adulthood.

The results presented in this report are based on a broadly designed systematic literature search in the relevant medical literature databases. The methodological approach of the literature search and selection conforms to the methodological standards of the German Agency for Health Technology Assessment (DAHTA) of the DIMDI.

Studies that examined a purely behavioural therapy or another therapeutic approach were ruled out.

6.1 Discussion of the methodology and comparison with other review studies

The search was performed computer-supported in numerous relevant databases and by examining the reference lists of the included publications.

For studies with negative results there is a danger of not being published. Given the availability of studies with predominantly positive study results, in the context of a systematic overview of their examined effects an intervention can be overestimated as a consequence.

Compared with other systematic review studies and meta-analyses, this study includes a number of studies in the processing of the evidence. The number of included studies fluctuates in the meta-analyses between six and 21 (Table 31: Comparison of the included studies). A significant difference between this HTA and the meta-analyses lies in the fact that in this work numerous studies were excluded due to the presence of serious methodological weaknesses and the year of publication was restricted. Furthermore, only two metaanalyses refer to all active ingredients for the treatment of ADHD in adulthood.

The results in this HTA show agreement compared with meta-analyses. All studies show efficacy to the benefit of the medication when compared with the placebo.

Table 31: Comparison of the included studies

Source	DIMDI-HTA	Kösters et al. 2009	Peterson et al. 2008	Faraone et al. 2002	Meszaros et al. 2009	Veerbeck et al. 2009
Adler et al. 2008					X	
Adler et al. 2009a	X					
Adler et al. 2009c	X					
Biederman et al. 2006		X	X			
Bouffard et al. 2003		X				
Carpentier et al. 2005		X	X			
Dorrego et al. 2002						X
Gualtieri et al. 1985		X		X		
Jain et al. 2007	X	X				
Kooij et al. 2004	X	X	X			
Kuperman et al. 2001		X		X	X	X
Levin et al. 2001		X	X			
Levin et al. 2006		X	X			X
Levin et al. 2007		X	X			
Mattes et al. 1984		X		X		
Medori et al. 2008	X					
Michelson et al. 2003	X		X		X	
Paterson et al. 1999			X			
Reimherr et al. 2007			X			
Reimherr et al. 2005		X	X			X

Table 31: Comparison of the included studies – continued

Source	DIMDI-HTA	Kösters et al. 2009	Peterson et al. 2008	Faraone et al. 2002	Meszaros et al. 2009	Veerbeck et al. 2009
Schubiner et al. 2002		X	X			
Spencer et al. 1995		X	X	X		
Spencer et al. 1998			X			
Spencer et al. 2001			X		X	
Spencer et al. 2005		X	X		X	
Spencer et al. 2007		X	X		X	
Spencer/Biederman 2002				X		
Tenenbaum et al. 2002		X				
Weisler et al. 2006			X		X	
Weiss et al. 2006	X		X			X
Wender et al. 1985		X	X	X		
Wilens et al. 1996					X	X
Wilens et al. 2001	X		X		X	
Wilens et al. 2005					X	X
Wilens et al. 2008b	X					

DIMDI = Deutsches Institut für Medizinische Dokumentation und Information (German Institute for Medical Documentation and Information). HTA = Health Technology Assessment.

6.2 Discussion of the assessment of publication quality

6.2.1 Randomised controlled studies (RCTs)

In the following, factors affecting the results and limitations of the studies will be presented and discussed.

Study quality

The RCTs included in the analysis all fulfil a required minimum quality in methodology, but some studies exhibit various weaknesses relating to study design, performance and reporting.

The majority of studies is adequately randomised, detailed information on how the randomisation was performed is only missing from three.

The diagnosis formulation of the patients included in the studies was performed by the DSM throughout. Deviations are evident in the studies regarding the exclusion criteria. A limitation in the comparability of the study population is particularly evident, when patients without prior response to a therapy are excluded from a study but not from other studies. In patients who demonstrably have already responded once before to the study medication, a greater efficacy can also be assumed subsequently. By comparison, a comparably poorer effect in the overall assessment must be anticipated for studies in which non-responders are included and that undergo an ITT analysis. Comorbidities such as depression and anxiety disorders are another exclusion criterion. Since the stated illnesses have a strong effect on the overall well-being, study populations that differ due to the exclusion criterion “comorbidity” are difficult to compare.

The sex distribution of the participants does not reflect the often demonstrated preponderance of male subjects in ADHD. Whether the preponderance of male ADHD patients declines with age or women rather tend more toward having themselves treated and, therefore, become accessible to studies cannot be assessed. It cannot be assessed what distortions arise from this.

Number of drop-outs

The results of some studies must be considered with caution due to the many drop-outs. The drop-out rates of the studies are relatively inconsistent. Very high drop-out rates are reported by Adler et al.[4]. In the intervention group with ATX, they reach 43.3 % and in the control group 37.2 %. These high drop-out rates constitute a limiting factor in study quality. An analysis of the results can result in a major

distortion as a function of the high drop-out rate. Most studies use an ITT approach, but this approach is not unproblematic in the studies. If the results of drop-outs are continued with the last recorded value (LOCF), possible ADHD changes of the respective study participants will remain unrecorded. In which direction the results of the group comparison are distorted in the process cannot be predicted.

Furthermore, a difference in the drop-out rates between groups will result in methodological problems. If, as for example in Wilens et al.[148], the drop-out rate in the control group is much higher than in the intervention group, this results in a systematic error in the statistical analysis that is very difficult to estimate. A drop-out rate of zero was reported by Kooij et al.[67] for the entire study population. The reason for this is probably the relatively small study population that only comprised 45 participants.

Subgroup analyses

All included studies report a change of the ADHD symptoms as the average of the respective group. The interpretation of averages often raises the problem that a percentage of patients do not benefit from a therapy, and another part benefits more compared with the average.

To estimate the influence of patient-specific characteristics, such as age, sex or expression of the ADHD symptoms on the results, subgroup analysis can be helpful. Subgroup analyses must be determined in advance in the study plan.

In the study by Kooij et al.[67], the authors performed a subgroup analysis with the objective of uncovering possible associations between MPH response and age, sex and comorbidity. However, the response rates to MPH changed in none of the subgroups.

Long-term consequences

The duration of most studies was usually just a few weeks and was too short to reveal long-term effects.

Therefore, currently questions regarding the efficacy and safety in the long-term use of medication in the treatment of adults are still unanswered.

Meaning of the dose adjustment

The medication is partially administered in absolute doses, partially in doses related to body weight. Only in two studies[7, 59] was the dosage individually adjusted relative to the change in ADHD symptoms.

Overall, there is a tendency to recognize higher response rates to higher dosages of MPH. However, high doses often harbour the risk of side effects and result in some patients even in a worsening of the clinical profile. Therefore, lack of a demonstration of efficacy can either be due to the active ingredient not being effective or to the optimal individual dosage not being achieved because of a too rigid dosing schedule. For the other active ingredients, an effect of the dosage on the proportion of responders cannot be recognised.

Measurement of the ADHD symptoms

Another major problem is posed by the uneven measurement of the response to the medication. A uniform and standardised method for measuring the improvement of ADHD symptoms, such as the HAM-D, does not exist so far.

The quantitative assessment of the ADHD symptoms relies on self- and third-party rating scales that deviate significantly from each other, and are subjective and situation-dependent. As a result, partially contrary results can arise.

Clinical relevance of the ADHD symptom change

As another methodical problem, the question of clinical relevance of an observed effect will be discussed. Contrary to the hard end points such as survival rates, the clinical relevance of subjective end points such as change in symptoms of attentiveness, hyperactivity and impulsiveness can be doubted.

In this case, it is important to create a clear delimitation between the statistical significance and the clinical relevance. Method Paper 3.0 of the IQWiG explicitly points out that the clinical relevance of a study result cannot be read from the p-value[57].

There still is no standardised procedure for assessing the clinical relevance of study results. The calculation of strengths of effect according to Cohen's d, which can be used as a measure of efficacy, can be a possibility for quantification. However, this determination is subjective and arbitrary. The advantage of the calculation of these strengths of effect is the comparability of the results independently of the employed measurement scale and dosage.

The efficacy of the medications not only differs considerably between studies but even within studies there are sometimes great differences. An explanation for these differences in efficacy of the medication between studies could be the different methodological requirements of the individual studies and the unequal exclusion criteria and, consequently, the heterogeneous study populations.

6.2.2 Meta-analyses

In the context of the literature search, five relevant meta-analyses were identified that deal with the question of the efficacy in adults with ADHD.

The meta-analyses differ with regard to methodology and results but all exhibit qualitative weakness that must be taken into account in the interpretation of the results. Thus, the systematic literature search by Meszaros et al.[89] ignores important databases. Furthermore, in three meta-analyses the qualitative assessment of the individual studies and the description of the data extraction[50, 65, 89] is missing.

Meta-analyses are essentially meaningful if the entered studies are as close as possible in design and study population. In the present meta-analyses the selected studies vary particularly strongly with regard to the study design and the measurement scale. Performing a meta-analysis with heterogeneous studies is generally problematic, since it must be assumed that the studies do not represent the same therapy effect and, therefore, are not comparable. An examination of the heterogeneity of the studies is performed in merely two meta-analyses[89, 139] and documents these clearly. As a result, only conditional conclusions and recommendations can be derived for the general population from the five identified meta-analyses.

6.2.3 Economic studies

Starting with 2,081 hits in the literature search, 183 economic studies were identified, of which in the end three were classified as relevant. These are publications that perform a cost survey with respect to ADHD in adulthood. No hits were found for cost effectiveness in the systematic literature search, which is why an estimate of the cost effectiveness is not possible for adults with ADHD.

Since the various studies do not have a standardised methodological approach to determining cost components, comparability of the data cannot be assumed. However, it becomes clear that greater direct costs arise for patients with ADHD as compared with a control group without ADHD. Apart from the direct costs, additional economic losses in the form of indirect costs (loss of employment, absence from work) must be considered.

By means of a dataset of five million insurees of large company health insurance funds in the USA, absolute costs of 2,008 to 2,540 US-dollars can be demonstrated per person over a period of six months. However, the data must be interpreted with care because no comparison group without ADHD was examined and statements on the costs attributable to ADHD cannot be made.

Furthermore, the included economic publications comprise a systematic review by Matza et al.[87], in which an assessment and summary of the literature regarding the costs of the ADHD is performed. The assessment includes the studies by Swensen et al.[133], Birnbaum et al.[24] und Secnik et al.[115]. Methodological limitations result from the missing quality assessment and description of the data extraction of the individual studies.

The study by Secnik et al.[115] was identified in the present HTA as a primary publication and was included in the economic assessment. The objective of the retrospective case control study is the determination of the macroeconomic consequences of ADHD in adulthood. These are differentiated

according to the direct medical costs and the indirect costs. Apart from the costs, resource use is also presented. According to the inclusion criteria, only participants were included who had a year of continuous insurance coverage and steady employment. However, persons with ADHD in particular frequently experience loss and change of employment. Therefore, it is possible that costs were underestimated.

In summary, higher total costs are found in the study of Secnik et al.[115] than in that of Swensen et al.[133]. However, it should be noted that the reference years of the calculation are different and, therefore, only a limited base of comparison can be created. Also, the basis of the cost calculation differs in the two studies.

Overall, it can be stated that the number of performed studies on the economic aspects of ADHD in adulthood is low. The transferability of the study results to Germany is limited due to possible differences in patient characteristics and differing compensation systems.

6.2.4 Ethical, social and legal aspects

ADHD can result, through disturbances of attentiveness, lack of endurance, restless behaviour and impulsiveness, to severe impairment of social behaviour and in the social environment such as family, work and leisure. People who suffer from ADHD stand a high risk of developing additional psychological disorders. They also have more accidents at home, at school, at work and during leisure activities. Persons with ADHD change their employment more often and are terminated more often than other employees.

An adequate drug treatment may be required, in cases of pronounced psychological and social impairments, to reduce the symptoms of ADHD. The objective of a therapy of this type is to enable affected persons to establish a stable sense of self-esteem, to integrate socially and to be professionally successful according to their gifts. Active ingredients, such as MPH, have been granted statutory pharmaceutical approval for the treatment of ADHD from age 6 to the age of majority. They are not approved for the treatment of adults. Usually, therefore, they are not paid for by the mandatory insurance schemes. This results in many of the affected adults not receiving a suitable medication. For example, according to the Red List[105] 2009, 50 Ritalin® 10 mg tablets cost 27.07 euros. If the daily maximum dose of 60 mg is assumed, the patient must pay about 97 euros monthly for the medication.

Furthermore, it should be noted that treatment of ADHD in adulthood does not involve a medication for a disease other than the one for which it is approved but rather a continuation of therapy begun in childhood. Especially in patients with an inattentive type of ADHD who were not noticed during childhood due to a disruptive set of symptoms, an often adequate therapy was missed in childhood. The missing approval of the medications is contradictory, especially in view of the genetic component of ADHD, since disease due to genetic causes also requires treatment after the 18th year of life.

If the medication is discontinued after age 18, this can cause the adolescent to drop out of school or discontinue their training. Furthermore, developing addictions and possible criminal prosecutions must be expected, so that the effects in sum can have grave consequences on personal and professional development.

6.2.5 Aspects of society and care

The lacking approval of drug therapy affects more than social and legal aspects. It can also lead to an undersupply of medication for adult ADHD patients having a need for treatment, since many physicians prescribe fewer medications due to the possibility of recourse claims. Furthermore, MPH is subject to the regulations of the BtMG. This keeps many physicians from prescribing it to adults even if they are willing and able to bear the costs themselves. Therefore, it must currently be assumed that many persons who are severely affected by ADHD and, therefore, adults whose quality of life is impaired are blocked from adequate medication despite their need for treatment.

The question presents itself as to whether a lack of adequate treatment due to a lack of approval for the drug therapy form of ADHD in adulthood does not ultimately produce significant economic effects through the treatment of psychiatric secondary illnesses, such as depression, anxiety disorders, personality disorders or the loss of work days, or premature inability to work, and possibly increased criminality. Usually, society bears these costs.

6.3 Summary assessment of the research questions

6.3.1 Answer to the question of efficacy

1. How does the efficacy of drug therapy compare with no treatment?

Using high quality RCT, there is strong evidence for the medical efficacy of MPH and ATX in the treatment of adults with ADHD with regard to symptom improvement. There are also statistically significant results for the active ingredient dextroamphetamine, though not for paroxetine. Significant results were found in the two studies with the active ingredients bupropion and NS2359, but the evidence is based on RCT of limited quality.

To answer this research question, five meta-analyses were also drawn upon. Three of these meta-analyses[50, 89, 95] document the superiority of MPH compared with the placebo. The authors of another meta-analysis[65] also show the efficacy of MPH. However, it is markedly lower in this instance. In the study by Veerbeck et al.[139], in which explicitly only antidepressants are compared with a placebo, treatment with bupropion achieved a strength of effect in the average range.

2. How does the efficacy of various drug therapies appear?

Regarding the medical efficacy in the comparison of different pharmaceutical active ingredients against each other, no definitive statement can be made due to a lack of direct comparisons. Overall, studies with ATX exhibit the greatest improvement of ADHD symptoms measured against various scales in the intervention groups. However, in a meta-analyses[89] higher strengths of effect in favour of stimulants were shown.

3. How does the efficacy of a drug treatment as a supplementary therapy with a behavioural-therapeutic treatment compare with no treatment?

The question of the efficacy of a drug treatment as a supplementary therapy with a behaviour-therapeutic treatment compare with no treatment cannot be definitively answered due to the deficient data. The only study in which patients received psychotherapy and stimulant treatment with a group receiving the same psychotherapy and placebo, shows a highly significant superiority of the effect of the combination of psychotherapy and medication on ADHD symptoms compared with that of psychotherapy alone[144].

4. How does the efficacy of a drug treatment as a supplementary therapy to a behavioural-therapeutic treatment compare with a purely drug therapy?

The question of the efficacy of a drug therapy as supplementary therapy with a behaviour-therapeutic treatment compared with a purely drug therapy cannot be definitively answered due to the deficient data situation.

6.3.2 Answer to the question of an economic assessment

1. What costs arise from a drug therapy in adult patients with ADHD as monotherapy and/or a supplementary therapy with a behaviour-therapeutic treatment (annually)?

High direct and indirect costs can be determined for the disease profile of ADHD in adulthood, with the indirect costs exceeding the direct costs by a multiple. The annual costs of drug therapy of ADHD patients amounted in 2009 to between 1,270 euros and 1,619 euros (currency-converted and inflation-adjusted).

The costs for a behaviour-therapeutic intervention cannot be estimated, since data was not collected for this purpose.

2. How should the cost effectiveness of the drug therapy in adult patients with ADHD as monotherapy and/or supplementary therapy be evaluated compared with a behaviour-therapeutic intervention?

The question of cost effectiveness cannot be answered due to a lack of data.

6.3.3 Answer to the additional questions

The research questions cannot be sufficiently answered by means of the systematic literature and the manual searches due to a lack of data/publications. Therefore, the following statements will refer to the scientific background.

1. What ethical, social and legal aspects must be considered in the use of drug therapy?

ADHD can cause considerable psychological and social problems that affect numerous aspects of life. A drug treatment can relieve the symptoms of ADHD and enable an adequate lifestyle. Ethical problems of an untreated ADHD not only arise primarily from the disease, but also from the fact that ADHD frequently favours other psychological diseases.

It must be noted in the treatment of ADHD with psychostimulants that considering all eventualities psychostimulants can also be used as lifestyle drugs and, therefore, abuse cannot be entirely ruled out.

Legal issues with regard to ADHD result primarily in the context of medication with stimulating substances, since they are subject to the Narcotics Law. When using stimulants, particular legal requirements must be taken into account, especially in the areas of road traffic, travel, military service and high-performance sports.

2. How do these aspects affect the assessment of the therapy in terms of economics/healthcare policy?

Apart from the considerable direct treatment costs, the macroeconomic damage caused by ADHD are also of great significance.

ADHD and the frequently associated psychological illnesses can result in occupational problems, since the patient is restricted in his work performance and problems can also arise in communications with employees and superiors. This can subsequently lead to more frequent terminations of the work relationship with financial losses for the affected person. Indirect costs also arise from the frequent absences of employees suffering from ADHD[133].

The drug treatment of ADHD is also a relevant topic in economics and healthcare policy because of the high risk that this disease favours other psychological disease, that it can lead to social impairment, and that large social costs result from it. Therefore, economic analyses will increase in importance in the context of providing for ADHD. To what extent the scales will be balanced between the observed increase of drug therapy in general and remuneration exclusions in the context of the mandatory health insurance is difficult to estimate. With regard to this point, a growing acceptance of pharmacotherapy for the treatment of adults with ADHD is to be expected in the healthcare policy environment. However, framework conditions must be created for this purpose in compensation law. Further support may be provided by the results of international studies, the German study in progress and the DGPPN guidelines which rate pharmacotherapy highly in the treatment of ADHD in adults.

3. What is the estimation/acceptance of the need for care by the affected persons/the public?

Acceptance of the need for care by the affected persons/the public cannot be assessed by means of the literature search.

However, on the Internet a multitude of information portals can be found, by means of which not only do affected persons provide information and help regarding the issue of ADHD in adulthood, but the public and relatives are also informed. For example, on the Internet pages of the ADHD information portal[8] quick tests and knowledge tests on the topic ADHD can be conducted. Furthermore, in a separate section, FAQ answers can be found.

Also, there is literature and advice (apart from academic literature) specifically for affected persons. They provide concrete help and practical tips for better handling of ADHD[30, 107].

In summary, an increased awareness of the problems by the affected persons, relatives and the public can be identified.

4. What is the assessment/acceptance of the need for care by the service providers and what are the consequences for affected persons and service providers?

ADHD in adulthood must not necessarily be treated. The decision for a treatment depends on the expression of the ADHD symptoms and the psychological and social impairment of the affected party[43]. Since the disease profile of ADHD in adulthood was unknown in medical studies and psychiatric training until a few years ago, the diagnosis was rejected by many doctors active in care. This has had dire consequences for the affected persons. In the meantime, the disease profile is established and there are a number of specialised psychiatrists in practice and outpatient clinics that perform the diagnostics and therapies. However, due to the required expensive diagnostics and the therapeutic guidance of these patients, there is, in the light of the minimal flat-rate remuneration offered by the mandatory health insurance funds, often little willingness, for economic reasons, to take on this patient group.

5. What is the estimation/acceptance of the need for care by the cost bearers and what consequences does this have for affected persons and service providers?

Service providers are not permitted to prescribe the medications for the treatment of ADHD at the expense of the mandatory healthcare funds. Doctors are not required to issue a healthcare fund prescription, if a recourse claim is expected in the context of an audit. In the presence of an indication of this kind, they must prescribe an effective medication in order not to make themselves criminally liable. This can only be accomplished with a private prescription. Due to the current data situation, the mandatory healthcare funds are willing, in individual cases with an appropriate indication for the patient, to carry the costs.

7 Conclusion/recommendation

An early start of drug treatment of ADHD is highly relevant for reasons of economics and politics, due to:

- the social impairment that can impact on numerous areas of life,
- the high risks of developing other psychological illnesses, and
- the high societal costs.

Apart from the undoubtedly psychiatric disease profile, we recommend for reasons of healthcare economics alone that the preconditions should be created for an appropriate supply of these medications also to adults.

In summary, positive effects (reduction of the symptoms or the symptom severity) of the active ingredients MPH, dextroamphetamine and ATX in the treatment of ADHD in adults can be demonstrated from the literature. Furthermore, there is evidence for a dose-effect principle. Individual dose finding in adulthood is important to achieve an optimal response to the medication.

The conclusion relates to the nine RCT, five meta-analyses and three economic studies that are presented in this report. The duration of the studies was usually just a few weeks and is too short to assess long-term effects. Therefore, negative long-term effects as a result of drug treatment cannot be ruled out as a result. Additional research in this area is needed.

Furthermore, the active ingredients are tested against placebos. High-quality direct comparison studies between the active ingredients, which are relevant for the issue of medical effectiveness of the therapy, are lacking.

To make a statement on the cost effectiveness of the drug therapy in adults with ADHD, additional economic studies are required that can be transferred to the German healthcare system.

8 Index of literature

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9 Appendix

9.1 Literature search

Table 32: Research results

No	Hits	Search Expression
1	88642632	INAHTA; DAHTA; NHSEED; CDAR94; CDSR93; ME83; EM83; CB85; BA83; MK77; CCTR93; GA03; SM78; CV72; II78; ED93; AZ72; AR96; EA08; IS83; CC00; IN73; KR03; KL97; SP97; SPPP; TV01; DD83; IA70; GM03; LQ97; HN69; HG05; TVPP; KP05
2	11341	ATTENTION DEFICIT HYPERACTIVITY AND ADULT?/SAME SENT
3	11149	ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ADULT?/SAME SENT
4	10504	ATTENTION DEFICIT DISORDER AND ADULT?/SAME SENT
5	5235	(ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY) AND ADULT?/SAME SENT
6	10552	ADHD AND ADULT?/SAME SENT
7	302	ADHS AND ERWACHSENE?/SAME SENT
8	25	HKS AND ERWACHSENE?/SAME SENT
9	144	AUFMERKSAMKEITSDEFIZIT-HYPERAKTIVITAETSSTOERUNG AND ERWACHSENE?/SAME SENT
10	153	AUFMERKSAMKEITSDEFIZIT-HYPERAKTIVIT%TSST%RUNG AND ERWACHSENE?/SAME SENT
11	12	AUFMERKSAMKEITSDEFIZIT-HYPERAKTIVIT%TSSYNDROM AND ERWACHSENE?/SAME SENT
12	0	AUSMERKSAMKEITSDEFIZIT-HYPERAKTIVITAETSSYNDROM AND ERWACHSENE?/SAME SENT
13	15	HYPERKINETISCHE STOERUNG AND ERWACHSENE?/SAME SENT
14	15	HYPERKINETISCHE ST%RUNG AND ERWACHSENE?/SAME SENT
15	17438	2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16	35193	CT=ATTENTION DEFICIT HYPERACTIVITY DISORDER
17	36783	CT=ATTENTION#DEFICIT#HYPERACTIVITY DISORDER
18	18249	CT=ADHD
19	37719	CT=ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY
20	2134	CT=ATTENTION DEFICIT DISORDER AND CT=HYPERACTIVITY
21	682	UT=ATTENTION DEFICIT HYPERACTIVITY DISORDER
22	4766	UT=ATTENTION#DEFICIT#HYPERACTIVITY DISORDER
23	4281	UT=ADHD
24	191	UT=ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY
25	196	UT=ATTENTION#DEFICIT DISORDER WITH HYPERACTIVITY
26	166	UT=ATTENTION#DEFICIT DISORDER AND UT=HYPERACTIVITY
27	993	IT=ATTENTION DEFICIT HYPERACTIVITY DISORDER
28	3099	IT=ATTENTION#DEFICIT#HYPERACTIVITY DISORDER
29	129	IT=ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY
30	2774	IT=ADHD
31	149	IT=ATTENTION#DEFICIT DISORDER WITH HYPERACTIVITY
32	53	IT=ATTENTION#DEFICIT DISORDER AND IT=HYPERACTIVITY
33	4	CT=ADHS
34	53	CT=ADD
35	3	CT=HKS
36	50550	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
37	5475547	CT=ADULT
38	2696583	CT=ADULTS
39	4859	CT=ADULTHOOD
40	6475	CT=ERWACHSENE?
41	48237	UT=ADULT
42	47877	UT=ADULTS
43	3195	UT=ADULTHOOD

Table 32: Research results – continued

No	Hits	Search Expression
44	368	UT=ERWACHSENE?
45	3637	IT=ADULT
46	2834	IT=ADULTS
47	310	IT=ADULTHOOD
48	0	IT=ERWACHSENE?
49	5621997	37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48
50	7892	36 AND 49
51	17440	15 OR 50
52	4172	ATOMOXETIN#
53	27972	METHYLPHENIDAT#
54	400059	MEDICATION
55	2552	MEDIKATION
56	440583	MEDIKAMENTE OR ARZNEIMITTEL
57	515692	PHARMACOLOGICAL
58	544	PHARMAKOLOGISCH
59	9152	PSYCHOPHARMACOLOGICAL
60	1353595	52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59
61	5238	51 AND 60
62	4408	61 AND PY>=2000
63	2119	check duplicates: unique in s=62
64	0	63 AND CT D TECHNOLOGY ASSESSMENT, BIOMEDICAL
65	0	63 AND CT D BIOMEDICAL TECHNOLOGY ASSESSMENT
66	0	63 AND CT=EVALUATION STUDIES AND CT D TECHNOLOGY
67	0	63 AND HEALTH CARE, TECHNOLOGY ASSESS?
68	2	63 AND HEALTH TECHNOLOGY ASSESS?
69	0	63 AND HEALTH CARE TECHNOLOGY EVALUAT?
70	0	63 AND HEALTH TECHNOLOGY EVALUAT?
71	0	63 AND BIOMEDICAL, TECHNOLOGY ASSESS?
72	0	63 AND HTA
73	0	63 AND MEDICAL, TECHNOLOGY ASSESS?
74	0	63 AND TECHNOLOGY, ASSESS? ? BIOMEDICAL?
75	0	63 AND TECHNOLOGI?, BEWERT?
76	0	63 AND TECHNOLOGI?, BEURTEIL?
77	0	63 AND EVALUATION#, MEDICAL?
78	0	63 AND EVALUATION#, BIOMEDICAL?
79	0	63 AND EVALUATION#, HEALTH CARE
80	2	64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79
81	3	63 AND CT=REVIEW LITERATURE
82	18	63 AND CT=SYSTEMATIC REVIEW
83	0	63 AND CTG=UEBERSICHTSARBEIT
84	243	63 AND DT=REVIEW LITERATURE
85	460	63 AND DT=REVIEW, ACADEMIC
86	77	63 AND REVIEW/TI
87	32	63 AND CT=PRACTICE GUIDELINE#
88	2	63 AND DT=PRACTICE GUIDELINE#
89	2	63 AND REVIEW LITERATURE
90	0	63 AND REVIEW SYSTEMATIC
91	0	63 AND REVIEW ACADEMIC
92	25	63 AND LITERATURE REVIEW#
93	40	63 AND SYSTEMATIC REVIEW#
94	0	63 AND ACADEMIC REVIEW#

Table 32: Research results – continued

No	Hits	Search Expression
95	3	63 AND (ÜBERSICHTSARBEIT OR UEBERSICHTSARBEIT)
96	55	63 AND PRACTICE GUIDELINE#
97	529	81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96
98	12	63 AND CT=META ANALYSIS
99	50	63 AND META-ANALYSIS
100	12	63 AND CT=META-ANALYSIS
101	14	63 AND DT=META-ANALYSIS
102	63	63 AND (METAANALY? OR META ANALY? OR META#ANALY?)
103	63	98 OR 99 OR 100 OR 101 OR 102
104	555	97 OR 103
105	118	63 AND DT=RANDOMIZED CONTROLLED TRIAL
106	44	63 AND CT=RANDOMIZED CONTROLLED TRIAL
107	4	63 AND CTG=RANDOMISIERUNG
108	5	63 AND CT D RANDOM ALLOCATION
109	4	63 AND CT=ALLOCATION, RANDOM
110	1	63 AND CT=SINGLE BLIND PROCEDURE
111	4	63 AND CT=SINGLE BLIND METHOD
112	26	63 AND CT D DOUBLE BLIND PROCEDURE
113	115	63 AND CT=DOUBLE-BLIND METHOD
114	143	63 AND CT D PLACEBO?
115	53	63 AND CT D CROSS-OVER STUDIES
116	13	63 AND CT=CROSSOVER PROCEDURE
117	14	63 AND RCT
118	258	63 AND (RANDOMI%ED? ? CONTROLLED? ? TRIAL? OR RANDOMI%ED? ? CONTROLLED? ? STUD?)
119	90	63 AND (RANDOMI%ED? ? CLINICAL? ? TRIAL? OR RANDOMI%ED? ? CLINICAL? ? STUD?)
120	292	63 AND (RANDOMI%ED? ? TRIAL? OR RANDOMI%ED? ? STUD?)
121	42	63 AND (RANDOMISIERT? ? STUDIE? OR RANDOMISIERT? ? VERSUCH?)
122	12	63 AND (RANDOM? ? ALLOCAT? OR ALLOCAT? ? RANDOM?)
123	7	63 AND (SINGLE#BLIND? OR SINGLE BLIND?)
124	240	63 AND (DOUBLE#BLIND? OR DOUBLE BLIND?)
125	0	63 AND (TRIPLE#BLIND? OR TRIPLE BLIND?)
126	0	63 AND EINFACH? ? BLIND?
127	0	63 AND DOPPEL? ? BLIND?
128	0	63 AND DREIFACH? ? BLIND?
129	254	63 AND ?BLIND#### AND (STUD? OR TRIAL? OR VERSUCH?)
130	2	63 AND ZUFALL?
131	96	63 AND (CROSS#OVER? OR CROSS OVER?)
132	0	63 AND (ÜBERKREUZ? OR UEBERKREUZ?)
133	379	63 AND PLA%EBO?
134	4	63 AND MASK?
135	528	105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118 OR 119 OR 120 OR 121 OR 122 OR 123 OR 124 OR 125 OR 126 OR 127 OR 128 OR 129 OR 130 OR 131 OR 132 OR 133 OR 134
136	190	63 AND (DT=CCT OR DT=CLINICAL TRIAL)
137	47	63 AND CT D CONTROLLED CLINICAL TRIAL
138	44	63 AND CTG D KONTROLLIERTE KLINISCHE STUDIEN
139	5	63 AND CCT
140	224	63 AND (CONTROLLED? ? CLINICAL? ? TRIAL? OR CONTROLLED? ? CLINICAL? STUD?)
141	5	63 AND (KONTROLLIERT? ? KLINISCH? ? STUDIE? OR KONTROLLIERT? ? KLINISCH? ? VERSUCH?)

Table 32: Research results – continued

No	Hits	Search Expression
142	570	63 AND (CONTROLLED? ? TRIAL? OR CONTROLLED? ? STUD?)
143	49	63 AND (KONTROLLIERT? ? STUDIE? OR KONTROLLIERT? ? VERSUCH?)
144	619	136 OR 137 OR 138 OR 139 OR 140 OR 141 OR 142 OR 143
145	22	63 AND CT D PROSPECTIVE STUD?
146	15	63 AND CTG=PROSPEKTIVE STUDIEN
147	34	63 AND PROSPE%TIVE# (STUD? OR TRIAL? OR VERSUCH?)
148	34	145 OR 146 OR 147
149	770	135 OR 144
150	549	135 OR 148
151	625	144 OR 148
152	774	135 OR 144 OR 148
153	0	63 AND CTD (TRIAL OR TRIALS)
154	0	63 AND CT=(STUDY OR STUDIES)
155	2	63 AND DT=VALIDATION STUDIES
156	0	63 AND DT=REPORT
157	186	63 AND DT=CLINICAL TRIAL
158	4	63 AND DT=EVALUATION STUDIES
159	0	63 AND DT=(RESEARCH ARTICLE OR RESEARCH-ARTICLE)
160	32	63 AND DT=MULTICENTER STUDY
161	0	63 AND DT=TECHNICAL REPORT
162	1391	63 AND (STUDY OR STUDIE?)
163	676	63 AND (TRIAL? OR VERSUCH?)
164	603	63 AND REPORT?
165	1	63 AND RESEARCH ARTICLE?
166	1	63 AND TECHNICAL REPORT?
167	1696	153 OR 154 OR 155 OR 156 OR 157 OR 158 OR 159 OR 160 OR 161 OR 162 OR 163 OR 164 OR 165 OR 166
168	1832	80 OR 104 OR 152 OR 167
169	41	63 AND CT D ECONOMICS
170	36	63 AND CTG D ÖKONOMIE
171	8	63 AND CT D SOCIOECONOMICS
172	3	63 AND CT D MODELS, ECONOMIC
173	0	63 AND (ÖKONOMISCH## MODELL# OR OEKONOMISCH## MODELL#)
174	62	63 AND CT D ECONOMIC ASPECT
175	51	63 AND CT D ECONOMICS, MEDICAL
176	51	63 AND CT D HEALTH ECONOMICS
177	63	63 AND CT D COST?
178	13	63 AND CTG D KOSTEN?
179	27	63 AND CT D EFFICIENCY?
180	19	63 AND CT D COST ANALYSIS
181	82	63 AND (ECONOMI? OR OEKONOMI? OR ÖKONOMI?)
182	0	63 AND (GESUNDHEITSOEKONOMIE OR GESUNDHEITSÖKONOMIE)
183	17	63 AND EFFICIENC?
184	4	63 AND ECONOMIC EVALUATION?
185	0	63 AND HEALTH CARE FINANCING?
186	15	63 AND (COST? ? BENEFIT? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
187	5	63 AND (COST? ? UTILIT? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
188	20	63 AND (COST? ? EFFECTIVENESS? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
189	6	63 AND (COST? ? EVALUATION? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
190	0	63 AND (COST? ? EFFICIENC? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))

Table 32: Research results – continued

No	Hits	Search Expression
191	13	63 AND (COST? ? CONTROL? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
192	0	63 AND (COST? ? MINIMI%ATION? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
193	6	63 AND (COST? ? ILLNESS? ? AND (STUD? OR TRIAL? OR RATIO? OR ANALYSIS?))
194	30	63 AND (COST? ? ANALYS? AND (STUD? OR TRIAL?))
195	5	63 AND (KOSTEN? ? NUTZEN? AND (STUDIE? OR ANALYS?))
196	0	63 AND (KOSTEN? ? NUTZWERT? AND (STUDIE? OR ANALYS?))
197	2	63 AND (KOSTEN? ? WIRKSAMKEIT? AND (STUDIE? OR ANALYS?))
198	0	63 AND (KOSTEN? ? EFFEKTIVIT? AND (STUDIE? OR ANALYS?))
199	0	63 AND (KOSTEN? ? EFFIZIENZ? AND (STUDIE? OR ANALYS?))
200	3	63 AND (KOSTEN? ? ANALYS?) AND STUDIE?
201	181	169 OR 170 OR 171 OR 172 OR 173 OR 174 OR 175 OR 176 OR 177 OR 178 OR 179 OR 180 OR 181 OR 182 OR 183 OR 184 OR 185 OR 186 OR 187 OR 188 OR 189 OR 190 OR 191 OR 192 OR 193 OR 194 OR 195 OR 196 OR 197 OR 198 OR 199 OR 200
202	2	63 AND CT=PHARMACOECONOMICS
203	31	63 AND (PHARMACOECONOMI? OR PHARMAKOOEKONOMI? OR PHARMAKOÖKONOMI?)
204	31	202 OR 203
205	183	201 OR 204
206	7	63 AND CT D ETHICS
207	0	63 AND CT D MORALS
208	4	63 AND CT D INFORMED CONSENT
209	0	63 AND CT=MORALITY
210	0	63 AND CT=SOCIAL JUSTICE
211	0	63 AND HEALTH SERCVICES ACCESSIBILITY
212	3	63 AND CT=HEALTH CARE ACCESS?
213	0	63 AND CT=FREEDOM
214	0	63 AND CT=ALTRUISM
215	0	63 AND CT=HUMAN RIGHTS
216	18	63 AND ETHIC?
217	0	63 AND BIOETHIC?
218	0	63 AND HUMAN RIGHTS
219	1	63 AND PATIENT# RIGHT#
220	6	63 AND CONSUMER?
221	4	63 AND MORAL?
222	0	63 AND JUSTICE
223	3	63 AND AUTONOMY
224	0	63 AND BENEFICIENC?
225	6	63 AND ETHIK?
226	3	63 AND ETHISCH##
227	0	63 AND MENSCHENRECHTE
228	11	63 AND RECHTSPRECHUNG?
229	1	63 AND JURISDICTION
230	20	63 AND LEGAL?
231	6	63 AND LAW#
232	66	206 OR 207 OR 208 OR 209 OR 210 OR 211 OR 212 OR 213 OR 214 OR 215 OR 216 OR 217 OR 218 OR 219 OR 220 OR 221 OR 222 OR 223 OR 224 OR 225 OR 226 OR 227 OR 228 OR 229 OR 230 OR 231
233	1846	168 OR 205 OR 232
234	1846	check duplicates: unique in s=233
235	1832	168
236	183	205
237	66	232

9.2 List of the literature ordered as full texts

No.	Reference (literature ordered as full texts)
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No.	Reference (literature ordered as full texts)
226.	Spencer T, Biederman J, Wilens T, Faraone S, Prince J, Gerard K, Doyle R, Parekh A, Kagan J, Bearman SK. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. Archives of general psychiatry 2001; 58(8): 775-782.
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262.	Weiss M, Hechtman L, The Adult ARG. A randomized double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. The Journal of clinical psychiatry 2006; 67(4): 611-619.
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265.	Wender PH, Reimherr FW, Marchant B, Czajkowski L, Sanford ME. A placebo-controlled, long-term trial of methylphenidate in the treatment of adults with ADHD. 2001 Annual Meeting of the American Psychiatric Association 2001.
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9.3 List of literature included after viewing the full text

No.	Reference (Literature included after viewing the full text))	Study design
1.	Adler LA, Goodman DW, Kollins SH, Weisler RH, Krishnan S, Zhang Y, Biederman J, Study G. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. The Journal of clinical psychiatry 2008; 69(9): 1364-1373.	Efficacy; RCT
2.	Adler LA, Liebowitz M, Kronenberger W, Qiao M, Rubin R, Hollandbeck M, Deldar A, Schuh K, Durell T. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. Depression and Anxiety 2009; 26(3): 212-221.	Efficacy; RCT
3.	Adler LA, Spencer T, Brown TE, Holdnack J, Saylor K, Schuh K, Trzepacz PT, Williams DW, Kelsey D. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: a 6-month, double-blind trial. Journal of Clinical Psychopharmacology 2009; 29(1): 44-50.	Efficacy; RCT
4.	Adler LA, Spencer TJ, Levine LR, Ramsey JL, Tamura R, Kelsey D, Ball SG, Allen AJ, Biederman J. Functional outcomes in the treatment of adults with ADHD. Journal of Attention Disorders 2008; 11(6): 720-727.	Efficacy; RCT

No.	Reference (Literature included after viewing the full text))	Study design
5.	Adler LA, Zimmerman B, Starr HL, Silber S, Palumbo J, Orman C, Spencer T. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/ hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. Journal of Clinical Psychopharmacology 2009; 29(3): 239-247.	Efficacy; RCT
6.	Barkley RA, Anderson DL, Kruesi M. A pilot study of the effects of atomoxetine on driving performance in adults with ADHD. Journal of attention disorders 2007; 10(3): 306-316.	Efficacy; RCT
7.	Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, Dunkel S, Dougherty M, Aleardi M, Spencer T. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 2006; 59(9): 829-835.	Efficacy; RCT
8.	Carpentier PJ, de Jong CA, Dijkstra BA, Verbrugge CA, Krabbe PF. A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. Addiction (Abingdon, England) 2005; 100(12): 1868-1874.	Efficacy; RCT
9.	Chamberlain SR, Del Campo N, Dowson J, Müller U, Clark L, Robbins TW, Sahakian BJ. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biological psychiatry 2007; 62(9): 977-984.	Efficacy; Cross-over
10.	Collins P, White T. Forensic implications of attention deficit hyperactivity disorder (ADHD) in adulthood. Journal of Forensic Psychiatry 2002; 13(2): 263-284.	Legal aspects
11.	Dorrego MF, Canevaro L, Kuzis G, Sabe L, Starkstein SE. A randomized, double-blind, crossover study of methylphenidate and lithium in adults with attention-deficit/hyperactivity disorder: preliminary findings. The Journal of neuropsychiatry and clinical neurosciences 2002; 14(3): 289-295.	Efficacy; RCT, Cross-over
12.	Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J. Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. Journal of clinical psychopharmacology 2004; 24(1): 24-29.	Efficacy; Metaanalysis
13.	Godfrey J. Safety of therapeutic methylphenidate in adults: a systematic review of the evidence. Journal of Psychopharmacology (Oxford, England) 2009; 23(2): 194-205.	Efficacy; Systematic review
14.	Hässler F, Reis O, Buchmann J, Bohne-Suraj S. HKS/ADHS und rechtliche Aspekte. Legal aspects of hyperkinetic disorders/ADHD. Der Nervenarzt 2008; 79(7): 820-826.	Legal aspects
15.	Jain U, Hechtman L, Weiss M, Ahmed TS, Reiz JL, Donnelly GA, Harsanyi Z, Darke AC. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. The Journal of clinical psychiatry 2007; 68(2): 268-277.	Efficacy; RCT, Cross-over
16.	Kösters M, Becker T, Kilian R, Fegert JM, Weinmann S. Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. Journal of psychopharmacology 2009; 23(7): 733-744.	Efficacy; Metaanalysis
17.	Kooij JJ, Burger H, Boonstra AM, Van der Linden PD, Kalma LE, Buitelaar JK. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/ hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. Psychological Medicine 2004; 34(6): 973-982.	Efficacy; RCT, Cross-over
18.	Kuperman S, Perry PJ, Gaffney GR, Lund BC, Bever-Stille KA, Arndt S, Holman TL, Moser DJ, Paulsen JS. Bupropion SR vs. methylphenidate vs. placebo for attention deficit hyperactivity disorder in adults. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists 2001; 13(3): 129-134.	Efficacy; RCT
19.	Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug and Alcohol Dependence 2007; 87(1): 20-29.	Efficacy; RCT
20.	Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug and Alcohol Dependence 2006; 81(2): 137-148.	Efficacy; RCT
21.	Matza LS, Paramore C, Prasad M. A review of the economic burden of ADHD. Cost Effectiveness and Resource Allocation 2005; 3: 5.	Economic study

No.	Reference (Literature included after viewing the full text))	Study design
22.	Medori R, Ramos-Quiroga JA, Casas M, Kooij JJ, Niemelä A, Trott GE, Lee E, Buitelaar JK. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 2008; 63(10): 981-989.	Efficacy; RCT
23.	Meszaros A, Czobor P, Balint S, Komlosi S, Simon V, Bitter I. Pharmacotherapy of adult attention deficit hyperactivity disorder (ADHD): a meta-analysis. The international journal of neuropsychopharmacology/official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 2009; 12(8): 1137-1147.	Efficacy; Metaanalysis
24.	Michelson D, Adler L, Spencer T, Reimherr FW, West SA, Allen AJ, Kelsey D, Wernicke J, Dietrich A, Milton D. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biological Psychiatry 2003; 53(2): 112-120.	Efficacy; RCT
25.	Peterson K, McDonagh MS, Fu R. Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. Psychopharmacology 2008; 197(1): 1-11.	Efficacy; Metaanalysis
26.	Purdie N, Hattie J, Carroll A. A review of the research on interventions for attention deficit hyperactivity disorder: what works best. Review of Educational Research 2002; 72(1): 61-99.	Efficacy; Metaanalysis
27.	Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. The Journal of Clinical Psychiatry 2007; 68(1): 93-101.	Efficacy; RCT
28.	Rösler M, Fischer R, Ammer R, Ose C, Retz W, on behalf of the study. A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder. European Archives of Psychiatry and Clinical Neuroscience 2009; 259(2): 120-129.	Efficacy; RCT
29.	Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, Edwards A, Donlin J, Pihlgren E. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Experimental and Clinical Psychopharmacology 2002; 10(3): 286-294.	Efficacy; RCT
30.	Secnik K, Swensen A, Lage MJ. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. PharmacoEconomics 2005; 23(1): 93-102.	Economic study
31.	Spencer T, Biederman J, Wilens T, Doyle R, Surman C, Prince J, Mick E, Aleardi M, Herzig K, Faraone S. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 2005; 57(5): 456-463.	Efficacy;
32.	Spencer T, Biederman J, Wilens T, Faraone S, Prince J, Gerard K, Doyle R, Parekh A, Kagan J, Bearman SK. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. Archives of General Psychiatry 2001; 58(8): 775-782.	Efficacy; RCT
33.	Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, Pestreich L, Adult ARG. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 2007; 61(12): 1380-1387.	Efficacy; RCT
34.	Spencer TJ, Adler LA, Weisler RH, Youcha SH. Triple-bead mixed amphetamine salts (SPD465), a novel, enhanced extended-release amphetamine formulation for the treatment of adults with ADHD: a randomized, double-blind, multicenter, placebo-controlled study. The Journal of Clinical Psychiatry 2008; 69(9): 1437-1448.	Efficacy; RCT
35.	Spencer TJ, Landgraf JM, Adler LA, Weisler RH, Anderson CS, Youcha SH. Attention-deficit/hyperactivity disorder-specific quality of life with triple-bead mixed amphetamine salts (SPD465) in adults: results of a randomized, double-blind, placebo-controlled study. The Journal of Clinical Psychiatry 2008; 69(11): 1766-1775.	Efficacy; RCT
36.	Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. Journal of Clinical Psychopharmacology 2001; 21(N2): 223-228.	Efficacy; RCT, Cross-over
37.	Tenenbaum S, Paull JC, Sparrow EP, Dodd DK, Green L. An experimental comparison of Pycnogenol and methylphenidate in adults with Attention-Deficit/Hyperactivity Disorder (ADHD). Journal of Attention Disorders 2002; 6(2): 49-60.	Efficacy; RCT, Cross-over

No.	Reference (Literature included after viewing the full text))	Study design
38.	Turner DC, Blackwell AD, Dowson JH, McLean A, Sahakian BJ. Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. Psychopharmacology 2005; 178(2-3): 286-295.	Efficacy; RCT, Cross-over
39.	Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. Biological psychiatry 2004; 55(10): 1031-1040.	Efficacy; RCT, Cross-over
40.	Verbeeck W, Tuinier S, Bekkering GE. Antidepressants in the treatment of adult attention-deficit hyperactivity disorder: a systematic review. Advances in Therapy 2009; 26(2): 170-184.	Efficacy; RCT
41.	Verster JC, Bekker EM, de Roos M, Minova A, Eijken EJ, Kooij JJ, Buitelaar JK, Kenemans JL, Verbaten MN, Olivier B, Volkerts ER. Methylphenidate significantly improves driving performance of adults with attention-deficit hyperactivity disorder: a randomized crossover trial. Journal of Psychopharmacology (Oxford, England) 2008; 22(3): 230-237.	Efficacy; RCT, Cross-over
42.	Weiss M, Hechtman L, The Adult ARG. A randomized double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. The Journal of Clinical Psychiatry 2006; 67(4): 611-619.	Efficacy; RCT
43.	Wilens TE, Adler LA, Weiss MD, Michelson D, Ramsey JL, Moore RJ, Renard D, Brady KT, Trzepacz PT, Schuh LM, Ahrbecker LM, Levine LR, Atomoxetine ASUD. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. Drug and Alcohol Dependence 2008; 96(1-2): 145-154.	Efficacy; RCT
44.	Wilens TE, Haight BR, Horrigan JP, Hudziak JJ, Rosenthal NE, Connor DF, Hampton KD, Richard NE, Modell JG. Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. Biological Psychiatry 2005; 57(7): 793-801.	Efficacy; RCT
45.	Wilens TE, Klint T, Adler L, West S, Wesnes K, Graff O, Mikkelsen B. A randomized controlled trial of a novel mixed monoamine reuptake inhibitor in adults with ADHD. Behavioral and Brain Functions 2008; 4: 24.	Efficacy; RCT
46.	Wilens TE, Spencer TJ, Biederman J, Girard K, Doyle R, Prince J, Polisner D, Solhkhah R, Comeau S, Monuteaux MC, Parekh A. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. The American Journal of Psychiatry 2001; 158(2): 282-288.	Efficacy; RCT
47.	Wu EQ, Birnbaum HG, Zhang HF, Ivanova JI, Yang E, Mallet D. Health care costs of adults treated for attention-deficit/hyperactivity disorder who received alternative drug therapies. Journal of Managed Care Pharmacy: JMCP 2007; 13(7): 561-569.	Economic study

RCT = Randomised controlled trial.

9.4 Literature excluded after viewing in full text with reason for exclusion

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
48.	Adler L, Dietrich A, Reimherr FW, Taylor LV, Sutton VK, Bakken R, Allen AJ, Kelsey D. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists 2006; 18(2): 107-113.	Comparison intervention: This study is a dose finding study; methylphenidate was administered in both groups
49.	Adler L, Dittmann RW, Kelsey D, Reimherr FW, Sangal BR, Saylor KE, Secnik K, Sutton V, Moore RJ, Suppl. Atomoxetin in the treatment of attention deficit/hyperactivity disorders in adults: effects on quality of life. Conference abstract: German Society for Psychiatry, Psychotherapy and Neuropathy, Congress 2004, Berlin, Germany, November 24-27, 2004.	This is an abstract
50.	Adler L, Spencer TJ, Williams DW, Moore R, Dittmann RW, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: final report of a 4-year study. Pharmacopsychiatry 2007; 40(5): 241.	This is an abstract

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
51.	Adler LA, Faraone SV, Spencer TJ, Michelson D, Reimherr FW, Glatt SJ, Marchant BK, Biederman J. The reliability and validity of self- and investigator ratings of ADHD in adults. Journal of attention disorders 2008; 11(6): 711-719.	Study design: Data of 2 studies are analysed
52.	Adler LA, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. Journal of attention disorders 2009; 12(5): 449-459.	Study design: Open-label study
53.	Adler LA, Spencer TJ, Milton DR, Moore RJ, Michelson D. Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: an interim analysis. The Journal of Clinical Psychiatry 2005; 66(3): 294-299.	Study design: Open-label study
54.	Adler LA, Spencer TJ, Stein MA, Newcorn JH. Best practices in adult ADHD: Neurobiology, pharmacology, and emerging treatments. CNS Spectrums 2008; 13(9 Suppl. 13): 2-16.	This is an abstract
55.	Adler LA, Spencer TJ, Williams DW, Moore RJ, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: Final report of a 4-year study. International Journal of Neuropsychopharmacology 2006; 9(Suppl. 1): 134-135.	This is an abstract
56.	Adler LA, Spencer TJ, Williams DW, Moore RJ, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: final report of a 4-year study. Journal of Attention Disorders 2008; 12(3): 248-253.	Belongs to Adler et al. 2005
57.	Adler LA, Sutton VK, Moore RJ, Dietrich AP, Reimherr FW, Sangal RB, Saylor KE, Secnik K, Kelsey DK, Allen AJ. Quality of life assessment in adult patients with attention-deficit/hyperactivity disorder treated with atomoxetine. Journal of Clinical Psychopharmacology 2006; 26(6): 648-652.	Study design: Uncontrolled study; data relate to a dose-finding study
58.	Adler LA. Non-stimulant trials of adult ADHD. CNS Spectrums 2007; 12(4 Suppl 6): 11-13.	Study design: This is a discussion paper
59.	Aharonovich E, Garawi F, Bisaga A, Brooks D, Raby WN, Rubin E, Nunes EV, Levin FR. Concurrent cannabis use during treatment for comorbid ADHD and cocaine dependence: effects on outcome. The American Journal of Drug and Alcohol Abuse 2006; 32(4): 629-635.	Study question: Does not aim at assessing the effectiveness of a pharmacotherapy
60.	Asherson P, Libretto SE. Long-acting methylphenidate for the treatment of adults with attention deficit hyperactivity disorder. British Journal of Developmental Disabilities 2004; 50(2): 143-151.	Study design: Case study
61.	Asherson P. Clinical assessment and treatment of attention deficit hyperactivity disorder in adults. Expert Review of Neurotherapeutics 2005; 5(4): 525-539.	Study design: unsystematic review
62.	Ashton H, Gallagher P, Moore B. The adult psychiatrist's dilemma: psychostimulant use in attention deficit/hyperactivity disorder. Journal of Psychopharmacology (Oxford, England) 2006; 20(5): 602-610.	Study design: unsystematic review; no description of the inclusion and exclusion criteria
63.	Bangs ME, Jin L, Zhang S, Desaiah D, Allen AJ, Read HA, Regev A, Wernicke JF. Hepatic events associated with atomoxetine treatment for attention-deficit hyperactivity disorder. Drug safety: An International Journal of Medical Toxicology and Drug Experience 2008; 31(4): 345-354.	Patient-relevant end point does not fulfil the inclusion criteria (hepatic events)
64.	Barkley RA, Cox D. A review of driving risks and impairments associated with attention-deficit/hyperactivity disorder and the effects of stimulant medication on driving performance. Journal of Safety Research 2007; 38(N1): 113-128.	Study design: unsystematic review
65.	Becker K, Wehmeier PM. Atomoxetin zur Behandlung der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (ADHS). Atomoxetine for the treatment of attention deficit/hyperactivity disorder (ADHD). PsychoNeuro 2003; 29(10): 472-476.	Study design: unsystematic review
66.	Bekker EM, Verster JC, Kenemans JL, Suppl. Neurocognitive effects of methylphenidate in adult attention deficit/hyperactivity disorder. Conference abstract: 19th Congress of the European College of Neuropsychopharmacology, Paris, France, 16/09/2006-20/09/2006.	This is an abstract

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
67.	Berman SM, Kuczenski R, McCracken JT, London ED. Potential adverse effects of amphetamine treatment on brain and behavior: a review. Molecular Psychiatry 2009; 14(2): 123-142.	Study design does not conform to the inclusion criteria
68.	Biederman J, Faraone S, Spencer T, Michelson D, Jones D, Adler L. Effects of atomoxetine treatment on executive functioning in adults with attention-deficit/hyperactivity disorder (ADHD). European Neuropsychopharmacology 2003; 13(Supplement 4): 458.	This is an abstract
69.	Biederman J, Mick E, Spencer T, Surman C, Hammerness P, Doyle R, Dougherty M, Aleardi M, Schweitzer K. An open-label trial of OROS methylphenidate in adults with late-onset ADHD. CNS Spectrums 2006; 11(5): 390-396.	Study design: Open-label study without comparison intervention or control group
70.	Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, Dunkel S, Dougherty M, Aleardi M, Spencer T. A randomized, double-blind, placebo-controlled study of OROS methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. European Neuropsychopharmacology 2005; 15(Suppl. 3): 631-632.	This is an abstract
71.	Biederman J, Mick EO, Surman C, Doyle R, Hammerness P, Michel E, Martin J, Spencer TJ. Comparative acute efficacy and tolerability of OROS and immediate release formulations of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. BMC Psychiatry 2007; 7: 49.	Study design does not conform to the inclusion criteria Data of 2 RCTs were pooled
72.	Biederman J, Seidman LJ, Petty CR, Fried R, Doyle AE, Cohen DR, Kenealy DC, Faraone SV. Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. The Journal of Clinical Psychiatry 2008; 69(7): 1150-1156.	Patient-relevant end point
73.	Biederman J, Spencer T, Surman C, Aleardi M, Dougherty M, Schweitzer K, Mick E. Open-label study of OROS methylphenidate in the treatment of adults with ADHD – Not otherwise specified (NOS). Biological Psychiatry 2005; 57(8): 106.	This is an abstract
74.	Biederman J, Spencer T. Methylphenidate in treatment of adults with Attention-Deficit/Hyperactivity Disorder. Journal of Attention Disorders 2002; 6(Suppl 1): 101-107.	Study design: unsystematic review
75.	Biederman J, Spencer TJ, Mick E, Suppl. Comparative acute efficacy and tolerability of OROS and immediate release formulations of methylphenidate in the treatment of adults with ADHD. Eur Neuropsychopharmacol. 2006; 16: 8-21.	Study design: No comparison group present
76.	Biederman J, Spencer TJ, Wilens TE, Weisler RH, Read SC, Tulloch SJ, Study G. Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. CNS Spectrums 2005; 10(12 Suppl 20): 16-25.	Study design: Open-label study; no comparison group present
77.	Biederman J, Spencer TJ. Psychopharmacology of adults with attention-deficit/hyperactivity disorder. Primary Psychiatry 2004; 11(7): 57-62.	Study design: unsystematic review
78.	Biederman J. Comparative and acute efficacy and tolerability of OROS and immediate release formulations of methylphenidate in the treatment of adults with attention deficit hyperactivity disorder. Biological Psychiatry 2006; 59(8, Suppl. S): 115.	This is an abstract
79.	Blix O, Dalteg A, Nilsson P. Treatment of opioid dependence and ADHD/ADD with opioid maintenance and central stimulants. Heroin Addiction and Related Clinical Problems 2009; 11(1): 5-14.	Intervention does not conform to the inclusion criteria: No drug therapy, no behaviour-therapeutic/drug therapy
80.	Boerner RJ, Rupprecht R, Martinius J, Müller HJ. Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung des Erwachsenenalters (ADHD), Alkoholabhängigkeit sowie kombinierte Persönlichkeitsstörung. Attention-deficit/ hyperactivity disorder in adult (ADHD), alcohol dependency, and combined personality disorder. Nervenheilkunde 2001; 20(7): 403-407.	Study design does not conform to the inclusion criteria
81.	Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJ. Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 2007; 30(4): 433-442.	The patient relevant end points do not fulfil the inclusion criteria

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
82.	Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK. Executive functioning in adult ADHD: a meta-analytic review. Psychological Medicine 2005; 35(N8): 1097-1108.	Study question does not aim at assessing the drug therapy
83.	Bouffard R, Hechtman L, Minde K, Iaboni-Kassab F. The efficacy of 2 different dosages of methylphenidate in treating adults with attention-deficit hyperactivity disorder. Canadian journal of psychiatry. Revue Canadienne de Psychiatrie 2003; 48(8): 546-554.	Study design: Dosing comparison study
84.	Bright GM. Abuse of medications employed for the treatment of ADHD: Results from a large-scale community survey. MedGenMed Medscape General Medicine 2008; 10(5).	Study design: Not a controlled study, no comparative intervention
85.	Brown TE. Atomoxetine and stimulants in combination for treatment of attention deficit hyperactivity disorder: four case reports. Journal of Child and Adolescent Psychopharmacology 2004; 14(1): 129-136.	Study design: Case study
86.	Buddensiek N, Te Wildt BT, Ziegenbein M, Emrich HM, Ohlmeier MD. Einsatz von atomoxetin bei erwachsenen mit ADHS und sucht: Vier fallberichte Medical therapy of adults with ADHD and addiction: Four case reports. Psychopharmakotherapie 2007; 14(2): 76-81.	Study design: Case study
87.	Buitelaar JK. Pharmacological treatment of adult ADHD. European Neuropsychopharmacology 2006; 16(Suppl. 4): 576-577.	Language
88.	Caballero J, Nahata MC. Atomoxetine hydrochloride for the treatment of attention-deficit/hyperactivity disorder. Clinical Therapeutics 2003; 25(12): 3065-3083.	Study design: Methodology not sufficiently described
89.	Centre for Reviews and. Efficacy of stimulants in adult ADHD (Structured abstract). Database of Abstracts of Reviews of Effectiveness 2003; (2009 Issue 3): 12003002537.	Doubled up
90.	Centre for Reviews and. Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder (Provisional abstract). Database of Abstracts of Reviews of Effectiveness 2004; (2009 Issue 3): 12004009139.	Doubled up
91.	Centre for Reviews and. The efficacy, safety, and practicality of treatments for adolescents with attention-deficit/hyperactivity disorder (ADHD) (Structured abstract). Database of Abstracts of Reviews of Effectiveness 2000; (2009 Issue 3): 12001003548.	Study population: children are also included
92.	Centre for Reviews and. The use of antidepressants to treat attention deficit hyperactivity disorder in adults (Structured abstract). Database of Abstracts of Reviews of Effectiveness 2003; (2009 Issue 3): 12003006908.	Doubled up
93.	Christman AK, Fermo JD, Markowitz JS. Atomoxetine, a novel treatment for attention-deficit-hyperactivity disorder. Pharmacotherapy 2004; 24(8): 1020-1036.	Study design: unsystematic review, no methodological description
94.	Chronis-Tuscano A, Seymour KE, Stein MA, Jones HA, Jiles CD, Rooney ME, Conlon CJ, Efron LA, Wagner SA, Pian J, Robb AS. Efficacy of osmotic-release oral system (OROS) methylphenidate for mothers with attention-deficit/hyperactivity disorder (ADHD): preliminary report of effects on ADHD symptoms and parenting. The Journal of Clinical Psychiatry 2008; 69(12): 1938-1947.	Study population is not representative: Only mothers were included
95.	Coetzee M, Kaminer Y, Morales A. Megadose intranasal methylphenidate (ritalin) abuse in adult attention deficit hyperactivity disorder. Substance abuse: official publication of the Association for Medical Education and Research in Substance Abuse 2002; 23(3): 165-169.	Study design: Case study
96.	Collins SL, Levin FR, Foltin RW, Kleber HD, Evans SM. Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD. Drug and Alcohol Dependence 2006; 82(2): 158-167.	Also persons without ADHD
97.	Corman SL, Fedutes BA, Culley CM. Atomoxetine: the first nonstimulant for the management of attention-deficit/hyperactivity disorder. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists 2004; 61(22): 2391-2399.	Study design: unsystematic review

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
98.	Cowles BJ. Lisdexamfetamine for treatment of attention-deficit/hyperactivity disorder. Annals of Pharmacotherapy 2009; 43(4): 669-676.	Study design: deficient methodological description; no standardised data extraction or assessment of the studies
99.	Cox DJ, Merkel RL, Kovatchev B, Seward R. Effect of stimulant medication on driving performance of young adults with attention-deficit hyperactivity disorder: a preliminary double-blind placebo controlled trial. The Journal of Nervous and Mental Disease 2000; 188(4): 230-234.	Study design: Not randomised, preliminary results, not a final paper
100.	Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate versus mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. Pediatrics 2006; 118(3): 704-710.	Study population: very young patients (16-19 years); Study design: small case number; no case number estimate
101.	Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. Journal of the American Academy of Child and Adolescent Psychiatry 2004; 43(3): 269-275.	Study population does not relate to adults
102.	Cox DJ, Mikami AY, Cox BS, Coleman MT, Mahmood A, Sood A, Moore M, Burket R, Merkel RL. Effect of long-acting OROS methylphenidate on routine driving in young adults with attention-deficit/hyperactivity disorder. Archives of Pediatrics & Adolescent Medicine 2008; 162(8): 793-794.	Study design: Case study of 2 persons
103.	Cox DJ, Moore M, Burket R, Merkel RL, Mikami AY, Kovatchev B. Rebound effects with long-acting amphetamine or methylphenidate stimulant medication preparations among adolescent male drivers with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 2008; 18(1): 1-10.	Study population: very young patients (17-19 years); Study design: No case number estimation
104.	Darredeau C, Barrett SP, Jardin B, Pihl RO. Patterns and predictors of medication compliance, diversion, and misuse in adult prescribed methylphenidate users. Human Psychopharmacology 2007; 22(8): 529-536.	Study question was not answered
105.	Davids E, Gastpar M. Atomoxetin in der Behandlung der Aufmerksamkeitsdefizit-/Hyperaktivitatsstörung bei Kindern und Erwachsenen Atomoxetine for the treatment of attention-deficit/hyperactivity disorder. Fortschritte der Neurologie-Psychiatrie 2004; 72(10): 586-591.	Study design: unsystematic review, no quality assessment of the studies, but just a simple list
106.	Davids E, Kis B, Specka M, Gastpar M. A pilot clinical trial of oxcarbazepine in adults with attention-deficit hyperactivity disorder. Progress in Neuro-psychopharmacology & Biological Psychiatry 2006; 30(6): 1033-1038.	Study design: no comparison or control group present
107.	Davidson MA. ADHD in adults: a review of the literature. Journal of Attention Disorders 2008; 11(6): 628-641.	Study question does not aim at the medical effectiveness of the pharmacotherapy
108.	De Lucas Taracena MT, Rada FM. Atomoxetina: Luces y sombras Atomoxetine: Lights and shadows. Psiquiatria Biologica 2007; 14(1): 13-23.	Language
109.	Dittmann RW, Adler L, Michelson D, Wernicke J. Efficacy and safety of atomoxetine in adults with attention deficit/hyperactivity disorder. Pharmacopsychiatry 2003; 36(5): 221.	This is an abstract
110.	Dodson WW. Pharmacotherapy of adult ADHD. Journal of Clinical Psychology 2005; 61(5): 589-606.	Study design: unsystematic review
111.	Downey KK, Sclrubiner H, Schuster CR. Double-blind placebo controlled stimulant trial for cocaine dependent ADHD adults. NIDA Research Monograph 2000; 180: 116.	This is an abstract
112.	Dowson JH. Pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD) in adults. Current Psychiatry Reviews 2006; 2(3): 317-331.	This is an abstract
113.	Drimmer EJ. Stimulant treatment of bulimia nervosa with and without attention-deficit disorder: three case reports. Nutrition 2003; 19(1): 76-77.	Study design: Case study

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
114.	Ebert D, Krause J, Roth-Sackenhelm C. ADHS im Erwachsenenalter: Leitlinien auf der Basis eines Expertenkonsensus mit Unterstuetzung der DGPPN. Nervenarzt 2003; 74(10): 939-946.	Study design: No detailed methodological description and description of the inclusion and exclusion criteria
115.	Edel MA, Pütze EM, Lieder A, Assion HJ, Ribbert H, Juckel G, Brüne M. Self concept, action control and ADHD symptoms under methylphenidate treatment in adults with ADHD. Pharmacopsychiatry 2009; 42(3): 109-113.	No control group
116.	Eiland LS, Guest AL. Atomoxetine treatment of attention-deficit/hyperactivity disorder. The Annals of Pharmacotherapy 2004; 38(1): 86-90.	No description of the methodology
117.	Fallu A, No. OROS*-Methylphenidate and executive functioning in adults with attention deficit hyperactivity disorder. Conference abstract: 39th International Danube Symposium for Neurological Science and Continuing Education 1st International Congress on ADHD from Childhood to Adult Disease, Würzburg, Germany, 02/06/2007-05/06/2007.	This is an abstract
118.	Fallu A, Prinzo R, Binder C. Safety and effectiveness of OROS*Methylphenidate in adults with Attention Deficit Hyperactivity Disorder (ADHD): Results of an open label study. International Journal of Neuropsychopharmacology 2006; 9(Suppl. 1): 134.	This is an abstract
119.	Fallu A, Richard C, Prinzo R, Binder C. Does OROS-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. Current Medical Research and Opinion 2006; 22(12): 2557-2566.	Uncontrolled study
120.	Fallu A, Richard C, Prinzo R, Binder C. Executive functioning in adult attention deficit hyperactivity disorder: Results of an open label study evaluating OROS*Methylphenidate. International Journal of Neuropsychopharmacology 2006; 9(Suppl. 1): 134.	This is an abstract
121.	Fallu A, Richard C, Prinzo R, Binder C. OROS-methylphenidate – How safe and how effective is it in ameliorating executive functioning deficits in adults with attention deficit hyperactivity disorder? Results of an open label study. Biological Psychiatry 2006; 59(8, Suppl. S): 203.	This is an abstract
122.	Faraone SV, Biederman J, Spencer T, Michelson D, Adler L, Reimherr F, Glatt SJ. Efficacy of atomoxetine in adult attention-deficit/hyperactivity disorder: a drug-placebo response curve analysis. Behavioral and Brain Functions : BBF 2005; 1: 16.	Study design does not fulfil the inclusion criteria: Data from 2 RCTs are compared (curve analysis)
123.	Faraone SV, Biederman J, Spencer T, Michelson D, Adler L, Reimherr F, Seidman L. Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 2005; 15(4): 664-670.	Inclusion of only 2 studies
124.	Faraone SV, Biederman J. Efficacy of Adderall for Attention-Deficit/ Hyperactivity Disorder: a meta-analysis. Journal of Attention Disorders 2002; 6(2): 69-75.	Study population: Children and adolescents included
125.	Frölich J, Lehmkuhl G. Die medikamentöse Behandlung der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung im Erwachsenenalter. Pharmacological treatment in adults with attention deficit hyperactivity disorder. Der Nervenarzt 2004; 75(11): 1074-1082.	Study design: unsystematic review
126.	Frölich J, Lehmkuhl G. Die Psychopharmakotherapie der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung im Erwachsenenalter. The psychopharmacological treatment in adults with attention deficit hyperactivity disorder. Nervenheilkunde 2004; 23(6): 343-353.	Study design: unsystematic review
127.	Gagne JJ, Singh M, Talati AR. Manifestation of adult attention-deficit/ hyperactivity disorder available treatment options. P and T 2006; 31(12): 736-741.	Study design
128.	Garces K. Atomoxetine for attention deficit/hyperactivity disorder. Issues in emerging health technologies 2003; (46): 1-4.	Study design: unsystematic review, no methodological description
129.	Gerwe M, Philipsen A, Roesler M, Sobanski E, Schauble B, Medori R, Trott GE. Effectiveness and compatibility of OROS (R)-methylphenidate for adult with ADHS - The long-acting methylphenidate in adult ADHD (LAMDA) trial. Nervenarzt 2007; 78(S2): 208-209.	This is an abstract

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
130.	Gerwe M, Rosler M, Trott GE, Philipsen A, Sobanski E, Medori R, Schauble B. Offene extensions-study for compatibility of OROS-methylphenidate for adult with ADHD - The long-acting methylphenidate in adult ADHD (LAMDA) trial. Nervenarzt 2007; 78(S2): 208.	No control or comparison group
131.	Gomatos OG, Antonopoulos MS, Delorme AJ, DePamphilis JL, Garalis DD. Buproprion SR versus methylphenidate in the treatment of adults with ADHD with or without comorbid depression: A cost-effective study. ASHP Midyear Clinical Meeting 2002; 37(DEC): 667.	This is an abstract
132.	Goodman DW, Ginsberg L, Weisler RH, Cutler AJ, Hodgkins P. An interim analysis of the quality of life, effectiveness, safety, and tolerability (QUEST) evaluation of mixed amphetamine salts extended release in adults with ADHD. CNS Spectrums 2005; 10(N12,S20): 26-34.	This is an abstract
133.	Greenfield B, Hechman L. Treatment of attention deficit hyperactivity disorder in adults. Expert Review of Neurotherapeutics 2005; 5(1): 107-121.	Study design: Methodology insufficiently described; no systematic review
134.	Greenhill LL, Pliszka S, Dulcan MK, Bernet W, Arnold V, Beitchman J, Benson RS, Bukstein O, Kinlan J, McClellan J, Rue D, Shaw JA, Stock S, Kroeger K. Summary of the practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. Journal of the American Academy of Child and Adolescent Psychiatry 2001; 40(11): 1352-1355.	No full text, only summary
135.	Greenhill LL, Pliszka S, Dulcan MK, Bernet W, Arnold V, Beitchman J, Benson RS, Bukstein O, Kinlan J, McClellan J, Rue D, Shaw JA, Stock S, American Academy of Child and Adolescent. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. Journal of the American Academy of Child and Adolescent Psychiatry 2002; 41(2 Suppl): 26.	Study population: Children and adolescents are included
136.	Gross-Tsur V, Shalev RS, Badihi N, Manor O. Efficacy of Methylphenidate in patients with Cerebral Palsy and attention-deficit hyperactivity disorder (ADHD). Journal of Child Neurology 2002; 17(12): 863-866.	Not a representative study population (cerebral palsy)
137.	Haasen C, Fink T, Schäfer I, Reimer J. ADHS und Sucht: erste Erfahrungen in der Behandlung mit Atomoxetin. Suchttherapie. 2005; 6: 133-136.	Study design: Case study
138.	Hammerness P. Stimulant therapy in adult ADHD. International Journal of Neuropsychopharmacology 2006; 9(Suppl. 1): 51.	This is an abstract
139.	Hargarter L, Gerwe M, Czekalla J, Mattejat F, Schauble B. Transition from IR methylphenidate (IR-MPH) to OROS (R)-MPH (concerta((R))) is associated with an improvement in quality of life in patients with ADRD – results from an open label study. Journal of Neural Transmission 2007; 114(7).	This is an abstract
140.	Hässler F, Reis O, Buchmann J, Bohne-Suraj S. HKS/ADHS und rechtliche Aspekte. Der Nervenarzt – Organ der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde 2008. Springer-Verlag – Berlin/Heidelberg.	Doubled up
141.	Hazell P. Review of new compounds available in Australia for the treatment of attention-deficit hyperactivity disorder. Australasian psychiatry: bulletin of Royal Australian and New Zealand College of Psychiatrists 2004; 12(4): 369-375.	Study design: unsystematic review, no methodological description
142.	Heinzl S. Atomoxetin für Kinder und Erwachsene mit ADHS. Psychopharmakotherapie 2003; 10(3): 120-124.	Study design: no systematic review
143.	Himpel S, Banaschewski T, Heise CA, Rothenberger A. The safety of non-stimulant agents for the treatment of attention-deficit hyperactivity disorder. Expert Opinion on Drug Safety 2005; 4(2): 311-321.	Study design: no systematic review
144.	Hornig-Rohan M, Amsterdam JD. Venlafaxine versus stimulant therapy in patients with dual diagnosis ADD and depression. Progress in Neuropsychopharmacology & Biological Psychiatry 2002; 26(3): 585-589.	Study design: retrospective study
145.	Horrigan JP, Barnhill LJ. Low-dose amphetamine salts and adult attention-deficit/hyperactivity disorder. The Journal of Clinical Psychiatry 2000; 61(6): 414-417.	No control group

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
146.	Horrigan JP. Present and future pharmacotherapeutic options for adult attention deficit/hyperactivity disorder. Expert Opinion on Pharmacotherapy 2001; 2(4): 573-586.	Study design: unsystematic review
147.	Jerome L, Segal A. Benefit of long-term stimulants on driving in adults with ADHD. The Journal of Nervous and Mental Disease. 2001; 189: 63-64.	Commentary on another publication
148.	Johnson M, Cederlund M, Rastam M, Areskoug B, Gillberg C. Open-Label Trial of Atomoxetine Hydrochloride in Adults With ADHD. Journal of Attention Disorders 2009 May 20.	Open-label study
149.	Kay GG, Michaels MA, Pakull B. Simulated driving changes in young adults with ADHD receiving mixed amphetamine salts extended release and atomoxetine. Journal of Attention Disorders 2009; 12(4): 316-329.	Study design: Pilot study; no case number; Generalisability is doubted by the authors themselves
150.	Kemner JE, Lage MJ. Effect of methylphenidate formulation on treatment patterns and use of emergency room services. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2006; 63(4): 317-322.	Study population: Emergency patients
151.	Kinsbourne M, De Quiros GB, Rufo DT. Adult ADHD: Controlled medication assessment. Annals of the New York Academy of Sciences 2001; 931: 287-296.	Deficient methodological description
152.	Kollins SH, English J, Robinson R, Hallyburton M, Chrisman AK. Reinforcing and subjective effects of methylphenidate in adults with and without attention deficit hyperactivity disorder (ADHD). Psychopharmacology 2009; 204(1): 73-83.	Study population: patients without ADHD also included
153.	Kollins SH. ADHD, substance use disorders, and psychostimulant treatment: current literature and treatment guidelines. Journal of Attention Disorders 2008; 12(2): 115-125.	Study question: No assessment of the medical effectiveness of a pharmacotherapy
154.	Kollins SH. Comparing the abuse potential of methylphenidate versus other stimulants: a review of available evidence and relevance to the ADHD patient. The Journal of Clinical Psychiatry 2003; 64(Suppl 11): 14-18.	Study question: Examination of the dependency potential of methylphenidate
155.	Koo PJ. Once daily formulation of MPH for treatment of adolescents and adults ADHD: interim results. ASHP Summer Meeting 2002; 59(Jun): 18.	Abstract
156.	Kooij JJ, Middelkoop HA, van Gils K, Buitelaar JK. The effect of stimulants on nocturnal motor activity and sleep quality in adults with ADHD: an open-label case-control study. The Journal of Clinical Psychiatry 2001; 62(12): 952-956.	Study design: Case control study
157.	Kooij S, Medori R, Buitelaar J, Ramos-Quiroga JA, Lee E, Casas M. Open-label extension trial of the safety and tolerability of OROSO methylphenidate in adults with ADHD - the long-acting methylphenidate in adult ADHD (lamda) trial. Journal of Neural Transmission 2007; 114(7).	This is an abstract
158.	Kordon A, Hofecker FM. Pharmakotherapie der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) im Erwachsenenalter – Allgemeine Grundlagen, Epidemiologie, Psychopathologie, Klassifikation, Verlauf, Neurobiologie und soziale Adaptation. Zeitschrift für Psychiatrie, Psychologie und Psychotherapie 2006; 54(2): 99-110.	Study design: unsystematic review
159.	Kratochvil CJ, Vaughan BS, Daughton JM, Mayfield-Jorgensen ML, Burke WJ. Atomoxetine in the treatment of attention deficit hyperactivity disorder. Expert Review of Neurotherapeutics 2004; 4(4): 601-611.	Study design: unsystematic review
160.	Kratochvil CJ, Vaughan BS, Harrington MJ, Burke WJ. Atomoxetine: a selective noradrenaline reuptake inhibitor for the treatment of attention-deficit/hyperactivity disorder. Expert Opinion on Pharmacotherapy 2003; 4(7): 1165-1174.	Study design: unsystematic review
161.	Krause J, Trott GE, Krause KH. Medikamentöse Therapie der ADHS im Erwachsenenalter Pharmacological therapy in ADHD of adulthood. PsychoNeuro 2005; 31(11): 569-575.	Study design: No systematic review

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
162.	Krause J. Die Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung bei Erwachsenen. Attentiondeficit-/hyperactivity disorder in adults. Fortschritte der Neurologie Psychiatrie 2007; 75(5): 293-305.	Study design: No systematic review
163.	Krause KH, Krause J. Ist Methylphenidat bei Komorbidität von Epilepsie und Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung kontraindiziert oder nicht? Is methylphenidate contraindicated or not in comorbidity of epilepsy and attention deficit/hyperactivity disorder? Aktuelle Neurologie 2000; 27(2): 72-76.	Study population: Patients with epileptic attacks
164.	Kurscheidt JC, Peiler P, Behnken A, Abel S, Pedersen A, Suslow T, Deckert J. Acute effects of methylphenidate on neuropsychological parameters in adults with ADHD: possible relevance for therapy. Journal of neural transmission (Vienna, Austria : 1996) 2008; 115(2): 357-362.	Analysis of neuropsychological tests
165.	Laing A, Aristides M. Attention deficit hyperactivity disorder (ADHD) in adults: SF-6D utilities from SF-36 scores in a randomised trial of atomoxetine. Value in Health 2005; 8(N6): 199.	This is an abstract
166.	Landgraf JM. Monitoring quality of life in adults with ADHD: reliability and validity of a new measure. Journal of Attention disorders 2007; 11(3): 351-362.	No intervention group
167.	Leibson CL, Long KH. Economic implications of attention-deficit hyperactivity disorder for healthcare systems. PharmacoEconomics 2003; 21(17): 1239-1262.	Study population: Inclusion of children and adolescents
168.	Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. Human psychopharmacology 2004; 19(3): 151-180.	Study design: unsystematic review
169.	Levin FR, Bisaga A, Raby W, Aharonovich E, Rubin E, Mariani J, Brooks DJ, Garawi F, Nunes EV. Effects of major depressive disorder and attention-deficit/hyperactivity disorder on the outcome of treatment for cocaine dependence. Journal of Substance Abuse Treatment 2008; 34(1): 80-89.	Patient-relevant end points do not fulfil the requirements of the inclusion criteria
170.	Levin FR, Evans SM, McDowell DM, Brooks DJ, Nunes E. Bupropion treatment for cocaine abuse and adult attention-deficit/hyperactivity disorder. Journal of Addictive Diseases 2002; 21(2): 1-16.	No comparison group present
171.	Levin FR, Mariani JJ, Secora A, Brooks D, Cheng WY, Bisaga A, Nunes E, Aharonovich E, Raby W, Hennessy G. Atomoxetine Treatment for Cocaine Abuse and Adult Attention-Deficit Hyperactivity Disorder (ADHD): A Preliminary Open Trial. Journal of Dual Diagnosis 2009; 5(1): 41-56.	No comparison group present
172.	Levine L, Tamura RN, Kelsey DK, Schoepp DD, Allen AJ. Functional outcomes in adults with attention-deficit/hyperactivity disorder following treatment with atomoxetine vs. placebo. Neuropsychopharmacology 2005; 30(Suppl. 1): 137.	This is an abstract
173.	Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. Annals of Pharmacotherapy 2006; 40(N10): 1829-1833.	Study design: no methodological description
174.	Loncarek E, Unglaub W, Lermer E, Guerlach G, Eilles C, Suppl. Stationary treatment of polytoxicomania and ADHD in adults using slow-release methylphenidate. (Ger.). Nervenarzt. 2002; 73: 203-204.	This is an abstract
175.	Madaan V, Daughton J, Lubberstedt B, Mattai A, Vaughan BS, Kratochvil CJ. Assessing the efficacy of treatments for ADHD: Overview of methodological issues. CNS Drugs 2008; 22(4): 275-290.	Study design does not fulfill the inclusion criterian
176.	Maidment ID. Efficacy of stimulants in adult ADHD. The Annals of Pharmacotherapy 2003; 37(12): 1884-1890.	Study design: no systematic search described
177.	Maidment ID. The use of antidepressants to treat attention deficit hyperactivity disorder in adults. Journal of Psychopharmacology (Oxford, England) 2003; 17(3): 332-336.	Only studies that examined antidepressants were included; methodology deficiently described (inclusion and exclusion criteria); no quality assessment of the study, no comparative presentation of the study results

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
178.	Martsenkovsky I, Melakh I, Bikshaeva Y, Suppl. Milnacipran and atomoxetine efficacy over time in adolescents and adults with depression who have comorbid attention-deficit/hyperactivity disorder. Conference abstract: 26th Collegium Internationale Neuro-Psychopharmacology Congress, Munich, Germany, 13/07/2008-17/07/2008.	This is an abstract
179.	Matza LS, Stoeckl MN, Shorr JM, Johnston JA. Impact of atomoxetine on health-related quality of life and functional status in patients with ADHD. Expert Review of Pharmacoeconomics and Outcomes Research 2006; 6(4): 379-390.	Study population: Inclusion of children and adolescents
180.	Medori R, Kooij S, Buitelaar J, Ramos-Quiroga JA, Trott GE, Lee E, Casas M, Suppl. Double-blind study of the efficacy and safety of prolonged-re lease methylphenidate in adults with ADHD – the LAMDA trial. Eur Neuropsychopharmacol. 2007; 17: 8.	This is an abstract
181.	Medori R, Kooij JJ, Ramos-Quiroga JA, Buitelaar J, Lee E, Casas M. Efficacy and safety of OROS methylphenidate in Adults with ADHD-the long acting methylphenidate in adult ADHD (LMDA) trial. Paper presented at: The 160th Annual Meeting of the American Psychiatric Association, 2007; San Diego, CA	Abstract
182.	Meijer WM, Faber A, van den Ban E, Tobi H. Current issues around the pharmacotherapy of ADHD in children and adults. Pharmacy World & Science : PWS 2009.	Study question: No assessment of the medical effectiveness of a pharmacotherapy
183.	Meszaros A, Czobor P, Balint S, Simon V, Bitter I. Pharmacotherapy of adult Attention Deficit/Hyperactivity Disorder (ADHD): a systematic review. Psychiatria Hungarica 2007; 22(4): 259-270.	Language
184.	Michelson D, Adler L, Spencer T, Milton D, Jones D. Long-term treatment effects of atomoxetine in adults with attention-deficit/hyperactivity disorder (ADHD). European Neuropsychopharmacology 2003; 13(Supplement 4): 458.	Abstract
185.	Michelson D, Milton D, Spencer T, Adler L, Dittmann RW, Suppl. Efficacy and tolerability of atomoxetine in the treatment of attention deficit/ hyperactivity disorder in adults. (Ger.). Nervenarzt. 2003; 74: 0766.	Abstract
186.	Montanes-Rada F, Gangoso-Fermoso AB, Martiinez-Granero MA. Drugs for attention deficit hyperactivity disorder. Revista de Neurologia 2009; 48(9): 469-481.	Language
187.	N. N. A naturalistic study of the effects of pharmacotherapy on substance use disorders among ADHD adults. Psychological Medicine 2007; 37(N12): 1743-1752.	Not a controlled study
188.	N. N. Effectiveness of attention-deficit/hyperactivity treatment and diagnosis methods tested. 2000; 11: 1-2.	No full text available
189.	N. N. Erste Ergebnisse der europäischen LAMDA-Studie zu ADHS: Retardiertes Methylphenidat ist auch bei Erwachsenen effektiv und verträglich. Journal für Pharmakologie und Therapie 2007; 16(6): 181.	Not available as a full text (could not be ordered by DIMDI)
190.	N. N. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. Journal of the American Academy of Child and Adolescent Psychiatry 2002; 41(2 Suppl.): 26.	Doubled up
191.	N. N. Summary of the practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. Journal of the American Academy of Child and Adolescent Psychiatry 2001; 40(11): 1352-1355.	Doubled up
192.	Najib J. The efficacy and safety profile of lisdexamfetamine dimesylate, a prodrug of d-amphetamine, for the treatment of attention-deficit/ hyperactivity disorder in children and adults. Clinical Therapeutics 2009; 31(1): 142-176.	Study population not restricted to adults
193.	Newcorn JH. Nonstimulants and emerging treatments in adults with ADHD. CNS Spectrums 2008; 13(N9,S13): 12-16.	Study design: unsystematic review

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
194.	Nutt DJ, Fone K, Asherson P, Bramble D, Hill P, Matthews K, Morris KA, Santosh P, Sonuga-Barke E, Taylor E, Weiss M, Young S. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: Recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 2007; 21(1): 10-41.	Study design: unsystematic review, no methodological description, presentation of the results deficient
195.	Ohlmeier MD, Prox V, Zhang Y, Zedler M, Ziegenbein M, Emrich HM, Dietrich DE. Effects of methylphenidate in ADHD adults on target evaluation processing reflected by event-related potentials. Neuroscience Letters 2007; 424(3): 149-154.	Patient-relevant end points and study design do not conform to the specified inclusion criteria
196.	Ohlmeier MD. Pharmakotherapie der ADHS im Erwachsenenalter bei komorbider Depression Pharmacotherapy of ADHD in adults with comorbid depression. Psychiatrische Praxis 2007; 34 Suppl 3: 296-299.	Study design: unsystematic review
197.	Olfson M, Marcus SC, Zhang HF, Wan GJ. Stimulant dosing in the community treatment of adult attention-deficit/hyperactivity disorder. Journal of clinical psychopharmacology. 2008; 28: 255-257.	Letters to the editor; no detailed full text
198.	Overtoom CC, Bekker EM, van der Molen MW, Verbaten MN, Kooij JJ, Buitelaar JK, Kenemans JL. Methylphenidate restores link between stop-signal sensory impact and successful stopping in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 2009; 65(7): 614-619.	Study end points do not conform to the required inclusion criteria
199.	Overtoom CCE, Bekker EM, Kenemans JL, Verbaten MN, van der Molen MW, Kooij JJS, Buitelaar JK. A dose-response study of methylphenidate and paroxetine on inhibition and attention in adults with Attention Deficit/Hyperactivity Disorder. Journal of Cognitive Neuroscience 2005; 221.	This is an abstract
200.	Perry Paul J. Bupropion sustained release versus methylphenidate versus placebo in the treatment of adult adhd. 155th Annual Meeting of the American Psychiatric Association. 2002.	This is an abstract
201.	Perry PJ, Gaffney GR, Bever Stille K, Holman T, Paulsen J. Bupropion sustained release versus methylphenidate versus placebo in the treatment of adult adhd. 153rd Annual Meeting of the American Psychiatric Association 2000.	This is an abstract
202.	Philipsen A, Heßlinger B, van Elst LT. Attention deficit and hyperactivity disorder in adulthood. Deutsches Arzteblatt 2008; 105(17): 311-317.	Study design: unsystematic review
203.	Philipsen A, Hesslinger B, van Elst LT. Attention Deficit Hyperactivity Disorder in Adulthood. Deutsches Ärzteblatt International 2009; 105(N17): 311-319.	Study design: unsystematic review
204.	Philipsen A, Trott GE, Roesler M, Gerwe M, Lee E, Medori R, Schauble B, No. Open-label (OL) extension trial of the safety and tolerability of OROS((R)) methylpheniclate in adults with ADHD – the long-acting methylpheniclate in adult ADHD (LAMDA) trial. Pharmacopsychiatry. 2007; 40: 204.	This is an abstract
205.	Pietras CJ, Cherek DR, Lane SD, Tcheremissine OV, Steinberg JL. Effects of methylphenidate on impulsive choice in adult humans. Psychopharmacology 2003; 170(4): 390-398.	Study population not representative: only male subjects with criminal past
206.	Pliszka SR. Pharmacologic treatment of attention-deficit/hyperactivity disorder: efficacy, safety and mechanisms of action. Neuropsychology Review 2007; 17(1): 61-72.	Study design: unsystematic review
207.	Pohl GM, Van Brunt DL, Ye W, Stoops WW, Johnston JA. A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD). BMC Health Services Research 2009; 9: 95.	Study design does not fulfil the required inclusion criteria: retrospective "claim analysis"
208.	Prasad S, Arellano J, Steer C, Libretto SE. Assessing the value of atomoxetine in treating children and adolescents with ADHD in the UK. International Journal of Clinical Practice 2009; 63(7): 1031-1040.	Study population relates to children
209.	Preuss U. ADHD for neurologists: ADHD in children, adolescents and adults. Aktuelle Neurologie 2007; 34(5): 291-310.	Study design: unsystematic review
210.	Quinn PO. Treating adolescent girls and women with ADHD: gender-specific issues. Journal of Clinical Psychology 2005; 61(5): 579-587.	Study design: unsystematic review

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
211.	Radigan M, Lannon P, Roohan P, Gesten F. Medication patterns for attention-deficit/hyperactivity disorder and comorbid psychiatric conditions in a low-income population. Journal of Child and Adolescent Psychopharmacology 2005; 15(1): 44-56.	Study population: Children and adolescents to age 19
212.	Ramos-Quiroga JA, Bosch R, Castells X, Valero S, Nogueira M, Gomez N, Yelmo S, Ferrer M, Martiinez Y, Casas M. Effect of switching drug formulations from immediate-release to extended-release OROS methylphenidate: a chart review of Spanish adults with attention-deficit hyperactivity disorder. CNS Drugs 2008; 22(7): 603-611.	Intervention: OROS-MPH vs. IR-MPH
213.	Ramos-Quiroga JA, Bosch R, Castells X, Valero S, Nogueira M, Yelmo S, Garcia E, Martinez I, Casas M. A 6 month study of the adherence, effectiveness and safety with methylphenidate adults with ADHD. European Psychiatry 2007; 22(S1): 63.	This is an abstract
214.	Ramos-Quiroga JA, Corominas M, Castells X, Bosch R, Casas M. OROS methylphenidate for the treatment of adults with attention-deficit/ hyperactivity disorder. Expert Review of Neurotherapeutics 2009; 9(8): 1121-1131.	Methodology of the literature search insufficiently described; no standardised data extraction, no quality assessment; possibly use in the discussion
215.	Ray R, Rukstalis M, Jepson C, Strasser A, Patterson F, Lynch K, Lerman C. Effects of atomoxetine on subjective and neurocognitive symptoms of nicotine abstinence. Journal of Psychopharmacology (Oxford, England) 2009; 23(2): 168-176.	Study question: The effects of atomoxetine are assessed for symptoms during nicotine abstinence
216.	Reimherr FW, Faraone SV, Marchant BK, Robison RJ, Strong R, Soni P, Adler L. Gender differences in adults with ADHD, pretreatment and following treatment with atomoxetine under double-blind conditions. European Neuropsychopharmacology 2005; 15(Suppl. 3): 604.	This is an abstract
217.	Reimherr FW, Marchant BK, Strong RE, Hedges DW, Adler L, Spencer TJ, West SA, Soni P. Emotional dysregulation in adult ADHD and response to atomoxetine. Biological Psychiatry 2005; 58(2): 125-131.	Study population is not representative: only patients with "brain dysfunction"
218.	Robinson DM, Keating GM. Dexmethylphenidate extended release: in attention-deficit hyperactivity disorder. Drugs 2006; 66(5): 661-668.	Study design: unsystematic review, no methodological description
219.	Roesler M, Trott GE, Philipsen A, Gerwe M, Lee E, Medori R, Schauble B, No. Efficacy and safety of OROS((R)) methylpheniclate in adults with ADHD: the long-acting methylphenidate in adult ADHD (LAMDA) trial. Pharmacopsychiatry. 2007; 40: 205.	This is an abstract
220.	Ron E, Dolan P, Ringer AF, DeLuca JE, Shah P. Cost-utility of osmotic release as compared to immediate release methylphenidate in an adult attention deficit hyperactivity disorder patient. ASHP Midyear Clinical Meeting 2001; 36(Dec): 660.	This is an abstract
221.	Rostain AL. Attention-deficit/hyperactivity disorder in adults: evidence-based recommendations for management. Postgraduate Medicine 2008; 120(3): 27-38.	Study design: unsystematic review
222.	Roy M, Dillo W, Bessling S, Emrich HM, Ohlmeier MD. Effective methylphenidate treatment of an adult Aspergers Syndrome and a comorbid ADHD: a clinical investigation with fMRI. Journal of Attention Disorders 2009; 12(4): 381-385.	Study design: Case study
223.	Rush CR, Higgins ST, Vansickel AR, Stoops WW, Lile JA, Glaser PE. Methylphenidate increases cigarette smoking. Psychopharmacology 2005; 181(4): 781-789.	Patient-relevant end points do not fulfil the inclusion criteria
224.	Sachdev PS, Trollor JN. How high a dose of stimulant medication in adult attention deficit hyperactivity disorder? The Australian and New Zealand Journal of Psychiatry 2000; 34(4): 645-650.	Study design: unsystematic review
225.	Safren SA, Duran P, Yovel I, Perlman CA, Sprich S. Medication adherence in psychopharmacologically treated adults with ADHD. Journal of Attention Disorders 2007; 10(3): 257-260.	Study objective is compliance with the medication and not the medical effectiveness

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
226.	Safren SA, Sprich SE, Cooper-Vince C, Knouse LE, Lerner JA. Life Impairments in Adults with Medication-Treated ADHD. Journal of Attention Disorders 2009.	Abstract
227.	Sandner F. Retardiertes methylphenidat ist auch bei erwachsenen effektiv und vertrÃ‘glich First results of the European LAMDA study on ADHD: Long-acting methylphenidate is effective and well tolerated in adults. Journal fur Pharmakologie und Therapie 2007; 16(6): 181-182.	Study design: unsystematic review
228.	Sargent E, Arnold SD, Costa M, De Maio YM, Vaughan F. Modeled cost-effectiveness analysis comparing atomoxetine and methylphenidate in adults with attention deficit hyperactivity disorder. ASHP Midyear Clinical Meeting 2004; 39: 433.	Abstract
229.	Sevecke K, Battel S, Dittmann RW, Lehmkuhl G, Döpfner M. The effectiveness of atomoxetine in children, adolescents, and adults with ADHD. A systematic overview. Der Nervenarzt 2006; 77(3): 294.	Study design: unsystematic review, no description of the methodology
230.	Simpson A, Kratochvil C, Spencer TJ, Buitelaar JK, Newcorn JH, Wilens TE, Allen AJ, Faries DE, Milton DR, Feldman PD, Michelson D, Biederman J. Efficacy of atomoxetine in placebo-controlled studies in children, adolescents, and adults with attention-deficit/hyperactivity disorder. European Psychiatry 2004; 19(S1): 240.	This is an abstract
231.	Simpson D, Plosker GL. Atomoxetine: a review of its use in adults with attention deficit hyperactivity disorder. Drugs 2004; 64(2): 205-222.	Study design: unsystematic review
232.	Simpson D, Plosker GL. Spotlight on atomoxetine in adults with attention-deficit hyperactivity disorder. CNS Drugs 2004; 18(6): 397-401.	Study design: unsystematic review
233.	Slatkoff J, Greenfield B. Pharmacological treatment of attention-deficit/ hyperactivity disorder in adults. Expert Opinion on Investigational Drugs 2006; 15(6): 649-667.	Study design: unsystematic review
234.	Sobanski E, Alm B, Krumm B, N. Methylphenidate in adults with attention-deficit/hyperactivity disorder. Nervenarzt. 2007; 78: 328-330.	Study design: open uncontrolled application observation
235.	Sobanski E, Alm B, Krumm B, No. Effect of subtype and psychiatric comorbidities on methylphenidate treatment in adults with attention-deficit hyperactivity disorder. (German). Nervenarzt. 2007; 78: 333-337.	Doubled up
236.	Sobanski E, Alm B, Krumm B, Suppl. Methylphenidate action in adult patients with attention deficit/hyperactivity disorder with reference to disorder subtype and psychiatric comorbidity. (Ger.). Conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Berlin, Germany, November 19-22, 2003.	This is an abstract
237.	Sobanski E, Alm B, Krumm B. Effect of subtype and psychiatric comorbidities on methylphenidate treatment in adults with attention-deficit hyperactivity disorder. Der Nervenarzt 2007; 78(3): 328-330.	Doubled up
238.	Sobanski E, Brueggemann D, Alm B, Kern S, Philipsen A, Schmalzried H, Hesslinger B, Waschkowski H, Rietschel M. Subtype differences in adults with attention-deficit/hyperactivity disorder (ADHD) with regard to ADHD-symptoms, psychiatric comorbidity and psychosocial adjustment. European Psychiatry 2008; 23(N2): 142-149.	Study design and intervention do not fulfil the inclusion criteria; not 2 groups in comparison
239.	Solhkhah R, Wilens TE, Daly J, Prince JB, Van Patten SL, Biederman J. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. Journal of Child and Adolescent Psychopharmacology 2005; 15(5): 777-786.	Study population: Inclusion of children and adolescents of ages 12-19
240.	Somoza EC, Winhusen TM, Bridge TP, Rotrosen JP, Vanderburg DG, Harrer JM, Mezinskis JP, Montgomery MA, Ciraulo DA, Wulsin LR, Barrett JA. An open-label pilot study of methylphenidate in the treatment of cocaine dependent patients with adult attention deficit/hyperactivity disorder. Journal of Addictive Diseases 2004; 23(1): 77-92.	No control group
241.	Spencer T, Biederman J, Mick E, Faraone SV. Efficacy in a 6 month trial of methylphenidate in adults with attention-deficit/hyperactivity disorder. European Neuropsychopharmacology 2004; 14: 369.	This is an abstract

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
242.	Spencer TJ, Faraone SV, Michelson D, Adler LA, Reimherr FW, Glatt SJ, Biederman J. Atomoxetine and adult attention-deficit/hyperactivity disorder: the effects of comorbidity. The Journal of Clinical Psychiatry 2006; 67(3): 415-420.	Study design does not fulfil the inclusion criteria: 2 RCTs are compared with each other
243.	Spencer TJ. Efficacy and safety of atomoxetine in adults with adhd. 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA. 2003; 32.	This is an abstract
244.	Spencer TJ. Pharmacology of adult ADHD with stimulants. CNS Spectrums 2007; 12(4 Suppl 6): 8-11.	Study design: unsystematic review
245.	Spencer TJ. Prelminary results of a six-month trial of methylphenidate in adults with adhd. 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA. 2003; 54.	This is an abstract
246.	Tcheremissine OV, Salazar JO. Pharmacotherapy of adult attention deficit/hyperactivity disorder: Review of evidence-based practices and future directions. Expert Opinion on Pharmacotherapy 2008; 9(8): 1299-1310.	No standardised data extraction, quality assessment
247.	Tepner R, Michelson D, Wernicke J, Allen AJ, Heiligenstein J, Laws H, Faries D, Suppl. Placebo controlled trials of atomoxetine for adhd in children, adolescents, and adults. International Journal of Neuropsychopharmacology. 2002; 5: 162.	This is an abstract
248.	Thanos PK, Michaelides M, Benveniste H, Wang GJ, Volkow ND. Effects of chronic oral methylphenidate on cocaine self-administration and striatal dopamine D2 receptors in rodents. Pharmacology, Biochemistry, and Behavior 2007; 87(4): 426-433.	Study design: animal experiment study
249.	Thomson A, Maltezos S, Paliokosta E, Xenitidis K. Amfetamine for attention deficit hyperactivity disorder in people with intellectual disabilities. Cochrane database of systematic reviews (Online) 2009; (1): 007009.	Restricted study population
250.	Tirado CF, Goldman M, Lynch K, Kampman KM, Obrien CP. Atomoxetine for treatment of marijuana dependence: a report on the efficacy and high incidence of gastrointestinal adverse events in a pilot study. Drug and Alcohol Dependence 2008; 94(1-3): 254-257.	Study question: Atomoxetine is used to fight marijuana addiction
251.	Tirado CF, Maullin N, Kyle K, Klein L, O'Brien C. An open label pilot trial of atomoxetine and four-session motivational interviewing for cannabis dependence. Neuropsychopharmacology 2005; 30(Suppl. 1): 216-217.	This is an abstract
252.	Tucha O, Mecklinger L, Laufkötter R, Klein HE, Walitza S, Lange KW. Methylphenidate-induced improvements of various measures of attention in adults with attention deficit hyperactivity disorder. Journal of Neural Transmission 2006; 113(10): 1575-1592.	Study design and inclusion criteria do not agree with the required inclusion criteria
253.	Turgay A. Atomoxetine in the treatment of children, adolescents and adults with attention deficit hyperactivity disorder. Therapy 2006; 3(1): 19-38.	Study design: unsystematic review, no methodological description
254.	Turner D. A review of the use of modafinil for attention-deficit hyperactivity disorder. Expert Review of Neurotherapeutics 2006; 6(4): 455-468.	Study design: unsystematic review, no methodological description
255.	Tutee O, Tutee L, Waltz S, Stasik D, Laufkotter R, Gerlach M, Klein HE, Lange KW. Differential effects of methylphenidate on problem solving of adults with attention deficit hyperactivity disorder. Journal of Neural Transmission. 2007; 114: 1004.	This is an abstract
256.	Unglaub W, Wismath M, Johann M, Wodarz N, Klein H. The addictive potential of methylphenidate. Psychiatrische Praxis, Supplement 2007; 34(1): 109-110.	Study objective: Addiction risk of methylphenidate
257.	Upadhyaya HP, Brady KT, Wang W. Bupropion SR in adolescents with comorbid ADHD and nicotine dependence: a pilot study. Journal of the American Academy of Child and Adolescent Psychiatry 2004; 43(2): 199-205.	Study population: Patients to age 19 included and from age 12
258.	Upadhyaya HP, Rose K, Wang W, O'Rourke K, Sullivan B, Deas D, Brady KT. Attention-deficit/hyperactivity disorder, medication treatment, and substance use patterns among adolescents and young adults. Journal of Child and Adolescent Psychopharmacology 2005; 15(5): 799-809.	Study design and intervention do not fulfil the required inclusion criteria

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
259.	Upadhyaya HP. Methylphenidate and pramipexole drug effects in adolescents and young adults with attention deficit hyperactivity disorder (ADHD) and nicotine dependence. Neuropsychopharmacology 2006; 31(Suppl. 1): 139.	This is an abstract
260.	Van Brunt DL, Johnston JA, Ye W, Pohl GM, O'Hara NN. Factors associated with initiation with atomoxetine versus stimulants in the treatment of adults with ADHD: retrospective analysis of administrative claims data. Journal of Managed Care Pharmacy : JMCP 2006; 12(3): 230-238.	Study design: "exploratory analysis"
261.	Vaughan B, Fegert J, Kratochvil CJ. Update on atomoxetine in the treatment of attention-deficit/hyperactivity disorder. Expert Opinion on Pharmacotherapy 2009; 10(4): 669-676.	Study design: unsystematic review
262.	Verster JC, Bekker EM, de Roos M, Minova A, Eijken EJE, Kooij JJS, Buitelaar JK, Kenemans JL, Verbaten MN, et a, Suppl. Driving ability in adults with attention-deficit hyperactivity disorder significantly improves when treated with methylphenidate. European Neuropsychopharmacology 2006; 16: 8-39.	This is an abstract
263.	Verster JC, Cox DJ. ADHD, methylphenidate and driving: Does some legislation endanger public health? Journal of Psychopharmacology 2008; 22(3): 227-229.	Study design: unsystematic review
264.	Weber J, Siddiqui MA. Lisdexamfetamine dimesylate: in attention-deficit hyperactivity disorder in adults. CNS Drugs 2009; 23(5): 419-425.	Study design: unsystematic review
265.	Wehmeier PM, Schacht A, Rothenberger A. Change in the direct cost of treatment for children and adolescents with hyperkinetic disorder in Germany over a period of four years. Child and Adolescent Psychiatry and Mental Health 2009; 3 (1): 3.	Study population: Children and adolescents
266.	Weih M, Thürauf N, Bleich S, Kornhuber J. Off-label use in psychiatry. Fortschritte der Neurologie-Psychiatrie 2008; 76(1): 7-13.	Study question: No assessment of the medical efficacy of a drug therapy
267.	Weisler RH, Biederman J, Spencer TJ, Wilens TE. Long-term cardiovascular effects of mixed amphetamine salts extended release in adults with ADHD. CNS Spectrums 2005; 10(12 Suppl 20): 35-43.	Patient-relevant end point: Cardiovascular illnesses
268.	Weiss MD, Gadow K, Wasdell MB. Effectiveness outcomes in attention-deficit/hyperactivity disorder. The Journal of clinical psychiatry 2006; 67(Suppl 8): 38-45.	Study design: unsystematic review
269.	Wender Paul H. A placebo-controlled, long-term trial of methylphenidate in the treatment of adults with adhd. 155th Annual Meeting of the American Psychiatric Association. 2002.	This is an abstract
270.	Wender PH, Reimherr FW, Marchant B, Czajkowski L, Sanford ME. A placebo-controlled, long-term trial of methylphenidate in the treatment of adults with ADHD. 2001 Annual Meeting of the American Psychiatric Association 2001.	This is an abstract
271.	Wender PH, Szajkowski L, Marchant B, Reimherr FW, Sanford E, Eden J. A Long-Term Study of Methylphenidate in the Treatment of ADHD in Adults. 156th Annual Meeting of the American Psychiatric Association, May 17-22, San Francisco CA. 2003; 708.	This is an abstract
272.	Wernicke JF, Adler L, Spencer T, West SA, Allen AJ, Heiligenstein J, Milton D, Ruff D, Brown WJ, Kelsey D, Michelson D. Changes in symptoms and adverse events after discontinuation of atomoxetine in children and adults with attention deficit/hyperactivity disorder: a prospective, placebo-controlled assessment. Journal of Clinical Psychopharmacology 2004; 24(1): 30-35.	Study design: unsystematic review; only 2 RCTs were used
273.	Wernicke JF, Faries D, Girod D, Brown J, Gao H, Kelsey D, Quintana H, Lipetz R, Michelson D, Heiligenstein J. Cardiovascular effects of atomoxetine in children, adolescents, and adults. Drug Safety: An International Journal of Medical Toxicology and Drug Experience 2003; 26(10): 729-740.	Patient-relevant end point Cardiovascular illnesses
274.	Wetzel MW, Burke WJ. Addressing attention-deficit/hyperactivity disorder in later adulthood. Clinical Geriatrics 2008; 16(11): 33-39.	Study design: unsystematic review
275.	Wigal SB. Efficacy and safety limitations of attention-deficit hyperactivity disorder pharmacotherapy in children and adults. CNS Drugs 2009; 23(Suppl. 1): 21-31.	Study design: unsystematic review

No.	Reference (Literature excluded after viewing in full text)	Reason for exclusion/ unfulfilled inclusion criterion
276.	Wilens TE, Adler LA, Weiss MD, Ramsey JL, Moore RF, Renard D, Trzepacz PT, Schuh LM, Dittmann RW, Levine LR, No. Atomoxetine treatment of adults with ADHD and comorbid alcohol abuse disorder. Pharmacopsychiatry. 2007; 40: 150.	This is an abstract
277.	Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003; 111(1): 179-185.	Study question: Link between stimulants and a dependency; no effectiveness
278.	Wilens TE, Hammerness PG, Biederman J, Kwon A, Spencer TJ, Clark S, Scott M, Podolski A, Ditterline JW, Morris MC, Moore H. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder. The Journal of Clinical Psychiatry 2005; 66(2): 253-259.	Patient-relevant end point: Blood pressure and pulse
279.	Wilens TE, Spencer TJ, Biederman J. A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. Journal of Attention Disorders 2002; 5(4): 189-202.	Deficient methodological description
280.	Wilens TE, Verlinden MH, Adler LA, Wozniak PJ, West SA. ABT-089, a neuronal nicotinic receptor partial agonist, for the treatment of attention-deficit/hyperactivity disorder in adults: results of a pilot study. Biological Psychiatry 2006; 59(11): 1065-1070.	Nicotine treatment
281.	Wilens TE, Zusman RM, Hammerness PG, Podolski A, Whitley J, Spencer TJ, Gignac M, Biederman J. An open-label study of the tolerability of mixed amphetamine salts in adults with attention-deficit/ hyperactivity disorder and treated primary essential hypertension. The Journal of Clinical Psychiatry 2006; 67(5): 696-702.	Patients suffer from high blood pressure and are treated for it; no comparative intervention
282.	Wilens TE. Attention-deficit/hyperactivity disorder and the substance use disorders: The nature of the relationship, who is at risk, and treatment issues. Primary Psychiatry 2004; 11(7): 63-70.	Study design: unsystematic review
283.	Wilens TE. Drug therapy for adults with attention-deficit hyperactivity disorder. Drugs 2003; 63(22): 2395-2411.	Study design: unsystematic review
284.	Williams E, Reimherr FW, Marchant BK, Strong RE, Halls C, Soni P. Personality Disorder Assessment in Adult ADHD Utilizing Subjects Enrolled in a Clinical Trial of OROS (R) Methylphenidate (OROS (R) MPH). Journal of Child and Adolescent Psychopharmacology 2008; 18(6): 635-636.	This is an abstract
285.	Young JL. Treatment of adult ADHD and comorbid disorders. CNS Spectrums 2006; 11(10 Suppl 11): 10-12.	Study design: no primary study, no systematic review

ADHD = attention[a] deficit/hyperactivity disorder. IR MPH = Immediate-release methylphenidate. OROS-MPH = Osmotic-controlled release delivery system-Methylphenidate extended release. RCT = Randomised controlled trial.

a Capitalise for consistency.

9.5 Check-lists of the included studies

9.5.1 Randomised controlled studies

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Efficacy and safety of OROS Methylphenidate in adults with attention-deficit/hyperactivity disorder. A randomized, placebo-controlled, double-blind, parallel group, dose-escalation study
Authors:	Adler LA, Zimmermen B, Starr L et al.
Source:	Journal of Clinical Psychopharmacology 2009; 29: 239-247

Document type	RCT:	☒	Cohort study:	☐	Case control study: ☐	Longitudinal study:	☐
			Case series:	☐		Other:	☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the “standard users” of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation	**Yes**	**No**	**?**
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis ?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Adler et al. 2009a – continued

	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
QB	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
I	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**						
Report No.:							
Title:	Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder						
Authors:	Adler LA, Liebowitz M, Kronenberger W						
Source:	Depression and Anxiety 2009; 26: 212-221						
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐			
		Case series: ☐		Other: ☐			

Class	**A Selection of the study participants**	**Yes**	**No**	**?**
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined.	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☒	☐	☐
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups treated in the same manner, with the exception of the intervention?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control groups?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐

Adler et al. 2009c – continued

	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis	**Yes**	**No**	**?**
QA	1. Are the described analytical methods correct and the information sufficient for a flawless analysis?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**			
Report No.:				
Title:	Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study			
Authors:	Jain U, Hechtman L, Weiss M et al.			
Source:	J Clin Psychiatry 2007; 68: 268-277			
Document type	RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐			
	Case series: ☐ Other: ☐			

Class	**A Selection of the study participants**	**Yes**	**No**	**?**
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☐	☐	☒
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒

Jain et al. 2007 – continued

	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs	**Yes**	**No**	**?**
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in the cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**					
Report No.:						
Title:	Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial					
Authors:	Kooij JJS, Burger H, Boonstra AM et al.					
Source:	Psychological Medicine 2004; 34(6): 973-982					
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐		
		Case series: ☐		Other: ☐		

Class	**A Selection of the study participants**	**Yes**	**No**	**?**
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined.	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐

Kooij et al. 2004 – continued

	D Study administration	Yes	No	?
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☐	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**					
Report No.:						
Title:	A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS Methylphenidate in adults with attention-deficit/hyperactivity disorder					
Authors:	Medori R, Ramos-Quiroga JA, Casas M et al.					
Source:	Biol Psychiatry 2008; 63: 981-989					
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐		
		Case series: ☐		Other: ☐		

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☒	☐	☐
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒

Medori et al. 2008 – continued

	C Intervention and exposure	Yes	No	?
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**			
Report No.:				
Title:	Atomoxetine in adults with adhd: two randomized, placebo-controlled studies			
Authors:	Michelson D, Adler L, Spencer T et al.			
Source:	Biol Psychiatry 2003; 53: 112-120			
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐

Michelson et al. 2003 – continued

	B Allocation and study participation	Yes	No	?
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis ?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	A randomized double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults
Authors:	Weiss M, Hechtman L et al.
Source:	J Clin Psychiatry 2006; 67: 611-619

Document type	RCT:	☒	Cohort study:	☐	Case control study: ☐	Longitudinal study:	☐
			Case series:	☐		Other:	☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☐	☒
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☐	☐	☒
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☒	☐
QA	2. Were reasons listed for study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Weiss et al. 2006 – continued

	G Statistical analysis	Yes	No	?
QA	1. Are the described analytical methods correct and the information sufficient for a flawless analysis?	☐	☐	☒
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**			
Report No.:				
Title:	A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults			
Authors:	Wilens TE, Spencer TJ, Biederman J et al.			
Source:	Am J Psychiatry 2001; 158: 282-288			
Document type	RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐			
	Case series: ☐ Other: ☐			

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☒	☐	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐

Wilens et al. 2001 – continued

	F Drop-outs	Yes	No	?
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis ?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**					
Report No.:						
Title:	A randomized controlled trial of a novel mixed monoamine reputake inhibitor in adults with ADHD					
Authors:	Wilens TE, Klingt T, Adler L et al.					
Source:	Behavioral and Brain Functions 2008; 4: 24-34					
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study:		☐
		Case series: ☐		Other:		☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒

Wilens et al. 2008b – continued

	E Outcome measurement	Yes	No	?
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☒	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis ?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☒ excluded ☐				

9.5.2 Metaanalyses

Check-list 1b:	**Systematic reviews and metaanalyses**			
Report No.:				
Title:	Meta-Analysis of the Efficacy of Methylphenidate for Treating Adult Attention-Deficit/Hyperactivity Disorder			
Authors:	Faraone S, Spencer T, Aleardi M et al.			
Source:	Journal of Clinical Psychopharmacology 2004; 24(1): 24-29			
This document contains: qualitative information syntheses ☐ quantitative information syntheses ☐				
		yes	**no**	**?**
Class	**A Question**			
QA	1. Is the research question relevant to our question?	☒	☐	☐
Class	**B Acquisition of information**			
	1. Documentation of the literature search:			
QA	a) Were the sources used documented?	☒	☐	☐
QB	b) Were the search strategies documented?	☐	☒	☐
QB	2. Were the inclusion criteria defined?	☐	☒	☐
QB	3. Were the exclusion criteria defined?	☐	☒	☐
	C Assessment of the information			
	1. Documentation of the study assessment:			
QA	a) Were validity criteria included?	☐	☒	☐
QB	b) Was the assessment performed independently by several persons?	☐	☒	☐
QC	c) Are excluded studies documented with the reasons for their exclusion?	☒	☐	☐
QC	2. Is the data extraction documented in a retraceable manner?	☐	☒	☐
QC	3. Was the data extraction performed independently by several persons?	☐	☒	☐
	D Information synthesis			
	1. Quantitative information syntheses:			
QA	a) Was the metaanalysis method stated?	☒	☐	☐
QB	b) Was heterogeneity testing performed?	☒	☐	☐
QC	c) Were the results in the sensitivity analysis tested for robustness?	☒	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the information synthesis documented in a retraceable manner?	☒	☐	☐
QB	b) Is there an assessment of the existing evidence?	☐	☒	☐

Faraone et al. 2004 – continued

	E Conclusions:	yes	no	?
QB	1. Was the research question answered?	☒	☐	☐
QB	2. Is the existing evidence thoroughly implemented in the conclusions?	☒	☐	☐
QA	3. Were limitations of the meaningfulness due to methodology critically discussed?	☒	☐	☐
I	4. Are recommendations for action stated?	☐	☒	☐
I	5. Is there a degree of differentiation in the recommendations?	☐	☒	☐
I	6. Is further need for research identified?	☒	☐	☐
I	7. Is an update of the review planned?	☐	☒	☐
	F Transferability of the international/foreign results and conclusions			
	Are there differences regarding the:			
	a) Epidemiology of the target condition?	☐	☒	☐
	b) Development status of the technology?	☐	☒	☐
	c) Formulation of the indication?	☐	☒	☐
	d) Care contexts, conditions, processes?	☐	☒	☐
	e) Remuneration systems?	☐	☒	☐
	f) Socio-economic consequences?	☐	☒	☐
	g) Patient and provider preferences?	☐	☒	☐
Concluding assessment: This publication will be: included ☒ excluded ☐				

Check-list 1b: Systematic reviews and metaanalyses				
Report No.:				
Title:	Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder			
Authors:	Kösters M, Becker T, Kilian R, Fegert JM, Weinmann S			
Source:	Journal of Psychopharmacology 2009; 23(7): 733-744			
This document contains: qualitative information syntheses **yes** quantitative information syntheses **yes**				
		yes	**no**	**?**
Class	**A Question**			
QA	1. Is the research question relevant to our question?	☒	☐	☐
Class	**B Acquisition of information**			
	1. Documentation of the literature search:			
QA	a) Were the sources used documented?	☒	☐	☐
QB	b) Were the search strategies documented?	☒	☐	☐
QB	2. Were the inclusion criteria defined?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☐	☒	☐
	C Assessment of the information			
	1. Documentation of the study assessment:			
QA	a) Were validity criteria included?	☐	☒	☐
QB	b) Was the assessment performed independently by several persons?	☐	☒	☐
QC	c) Are excluded studies documented with the reasons for their exclusion?	☒	☐	☐
QC	2. Is the data extraction documented in a retraceable manner?	☒	☐	☐
QC	3. Was the data extraction performed independently by several persons?	☒	☐	☐
	D Information synthesis			
	1. Quantitative information syntheses:			
QA	a) Was the metaanalysis method stated?	☒	☐	☐
QB	b) Was heterogeneity testing performed?	☒	☐	☐
QC	c) Were the results in the sensitivity analysis tested for robustness?	☒	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the information synthesis documented in a retraceable manner?	☒	☐	☐
QB	b) Is there an assessment of the existing evidence?	☒	☐	☐

Kösters et al. 2009 – continued

	E Conclusions:	yes	no	?
QB	1. Was the research question answered?	☒	☐	☐
QB	2. Is the existing evidence thoroughly implemented in the conclusions?	☐	☒	☐
QA	3. Were limitations of the meaningfulness due to methodology critically discussed?	☒	☐	☐
I	4. Are recommendations for action stated?	☒	☐	☐
I	5. Is there a degree of differentiation in the recommendations?	☐	☐	☐
I	6. Is further need for research identified?	☒	☐	☐
I	7. Is an update of the review planned?	☐	☒	☐
	F Transferability of the international/foreign results and conclusions			
	Are there differences regarding the:			
	a) Epidemiology of the target condition?	☐	☒	☐
	b) Development status of the technology?	☒	☐	☐
	c) Formulation of the indication?	☒	☐	☐
	d) Care contexts, conditions, processes?	☒	☐	☐
	e) Remuneration systems?	☐	☒	☐
	f) Socio-economic consequences?	☐	☐	☐
	g) Patient and provider preferences?	☐	☐	☐
Concluding assessment: This publication will be: included ☒ excluded ☐				

Check-list 1b:	**Systematic reviews and metaanalyses**
Report No.:	
Title:	Pharmacotherapy of adult attention deficit hyperactivity disorder (ADHD): a meta-analysis
Authors:	Meszaros A, Czober P, Balint S et al.
Source:	International Journal of Neuropsychopharmacology 2009; 12(8): 1137-1147

This document contains:
qualitative information syntheses **no** quantitative information syntheses **yes**

		yes	no	?
Class	**A Question**			
QA	1. Is the research question relevant to our question	☒	☐	☐
Class	**B Acquisition of information**			
	1. Documentation of the literature search:			
QA	a) Were the sources used documented?	☒	☐	☐
QB	b) Were the search strategies documented?	☐	☒	☐
QB	2. Were the inclusion criteria defined?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Assessment of the information			
	1. Documentation of the study assessment:			
QA	a) Were validity criteria included?	☐	☐	☒
QB	b) Was the assessment performed independently by several persons?	☐	☐	☒
QC	c) Are excluded studies documented with the reasons for their exclusion?	☐	☒	☐
QC	2. Is the data extraction documented in a retraceable manner?	☐	☐	☒
QC	3. Was the data extraction performed independently by several persons?	☐	☐	☒
	D Information synthesis			
	1. Quantitative information syntheses:			
QA	a) Was the metaanalysis method stated?	☒	☐	☐
QB	b) Was heterogeneity testing performed?	☐	☒	☐
QC	c) Were the results in the sensitivity analysis tested for robustness?	☐	☐	☒
	2. Qualitative information syntheses:			
QA	a) Is the information synthesis documented in a retraceable manner?	☒	☐	☐
QB	b) Is there an assessment of the existing evidence?	☐	☒	☐

Meszaros et al. 2009 – continued

	E Conclusions:	yes	no	?
QB	1. Was the research question answered?	☒	☐	☐
QB	2. Is the existing evidence thoroughly implemented in the conclusions?	☒	☐	☐
QA	3. Were limitations of the meaningfulness due to methodology critically discussed?	☒	☐	☐
I	4. Are recommendations for action stated?	☒	☐	☐
I	5. Is there a degree of differentiation in the recommendations?	☐	☒	☐
I	6. Is further need for research identified?	☒	☐	☐
I	7. Is an update of the review planned?	☐	☐	☒
	F Transferability of the international/foreign results and conclusions			
	Are there differences regarding the:			
	a) Epidemiology of the target condition?	☐	☒	☐
	b) Development status of the technology?	☐	☒	☐
	c) Formulation of the indication?	☐	☒	☐
	d) Care contexts, conditions, processes?	☐	☒	☐
	e) Remuneration systems?	☐	☒	☐
	f) Socio-economic consequences?	☐	☒	☐
	g) Patient and provider preferences?	☐	☒	☐
Concluding assessment: This publication will be: included ☒ excluded ☐				

Check-list 1b: Systematic reviews and metaanalyses				
Report No.:				
Title:	Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis			
Authors:	Peterson K, McDonagh MS, Fu R			
Source:	Psychopharmacology 2008; 197: 1-11			
This document contains: qualitative information syntheses ☒ quantitative information syntheses ☒				
		yes	**no**	**?**
Class	**A Question**			
QA	1. Is the research question relevant to our question?	☒	☐	☐
Class	**B Acquisition of information**			
	1. Documentation of the literature search:			
QA	a) Were the sources used documented?	☒	☐	☐
QB	b) Were the search strategies documented?	☒	☐	☐
QB	2. Were the inclusion criteria defined?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☐	☒	☐
	C Assessment of the information			
	1. Documentation of the study assessment:			
QA	a) Were validity criteria included?	☒	☐	☐
QB	b) Was the assessment performed independently by several persons?	☒	☐	☐
QC	c) Are excluded studies documented with the reasons for their exclusion?	☒	☐	☐
QC	2. Is the data extraction documented in a retraceable manner?	☒	☐	☐
QC	3. Was the data extraction performed independently by several persons?	☒	☐	☐
	D Information synthesis			
	1. Quantitative information syntheses:			
QA	a) Was the metaanalysis method stated?	☒	☐	☐
QB	b) Was heterogeneity testing performed?	☒	☐	☐
QC	c) Were the results in the sensitivity analysis tested for robustness?	☒	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the information synthesis documented in a retraceable manner?	☒	☐	☐
QB	b) Is there an assessment of the existing evidence?	☐	☒	☐

Peterson et al. 2008 – continued

	E Conclusions:	yes	no	?
QB	1. Was the research question answered?	☒	☐	☐
QB	2. Is the existing evidence thoroughly implemented in the conclusions?	☒	☐	☐
QA	3. Were limitations of the meaningfulness due to methodology critically discussed?	☒	☐	☐
I	4. Are recommendations for action stated?	☒	☐	☐
I	5. Is there a degree of differentiation in the recommendations?	☐	☐	☐
I	6. Is further need for research identified?	☒	☐	☐
I	7. Is an update of the review planned?	☐	☒	☐
	F Transferability of the international/foreign results and conclusions			
	Are there differences regarding the:			
	a) Epidemiology of the target condition?	☐	☒	☐
	b) Development status of the technology?	☒	☐	☐
	c) Formulation of the indication?	☐	☒	☐
	d) Care contexts, conditions, processes?	☒	☐	☐
	e) Remuneration systems?	☐	☒	☐
	f) Socio-economic consequences?	☐	☒	☐
	g) Patient and provider preferences?	☐	☒	☐
Concluding assessment: This publication will be: included ☒ excluded ☐				

Check-list 1b: Systematic reviews and metaanalyses				
Report No.:				
Title:	Antidepressants in the treatment of adult attention-deficit hyperactivity disorder: a systematic review			
Authors:	Verbeeck W, Tuinier S, Bekkering GE			
Source:	Adv Ther 2009; 26(2): 170-184			
This document contains: qualitative information syntheses **yes** quantitative information syntheses **yes**				
		yes	**no**	**?**
Class	**A Question**			
QA	1. Is the research question relevant to our question?	☒	☐	☐
Class	**B Acquisition of information**			
	1. Documentation of the literature search:			
QA	a) Were the sources used documented?	☒	☐	☐
QB	b) Were the search strategies documented?	☐	☒	☐
QB	2. Were the inclusion criteria defined?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☐	☒	☐
	C Assessment of the information			
	1. Documentation of the study assessment:			
QA	a) Were validity criteria included?	☐	☐	☒
QB	b) Was the assessment performed independently by several persons?	☒	☐	☐
QC	c) Are excluded studies documented with the reasons for their exclusion?	☐	☒	☐
QC	2. Is the data extraction documented in a retraceable manner?	☐	☒	☐
QC	3. Was the data extraction performed independently by several persons?	☐	☐	☒
	D Information synthesis			
	1. Quantitative information syntheses:			
QA	a) Was the metaanalysis method stated?	☒	☐	☐
QB	b) Was heterogeneity testing performed?	☐	☐	☒
QC	c) Were the results in the sensitivity analysis tested for robustness?	☐	☒	☐
	2. Qualitative information syntheses:			
QA	a) Is the information synthesis documented in a retraceable manner?	☒	☐	☐
QB	b) Is there an assessment of the existing evidence?	☐	☒	☐

Veerbeck et al. 2009 – continued

	E Conclusions:	**yes**	**no**	**?**
QB	1. Was the research question answered?	☒	☐	☐
QB	2. Is the existing evidence thoroughly implemented in the conclusions?	☒	☐	☐
QA	3. Were limitations of the meaningfulness due to methodology critically discussed?	☒	☐	☐
I	4. Are recommendations for action stated? ***	☒	☐	☐
I	5. Is there a degree of differentiation in the recommendations?	☐	☒	☐
I	6. Is further need for research identified?	☒	☐	☐
I	7. Is an update of the review planned?	☐	☐	☒
	F Transferability of the international/foreign results and conclusions			
	Are there differences regarding the:			
	a) Epidemiology of the target condition?	☐	☒	☐
	b) Development status of the technology?	☐	☒	☐
	c) Formulation of the indication?	☐	☐	☒
	d) Care contexts, conditions, processes?	☐	☐	☒
	e) Remuneration systems?	☐	☐	☒
	f) Socio-economic consequences?	☐	☐	☒
	g) Patient and provider preferences?	☐	☐	☒
Concluding assessment: This publication will be: included ☒ excluded ☐				

9.5.3 Economic studies

Check-list 1b:	**Systematic reviews and metaanalyses**			
Report No.:				
Title:	A review of the economic burden of ADHS			
Authors:	Matza LS, Paramore C, Prasad M			
Source:	Cost Effectiveness and Ressource Allocation 2005; 3(5): 1-9			
This document contains: qualitative information syntheses ☒ quantitative information syntheses ☒				
		yes	**no**	**?**
Class	**A Question**			
QA	1. Is the research question relevant to our question?	☒	☐	☐
Class	**B Acquisition of information**			
	1. Documentation of the literature search:			
QA	a) Were the sources used documented?	☒	☐	☐
QB	b) Were the search strategies documented?	☒	☐	☐
QB	2. Were the inclusion criteria defined?	☐	☒	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Assessment of the information			
	1. Documentation of the study assessment:			
QA	a) Were validity criteria included?	☐	☒	☐
QB	b) Was the assessment performed independently by several persons?	☐	☐	☒
QC	c) Are excluded studies documented with the reasons for their exclusion?	☐	☐	☒
QC	2. Is the data extraction documented in a retraceable manner?	☐	☐	☒
QC	3. Was the data extraction performed independently by several persons?	☐	☐	☒
	D Information synthesis			
	1. Quantitative information syntheses:			
QA	a) Was the metaanalysis method stated?	☐	☐	☒
QB	b) Was heterogeneity testing performed?	☐	☐	☒
QC	c) Were the results in the sensitivity analysis tested for robustness?	☐	☐	☒
	2. Qualitative information syntheses:			
QA	a) Is the information synthesis documented in a retraceable manner?	☐	☒	☐
QB	b) Is there an assessment of the existing evidence?	☐	☒	☐

Matza et al. 2005 – continued

	E Conclusions:	yes	no	?
QB	1. Was the research question answered?	☒	☐	☐
QB	2. Is the existing evidence thoroughly implemented in the conclusions?	☒	☐	☐
QA	3. Were limitations of the meaningfulness due to methodology critically discussed?	☒	☐	☐
I	4. Are recommendations for action stated? ***	☒	☐	☐
I	5. Is there a degree of differentiation in the recommendations?	☒	☐	☐
I	6. Is further need for research identified?	☒	☐	☐
I	7. Is an update of the review planned?	☐	☒	☐
	F Transferability of the international/foreign results and conclusions			
	Are there differences regarding the:			
	a) Epidemiology of the target condition?	☐	☒	☐
	b) Development status of the technology?	☐	☒	☐
	c) Formulation of the indication?	☐	☒	☐
	d) Care contexts, conditions, processes?	☐	☒	☐
	e) Remuneration systems?	☐	☐	☒
	f) Socio-economic consequences?	☐	☐	☐
	g) Patient and provider preferences?	☐	☐	☐
Concluding assessment: This publication will be: included ☒ excluded ☐				

Check-list for methodological quality			
Authors, title and publication: **Secnik K, Swensen A, Lage MA** **Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder** **Pharmacoeconomics 2005; 23(1): 93-102**	1 1/2 0 nr	= criterion fulfilled = criterion partially fulfilled = criterion not fulfilled = not relevant	1, ½, 0, nr
Question			
1. Was the question precisely formulated?			1
2. Was the context of the medical and economic problem sufficiently presented?			1
Evaluation framework			
3. Were all technologies included in the study presented in sufficient detail?			1/2
4. Were all technologies relevant in the framework of the question compared?			nr
5. Was the selection of the comparison technologies conclusively justified?			nr
6. Was the target population clearly described?			1
7. Was a suitable time frame selected for the question selected and stated?			1
8. Was the type of healthcare economic evaluation explicitly stated?			1
9. Were both costs and health effects examined?			0
10. Was the perspective of the examination clearly selected and explicitly stated?			1
Analysis method and modelling			
11. Were adequate statistical tests/models selected for data analysis and sufficiently thoroughly described?			nr
12. Were the model structure and all parameters completely and logically documented in the decision-analytical models (in the publication or a technical report)?			nr
13. Were the relevant assumptions explicitly formulated?			1
14. Were adequate data sources selected for the path probabilities and clearly stated in the decision-analytical models?			nr
Health effects			
15. Were all states of health relevant to the selected perspective and the selected time horizon considered and explicitly listed?			nr
16. Were adequate sources for the health effect data selected and unambiguously named?			nr
17. Were the epidemiological study design and the methods of analysis adequately selected and described and were the results presented in detail? (if based on a single study)			nr
18. Were suitable methods used for identification, extraction and synthesis of the effect parameters and were they described in detail? (if based on an information synthesis)			nr
19. Were the different health states assessed with preferences and suitable methods and measurement instruments selected and stated?			nr
20. Were adequate sources of the assessment data for the states of health selected and unambiguously stated?			nr
21. Was the evidence of the health effects sufficiently documented? (possibly see the context documents)			nr

Secnik et al. 2005 – continued

Costs	
22. Were the quantitative frameworks underlying the costs presented with sufficient thoroughness?	1
23. Were adequate sources and methods stated for the determination of the quantitative framework selected and unambiguously named?	1
24. Were the price structures underlying the costs sufficiently thoroughly described?	1
25. Were adequate sources and methods for determining prices selected and unambiguously named?	1
26. Were the included costs conclusively justified by means of the selected perspective and the selected time frame and were all relevant costs considered?	1

Check-list for methodological quality			
Authors, title and publication: **Wu E, Birnbaum HG, Zhang HF et al.** **Health care costs of Adult treatment for attention-deficit/ hyperactivity disorder who received alternative drugs** **Managed Care Pharmacy 2007; 13(7): 561-9**	1 1/2 0 nr	= criterion fulfilled = criterion partially fulfilled = criterion not fulfilled = not relevant	1, ½, 0, nr
Question			
1. Was the question precisely formulated?			1
2. Was the context of the medical and economic problem sufficiently presented?			1
Evaluation framework			
3. Were all technologies included in the study presented in sufficient detail?			1/2
4. Were all technologies relevant in the framework of the question compared?			nr
5. Was the selection of the comparison technologies conclusively justified?			nr
6. Was the target population clearly described?			1
7. Was a suitable time frame selected for the question and stated?			1/2
8. Was the type of healthcare economic evaluation explicitly stated?			nr
9. Were both costs and health effects examined?			nr
10. Was the perspective of the examination clearly selected and explicitly stated?			1
Analysis method and modelling			
11. Were adequate statistical tests/models for data analysis selected and sufficiently thoroughly described?			1
12. Were the model structure and all parameters completely and logically documented in the decision-analytical models (in the publication or a technical report)?			nr
13. Were the relevant assumptions explicitly formulated?			nr
14. Were adequate data sources for the path probabilities selected and clearly stated in the decision-analytical models?			nr
Health effects			
15. Were all states of health relevant to the selected perspective and the selected time horizon considered and explicitly listed?			nr
16. Were adequate sources for the health effect data selected and unambiguously named?			1
17. Were the epidemiological study design and the methods of analysis adequately selected and described and were the results presented in detail? (if based on a single study)			1
18. Were suitable methods used for identification, extraction and synthesis of the effect parameters and were they described in detail? (if based on an information synthesis)			1
19. Were the different health states assessed with preferences and suitable methods and measurement instruments selected and stated?			nr
20. Were adequate sources of the assessment data for the states of health selected and unambiguously stated?			nr
21. Was the evidence of the health effects sufficiently documented? (possibly see the context documents)			nr
Costs			
22. Were the quantitative frameworks underlying the costs presented with sufficient thoroughness?			1
23. Were adequate sources and methods stated for the determination of the quantitative framework selected and unambiguously named?			1
24. Were the price structures underlying the costs sufficiently thoroughly described?			0
25. Were adequate sources and methods selected for determining prices selected and unambiguously named?			0
26. Were the included costs conclusively justified by means of the selected perspective and the selected time frame and were all relevant costs considered?			

9.6 Extraction forms of the assessed studies (included after the third selection)

9.6.1 RCT

Study description	Randomised, placebo-controlled, multicentre, double-blind study
Study type (assessed)	RCT
Level of evidence (assessed)	Ib
Source	Adler et al. Efficacy and safety of OROS Methylphenidate in adults with attention-deficit/hyperactivity disorder. A randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. Journal of Clinical Psychopharmacology 2009; 29: 239-247.
Study period	08/05/2006 to 21/11/2006
Country of study	USA
Question/objective	Assessment of the medical efficacy and safety of OROS-MPH vs. Pl in adults with ADHD
Setting	n. i.
Relevant inclusion and exclusion criteria	Inclusion criteria: • Age between 18 and 65 years • Presence of ADHD according to DSM-IV criteria • Body weight of at least 45.4 kg • Persistence of the ADHD symptoms into adulthood • AISRS score ≥ 24 • GAF score between 41 and 60 Exclusion criteria: • Persons with signs of states of anxiety and tension, restlessness, signs of depression (according to HAM-A, HAM-D or DSM-IV) • Persons with known non-responsiveness to MPH, allergies to MPH • Medical conditions and medications with possible impairment of the MPH therapy • Known or suspected cardiac abnormalities • Diagnosis or family history of Tourette's syndrome, or motor or verbal ticks • Paroxysmal illnesses, hyper- or hypothyroidism in the medical history • Patients with a comorbid psychiatric diagnosis according to DSM-IV criteria • Persons who were in a state of drug or alcohol dependence in the last 6 months, had suicidal intent or showed suicidal behaviour in the last year • Persons who had an eating disorder in the last 3 years • Medication intake of antipsychotic medications, bupropion; modafinil, clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophyllin, coumarin anticoagulants, antiepileptics, monoaminoxidase inhibitors, guanethidine, serotonin re-uptake inhibitor (e.g. venlafaxin and duloxetin)
Number of groups	2
Intervention	• Start with 36 mg daily; dose titration by 18 mg every 7 d until custom dosing has been achieved • Custom dosing is achieved when the AISRS drops by 30 % since the baseline examination and the CGI-I rating is 1 (very strong improvement) or 2 (strong improvement) or the maximum dose titration of 108 mg daily has been achieved • In cases of intolerability, the dose can be reduced once by 18 mg • Dose reduction possible in case of cardiac abnormalities • Patients who do not tolerate 36 mg/day are excluded from the study
Control	Placebo
Possible other treatment groups	–
Number of centres	27
Details, if >1	–
Randomisation	Randomisation 1: 1 OROS-MPH to Pl Computer-generated stratified block randomisation with a block length of 4. Stratification according to study centre. The study personnel uses a voice recognition system for randomisation and records the birth date, sex and response therein. The system checks whether the subject is registered only once.

Adler et al. 2009a – continued

Concealment	Tablets with identical appearance At each scheduled physician contact, the patients return all medication and receive new medication.
Blinding	Yes
Study duration, total	7 weeks
Primary end points	The change of the AISRS score from the time of the first examination to the last examination/after 2 weeks (OROS-MPH vs. Pl).
Secondary end points	• Vital signs • Weight • ECG • Blood pressure, heart rate behaviour • Adverse events • Symptom improvement of ADHD assessed by means of the CGI-I between baseline and study end
Subgroup analyses	None performed/stated
Sample size calculation, incl. planned sample size	• Sample size of 83 patients per treatment arm, to determine a difference of 5.5 units in the AISRS score with a power of 90 % between OROS-MPH and Pl. • Assuming a 20 % drop-out rate, about 208 persons are required • Two-sided T-test with alpha-error = 0.05, SD = 10.8
Statistical methodology	• ITT analysis regarding the primary end point: all randomised patients who receive at least 1 study medication • LOCF estimate • Comparison of the 2 treatment groups in each examination by means of a covariance analysis (ANCOVA) (baseline as covariate) • Cochran-Mantel-Haenszel Test
Patient characteristics	Proportion of male patients: • OROS-MPH = 57.3 % • Pl = 55.2 % Proportion of patients with white skin colour: • OROS-MPH = 87.3 % • Pl = 85.3 % Average age (in years): • OROS-MPH = 39.9 (SD = 12.27; range: 18-65) • Pl = 38.2 (SD = 11.40; range: 19-64) Average BMI (kg/m^2): • OROS-MPH = 28.22 (SD = 6.3; range: 17.9-58.6) • Pl = 28.81 (SD = 5.44; range: 19.0-51.4) Proportion of patients with a combined ADHD type: • OROS-MPH = 79.1 % • Pl = 81 % Proportion of patients with the inattentive ADHD type: • OROS-MPH = 20 % • Pl = 18.1 % Proportion of patients with the hyperactive/impulsive ADHD type: • OROS-MPH = 0.9 % • Pl = 0.9 % Average GAF: • OROS-MPH = 53.1 (SD = 3.83; range: 41-60) • Pl = 53.0 (SD = 4.23; range: 42-60) Proportion of patients, who at the time of the first examination did not take ADHD medication: 93 % Proportion of patients, who already took ADHD medication before the study: 35.4 % Average AISRS score (start of study): • OROS-MPH = 38.6 (SD = 6.85) • Pl = 38.1 (SD = 7.31)
Number of screened patients	N = 348
Number of randomised patients	N = 229 N(OROS-MPH) = 113 N(Pl) = 116

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Number of analysed patients	N = 226 N(OROS-MPH) = 110 N(Pl) = 116
Lost-to-follow-up patients	Drop-outs: • OROS-MPH = 37.2 % (42/113) • Pl = 22.4 % (26/116) Reasons for dropping out: a) Adverse events • OROS-MPH = 16/42 (38 %) • Pl = 6/26 (23 %) b) At patient's wish: • OROS-MPH = 8/42 • Pl = 5/26 c) Deficient compliance with therapy instructions: • OROS-MPH = 5/42 • Pl = 5/26 d) Other reasons: • OROS-MPH = 2/42 • Pl = 6/26 Lost-to-follow-up: • OROS-MPH = 8 • Pl = 4
Patient flow	• 3 randomised patients of the group OROS-MPH do not fulfil the inclusion criteria and will be excluded from the study • 226 patients were included in the ITT analysis (N(OROS-MPH) = 110; N(Pl) = 116)
Comparability of the groups	Given The treatment groups exhibit the same demographic characteristics and the same characteristics at the start of the study.
Results of the dosing	Compliance with the therapy instructions: • OROS-MPH = 72.7 % • Pl = 84.5 % Average number of days with medication: • OROS-MPH = 38.9 (SD = 17.23) • Pl = 42.6 (SD = 14.06) Proportion of patients with at least 49 days of medication: • OROS-MPH = 59.1% • Pl = 57.8 Average last dose (mg/day): • OROS-MPH = 67.7 (SD = 27.9) • Pl = 86.9 (SD = 27.8) Lowest dosing (36 mg daily); as last dose: • OROS-MPH = 32.7 % of patients • Pl = 12.9 % of patients Highest dosing (108 mg daily); as last dose: • OROS-MPH = 20.9 % of patients • Pl = 58.6% of patients Last dosing in the OROS-MPH group: • 36 mg daily, 36 patients (32.7 %) • 54 mg daily, 16 patients (14.5 %) • 72 mg daily, 19 patients (17.3 %) • 90 mg daily, 16 patients (14.5 %) • 108 mg daily, 23 patients (20.9 %) Last dose in the placebo group: • 36 mg daily, 15 patients (12.9 %) • 54 mg daily, 16 patients (13.8 %) • 72 mg daily, 11 patients (9.5 %) • 90 mg daily, 6 patients (5.2 %) • 108 mg daily, 68 patients (58.6 %)

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Results regarding efficacy	Average change of the AISRS scores since start of the study: *Titration 1:* • OROS-MPH = -7.2 (SD = 0.82) • Pl = -4.0 (SD = 0.78) • p = 0.006 *Titration 2:* • OROS-MPH = -8.8 (SD = 0.95) • Pl = -5.9 (SD = 0.91) • p = 0.027 *Titration 3:* • OROS-MPH = -10.4 (SD = 1.11) • Pl = -7.4 (SD = 1.04) • p = 0.050 *Titration 4:* • OROS-MPH = -13.5 (SD = 1.19) • Pl = -8.2 (SD = 1.12) • p = 0.001 *Titration 5:* • OROS-MPH = -13.9 (SD = 1.29) • Pl = -8.6 (SD = 1.3) • p = 0.003 *2-week efficacy evaluation:* • OROS-MPH = -13.2 (SD = 1.33) • Pl = -7.5 (SD = 1.21) • p = 0.002 *Final (LOCF):* • OROS-MPH = -10.6 (SD = 1.09) • Pl = -6.8 (SD = 1.06) • p = 0.012 Average of the CGI-I score since the start of studies: *Titration 1:* • OROS-MPH = 3.28 (SD = 0.076) • Pl = 3.64 (SD = 0.072) • p < 0.001 *Titration 2:* • OROS-MPH = 3.07 (SD = 0.097) • Pl = 3.47 (SD = 0.092) • p = 0.003 *Titration 3:* • OROS-MPH = 3.02 (SD = 0.109) • Pl = 3.34 (SD = 0.103) • p = 0.035 *Titration 4:* • OROS-MPH = 2.70 (SD = 0.110) • Pl = 3.26 (SD = 0.104) • p < 0.001 *Titration 5:* • OROS-MPH = 2.68 (SD = 0.122) • Pl = 3.21 (SD = 0.117) • p = 0.002 *2-week efficacy evaluation:* • OROS-MPH = 2.73 (SD = 0.125) • Pl = 3.36 (SD = 0.115) • p < 0.001 *Final (LOCF):* • OROS-MPH = 3.02 (SD = 0.111) • Pl = 3.43 (SD = 0.106) • p = 0.008 Patients who respond to treatment (at least 30 % improvement of the AISRS and CGI-I score of 1 or 2): *Titration 1:* • OROS-MPH = 19.4 % • Pl = 5.2 % • p = 0.002

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Results regarding efficacy *(continued)*	*Titration 2:* • OROS-MPH = 23.5 % • PI = 12 % • p = 0.037 *Titration 3:* • OROS-MPH = 33.0 % • PI = 18.4% • p = 0.028 *Titration 4:* • OROS-MPH = 41.2% • PI = 21.6 % • p = 0.003 *Titration 5:* • OROS-MPH = 49.4% • PI = 23.7% • p < 0.001 *2-week efficacy evaluation:* • OROS-MPH = 44.6 % • PI = 24.4 % • p = 0.003 *Final (LOCF):* • OROS-MPH = 36.9 % • PI = 20.9 % • p = 0.009
Results for adverse events	Any adverse event: • OROS-MPH = 93 (84.5 %) • PI = 74 (63.8 %) Reduced appetite: • OROS-MPH = 28 (25.5 %) • PI = 7 (6 %) Headaches: • OROS-MPH = 28 (25.5 %) • PI = 16 (13.8 %) Dry mouth: • OROS-MPH = 22 (20.0 %) • PI = 6 (5.2 %) Anxieties: • OROS-MPH = 18 (16.4 %) • PI = 4 (3.4 %) Nausea: • OROS-MPH = 14 (12.7 %) • PI = 3 (2.6 %) Raised blood pressure: • OROS-MPH = 11 (10.0 %) • PI = 6 (5.2 %) Insomnia[b]: • OROS-MPH = 10 (9.1 %) • PI = 6 (5.2 %) Increased heart rate: • OROS-MPH = 8 (7.3 %) • PI = 5 (4.3 %) Initial insomnia: • OROS-MPH = 8 (7.3 %) • PI = 4 (3.4 %) Bruxism • OROS-MPH = 7 (6.4 %) • PI = 1 (0.9 %) Irritability: • OROS-MPH = 7 (6.4 %) • PI = 2 (1.7 %)

b These changes are fine though I wish to note that the source text uses less technical terms, which is reflected in our translation.

Adler et al. 2009a – continued

Results for adverse events *(continued)*	Muscle tightness: • OROS-MPH = 7 (6.4 %) • Pl = 0 (0.0 %) Diarrhoea: • OROS-MPH = 4 (3.6 %) • Pl = 6 (5.2 %) Somnolence: • OROS-MPH = 3 (2.7 %) • Pl = 8 (6.9 %) No deaths, no severe adverse events
Authors' conclusions	• Detailed description of the inclusion and exclusion criteria • Patients in both groups received the same treatment • Methodology (sample size calculation, randomisation, statistics) properly described. The conventional tests were used. • A large proportion of drop-outs that could lead to a distortion of results • Discontinuation due to adverse events greater in the OROS-MPH group • Result: OROS-MPH in comparison with Pl statistically significant improvement regarding AISRS and CGI-I score • Patients receiving OROS-MPH followed therapy instructions better than in Pl • Patients for whom non-responsiveness to MPH is known were excluded. This can lead to overestimating the results
Comments	• Keeping the instructions is checked by having everyone return the medication packages and the unused medication at every study visit. In cases of repeatedly missed intakes, the clinical investigator had to re-evaluate the suitability of the person regarding the study requirements. • The data of the other patients were continued according to LOCF method. • The discussion refers to other studies • No justification of the end points

ADHD = Attention deficit/hyperactivity disorder. AISRS = Adult ADHD Investigator Symptom Rating Scale. ANCOVA = Covariance analysis. BMI = Body Mass Index (BMI). CGI = Clinical Global Impression Scale. CGI-I = Clinical Global Impression Improvement scale. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ECG = Electrocardiogram. GAF = Global assessment of functioning. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. ITT = Intention-to-treat. LOCF = Last observation carried forward. MPH = Methylphenidate. OROS = Osmotic-controlled release delivery system. OROS-MPH = Osmotic-controlled release delivery system/methylphenidate extended release. Pl = Placebo. RCT = Randomised controlled trial. SD = Standard deviation.

Study description	Randomised, double-blind, multicentre, placebo-controlled, parallel study
Study type (assessed)	RCT
Level of evidence (assessed)	Ib
Source	Adler LA, Liebowitz M, Kronenberger W et al. Atomoxetine treatment in adult with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. Depression and Anxiety 2009; 26: 212-221.
Study period	July 2005 to May 2007
Country of study	USA, Puerto Rico
Question/objective	Assessment of the efficacy of ATX in adults with ADHD and comorbid social anxiety states. Assumption: ATX improves the therapeutic efficacy significantly.
Setting	Outpatient, multicentre
Relevant inclusion and exclusion criteria	Inclusion criteria: • Age: 18 to 65 year • Diagnosis: ADHD and social anxiety states according to DSM-IV-TR • Diagnostic criteria of ADHD: CAARS • Diagnostic criteria of the social anxiety states: Structured clinical interview according to DSM-IV-TR Axis I Disorders/Research Version • LSAS ≥ 50 (Examination 1) • LSAS improvement of ≤ 30% (Examination 2) • CGI-O-S Score ≥ 4 (Examination 1 and 2)

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Relevant inclusion and exclusion criteria *(continued)*	Exclusion criteria: • Major depression diagnosis is not more than 6 months old (Examination 1) • Acute or chronic compulsive-obsessive illnesses, bipolar disorders, psychoses, artificial disorders, somatoform disorders and/or acute panic disorders, post-traumatic stress disorders, eating disorders within a year (Examination 1) • Alcohol or drug abuse • Abuse of prescription medications
Number of groups	2
Intervention	ATX: • Twice daily, in the morning and afternoon/evening • 2-week initiation phase without medications • Dosing: at least 7 days 40 mg daily, then at least 7 days 80 mg daily. Patients with remaining significant symptoms at week 10 or later will receive a dose of maximally 100 mg daily • Dose reductions are possible, but not below 40 mg daily • Wash-out phase of stimulants: 24 hours • Evaluation after 2, 4, 8, 10, 12, 14 weeks following active intake of the medications
Control	Pl
Possible other treatment groups	–
Number of centres	30
Details, if > 1	All centres are located in the USA
Randomisation	• 1: 1 Randomisation ATX or Pl • Blinded, computer-generated randomisation
Concealment	n. i.
Blinding	Yes
Recording of compliance	No information
Study duration, total	16 weeks
Primary end points	• Change of the CAARS: CAARS:Inv:SV Total ADHD Symptom Score from start of study to end of study • Change of the CAARS:Inv:SV subscales inattentiveness, hyperactivity impulsiveness, ADHD index from start to end of study
Secondary end points	• LSAS • CGI-O-S • STAI • AAQoL • SAS • TEAE and vital signs to assess safety
Subgroup analyses	No information
Sample size calculation, including planned sample size	• Power (test strength) of 85 %, to show a difference of 3.64 points in the CAARS:Inv:SV scale • Level of significance: 0.05 • 2-sided T-test • SD of 9.98 points
Statistical methodology	Primary end point: • ANCOVA for CAARS:Inv:SV Total ADHD Symptom Score (value at start of the study, treatment group, centre) • Replacement of missing values according to the LOCF method • Assessment of general robustness, average change of the CAARS:Inv:SV Total ADHD Symptom Scores, LSAS total score and the CGI-O-S by means of the least squares method • Akaikes information criterion • Determination of the degrees of freedom using the Kenward-Rogers method • Efficacy analyses with the ITT population Secondary end points: • LSAS and CGI-O-S: LOCF ANCOVA and least squares method • STAI, SAS and AAQoL: LOCF ANCOVA Patient characteristics: • Fisher's Exact Test • ANCOVA

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Patient characteristics	Average age (in years) total: 38 Average proportion of male patients, total (%): 53.6 Average proportion of white patients, total (%): 74 Average proportion of patients with • Combined subtype, total (%): 57.2 • Social anxiety disorders, total (%): 86.9 • Anxiety disorders, total (%): 23.3 Average weight (kg): • ATX = 85.1 • PI = 81.3 Average last ATX dose: 82.9 mg daily Patients who complete the study (starting with randomisation). • ATX = 56.7 % • PI = 62.8 % Average CAARS:Inv:SV Total ADHD Symptoms Score: • ATX = 29.6 (SD = 10.4) • PI = 31.2 (SD = 9.4) Average CAARS:Inv:SV ADHD index subscale • ATX = 19.8 (SD = 6.8) • PI = 20.5 (SD = 5.8) Average CAARS:InV:SV Hyperactivity/Impulsiveness: • ATX = 12.7 (SD = 5.9) • PI = 12.7 (SD = 5.6) Average CAARS:Inv:SV Inattentiveness: • ATX = 17.0 (SD = 6.0) • PI = 18.5 (SD = 5.4) Average LSAS total score: • ATX = 85.3 (SD = 23.3) • PI = 82.1 (SD = 21.3) Average CGI-O-S: • ATX = 4.3 (SD = 0.8) • PI = 4.4 (SD = 0.9) Average STAI Trait: • ATX = 56.2 (SD = 10.4) • PI = 54.7 (SD = 10.2) Average SAS: • ATX = 2.4 (SD = 0.4) • PI = 2.4 (SD = 0.5) Average AAQoL total score: • ATX = 44.1 (SD = 15.2) PI = 45.3 (SD = 13.6)
Number of screened patients	N = 590
Number of randomised patients	N = 442; N(ATX) = 224; N(PI) = 218
Number of analysed patients	ITT analysis
Lost-to-follow-up patients	During PI introduction phase: • N(ATX) = 15 • N(PI) = 14 After the PI introduction phase: • N(ATX) = 82 • N(PI) = 87
Patient flow	Reasons for dropping out during the PI introduction phase: *ATX:* • Lost-to-follow-up: N = 9 • AE: N = 1 • Patient decision: N = 4 • Protocol violation: N = 1 *PI:* • Lost-to-follow-up: N = 7 • AE: N = 5 • Patient decision: N = 1 • Non-fulfilment of the inclusion criteria: N = 1

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Patient flow *(continued)*	Reasons for dropping out after the PI introduction phase: *ATX:* • Lost-to-follow-up: N = 30 • AE: N = 30 • Patient decision: N = 11 • Protocol violation: N = 3 • Non-fulfilment of the inclusion criteria: N = 1 • Lack of effectiveness: N = 9 • Other reasons: N = 6 *PI:* • Lost-to-follow-up: N = 29 • AE: N = 13 • Patient decision: N = 12 • Protocol violation: N = 1 • Non-fulfilment of the inclusion criteria: N = 1 • Lack of effectiveness: N = 8 • Other reasons: N = 3
Comparability of the groups	No significant results
Results regarding effectiveness	Analyses according to LOCF, ANCOVA: Average CAARS:Inv:SV Total Score change between start and end of the study: • ATX = -8.7 (SD = 10.0) • PI = -5.6 (SD = 10.2) • p < 0.001; 95 % CI (-6.0;-2.2) • Strength of effect = 0.47 Average CAARS:Inv:SV ADHD index subscale change between start and end of the study: • ATX = -5.7 (SD = 7.3) • PI = -3.2 (SD = 6.7) • p < 0.001; 95 % CI (-6.0;-2.2) • Strength of effect = 0.47 Average CAARS:Inv:SV change of hyperactivity/impulsiveness between start and end of the study: • ATX = -3.9 (SD = 5.3) • PI = -2.0 (SD = 5.2) • p < 0.001; 95 % CI (-6.0;-2.2) • Strength of effect = 0.47 Average CAARS:Inv:SV change of inattentiveness between the start and end of the study: • ATX = -4.8 (SD = 5.7) • PI = -3.6 (SD = 6.2) • p = 0.001; 95 % CI (-6.0;-2.2) • Strength of effect = 0.47 Average LSAS total score between the start and end of study: • ATX = -22.9 (SD = 25.3) • PI = -14.4 (SD = 20.3) • p < 0.001; 95% CI (-13.4;-3.9) • Strength of effect = 0.40 Average CGI-O-S change between start and end of the study: • ATX = -0.76 (SD = 1.1) • PI = -0.60 (SD = 1.0) • P = 0.02; 95 % CI (-0.39; -0.03) • Strength of effect = 0.23 Average STAI Trait change between the start and end of the study: • ATX = -8.9 (SD = 11.2) • PI = -6.0 (SD = 9.0) • p = 0.008; 95 % CI (-4.7;-0.7) • Strength of effect = 0.27 Average SAS change between the start and end of the study • ATX = -0.3 (SD = 0.4) • PI = -0.2 (SD = 0.4) • p = 0.0504; 95% CI (-0.1;0.0)

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Results regarding effectiveness *(continued)*	Average AAQoL total score change between the start and end of the study: • ATX = 14.9 (SD = 17.1) • Pl = 11.1 (SD = 15.0) • p = 0.03; 95 % CI (0.35;7.0) • Strength of effect = 0.24 Least squares method analysis of the primary end point CAARS:The Inv:SV Total ADHD symptoms score and subscales makes clear that ATX is statistically significant compared with the Pl (p < 0.001). The least squares method analysis shows significant reduction (p < 0.001) of the LSAS total score and a result of p = 0.014 of the CGI-O-S for ATX compared with Pl. Correlation coefficient according to Pearson (post hoc): There is a linear correlation between CAARS:Inv:SV Total Score and LSAS: r = 0.61; 95% CI (0.54;0.67) No significant differences for comorbid anxiety disorder (ATX vs. Pl) regarding CAARS:Inv:SV total score for ADHD symptoms (p = 0.586) and LSAS total score (0.526).
Results for AEs	Persons with AE (N(ATX) = 212; N(Pl) = 211) in %: At least 1 AE: • ATX = 86.3 • Pl = 79.1 • p = 0.05 Headaches: • ATX = 20.3 • Pl = 14.2 • p = 0.12 Insomnia: • ATX = 17.0 • Pl = 9.0 • p = 0.02 Nausea: • ATX = 16.0 • Pl = 7.6 • p = 0.01 Dry mouth: • ATX = 15.6 • Pl = 4.3 • p < 0.001 Change in diastolic blood pressure: • ATX = 1.4 mmHg • Pl = -0.4 mmHg • p = 0.003 Change in pulse: • ATX = 3.6 bpm • Pl = 1.3 bpm • p < 0.001 Change in weight: • ATX = -0.41 kg • Pl = -0.08 kg • p = 0.190
Authors' conclusions	Compared with Pl, ATX is effective in the treatment of adults with ADHD and comorbid social anxiety disorders
Comments	• Inclusion and exclusion criteria logical and understandable • Recruitment of the persons? • No information on compliance • No definition and information on responders • High drop-out rate

AAQoL = Adult ADHD Quality of Life Scale. ADHD = Attention deficit/hyperactivity disorder. ANCOVA = Covariance analysis. ATX = Atomoxetine. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. CAARS = Conners Adult ADHD Rating Scale. CAARS:Inv:SV = Conners Adult ADHD Rating Scale: Investigator-rated: Screening Version. CGI-O-S = Clinical Global Impression Overall Severity. DSM-IV-TR = Diagnostic and Statistical Manual of Psychological Disorders, 4th text revision. ITT = Intention-to-treat. n. i. = no information. CI = Confidence interval. LOCF = Last observation carried forward. LSAS = Liebowitz social anxiety scale. N = Number. Pl = Placebo. RCT = Randomised controlled trial. SAS = Social adjustment scale. SD = Standard deviation. STAI = State-Trait Anxiety Inventory TEAE = Treatment-emergent adverse event. AE = Adverse event.

Study description	Randomised, controlled crossover study.
Study type (assessed)	RCT
Level of evidence (assessed)	Ib
Source	Jain U, Hechtman L, Weiss M et al. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. Journal of Clinical Psychiatry 2007; 68: 268-277.
Study period	October 2003 to April 2004
Country of study	Finland, Helsinki
Question/objective	Efficacy of biphasic MPH in adults with ADHD
Setting	Multicentre, outpatient
Relevant inclusion and exclusion criteria	Inclusion criteria: • Age: 18 to 60 years • Diagnosis of ADHD according to DSM-IV criteria • Presence of an ADHD since childhood • Weight: 50 to 90 kg • IQ: at least 80 according to the Wechsler Intelligence Scale for Adults III in Examination 1 or in the last 5 years • CAARS-S or CAARS-O ≥ 65 Exclusion criteria: • Allergies to MPH or amphetamines • Known severe side effects to MPH or known unresponsiveness to MPH • Severe illnesses • Severe high blood pressure (values over 100 mm Hg diastolic and 170 mm Hg systolic) • Anxiety disorders according to HAM-A • Depression according to HAM-D • Drug or alcohol abuse in the past • Illnesses of the sensory organs • Autism • Psychoses or other volatile psychological states that require a treatment • Patients that are treated with the following medications: Guanethidine, blood pressure-enhancing medications, monoaminoxidase inhibitors, coumarin anticoagulants, etc.
Number of groups	2
Intervention	MPH: Wash-out: 1 week Oral administration once daily (10-, 15-, 20-, 30-, 40-, 50-, 60- or 80-mg capsules) Weekly dose titration up to optimal adjustment during the first 3 weeks 2 weeks constant dosing, then change of the treatment group The necessity and the time of a dose titration is estimated by means of the CGI scale
Control	Pl: Wash-out: 1 week Oral administration once daily
Possible other treatment groups	–
Number of centres	n. i.
Details, if > 1	n. i.
Randomisation	n. i.
Concealment	n. i.
Compliance recording	Return of the packages Exclusion of patients with a compliance < 80% and > 120%
Blinding	Patient, randomisation, clinical investigator
Study duration, total	5 to 11 weeks (depending on the dose titration)
Primary end points	• CGI during constant dose • CAARS, especially the E-scale (Conners' ADHD Index)
Secondary end points	• Other CAARS scales (self- and third-party assessment) • PSS • HAM-A, HAM-D • LIFE

Jain et al. 2007 – continued

Subgroup analyses	No information
Sample size calculation, incl. planned sample size	• Sample size calculation based on: Recognise 5 T units of the CAARS scale "ADHD Index" during the constant MPH dosing between MPH and Pl • Error 1. Type: 5 % • Error 2. Type: 20 %; thus power (test strength) of 80 % • Variance derived from other studies • The sample size is estimated to 40 patients to show a difference of 8 T units • 2-sided test
Statistical methodology	• All patients were analysed for the PPA population for whom the data of the primary end point was available during constant dosing but no protocol violations were present. • All patients for whom the data for the primary end point was available in some form were analysed for the ITT population. • PPA analysis: Average scores of the CGI and CAARS scales compared during constant dose (MPH vs. Pl). Here, a variance analysis (2-sided) was performed. • ITT: Last observation carried forward • PSS and LIFE: Wilcoxon rank sum test • Missing values were not substituted • Primary statistical tests: determined a priori • AE: Codification with COSTART IV • McNemar Test differentiates the frequency of side effects in the samples • Statistical significance: $p < 0.05$ (2-sided)
Patient characteristics	Average age (in years) ITT: 37.2 (18.8 to 57.1); PPA = 37.9 (18.8 to 57.1) Proportion of women: ITT = 37.5 %; PPA = 41 % Proportion of men: ITT = 62.5 %; PPA = 59 % Proportion of whites: ITT = 87.5 %; PPA = 92.3 % CAARS-S scale: ITT = 72.8 (SD = 8.4); PPA = 72.3 (SD = 8.2) CAARS-O scale: ITT = 73.5 (SD = 7); PPA = 73.4 (SD = 6.8)
Number of screened patients	N = 54
Number of randomised patients	N = 50
Number of analysed patients	In ITT: N = 48 In PPA: N = 39
Lost-to-follow-up patients	N = 6 (12 %)
Patient flow	Reasons for dropping out: 1 due to insufficient effectiveness 1 due to withdrawal of the declaration of consent 2 due to non-compliance 2 due to lost-to-follow-up For the PPA, 5 patients of the 44 patients who completed the study were excluded due to protocol violations. For the ITT, 2 patients were excluded due to a lack of data.
Comparability of the groups	n. i.
Results of the dosing	Average dosing (mg/d): • MPH = 57.8 (SD = 20.1) • Pl = 64.9 (SD = 17.5) Maximum dose titration: 1 mg/kg or 80 mg/d Patients who received the max. dose of 80 mg: 65 % Constant dose of MPH: 0.2 mg/kg to 1.0 mg/kg
Results regarding effectiveness	PPA (N = 39): MPH improvement measured in CGI Global Impr. against Pl: p = 0.0015 MPH improvement measured in CGI therapy effect against Pl: p = 0.0033 MPH improvement measured in CGI severity of the AEs against the Pl: p = 0.0066 MPH improvement “much improved” or “very much improved” (CGI): 48.7 %; Pl improvement “much improved” or “very much improved” (CGI): 23.1 %; p = 0.0158 Strength of effect (CGI) 0.90 (95 % CI 0.43;1.36) MPH improvement measured as CAARS-S at the start of the study to constant dosing: p = 0.0083 Strength of effect (CAARS-S): 0.53 (95 % CI 0.008 to 0.99) CAARS-S ADHD Index (T score < 65): MPH = 73.7 %; Pl = 33.3 %; p = 0.001

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Results regarding effectiveness *(continued)*	MPH vs. Pl: CAARS-S subscale • Inattentiveness/memory problems: p = 0.0037 • Problems of self-assessment: p = 0.0601 • Impulsiveness/affect volatility: p = 0.0899 MPH improvement measured as CAARS-O from baseline to constant dosing: p = 0.1404 CAARS-O-ADHD-Index: Normalisation rates: MPH = 65.8 %; Pl = 45.9 %; p = 0.0707 HAM-A: MPH vs. Pl no difference (p = 0.5312) HAM-D: MPH vs. Pl no difference (p = 0.1724) ITT (N = 48): MPH improvement measured as CGI-Global Impr. against Pl: p = 0.0005 MPH improvement measured as CGI: Therapy effect against Pl: p = 0.0006 MPH improvement measured as CGI: Therapy effect against Pl: p = 0.0014 MPH improvement measured as CAARS-S: Start of study at constant dosing: p = 0.0033 MPH improvement measured as CAARS-O: Start of study at constant dosing: p = 0.0967 The stated differences are statistically significant regarding LIFE
Results for AEs	Average weight loss during treatment: • MPH = 1.1 kg (SD = 0.9 kg); p = 0.0001 • Pl = 0.1 kg (SD = 1.6 kg); p = 0.5982 • P = 0.0001 Average change of the blood pressure during the treatment in mmHg: • MPH: syst. = 0.6 (SD = 10.4) p = 0.7055; diast. = 0 (SD = 6.7) p = 1.0 • Pl: syst. = 0.9 (SD = 10.6) p = 0.6719; diast. = 1.4 (SD = 8.3) p = 0.5719 Average change in the heart rate (beats per minute): • MPH = 1.8 (SD = 10.9); p = 0.2703 • Pl = 0.7 (SD = 12.8); p = 0.6981 No serious AEs were observed during the study At least 1 AE: • MPH = 84 % • Pl = 58 % Headaches: • MPH = 13 % • Pl = 12 % • p = 0.8083 Anorexia: • MPH = 11 % • Pl = 3 % • p = 0.0325 Insomnia: • MPH = 11 % • Pl = 4 % • p = 0.1088 Nervousness: • MPH = 10 % • Pl = 2 % • p = 0.0047 Nausea: • MPH = 8 % • Pl = 4 % • p = 0.2482 Anxiety: • MPH = 7 % • Pl = 0 • P = 0.0082 Dry mouth: • MPH = 6 % • Pl = 1 % • p = 0.0588

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Results for AEs *(continued)*	Emotional lability:[c] • MPH = 5 % • Pl = 1 % • p = 0.1025 Depression: • MPH = 4 % • Pl = 1 % • p = 0.0833 Asthenia: • MPH = 4 % • Pl = 4 % • p = 1.0 Sweating:[d] • MPH = 3 % • Pl = 0 • p = 0.0833
Authors' conclusions	Treatment with MPH is effective compared with Pl
Comments	• How is a responder defined? • The individual dose adjustment is positive • According to the CAARS scales, the patients have very pronounced ADHD symptoms at the start of the study. The initial level is relevant for the improvement since patients with pronounced symptoms can improve more than patients with milder symptoms. In weakly affected patients, an objective result is more difficult to achieve. • The discussion notes that the results are also clinically relevant. Statements on the clinical relevance are very difficult to determine in ADHD. For this purpose, one should rely on the patient's subjective statements. • The third-party assessment is only made during a particular period in the daytime. Therefore, behaviour and state of the patients over the entire day cannot be assessed.

ADHD = Attention deficit/hyperactivity disorder. CAARS = Conners Adult ADHA Rating Scale. CAARS = Conners Adult ADHA Rating Scale/Self-rated. CAARS-O = Conners Adult ADHA Rating Scale/Observer-rated. CGI = Clinical Global Impression. COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. IQ = Intelligence quotient. ITT = Intention-to-treat. n. i. = no information. CI = Confidence interval. LIFE = Longitudinal Interval Follow-up Evaluation. MPH = Methylphenidate. N = Number. Pl = Placebo. PPA = Per protocol analysis. PSS = Patient Satisfaction Survey RCT = Randomised controlled trial. SD = Standard deviation. AE = Adverse event.

Study description	Randomised, double-blind crossover study
Study type (assessed)	RCT
Level of evidence (assessed)	Ib
Source	Kooij JJS, Burger H, Boonstra AM et al. Efficacy and safety of Methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. Psychol Med 2004; 34(6): 973-982.
Study period	n.i.
Country of study	The Netherlands
Question/objective	Assessment of the efficacy and safety of MPH in the treatment of adults with ADHD
Setting	Outpatient
Relevant inclusion and exclusion criteria	Inclusion criteria: • Diagnosis of ADHD according to DSM-IV criteria • Comorbid psychiatric diseases Exclusion criteria: • Contraindication for MPH • Clinically significant internal and unstable psychological diseases • Abnormal laboratory values • Tick disorders • IQ < 75 • Psychotropic use • Former use of MPH/amphetamines • Pregnant/nursing

c See Fn. m.
d The source says Schweißausbrüche (sweat outbreaks), not Schwitzen (sweating). One tends to be periodic, the other persistant.

Kooij et al. 2004 – continued

Number of groups	2
Intervention	MPH • Start with 0.5 mg/kg daily in the 1st week • Titration to 0.75 mg/kg daily in the 2nd week • Titration to 1.00 mg/kg daily in the 3rd week
Control	Pl
Possible other treatment groups	–
Number of centres	n. i.
Details, if > 1	–
Randomisation	Computer-generated randomisation to determine the therapeutic series
Concealment	n.i.
Blinding	Yes
Compliance	Electronic monitoring of compliance
Study duration, total	2-times 3 weeks, 1 week wash-out between the therapy phases
Primary end points	• DSM-IV ADHD Rating Scale modified • CGI-ADHD
Secondary end points	• HAM-D • HAM-A • SDS • GAF • Effect Rating Scale of Barkley modified
Subgroup analyses	Link between MPH response and age, sex and comorbidities
Sample size calculation, incl. planned sample size	n. i.
Statistical methodology	• McNemar Test • T-test • Alpha: 0.05 (2-sided) • Subgroup analysis: Chi-square test or, for small sample size, Fisher's Exact Test
Patient characteristics	Proportion of male patients: 53.3 % Average age: 39.1 years (range: 20-56) Number of patients with major depression: 15 Number of patients with dysthymia: 7 Number of patients with bipolar disorders: 6 Average HAM-D (start of the study): 8.0 (SD = 5.8) Average HAM-A (start of the study): 7.8 (SD = 6.0) Number of patients with substance-dependent addiction diseases: 37 Number of patients with ADHD of "combined type“: 43 Number of patients with ADHD of "hyperactive/impulsive type": 2
Number of screened patients	N = 108
Number of randomised patients	N = 45 Treatment sequence MPH – Pl: N = 25 Treatment sequence Pl – MPH: N = 20
Number of analysed patients	N = 45
Lost-to-follow-up patients	All patients completed the study.
Patient flow	• 1 patient completed the study 1 week later • 1 patient used morphine in the 5th week • 13 patients were non-compliant, 18 compliant
Comparability of the groups	No statistically significant differences
Results of the dosing	Average daily dosing of MPH at the end of • Week 1: 0.5 mg/kg (0.31-0.55 mg/kg) and 0.5 mg/kg (0.45-0.55 mg/kg) • Week 2: 0.75 mg/kg (0.31-0.82 mg/kg) and 0.76 mg/kg (0.69-0.82 mg/kg) • Week 3: 0.91 mg/kg (0.54-1.04 mg/kg) and 0.98 mg/kg (0.71-1.04 mg/kg)

Kooij et al. 2004 – continued

Results regarding effectiveness	Response rate measured as DSM-IV ADHD-RS and CGI: • Pl = 7 % • MPH = 38 % • P = 0.003 Response rate only measured as DSM-IV ADHD-RS: • Pl = 13 % • MPH = 42 % • p = 0.011 Response rate only measured as CGI: • Pl = 18 % • MPH = 51 % • p = 0.011 With MPH, the average DSM-IV ADHD-RS is lower by 0.19 (p = 0.064) and the CGI by 0.72 (p = 0.026) as compared with Pl. Response rate in • Compliance patients = 43 % • Non-compliance patients = 23 % • p = 0.31 (Fisher's Exact Test) With MPH, the average SDS is lower by 0.93 (p = 0.029) compared with Pl. With MPH, the average GAF score is higher by 2.5 (p = 0.104) than with Pl. With MPH, the HAM-D and HAM-A are higher (2.4 (p = 0.002) and 2.9 (p = 0.002) than with Pl. However, the response rates to MPH are not affected by sex, age, comorbidity, degree of severity of the anxiety disorders and depression or intelligence.
Results for AEs	Any AE: • MPH = 82 % • Pl = 69 % • p = 0.11 The average number of AEs is higher with MPH than with Pl: • p = 0.004 Most common AEs: • Loss of appetite MPH = 22 %; Pl = 4 %; p = 0.039 • Sleep problems: MPH = 33 %; Pl = 22 %; p = 0.27 • Headaches: MPH = 16 %; Pl = 4 %; p = 0.18) • Tachycardia: MPH = 9 %; Pl = 2 %; p = 0.25 • Dizziness: MPH = 16 %; Pl = 7 %; p = 0.34 • Abdominal complaints: MPH = 13 %; Pl = 4 %; p = 0.22) • Dry mouth: MPH = 24 %; Pl = 7 %; p = 0.06 • Tics: MPH = 7 %; Pl = 2 %; p = 0.05 Due to side effects, eight patients reduced the MPH dosage. The systolic blood pressure is 0.13 mmHg higher with MPH than with Pl (p = 0.954).
Authors' conclusions	MPH is an effective and well tolerated treatment in adults with ADHD
Comments	• Age was not considered among the inclusion criteria • Baseline characteristics are not reported separately for MPH and Pl • Short therapy phases • No description of the sample size calculation • Crossover study, not multicentre • Dose titration • Performance of a subgroup analysis • Inclusion of comorbidities • Third-party and self-rating scale • Small study population

ADHD = Attention deficit/hyperactivity disorder. CGI-I-ADHD = Clinical Global Impression Improvement Scale for ADHD. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. GAF = Global assessment of functioning. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. n. i. = no information. MPH = Methylphenidate. N = Number. Pl = Placebo. RCT = Randomised controlled trial. SD = Standard deviation. SDS = Sheehan Disability Scale. AE = Adverse event.

Study description	Randomised, double-blind, placebo-controlled study
Study type (proven)	RCT
Level of evidence (proven)	Ib
Source	Medori R, Ramos-Quiroga A, Casas M et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS Methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2008; 63:981-989.
Study period	April 2005 to June 2006
Country of study	13 European countries
Question/objective	Assessment of the short-term efficacy and safety of long-lasting OROS-MPH in 3 different dosages (18 mg, 36 mg, 72 mg) in adults with ADHD
Setting	Multicentre
Relevant inclusion and exclusion criteria	Inclusion criteria: • Confirmed diagnosis according to DSM-IV and according to the Conners Adult ADHD Diagnostic Interview • Age: 16 to 65 years • Chronic course of the ADHD with presence of some ADHD symptoms before the 7th year • CAARS score ≥ 24 during screening Exclusion criteria • Minor response or intolerability for MPH • Presence of acute unstable psychiatric diseases (e.g. acute mood disorders, bipolar diseases, acute compulsive-obsessive neuroses) • Substance-dependent addiction diseases (abuse/dependency) according to DSM-IV criteria within the last 6 months • Schizophrenia or affective psychoses in the family • Severe illnesses (e.g. liver or renal insufficiency or cardiac, gastrointestinal, psychiatric or metabolic disorders), hyperthyroidism, myocardial infarction or stroke in the last 6 months before the screening • Paroxysmal diseases, glaucoma or unadjusted hypertension in the medical history
Number of groups	4
Intervention	MPH 18 mg: • Oral administration of 18 mg MPH once daily over 5 weeks MPH 36 mg: • Oral administration of 36 mg MPH once daily over 5 weeks MPH 72 mg: • Dosage titration; Days 1-4: 36 mg/d, then 54 mg/d for 3 days, then 72 mg/d for 4 weeks • Wash-out phase of 4 weeks before administration of the 1st study medication
Control	• Once daily one placebo tablet over 5 weeks • Wash-out phase of 4 weeks before administration of the 1st study medication
Possible other treatment groups	–
Number of centres	51
Details, if >1	Centres distributed over 13 European countries
Randomisation	• Computer-generated, permuted block randomisation • Stratification according to study centre
Concealment	n. i.
Blinding	Yes
Study duration, total	5 weeks
Primary end points	Change of the total score of the third-party rating scale CAARS-O with 18 items between the start and end of the study, or the last recorded value
Secondary end points	Change of the CAARS:-SV total score and subscale in weeks 1, 3 and 5. Changes from the start to the end of the study in: • Total score and subscale of the self-evaluation scale CAARS-S (short version with 26 items) • CGI-S • SDS Assessment of safety: Monitoring of adverse events, laboratory tests, vital signs, physical examination

Medori et al. 2008 – continued

Subgroup analyses	No information
Sample size calculation, incl. planned sample size	• Calculated sample size of 94 patients per group • Power (test strength) of ≥ 90% • Difference to be discovered: 6 units between the intervention and the placebo group from the start to the end of the study • 2-sided T-test • Alpha: 0.016 • SD: 11
Statistical methodology	• The change from start to end of the study (LOCF) is examined by means of a covariance analysis. ○ Treatment, sex, country as factors ○ Baseline scores as covariate • Effects of the treatment: Least squares method • Adjustment for multiple comparisons: Dunnett method • Paired comparisons of the MPH dosing groups: Covariance analysis with the factors treatment, sex, country and the covariate baseline scores • Responders to the treatment: Improvement of the CAARS:O total score of ≥ 30% from start to end of the study • Primary end point Cochran-Mantel-Haenszel Test • Sidak correction: Adjustment for multiple comparisons of the 3 MPH groups vs. Pl in the responder analysis • Additional analysis of all patients with a CAARS:O total score improvement of ≥ 50% • CGI-S Variance analysis; factors: Change since the start of study, treatment, sex, country; covariate: Baseline score • Performance of the statistical analyses in SAS Version 8.02
Patient characteristics	Average age (in years) • MPH 18 mg = 34.2 • MPH 36 mg = 33.8 • MPH 72 mg = 33.6 • Pl = 34.5 • Total = 34.0 Proportion of men (%): • MPH 18 mg = 57.4 • MPH 36 mg = 45.1 • MPH 72 mg = 53.9 • Pl = 61.5 • Total = 54.4 Proportion of white persons (%): • MPH 18 mg = 99 • MPH 36 mg = 96.1 • MPH 72 mg = 97.1 • Pl = 97.9 • Total = 97.5 Proportion of persons with another ethnicity (%): • MPH 18 mg = 1 • MPH 36 mg = 3.9 • MPH 72 mg = 2.9 • Pl = 2.1 • Total = 2.5 Average age at diagnosis (in years): • MPH 18 mg = 30.5 • MPH 36 mg = 29.2 • MPH 72 mg = 28.9 • Pl = 31.4 • Total = 29.9 Proportion of persons with ADHD in childhood (%): Combined subtype: • MPH 18 mg = 71.3 • MPH 36 mg = 78.4 • MPH 72 mg = 77.5 • Pl = 70.8 • Total = 74.6

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Patient characteristics *(continued)*	Inattentive subtype: • MPH 18 mg = 22.8 • MPH 36 mg = 15.7 • MPH 72 mg = 18.6 • PI = 21.9 • Total = 19.7 Hyperactive subtype • MPH 18 mg = 5 • MPH 36 mg = 5.9 • MPH 72 mg = 2.9 • PI = 5.2 • Total = 4.7 Proportion of persons with ADHD in adulthood (%): Combined subtype: • MPH 18 mg = 63.4 • MPH 36 mg = 74.5 • MPH 72 mg = 75.5 • PI = 69.8 • Total = 70.8 Inattentive subtype: • MPH 18 mg = 31.7 • MPH 36 mg = 18.6 • MPH 72 mg = 21.6 • PI = 25 • Total = 24.2 Hyperactive subtype • MPH 18 mg = 4 • MPH 36 mg = 6.9 • MPH 72 mg = 2.9 • PI = 2.1 • Total = 4 Proportion of persons with comorbidities: Current alcohol/substance-dependent illnesses • MPH 18 mg = 1 % • MPH 36 mg = 1 % • MPH 72 mg = 1 % • PI = 0 • Total = 0.7 % Alcohol/substance-dependent illnesses in the past • MPH 18 mg = 11. 9% • MPH 36 mg = 14. 7% • MPH 72 mg = 14. 7% • PI = 12.5 % • Total = 13.5 % Current mood and anxiety disorders • MPH 18 mg = 9.9 % • MPH 36 mg = 10.8 % • MPH 72 mg = 16.7 % • PI = 10.4 % • Total = 12 % Mood and anxiety disorders in the past • MPH 18 mg = 26.7 % • MPH 36 mg = 35.3 % • MPH 72 mg = 31.4 % • PI = 26 % • Total = 29.9 % Average CAARS:O Total Score (95 % CI): • MPH 18 mg = 35,6 (34.2;37.0) • MPH 36 mg =37.3 (35.9;38.6) • MPH 72 mg = 36.6 (35.2;37.8) • PI = 37.2 (35.8;38.6)

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Patient characteristics *(continued)*	Average CAARS:S Total Score (95 % CI): • MPH 18 mg = 48.5 (46.0;50.9) • MPH 36 mg = 51.2 (49.0;53.4) • MPH 72 mg = 50.6 (48.2;53.0) • Pl = 51.1 (49.0;53.2) Average CGI-S total score (95 % CI): • MPH 18 mg = 4.9 (4.7;5.0) • MPH 36 mg = 5.0 (4.8;5.1) • MPH 72 mg = 4.9 (4.7;5.1) • Pl = 4.9 (4.7;5.0)
Number of screened patients	N = 448
Number of randomised patients	N = 402
Number of analysed patients	Patients who have received at least 1 study dose and for whom a measured effectiveness value is available post-baseline are analysed. Analysis of the primary end point: N = 394 N(MPH 18 mg) = 99; N(MPH 36 mg) = 101; N(MPH 72 mg) = 99; N(Pl) = 95 Assessment of safety: N = 401 N(MPH 18 mg) = 101; N(MPH 36 mg) = 102; N(MPH 72 mg) = 102; N(Pl) = 96
Lost-to-follow-up patients	Number of drop-outs due to AE: • MPH 18 mg = 1 (1 %) • MPH 36 mg = 4 (3.9 %) • MPH 72 mg = 8 (7.8 %) • Pl = 1 (1 %) No other statements.
Patient flow	365 patients (91 %) completed the study. N(MPH 18 mg) = 94.1 % N(MPH 36 mg) = 90.2 % N(MPH 72 mg) = 86.3 % N(Pl) = 93.8 %
Comparability of the groups	No statistical comparisons given
Results of the dosing	Average intake: 33.9 days (SD = 6.53 days) Average daily dosing: MPH 18 mg = 0.24 mg/kg (SD = 0.048 mg/kg; range = 0.1-0.4 mg/kg) MPH 36 mg = 0.50 mg/kg (SD = 0.112 mg/kg; range = 0.3-0.8 mg/kg) MPH 72 mg = 0.96 mg/kg (SD =0.198 mg/kg; range = 0.6-1.7 mg/kg)
Results regarding effectiveness	Average change of the CAARS:O total score from start to end of the study in points (LOCF): • MPH 18 mg = -10.6 (SD = 10.34); 95 % CI (-12.7;-8.55); p = 0.015 • MPH 36 mg =-11.5 (SD = 9.97); 95 % CI (-13.4;-9.5); p = 0.013 • MPH 72 mg = -13.7 (SD = 11.11); 95 % CI (-15.9;-11.5);p < 0.001 • Pl = -7.6 (SD = 9.93); 95 % CI (-9.63;-5.59) Strength of effect: • MPH 18 mg = 0.38 • MPH 36 mg = 0.43 • MPH 72 mg = 0.62 Responder (≥ 30 % reduction of the CAARS:O): • MPH 18 mg = 50.5 % • MPH 36 mg = 48.5 % • MPH 72 mg = 59.6 % • Pl = 27.4 % • p < 0.001 Patients with an improvement of the CAARS:O of ≥ 50 %: • MPH 18 mg = 22.2 % • MPH 36 mg = 24.8 % • MPH 72 mg = 31.3 % • Pl = 13.7 % • p < 0.01

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Results regarding effectiveness *(continued)*	Average change of the CAARS:O subscale “inattentive type” from start to end of the study: • MPH 18 mg = -5.9; 95 % CI (-7.08;-4.78); p < 0.001 • MPH 36 mg = -6.5; 95 % CI (-7.7;-5.37); p < 0.001 • MPH 72 mg = -7.6; 95 % CI (-8.87;-6.36); p < 0.001 • PI = -3.7; 95 % CI (-4.74;-2.61) Average change of the CAARS:O subscale “hyperactive type” from start to end of the study: • MPH 18 mg = -47; 95 % CI (-5.78;-3.57); p = 0.272 • MPH 36 mg = -4.9; 95 % CI (-5.93;-3.94); p = 0.406 • MPH 72 mg = -6.0; 95 % CI (-7.28;-4.82); p = 0.003 • PI = -3.9; 95 % CI (-5.05;-2.82) Average change of the CAARS:S total score from start to end of the study: • MPH 18 mg = -10.4; 95 % CI (-13.0;-7.73); p = 0.003 • MPH 36 mg = -11.3; 95 % CI (-13.8;-8.73); p = 0.003 • MPH 72 mg = -14.4; 95 % CI (-17.6;-11.2); p < 0.001 • PI = -5.8; 95 % CI (-8.14;-3.45) Average change of the CAARS:S subscale from start to end of the study: Inattentiveness/memory problems • MPH 18 mg = -1.9; 95 % CI (-2.46;-1.25); p = 0.003 • MPH 36 mg = -2.1; 95 % CI (-2.70;-1.56); p < 0.001 • MPH 72 mg = -3.0; 95 % CI (-3.83;-2.25); p < 0.001 • PI = -0.9; 95 % CI (-1.49;-0.29) Hyperactivity • MPH 18 mg = -2.5; 95 % CI (-3.11;-1.87); p = 0.005 • MPH 36 mg = -2.2; 95 % CI (-2.78;-1.54); p = 0.109 • MPH 72 mg = -2.6; 95 % CI (-3.32;-1.93); p = 0.001 • PI = -1.4; 95 % CI (-1.99;-0.85) Impulsiveness/emotional volatility • MPH 18 mg = -1.8; 95 % CI (-2.45;-1.22); p = 0.049 • MPH 36 mg = -2.1; 95 % CI (-2.67;-1.51); p = 0.160 • MPH 72 mg = -2.8; 95 % CI (-3.45;-2.19); p < 0.001 • PI = -1.3; 95 % CI (-1.92;-0.76) Problems of self-awareness • MPH 18 mg = -1.8; 95 % CI (-2.50;-1.12); p = 0.016 • MPH 36 mg = -2.0; 95 % CI (-2.64;-1.38); p = 0.007 • MPH 72 mg = -2.3; 95 % CI (-3.04;-1.49); p < 0.001 • PI = -0.6; 95 % CI (-1.17;-0.01) ADHD Index • MPH 18 mg = -4.4; 95 % CI (-5.73;-3.14); p = 0.015 • MPH 36 mg = -5.5; 95 % CI (-6.82;-4.13); p = 0.002 • MPH 72 mg = -6.9; 95 % CI (-8.41;-5.34); p < 0.001 • PI = -2.7; 95 % CI (-3.78;-1.58) Average change of the CGI-S total score from start to end of the study: • MPH 18 mg = -0.9; 95 % CI (-1.16;-0.72); p = 0.003 • MPH 36 mg = -0.9; 95 % CI (-1.14;-0.72); p = 0.005 • MPH 72 mg = -1.2; 95 % CI (-1.45;-0.96); p < 0.001 • PI = -0.5; 95 % CI (-0.69;-0.32) Average change of the SDS total score from start to end of the study: • MPH 18 mg = -4.8; 95 % CI (-6.19;-3.34); p = 0.008 • MPH 36 mg = -4.1; 95 % CI (-5.31;-2.79); p = 0.061 • MPH 72 mg = -5.1; 95 % CI (-6.69;-3.49); p = 0.004 • PI = -2.2; 95 % CI (-3.08;-1.27) Average change of the CAARS:O total score Week 1 • MPH 18 mg = -8.0; 95 % CI (-9.71;-6.33); p = 0.009 • MPH 36 mg = -9.1; 95 % CI (-10.9;-7.42); p = 0.001 • MPH 72 mg = -9.5; 95 % CI (-11.3;-7.73); p < 0.001 • PI = -5.5; 95 % CI (-6.93;-4.09) Week 3 • MPH 18 mg = -9.6; 95 % CI(-11.4;-7.77); p = 0.059 • MPH 36 mg = -11.2; 95 % CI(-13.2;-9.21; p = 0.011 • MPH 72 mg = -13.3; 95 % CI(-15.5;-11.1); p < 0.001 • PI = -7.5; 95 % CI(-9.42;-5.66)

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Results regarding effectiveness *(continued)*	Week 5 • MPH 18 mg = -10.6; 95 % CI (-12.8;-8.4); p = 0.036 • MPH 36 mg = -12.4; 95 % CI (-14.5;-10.2); p = 0.008 • MPH 72 mg = -13.6; 95 % CI (-15.9;-11.2); p < 0.001 • PI = -8.0; 95 % CI (-10.1;-5.83) Average change of the CAARS:O (subscale inattentiveness) Week 1 • MPH 18 mg = -4.5; 95 % CI (-5.50;-3.52); p = 0.010 • MPH 36 mg = -5.5; 95 % CI (-6.48;-4.47); p < 0.001 • MPH 72 mg = -5.6; 95 % CI (-6.59;-4.58); p < 0.001 • PI = -3.1; 95 % CI(-3.82;-2.28) Week 3 • MPH 18 mg = -5.3; 95 % CI (-6.31;-4.26); p = 0.030 • MPH 36 mg = -6.6; 95 % CI (-7.79;-5.41); p < 0.001 • MPH 72 mg = -7.6; 95 % CI (-8.90;-6.39); p < 0.001 • PI = -3.8; 95 % CI (-4.82;-2.83) Week 5 • MPH 18 mg = -5.9; 95 % CI (-7.14;-4.71); p = 0.003 • MPH 36 mg = -7.2; 95 % CI (-8.42;-5.92); p < 0.001 • MPH 72 mg = -7.7; 95 % CI (-8.99;-6.33); p < 0.001 • PI = -3.7; 95 % CI (-4.86;-2.62) Average change of the CAARS:O (subscale hyperactivity) Week 1 • MPH 18 mg = -3.5; 95 % CI (-4.47;-2.55); p = 0.046 • MPH 36 mg = -3.7; 95 % CI (-4.63;-2.72); p = 0.077 • MPH 72 mg = -3.9; 95 % CI (-4.85;-2.96); p = 0.013 • PI = -2.5; 95 % CI (-3.27;-1.64) Week 3 • MPH 18 mg = -4.3; 95 % CI (-5.35;-3.27); p = 0.320 • MPH 36 mg = -4.6; 95 % CI (-5.67;-3.59); p = 0.420 • MPH 72 mg = -5.7; 95 % CI (-6.92;-4.43); p = 0.002 • PI = -3.7; 95 % CI (-4.78;-2.64) Week 5 • MPH 18 mg = -4.6; 95 % CI (-5.81;-3.47); p = 0.496 • MPH 36 mg = -5.2; 95 % CI (-6.26;-4.12); p = 0.536 • MPH 72 mg = -5.9; 95 % CI (-7.21;-4.60); p = 0.019 • PI = -4.2; 95 % CI (-5.37;-3.06)
Results for AEs	Number of severe AEs: • MPH 18 mg = 2 (2 %) • MPH 36 mg = 0 • MPH 72 mg = 2 (2 %) • PI = 0 • All MPH = 4 (1.3 %) Number of drop-outs due to AE: • MPH 18 mg = 1 (1 %) • MPH 36 mg = 4 (3.9 %) • MPH 72 mg = 8 (7.8 %) • PI = 1 (1 %) • All MPH = 13 (4.3 %) Number of AEs total: • MPH 18 mg = 76 (75.2 %) • MPH 36 mg = 77 (75.5 %) • MPH 72 mg = 84 (82.4 %) • PI = 63 (65.6 %) • All MPH = 237 (77.7 %) Possible relationship to the study medication: • MPH 18 mg = 52 (51.5 %) • MPH 36 mg = 60 (58.8 %) • MPH 72 mg = 70 (68.6 %) • PI = 41 (42.7 %) • All MPH = 182 (59.7 %)

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Results for AEs *(continued)*	Reduced appetite: • MPH 18 mg = 20 (19.8 %) • MPH 36 mg = 22 (21.6 %) • MPH 72 mg = 35 (34.3 %) • PI = 7 (7.3 %) • All MPH = 77 (25.2 %) Headaches: • MPH 18 mg = 26 (25.7 %) • MPH 36 mg = 21 (20.6 %) • MPH 72 mg = 17 (16.7 %) • PI = 17 (17.7 %) • All MPH = 64 (21 %) Insomnia: • MPH 18 mg = 12 (11.9 %) • MPH 36 mg = 12 (11.8 %) • MPH 72 mg = 17 (16.7 %) • PI = 7 (7.3 %) • All MPH = 41 (13.4 %) Nausea: • MPH 18 mg = 8 (7.9 %) • MPH 36 mg = 16 (15.7 %) • MPH 72 mg = 15 (14.7 %) • PI = 4 (4.2 %) • All MPH = 39 (12.8 %) Dry mouth: • MPH 18 mg = 8 (7.9 %) • MPH 36 mg = 7 (6.9 %) • MPH 72 mg = 21 (20,6 %) • PI = 2 (2.1 %) • All MPH = 36 (11.8 %) Dizziness: • MPH 18 mg = 6 (5.9 %) • MPH 36 mg = 10 (9.8 %) • MPH 72 mg = 9 (8.8 %) • PI = 7 (7.3 %) • All MPH = 25 (8.2 %) Weight loss: • MPH 18 mg = 3 (3.0 %) • MPH 36 mg = 8 (7.8 %) • MPH 72 mg = 11 (10.8 %) • PI = 5 (5.2 %) • All MPH = 22 (7.2 %) Nasopharyngitis: • MPH 18 mg = 7 (6.9 %) • MPH 36 mg = 8 (7.8 %) • MPH 72 mg = 4 (3.9 %) • PI = 9 (9.4 %) • All MPH = 19 (6.2 %) Tachycardia: • MPH 18 mg = 4 (4.0 %) • MPH 36 mg = 5 (4.9 %) • MPH 72 mg = 8 (7.8 %) • PI = 0 • All MPH = 17 (5.6 %) Irritability: • MPH 18 mg = 4 (4 %) • MPH 36 mg = 4 (3.9 %) • MPH 72 mg = 9 (8.8 %) • PI = 1 (1.0 %) • All MPH = 17 (5.6 %)

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Results for AEs *(continued)*	Anxiety: • MPH 18 mg = 3 (3.0 %) • MPH 36 mg = 5 (4.9 %) • MPH 72 mg = 8 (7.8 %) • Pl = 1 (1.0 %) • All MPH = 16 (5.2 %) Hyperhidrosis: • MPH 18 mg = 5 (5.0 %) • MPH 36 mg = 3 (2.9 %) • MPH 72 mg = 8 (7.8 %) • Pl = 1 (1.0 %) • All MPH = 16 (5.2 %) Fatigue: • MPH 18 mg = 4 (4.0 %) • MPH 36 mg = 4 (3.9 %) • MPH 72 mg = 6 (5.9 %) • Pl = 6 (6.3 %) • All MPH = 14 (4.6 %) Depressed mood: • MPH 18 mg = 6 (5.9 %) • MPH 36 mg = 3 (2.9 %) • MPH 72 mg = 5 (4.9 %) • Pl = 1 (1.0 %) • All MPH = 14 (4.6 %) Palpitations: • MPH 18 mg = 2 (2.0 %) • MPH 36 mg = 5 (4.9 %) • MPH 72 mg = 5 (4.9 %) • Pl = 0 • All MPH = 12 (3.9 %) Nervousness: • MPH 18 mg = 0 • MPH 36 mg = 3 (2.9 %) • MPH 72 mg = 8 (7.8 %) • Pl = 1 (1.0 %) • All MPH = 11 (3.6 %) Initial insomnia: • MPH 18 mg = 3 (3.0 %) • MPH 36 mg = 2 (2.0 %) • MPH 72 mg = 5 (4.9 %) • Pl = 2 (2.1 %) • All MPH = 10 (3.3 %)
Authors' conclusions	Treatment with MPH is effective in all 3 dosages compared with Pl. The largest improvement was evident in the 72-mg group. The safety is comparable to administration of MPH in childhood.
Comments	1. Compliance is checked by having all tablet packages returned 2. The scales were translated into the respective language of the country 3. AEs are more frequent in the treatment groups 4. Highest percent rate of AEs: MPH 72 mg 5. The results of the study must be considered globally and cannot be transferred to individual patients. An optimal effectiveness of MPH can only occur with a dose adjustment and not with a fixed dose. Therefore, it is possible, for example, that the dose of patients in the 18-mg and 36-mg groups is too high and an optimal result was not achieved. With a too high dosage, the effect of MPH can be negative and hyperactive patients will exhibit, e.g. more hyperactivity. 6. It is not clearly evident in this study to what extent patients with depression are included or how many patients suffer from depression 7. The primary end point is a third-party rating form. It needs to be discussed whether a self-assessment form would not be more suitable 8. Sponsor: Janssen Pharmaceutica N. V. Belgium

ADHD = Attention deficit/hyperactivity disorder. AE = Adverse event. CAARS = Conners Adult ADHA Rating Scale. CAARS-O = Conners Adult ADHA Rating Scale/Observer-rated. CAARS-S = Conners Adult ADHD Rating Scale/Self-rated. CGI-S = Clinical Global Impression-Severity of Illness subscale. n. i. = no information. CI = Confidence interval LOCF = Last observation carried forward. MPH = Methylphenidate. N = Number. Pl = Placebo. RCT = Randomised controlled trial. SAS = Social adjustment scale. SD = Standard deviation. SDS = Sheehan Disability Scale.

Study description	Randomised, double-blind, multicentre, parallel study
Study type (proven)	RCT
Level of evidence (proven)	Ib
Source	Michelson D, Adler L, Spencer T et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled Studies.
Study period	No information
Country of study	No information
Question/objective	Assessment of the effectiveness and safety of MPH in the treatment of adults with ADHD
Setting	Outpatient Recruitment by advertising
Relevant inclusion and exclusion criteria	Inclusion criteria: • Adult patients • Diagnosis: ADHD according to DSM-IV criteria and CAARS • At least a moderate degree of severity of ADHD • Confirmation of the diagnosis by a 2nd appraiser or because the symptoms have been present since childhood Exclusion criteria: • Comorbid major depression, anxiety disorders, bipolar/psychotic disorders • Patients with severe illnesses • Patients with alcohol dependency • Current drug abuse
Number of groups	4; 2 groups per study
Intervention	ATX: • Administration in the morning and the evening • Start with 60 mg daily • If necessary, titration to 90 mg daily after 2 weeks • If necessary, titration to 120 mg after 4 weeks
Control	Pl
Possible other treatment groups	–
Number of centres	Study I: 17 centres Study II: 14 centres
Details, if >1	All centres are located in North America
Randomisation	Computer-generated randomisation
Concealment	No information
Blinding	Yes
Study duration, total	10 weeks
Primary end points	Third-party assessment after CAARS sum score for inattentiveness and hyper-activity/impulsiveness
Secondary end points	• CGI severity • WRAADDS • HAM-A, HAM-D • Sheehan Disability
Subgroup analyses	No information
Sample size calculation, incl. planned sample size	No information
Statistical methodology	• ITT analysis; LOCF • Mixed model • Transformation of the results of the CAARS self-assessment as t-scores • ANOVA • Fisher's Exact Test • Level of significance: 0.05 (2-sided)
Patient characteristics	Study I: Proportion of male patients (%): • ATX = 64.5 • Pl = 62.6 • p = 0.804

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Patient characteristics *(continued)*	Average age in years: • ATX = 40.2 (SD = 11.7) • Pl = 40.3 (SD = 11.6) • p = 0.976 ADHD subtype: Combined • ATX = 71.6 % • Pl = 71.9 % • P = 1.00 Inattentiveness • ATX = 27.7 % • Pl = 27.3 % Hyperactivity/impulsiveness • ATX = 0.7 • Pl = 0.7 Previous taking of stimulants: • ATX = 44.0 % • Pl = 48.9 % • p = 0.427 Average CAARS-Inv score Total ADHD Symptom Score • ATX = 33.6 (SD = 7.2) • Pl = 33.2 (SD = 7.8) • p = 0.603 Inattentiveness • ATX = 18.4 (SD = 4.2) • Pl = 18.6 (SD = 4.4) • p = 0.736 Hyperactivity/impulsiveness • ATX = 15.2 (SD = 5.0) • Pl = 14.5 (SD = 5.4) • p = 0.309 Average CAARS according to self-assessment Total ADHD Symptom Score: • ATX = 82.6 (SD = 12.7) • Pl = 80.8 (SD = 12.3) • p = 0.291 Inattentiveness: • ATX = 87.5 (SD = 12.5) • Pl = 85.6 (SD = 12.7) • p = 0.249 Average CGI-ADHD-S: • ATX = 4.7 (SD = 0.8) • Pl = 4.7 (SD = 0.7) • p = 0.886 Average WRAADDS: • ATX = 18.3 (SD = 4.7) • Pl = 17.6 (SD = 4.2) • p = 0.073 Average HAM-D: • ATX = 5.1 (SD = 3.6) • Pl = 5.9 (SD = 3.9) • p = 0.073 Average HAM-A: • ATX = 7.4 (SD = 5.2) • Pl = 8.2 (SD = 4.8) • p = 0.169 Study II: Results are not included due to the high drop-out rate.
Number of screened patients	Study I: N = 448 Study II: N = 388
Number of randomised patients	Study I: N = 280; N(ATX) = 141, N(Pl) = 139 Study II: N = 256; N(ATX) = 129, N(Pl) = 127

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Number of analysed patients	All randomised Patients (ITT analysis)
Lost-to-follow-up patients	Study I: N(ATX) = 39 (28 %), N(Pl) = 32 (23 %) Study II: N(ATX) = 47 (36 %), N(Pl) = 32 (25 %)
Patient flow	Reasons for dropping out, Study I: • AE: ATX = 11, Pl = 6 • Lost-to-follow-up: ATX = 11, Pl = 11 • Patient decision: ATX = 11, Pl = 7 • Protocol violations: ATX = 1, Pl = 4 • Physician's decision: ATX = 1 • Sponsor's decision: ATX = 1, Pl = 1 • LOE: ATX = 3, Pl = 3 Reasons for dropping out, Study II: • AE: ATX = 12, Pl = 3 • Lost-to-follow-up: ATX = 8, Pl = 4 • Patient decision: ATX = 8, Pl = 5 • Protocol violations: ATX = 1, Pl = 3 • Physician's decision: ATX = 1, Pl = 1 • Sponsor's decision: ATX = 13, Pl = 15 • LOE: ATX = 5, Pl = 6 • Patient has moved: Pl = 1
Comparability of the groups	No statistically significant differences
Results of the dosing	Most frequent dosing Study I: 90 mg: 40.4 % 120 mg: 39.7 % 60 mg: 19.9 %
Results regarding effectiveness	Results, Study I: Change from start to end of study in the CAARS-Inv Total ADHD Symptom Score: • ATX = -9.5 (SD = 10.1) • Pl = -6.0 (SD = 9.3) • p = 0.005; 95 % CI (-5.61;-0.99) Inattentiveness: • ATX = -5.0 (SD = 5.7) • Pl = -3.1 (SD = 5.8) • p = 0.010; 95 % CI (-3.21;-0.45) Hyperactivity/impulsiveness: • ATX = -4.5 (SD = 5.1) • Pl = -2.9 (SD = 4.9) • p = 0.17; 95 % CI (-2.67;-0.27) Change from start to end of study in the CAARS self-assessment Total ADHD Symptom Score: • ATX = -16.0 (SD = 16.2) • Pl = -9.3 (SD = 14.0) • p = 0.002; 95 % CI (-10.53;-2.47) Inattentiveness: • ATX = -15.9 (SD = 16.3) • Pl = -8.6 (SD = 13.8) • p < 0.001; 95 % CI (-11.00;-2.94) Hyperactivity/impulsiveness: • ATX = -11.9 (SD = 13.5) • Pl = -7.5 (SD = 12.1) • P = 0.013; 95 % CI (-7.75;-0.94) CGI-ADHD-S: • ATX = -0.8 (SD = 1.2) • Pl = -0.4 (SD = 1.0) WRAADS: • ATX = -5.3 (SD = 6.6) • Pl = -2.9 (SD = 4.8) HAM-D: • ATX = -0.3 (SD = 3.8) • Pl = -0.6 (SD = 4.2) HAM-A: • ATX = -1.0 (SD = 5.3) • Pl = -1.2 (SD = 4.8) Strength of effect of the primary end point for Study I: 0.35

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Results for AEs	Study I: No serious AEs: Change in diastolic blood pressure: • ATX = 2.3 mmHg (SD = 8.1 mmHg) • Pl = 0.5 mmHg (SD = 7.8 mmHg) • p = 0.063 Change of systolic blood pressure: • ATX = 2.3 mmHg (SD = 11.1 mmHg) • Pl = -0.8 mmHg (SD = 9.8 mmHg) • P = 0.015 Change in the heart rate, beats per minute: • ATX = 6.7 (SD = 11.6) • Pl = -0.5 (SD = 9.3) • p < 0.001 Most common AEs: • Dry mouth: p < 0.001 • Sleeplessness: p < 0.001 • Nausea: p = 0.003 • Reduced appetite: p < 0.001
Authors' conclusions	ATX is effective in the treatment of adults with ADHD
Comments	• Exclusion of patients with comorbid disorders • Short study period for ATX • No description of the sample size calculation • How were the two studies randomised? • Sponsor influence uncertain • Values do not lie in the CI • CI very broad • Self-assessment turns out better • Statistics, randomisation and sample size calculation designed for 2 studies

ADHD = Attention deficit/hyperactivity disorder. AE = Adverse event. ANOVA = Variance analysis. ATX = Atomoxetine. CAARS = Conners Adult ADHA Rating Scale. CGI = Clinical Global Impression. CGI-ADHD-S = Clinical Global Impression Improvement Scale for ADHD symptoms. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. ITT = Intention-to-treat. n. i. = no information. CI = Confidence interval. LOCF = Last observation carried forward. LOE = Loss of efficacy. N = Number. Pl = Placebo. RCT = Randomised controlled trial. SAS = Social adjustment scale. SD = Standard deviation. WRAADS = Wender Reimherr ADHD Scale.

Study description	Randomised, multicentre, placebo-controlled study
Study type (proven)	RCT
Level of evidence (proven)	Ib
Source	Weiss M, Hechtman L et al. A randomized double-blind trial of Paroxetine and/or Dextroamphetamine and problem-focused therapy for attention-deficit/ hyperactivity disorder in adults. J Clin Psychiatry 2006; 67:611-619.
Study period	August 2000 to May 2002
Country of study	USA and Canada
Question/objective	Assessment of the effectiveness and safety of paroxetine and dextroamphetamine in monotherapy and combination therapy
Setting	Multicentre Recruiting: psychiatric, clinical outpatient clinics
Relevant inclusion and exclusion criteria	Inclusion criteria: • Age: 18 to 66 years • Diagnosis of ADHD according to DSM-IV criteria Exclusion criteria: • Persons with eating disorders, substance abuse, organic brain psychosyndrome, neurological disorders, psychoses, acute risk of suicide • Other comorbid disorders
Number of groups	4

Weiss et al. 2006 – continued

Intervention	• Wash-out phase of 1 week before start of study • Weekly dose titration over a period of 4 weeks (defined according to CGI-I) • During the titration phase: Follow-up every 2 weeks (6 sessions) • PAR: Oral administration of 20 mg daily; dose titration by 10 mg to a maximum of 40 mg daily • DEX: Oral administration of 5 mg daily; dose titration by 5 mg to a maximum of 20 mg daily • Paroxetine in combination with dextroamphetamine (PAR/DEX): Simultaneous administration of both active ingredients; no information on precise dosing • 9 sessions of a problem-oriented psychotherapy (developed by the authors)
Control	• Pl: No information on dosing and duration of intake • 9 sessions of a problem-oriented psychotherapy (developed by the authors)
Possible other treatment groups	–
Number of centres	5
Details, if >1	2 centres in the USA: Yale and Duke Universities 3 centres in Canada: McGill University, University of Toronto, University of British Columbia
Randomisation	Block randomisation
Concealment	Identical tablets for intervention groups and Pl
Blinding	Double-blind
Study duration, total	5 months
Primary end points	• Change in the ADHD-RS • HAM-D • HAM-A
Secondary end points	• Changes of the CGI-I from start to end of the study or to the last recorded value • Measurements at study end: ADHD symptoms (CGI-I-ADHD), mood and anxiety symptoms (CGI-I-Int), total improvement (CGI-I), GAF, Proportion of the mood disorders and anxiety disorders occurring. • Recording in each examination: Weight, blood pressure, pulse, adverse events, simultaneously taken medication
Recording of compliance	• Recording with each examination • Counting of the tablets • Subjects must show a minimum compliance of 75 % regarding the medi-cation intake
Subgroup analyses	No information
Sample size calculation, incl. planned sample size	• Alpha: 0.05 • Power (test strength): 80 % • 2-sided test • Strength of effect: 0.89 • Calculated sample size per group: 20 subjects • Assumption: Drop-out of 20 % • Calculated sample size total: 100 subjects
Statistical methodology	• Primary: Analysis of the results of study participants in Week 20 • Additional ITT analysis; with imputation of missing values according to LOCF • 2 x 2 factor model • DEX and PAR/DEX vs. PAR and Pl x PAR and PAR/DEX vs. DEX and Pl • Secondary end points Chi-square test/Fisher's Exact Test • Change from baseline to study end of the vital signs: paired t-test • Level of significance: p = 0.05 • No statistical analysis of the adverse results
Patient characteristics	• Average age (in years) total: 37.5 (SD = 10.75) • Proportion of men, total (%): 64 • Proportion of "inattentive subtype" total (%): 36 • Proportion of "hyperactive subtype" total (%): 4 • Proportion of "combined subtype" total (%): 60 • Average GAF score total: 53.1 (SD = 7.93) • Proportion of white persons (%): 85

Weiss et al. 2006 – continued

Patient characteristics *(continued)*	• Proportion of persons with at least one mood disorder or anxiety disorders according to SCID (%) total: 33 • Proportion of persons with chronic mood disorders or anxiety disorders (%) total: 53 • Average ADHD-RS total: 32.20 (SD = 7.55) • Average HAM-A total score: 12.70 (SD = 6.56) • Average HAM-D total score: 9.20 (SD = 5.71)
Number of screened patients	N = 140
Number of randomised patients	N = 98
Number of analysed patients	According to LOCF N = 98 N(PAR) = 24 N(DEX) = 23 N(PAR/DEX) = 25 N(Pl) = 26
Lost-to-follow-up patients	65% of patients completed the study (20 weeks) • Intervention: 62 % • Pl: 77 %
Patient flow	Reasons for dropping out: • 18 patients due to adverse events N(PAR) = 6 N(DEX) = 3 N(PAR/DEX) = 7 N(Pl) = 2 • 5 patients due to lacking effectiveness • 1 patient due to protocol violations • 5 patients due to non-compliance • 5 patients due to lost-to-follow-up • 2 patients without reason
Comparability of the groups	Patient characteristics not shown according to groups Randomised proportion of women in the group PAR larger (p = 0.04) No further statistical differences stated
Results of the dosing	Maximum dosing of PAR 40 mg/d and DEX 40 mg/d: 52.6 % Maximum dosing in Pl: 68 % No statistically significant differences between the 4 groups
Results regarding effectiveness	Persons who received DEX (mono- or combination therapy) exhibit statistically non-significantly fewer symptoms according to ADHD-RS than persons who received Pl or PAR (ITT analysis): • F = 3.51 • Df = 1.94 • p = 0.064 ADHD symptoms in patients in the group with DEX (mono- or combination therapy) and who remained to the end are significantly less after 20 weeks compared with Pl and PAR: • F = 6.694 • Df = 1.58 • p = 0.012 Persons who terminate the studies and DEX (mono- or combination therapy), have significantly higher GAF compared with persons in the Pl or PAR group: • F = 4.53 • Df = 1.60 • p = 0.037 The other primary end points do not show a significant result either in the ITT analysis or in the analysis of the patients who have completed the study after 20 weeks Average ADHD-RS at study end according to ITT: • PAR = 24.71 (SD = 9.47) • DEX = 20.78 (SD = 9.65) • PAR/DEX = 19.52 (SD = 10.07) • Pl = 23.50 (SD = 12.14)

Weiss et al. 2006 – continued

Results regarding effectiveness *(continued)*	Average ADHD-RS at study end according to CC: • PAR = 23.73 (SD = 9.56) • DEX = 16.83 (SD = 8.18) • PAR/DEX = 16.93 (SD = 10.02) • PI = 23.55 (SD = 11.51) Average HAM-A at study end according to ITT: • PAR = 7.29 (SD = 4.60) • DEX = 9.17 (SD = 7.80) • PAR/DEX = 8.28 (SD = 7.36) • PI = 7.69 (SD = 4.47) Average HAM-A at the end of study according to CC: • PAR = 5.73 (SD = 4.43) • DEX = 8.27 (SD = 6.69) • PAR/DEX = 7.07 (SD = 6.69) • PI = 7.15 (SD = 3.51) Average HAM-D at end of study according to ITT: • PAR = 4.83 (SD = 4.26) • DEX = 7.56 (SD = 7.25) • PAR/DEX = 6.44 (SD = 6.71) Average HAM-D at end of study according to CC: • PAR = 3.60 (SD = 3.96) • DEX = 7.00 (SD = 6.46) • PAR/DEX = 5.40 (SD = 6.87) • PI = 5.30 (SD = 3.11) Average GAF at end of study according to ITT: • PAR = 61.04 (SD = 13.31) • DEX = 60.00 (SD = 15.89) • PAR/DEX = 62.88 (SD = 14.66) • PI = 58.88 (SD = 9.84) Average GAF at end of study according to CC: • PAR = 66.93 (SD = 6.97) • DEX = 68.71 (SD = 9.08) • PAR/DEX = 69.6 (SD = 14.21) • PI = 60.05 (SD = 10.52) CGI-I-ADHD responder according to ITT: significant group difference in DEX (DEX and PAR/DEX): • Chi square = 15.975 • Df = 3.95 • $p < 0.001$ CGI-I-ADHD responders according to ITT population: • DEX = 64 % • PAR/DEX = 44 % • PAR = 17 % • PI = 16 % CGI-I-ADHD responder according to CC: significant group difference at DEX (DEX and PAR/DEX): • Chi square = 20.309 • Df = 3.63 • $p < 0.001$ CGI-I-ADHD responder according to CC: • DEX = 86 % • PAR/DEX = 67 % • PAR = 20 % • PI = 21 % CGI-I-Int responders according to CC: • DEX = 57 % • PAR/DEX = 73 % • PAR = 100 % • PI = 47 % CGI-I-Int responders were highest in administration of: • Chi-square = 11.78 • Df = 3.63 • p = 0.003

Weiss et al. 2006 – continued

Results regarding effectiveness *(continued)*	CGI-I-Int responders according to ITT: • DEX = 46 % • PAR/DEX = 48 % • PAR = 70 % • Pl = 36 % • Difference not statistically significant CGI-I responders in the medication groups greater than with Pl in the ITT population: • Chi-square = 8.728 • Df = 3.95 • p = 0.033 CGI-I responders in the medication groups greater than with Pl in the CC population: • Chi-square = 16.604 • Df = 3.63 • p = 0.001
Results for AEs	83% of persons reported at least 1 AE No significant differences between medication groups regarding those who drop out due to 1 AE (PAR: N = 6; DEX: N = 3; PAR/DEX: N = 7 Pl: N = 2) (chi-square = 4.662; df = 3.98; p = 0.198) and the average number of AEs (F = 2.121; df = 3.90; p = 0.130). In the PAR/DEX group, significantly more serious AEs were reported (chi-square = 18.662; df = 9.471; p = 0.028). Weight loss from baseline to end of study is significant in the DEX and PAR/DEX group: • DEX: 3 kg; t = 4.354; df = 21; p < 0.001 • PAR/DEX: 1.7 kg; t = 3.422; df = 24; p = 0.002 Weight increase from 1.3 kg in the PAR group significant (t = 2.248; df = 21; p = 0.035) Increased pulse of 9.8 bpm in the PAR/DEX group (t = 4.325; df = 24; p < 0.001) Diastolic blood pressure: significantly lower with Pl (t = 2.136; df = 23; p = 0.044)
Authors' conclusions	ADHD symptoms improve with taking DEX. No statement can be made on the use of psychotherapy.
Comments	• Long study period • Drop-out rate is 35 % (20 % were assumed) • Most common reason for drop-out: AE • A recommendation for clinical action is made • The study has considerable qualitative deficiencies

ADHD = Attention deficit/hyperactivity disorder. ADHD-RS = ADHD Rating Scale. AE = Adverse event. CGI = Clinical Global Impression. CGI-I = Clinical Global Impression Improvement scale. CGI-I-ADHD = Clinical Global Impression Improvement scale ADHD. CGI-I-Int = Clinical Global Impression-Improvement scale mood and anxiety symptoms. CC = Complete Condition (patients who complete the study). DEX = Dextroamphetamine. Df = Degrees of freedom. -DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. F = F-statistic. GAF = Global assessment of functioning. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. ITT = Intention-to-treat. n. i. = no information. LOCF = Last observation carried forward. N = number. p = p-value. PAR = Paroxetine PAR/DEX = Paroxetine/dextroamphetamine. Pl = Placebo. RCT = Randomised controlled trial. SCID = Structured Clinical Interview for DSM-IV Axis I Disorders. SD = Standard deviation.

Study description	Randomised, double-blind, placebo-controlled study
Study type (assessed)	RCT
Level of evidence (assessed)	Ib
Source	Wilens TE, Spencer TJ, Biederman J et al. A controlled clinical trial of Bupropion for attention deficit hyperactivity disorder in adults. Am J Psychiatry 2001; 158: 282-288.
Study period	No information
Country of study	No information
Question/objective	Assessment of the effectiveness of Bp in adults with ADHD in comparison with Pl Assumption: Bp is superior to the Pl therapy
Setting	Outpatient

Wilens et al. 2001 – continued

Relevant inclusion and exclusion criteria	Inclusion criteria: • Age: 20 to 59 years • Recruiting: Advertising and referral • Diagnosis: ADHD according to DSM-III-R or DSM-IV Exclusion criteria: • Severe chronic diseases • Heart rhythm disorders or paroxysmal illnesses in the past • IQ < 75 • Organic brain syndrome • Unstable psychological constitution • Bipolar disorders • Alcohol or drug abuse or dependencies 6 months before the start of the study • Current intake of psychopharmaceuticals
Number of groups	2
Intervention	Bp: • Oral administration of 100 mg bupropion in the morning • Dose titration of 100 mg weekly • Maximum dose: 200 mg twice daily
Control	Pl: Pl administration identical to Bp administration
Possible other treatment groups	–
Number of centres	No information
Details, if > 1	
Randomisation	No information
Concealment	Pl capsule identical to Bp capsule
Blinding	Yes
Recording of compliance	Return of the medication at each examination
Study duration, total	6 weeks
Primary end points	• CGI scale • ADHD rating scale
Secondary end points	• HAM-D • Beck Depression Inventory • HAM-A
Subgroup analyses	No information
Sample size calculation, incl. planned sample size	• Planned sample size: 20 patients per treatment arm • Assumption: Bp response rate of 60%, Pl response rate of 10 % • Alpha: 0.05 • Power (test strength): 89 % (1-beta); beta = 0.11 • Improvement of the ADHD symptoms: min. 30% reduction of the ADHD rating scale
Statistical methodology	• Continuation of the missing values of the CGI and ADHD Rating Scale according to LOCF (ITT method) • Fisher's Exact Test for comparison of patients who exhibit improvement with Bp and Pl treatment • Wilcoxon signed rank test for comparison of ordinal data between 2 points in time • Wilcoxon rank sum test • Fisher's Exact Test for comparing study group for binary end points. • Linear regression and GEE method: Treatment (Bp vs. Pl), time (week in study), effect on variables • Level of significance: 0.05 • Performance of the statistical analyses in strata
Patient characteristics	Average age (in years) • Bp = 37 (SD = 11.8) • Pl = 39.6 (SD = 10.4) • Total = 38.3 (SD = 11.1) Average proportion of male patients (%): • Bp = 57 • Pl = 53 • Total = 55

Wilens et al. 2001 – continued

Patient characteristics *(continued)*	Average proportion of patients with current depression (%): • Bp = 32 • Pl = 6 • Total = 19 Average proportion of patients with depression in the past (%): • Bp = 58 • Pl = 61 • Total = 59 Average proportion of patients with current other comorbid disorders (%): • Bp = 58 • Pl = 39 • Total = 49 Average proportion of patients with other comorbid disorders in the past (%): • Bp = 89 • Pl = 89 • Total = 89 Average proportion of patients with ADHD total (%): • Inattentive subtype = 58 • Combined subtype = 35 • Hyperactive/inattentive subtype = 8 Average GAF score: • Bp = 50.7 (SD = 6.9) • Pl = 52.9 (SD = 7.1) • Total = 51.8 (SD = 7.0) Beck Depression Inventory: • Bp = 11.5 (SD = 8.9) • Pl = 9.4 (SD = 9.5) • Total = 10.5 (SD = 9.1) Average HAM-D: • Bp = 7.8 (SD = 5.1) • Pl = 6.7 (SD = 4.3) • Total = 7.3 (SD = 4.7) Average HAM-A: • Bp = 7.8 (SD = 5.1) • Pl = 8.5 (SD = 4.4) • Total = 8.2 (SD = 4.7)
Number of screened patients	N = 154
Number of randomised patients	N = 40
Number of analysed patients	N = 40
Lost-to-follow-up patients	N = 2
Patient flow	Reasons for dropping out: Non-compliance
Comparability of the groups	The groups are comparable
Results of the dosing	No link between response and daily Bp dosing: • T = -0.11; df = 19; p = 0.91 Average daily dosing at end of study (Week 6) with Bp and Pl: 379 mg and 362 mg Distribution of the daily Bp dosing: • 400 mg: 76 % • 300 mg: 10 % • 200 mg: 14 %
Results regarding effectiveness	Proportion of patients with CGI improvement: • Bp = 52 % • Pl = 11 % • p < 0.007 Proportion of patients with DSM improvement of ≥ 30 % (ADHD rating scale): • Bp = 76 % • Pl = 37 % • p = 0.02 Average improvement of the ADHD symptom check-list: • Bp = 42 % • Pl = 24 % • Linear regression; t = -2.02, df = 39, p = 0.05 ADHD symptom check-list (according to GEE model): • Time effect: z = -4.66; p < 0.001 • Effect on med. (Bp vs. Pl): z = 0.69; p = 0.49 • Drug-by-time: z = -1.29; p = 0.20

Wilens et al. 2001 – continued

Results regarding effectiveness *(continued)*	Effect of the treatment on the 18 DSM-IV specific ADHD symptoms (LOCF) (ADHD rating scale): • Bp: Significant improvement of all symptoms • Pl: Improvement of 8 (44 %) symptoms • $p < 0.001$ (Fisher's Exact Test) Regarding HAM-D, HAM-A and Beck Depression Inventory, no significant differences appear among groups.
Results for AEs	No serious AEs: Headaches: • Bp = 19 % • Pl = 16 % Gastrointestinal complaints: • Bp = 19 % • Pl = 16 % Sleep disorders: • Bp = 38 % • Pl = 16 % Strong pains: • Bp = 10 % • Pl = 5 % Dry mouth: • Bp = 10 % • Pl = 0 % Chest pains: • Bp = 10 % • Pl = 0 % No significant differences regarding AEs between Bp and Pl (Fisher's Exact Test; $p > 0.05$). No significant differences regarding the heart rate between Bp and Pl (Wilcoxon rank sum test; $z = -1.35$; $p = 0.18$). No significant differences regarding systolic (Wilcoxon rank sum test; $z = -0.83$, $p = 0.41$) and diastolic (Wilcoxon rank sum test; $z = -0.15$, $p = 0.88$) blood pressure between Bp and Pl
Authors' conclusions	In the treatment of adults with ADHD, Bp shows significant effects compared to the Pl
Comments	• Exclusion of comorbid disorders • Recruiting doubtful • Pl response is low • For a precise estimation of the effects and long-term effects, the therapy phases must be longer • Delayed onset of effect: The greatest effectiveness was observed in the last 2 weeks (with the highest dosages) • Small sample size • Only 26% of the screened patients were included • Study population is not representative: The majority of included subjects were from higher social levels

ADHD = Attention deficit/hyperactivity disorder. AE = Adverse event. Bp = Bupropion. CGI = Clinical Global Impression Scale. Df = Degrees of freedom. DSM-III-R = Diagnostic and Statistical Manual of Psychological Disorders, 3rd revision. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. GAF = Global assessment of functioning. GEE = Generalized Estimation Equation HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. IQ = Intelligence quotient .ITT = Intention-to-treat. n. i. = no information. LOCF = Last observation carried forward. N = Number. Pl = Placebo. RCT = Randomised controlled trial. SD = Standard deviation.

Study description	RCT = Randomised, controlled, double-blind study.
Study type (assessed)	RCT
Level of evidence (assessed)	Ib
Source	Wilens TE, Klingt T, Adler L et al. A randomized controlled trial of a novel mixed monoamine reuptake inhibitor in adults with ADHD. Behavioral and Brain Functions 2008; 4: 24-34.
Study period	No information
Country of study	USA
Question/objective	Assessment of the efficacy, safety and cognitive function of NS2359 in adults with ADHD.

Wilens et al. 2008b – continued

Setting	Outpatient, multicentre The recruiting used advertising in the local media.
Relevant inclusion and exclusion criteria	Inclusion criteria: • Age: 18 to 55 years • Diagnosis: ADHD according to DSM-IV criteria • CGI ≥ 4 Exclusion criteria: • Unstable state of health • Significant unusual laboratory values at the start of the study • Mental retardation • Psychotic disorders • Bipolar disorders • Presence of a depression (HAM-D > 15) • Eating disorders • Organic brain disorders with paroxysmal diseases (non-febrile) • Drug abuse, alcohol abuse, positive urine drug test (cocaine, heroine, marijuana) in the last 6 months. • Taking of stimulant 1 week before randomisation; benzodiazepine, anti-epileptics 2 weeks before randomisation, antidepressants 4 weeks before randomisation, antipsychotics and monoaminoxidase inhibitors 8 weeks before randomisation.
Number of groups	2
Intervention	NS2359: Oral administration of 0.5 mg in the morning for 8 weeks
Control	Pl
Possible other treatment groups	–
Number of centres	3
Details, if > 1	All in the USA
Randomisation	No information
Concealment	No information
Blinding	Yes
Study duration, total	8 weeks
Primary end points	• ADHD rating scale (ADHD-RS) (investigator-rated)
Secondary end points	• ADHD rating Scale (self-rating scale) • CGI • CAARS (Self-rating scale) • ADHD rating scale (self-rating scale) • HAM-D • HAM-A • AE
Subgroup analyses	No information
Sample size calculation, incl. planned sample size	• Assumption: The probability of achieving a responder effect is 55 % (min. 30% improvement of the primary end point within 8 weeks) for patients in NS2359 treatment. • Probability of achieving a responder effect in Pl is 25 %. • Level of significance: 1 % • Power (test strength): 80 % • 100 patients (50 per group) were to be included • Assumption: Drop-out rate of 20 %
Statistical methodology	Clinical scales: • ANOVA • Comparison of results using the spatial correlation model • Covariates: Examination, treatment, centre as categoric variables • Baseline variables: sex, alcohol consumption, smoking habit, age and weight were included • Patients were grouped into “inattentive” and “combined” type according to DSM-IV • All tests: 2-sided • Level of significance: 0.05 CDR data: • The factor structure is analysed using a main component analysis • ANOVA

Wilens et al. 2008b – continued

Patient characteristics	Average age in years as median (range): • N(NS) = 35 (18.8-54.1) • N(Pl) = 35.2 (19.0-51.1) Proportion of male patients (%): • N(NS) = 74.6 • N(Pl) = 66.7 Proportion of white patients (%): • N(NS) = 81.0 • N(Pl) = 85.7 Proportion of patients with early ADHD treatment (%): • N(NS) = 27.0 • N(Pl) = 28.6 Proportion of patients with ADHD subtype (%): Inattentiveness: • N(NS) = 27.0 • N(Pl) = 46.0 Hyperactivity/impulsiveness (%): • N(NS) = 0 • N(Pl) = 1.6 Combined subtype (%): • N(NS) = 60.3 • N(Pl) = 50.8 Not classifiable subtype (%): • N(NS) = 12.7 • N(Pl) = 1.6 Average weight in kg (range): • N(NS) = 80.3 (54.9-142.9) • N(Pl) = 78.9 (48.5-133.4) Average size in cm (range): • N(NS) = 173 (152-197) • N(Pl) = 175 (151-188) Proportion of smokers (%): • N(NS) = 25.4 • N(Pl) = 23.8 Proportion of patients with occasional alcohol consumption (%): • N(NS) = 84.1 • N(Pl) = 92.1 Proportion of patients with no alcohol consumption (%): • N(NS) = 15.9 • N(Pl) = 7.9 Average HAM score (range): • N(NS) = 3.0 (0.0-15.0) • N(Pl) = 4.0 (0.0-12.0) Proportion of persons, with a CGI Severity of Illness (%): Moderate: • N(NS) = 47.6 • N(Pl) = 46.0 Pronounced: • N(NS) = 44.4 • N(Pl) = 49.2 Severe: • N(NS) = 6.3 • N(Pl) = 4.8 Very severe: • N(NS) = 1.6 • N(Pl) = 0
Number of screened patients	N = 180
Number of randomised patients	N = 126 N(NS) = 63 N(Pl) = 63

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Number of analysed patients	ITT analysis; all randomised patients to be analysed
Lost-to-follow-up patients	Patients who complete the study: N(NS) = 51 N(Pl) = 44
Patient flow	31 persons did not complete the study Reasons for dropping out: • Protocol violation: N = 8 • AE: N = 3 • Patients' decision: N = 11 • Other reasons: 4 Lost-to-follow-up: N = 4 Lack of effectiveness: N = 2
Comparability of the groups	No statistically significant differences
Results regarding effectiveness	Third-party rating scale: No significant differences in the ADHD-RS total sum score between the groups: • NS = 7.8 (SD = 1.3) • Pl = 6.4 (SD = 1.3) • p < 0.45 No significant differences between the groups in the proportion of patients with an ADHD-RS score of more than 30 %: • NS = 33 % • Pl = 27 % • p = 0.55 Patients in the inattentive subgroup have a significantly larger proportion of responders in the NS group compared with the Pl group: • NS = 41 % • Pl = 7 % • p < 0.001 Proportion of the responders in the combined subgroup: • NS = 30 % • Pl = 42 % • p = 0.23 Self-rating scales: ADHD-RS improvement: • NS = 7.2 (SD = 1.6) • Pl = 3.2 (SD = 1.2) • p = 0.052 ADHD-RS improvement in patients of the inattentive subgroup: • NS = 8.1 (SD = 3.1) • Pl = 0.3 (SD = 1.7) • p < 0.05 ADHD-RS improvement in patients of the combined subgroup: • NS = 6.9 (SD = 1.8) • Pl = 6.3 (SD = 1.7) • p = 0.82 CAARS total sum score improvement: • NS = 6.4 (SD = 1.5) • Pl = 4.7 (SD = 1.5) • p = 0.42 CAARS improvement in patients of the inattentive subgroup: • NS = 7.0 (SD = 1.9) • Pl = 2.0 (SD = 1.5) • p < 0.05 CAARS improvement in patients of the combined subgroup: • NS = 6.3 (SD = 1.9) • Pl = 6.9 (SD = 2.2) • p = 0.86

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Results regarding effectiveness *(continued)*	BROWN-AS improvement: • NS = 10.6 (SD = 2.8) • Pl = 10.8 (SD = 2.8) • p = 0.97 BROWN-AS improvement in patients of the inattentive subgroup: • NS = 15.8 (SD = 4.1) • Pl = 2.5 (SD = 3.1) • p <0.01 BROWN-AS improvement in patients of the combined subgroup: • NS = 10.8 (SD = 3.6) • Pl = 19.8 (SD = 4.3) • p = 0.11 • At no time can a CGI Severity difference be found between NS and Pl (Week 8: 3.9 (SD = 1.1) and 4.0 (SD = 1.1; p = 0.94). • Significant reduction of the CGI severity between NS and Pl in patients of the inattentive subgroup at the end of the study (Week 8: 3.3 (SD = 0.9) and 4.2 (SD = 0.8; p < 0.01) • No significant reduction of the CGI severity between NS and Pl in patients of the combined subgroup (Week 8: 4.0 (SD = 1.1) and 3.8 (SD = 1.3; p = 0.63)) • At no time could a CGI improvement between NS and Pl (Week 8: 3.2 (SD = 1.0) and 3.4 (SD = 1.1; p = 0.10)) be identified. • Significantly larger response among patients of the inattentive subgroup between NS and Pl regarding CGI improvement (Week 8: 3.0 (SD = 1.1) and 3.8 (SD = 0.9; p < 0.5)) at end of study. • No significantly greater response in patients of the combined subtype between NS and Pl regarding CGI improvement (Week 8: 3.2 (SD = 1,0) and 3.0 (SD = 1.2; p = 0.27) at any time. • No significant difference of the HAM-D between groups at the end of the study • Significant difference of the HAM-D between NS and Pl in patients of the inattentive subgroup (average HAM-D 3.7 (SD = 0.4) vs. 4.6 (SD = 0.4; p = 0.04)). • No significant difference in the HAM-A between NS and Pl at the end of the study (average HAM-A 5.7 (SD = 0.5) vs. 6.3 (SD = 0.5; p = 0.12)). • Results of the computer-generated cognitive assessment between the groups: Strength of attentiveness = p < 0.015 Quality of the secondary episodic memory = p < 0.01 Quality of the working memory = p < 0.1
Results for AEs	• No serious AEs: • No significant differences regarding the measured blood and urine laboratory values • No significant differences regarding blood pressure, pulse and ECG • Most common AE with NS2359: Weight loss
Authors' conclusions	A significant superiority of NS2359 cannot be demonstrated regarding the primary and secondary end points.
Comments	• No transferability of the study population to the general population • Small sample size (limited power for finding differences) • Furthermore, the study only includes a low dosage of NS2359, which may be insufficient for the treatment of ADHD patients. • Problem: optimal dosing • Short therapy phase • Drop-out rate in the Pl group > 20 %

ADHD = Attention deficit/hyperactivity disorder. ADHD-RS = ADHD-Rating Scale. AE = Adverse event. ANOVA = Variance analysis. BROWN-AS = Brown Adult Scale. CAARS = Conners Adult ADHD Rating Scale. CDR = Cognitive Drug Research. CGI = Clinical Global Impression. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ECG = Electrocardiogram. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. ITT = Intention-to-treat. n. i. = no information. N = Number. NS = NS2359. Pl = Placebo. RCT = Randomised controlled trial. SD = Standard deviation.

9.6.2 Metaanalyses

Study description	Metaanalysis
Study type (assessed)	Systematic review and metaanalysis
Level of evidence (assessed)	Ia
Source	Faraone SV, Spencer T, Aleardi M et al. Meta-Analysis of the efficacy of Methylphendidate for treating adult attention-deficit/hyperactivity disorder. Journal of Clincal Psychiatry 2004; 24(1): 24-29.
Question/objective	Effectiveness of MPH in adult patients with ADHD compared with Pl
Methods	
Literature search	• Databases: PubMed, Ovid, ERIC, Cinahl, MEDLINE, PreMEDLINE, Cochrane database, e-psyche, social science abstracts • No limitation of the year of publication • The literature index of the identified article was searched for relevant publications • Search strategy missing
Inclusion and exclusion criteria: Study design	Inclusion: • Randomised, placebo-controlled, double-blind studies • To ascertain the relevance of the studies with respect to the current diagnostic concepts, studies were used that selected the patients according to the diagnostic criteria of DSM-III, DSM-III-R or DSM-IV
Inclusion and exclusion criteria: Patients	Inclusion: Adults with ADHD
Inclusion and exclusion criteria: Intervention	Inclusion: MPH against Pl
Inclusion and exclusion criteria: Target criteria	Inclusion: Only studies were included that stated the average values or standard deviation either as a change or as the end point for the medication or the Pl
Quality assessment of the studies	No quality assessment
Data extraction	No information
Data analysis	• The homogeneity of the studies was not mathematically examined, the difficulties of comparability are only discussed in words; the "concept of effect size" (concept of the effect strengths) is developed to make the studies comparable • Every variable size in every study is stated as SMD between medication and Pl • The SMD is calculated from the difference of the average end point values of the medication group and the Pl group • When studies report change values (end point scores minus baseline scores), then the SMD is calculated from the difference of the change values • If studies only report end point scores, then the SMD is calculated from the end point scores • The studies are weighted according to the precision of the SMD estimator • For the metaanalysis, the estimator-based DerSimonian & Laird Random Effects Model is used • Excluding an oversized effect of an individual study by calculating a pooled SMD in which one study each was omitted • Estimation of the publication bias according to the method of Egger et al. • Some studies report more than one variable; in those cases, deviating estimators are adjusted according to the formula of Huber, to dissolve intrafamilial cluster formation
Assessed literature sources	
Overview	• 6 studies (4 with crossover design, 2 with parallel design) • These 6 studies include 10 medication-to-Pl comparisons that can be used to calculate the strength of effect • Mattes et al. 1984, Wender et al. 1985, Gualtieri et al. 1985, Spencer et al. 1995, Kuperman et al. 2001, Spencer and Biederman 2002
Participants	Number of patients in all studies N = 235; N(MPH) = 140; N(Pl) = 113 • Mattes et al.: N(MPH) = 8; N(Pl) = 8; average age in years = no information, proportion of male patients: No information; diagnosis system: DSM-III • Wender et al. N(MPH) = 37; N(Pl) = 37; average age in years = 31, proportion of male patients: 54; Diagnostic system: DSM-III

Faraone et al. 2004 – continued

Participants *(continued)*	• Gualtieri et al. N(MPH) = 8; N(PI) = 8; average age in years = 27, proportion of male patients: 100; diagnosis system: DSM-III • Spencer et al. N(MPH) = 23; N(PI) = 23; average age in years = 40, proportion of male patients: 43; diagnostic system: DSM-III-R • Kuperman et al.: N(MPH) = 8; N(PI) = 11; average age in years = 31, proportion of male patients: 75; diagnostic system: DSM-IV • Spencer and Biederman: N(MPH) = 56; N(PI) = 26; average age in years = 39, proportion of male patients: 59; diagnostic system: DSM-IV
Country	No information
Inclusion of baseline, titrations, assessment and phase-out phase	• Definition "highly dosed MPH": 0.9 mg/kg daily or more • Average daily dose (low-dosed) is 44 mg (0.63 mg/kg daily) • Average daily dose (high dosed) is 70 mg (0.63 mg/kg daily) • 1 study contains no information on the dosing (Kuperman et al.) and is excluded from the comparison "Amount of the dosing vs. strength of effect" • Best/fixed dosing method stated
Assessment of the studies after the intervention	No information
Target variables	Primary end points: Efficiency of the use of MPH in adults with ADHD • Global improvement: 1 study • Global rating: 1 study • Global assessment scale: 1 study • ADHD symptoms: 1 study • ADHD Rating scale hyperactivity: 1 study • ADHD Rating scale impulsiveness: 1 study • ADHD Rating scale inattention 1. Study • ADHD Rating scale total: 2 studies With 2 scores there is self-assessment, with 7 scores, the physician assesses
Methodological quality of the studies	Studies are not assessed
Results for the target criteria	• The average strength of effect of the SMD is significant at 0.9 ($z = 4.3$, $p < 0.001$) • The Egger Publication Bias statistic is low (0.5) and not significant ($t = 0.2$, $p = 0.9$) • The larger and more precise a study, the visibly stronger the effect and, therefore, the stronger the evidence for the difference between MPH/Pl • The SMD varies from -0.24 to 2.3 • The strength of effect of the crossover studies is not significantly greater than that of the parallel studies • The following data have no effect on the study result. Time of study, sex ratio, length of the study protocol (all $p > 0.05$)
Authors' conclusions	
Comments	• Some studies such as Levin et al. 2001, Tenenbaum et al. 2002 and Bouffard et al. 2003 were neither included nor mentioned • Included studies are differently weighted; the metaanalysis was calculated according to the values published there • Studies such as those of Spencer are given more weight due to the use of a greater number of measurement scales • Inclusion of the Egger Publication Bias • The study question was answered: MPH is effective in the treatment of adult ADHD patients, especially when the correct dose adjustment to weight is applied (adjustment derived from paediatric studies) • Attempt to explain how the SMD should be interpreted (according to the guidelines of Cohen 1988) • The quality of the included studies was not checked

ADHD = Attention deficit/hyperactivity disorder. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders. DSM-III = Diagnostic and Statistical Manual of Psychological Disorders, version 3. DSM-III-R = Diagnostic and Statistical Manual of Psychological Disorders, 3rd revision. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ERIC = Educational Resources Information Center (database). n. i. = no information. MEDLINE = Medical Literature Analysis and Retrieval System Online (database). MPH = Methylphenidate. N = Number. Pl = Placebo. SMD = Average standard deviation.

Study description	Metaanalysis
Study type (assessed)	Metaanalysis with systematic literature search based on RCTs
Level of evidence (assessed)	Ia
Source	Kösters M, Becker T, Kilian R et al. Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. Journal of Psychopharmacology 2009; 23: 733-744.
Question/objective	Effectiveness of drug treatment with MPH in adults with ADHD
Methods	
Literature search	• Search in MEDLINE, Cochrane Clinical Trial Register, PsycINFO • No restriction with respect to year of publication • Manual search for references of all identified articles • 1. Search May 2006, weekly update with databases autoalert function • All databases were again searched in January 2008 • 2 independent reviewers sought and extracted the data without blinding of author and journal
Inclusion and exclusion criteria: Study design	Inclusion: • Placebo-controlled, double-blind studies that examined the effectiveness of MPH in adults with ADHD • Only English and German studies • Only studies that include DSM-III, DSM-IV or ICD for the diagnosis of ADHD and end point parameters, that describe ADHD symptoms
Inclusion and exclusion criteria: Patients	Inclusion: Adult patients with ADHD
Inclusion and exclusion criteria: Intervention	Inclusion: MPH against Pl
Inclusion and exclusion criteria: Target criteria	Inclusion: Only studies with end point parameters that describe ADHD symptoms
Quality assessment of the studies	No information
Data extraction	No information
Data analysis	• Calculation of an estimator: d/SD, where d = M1-M2 (M1 and M2 are the averages of the postscores of a study in the MHP and Pl group) and SD is the pooled SD between the treatment and the control group • The effects are corrected according to the formula of Hedges 1981 to avoid a bias due to small sample size • Only variables that are relevant to ADHD symptoms are estimated • If several values are reported, then an average strength of effect is calculated • Where possible, additional effect estimators are stated for the subgroups • Subgroup formation in the manner of the rating scales (self- or third-party estimate) • Subgroup formation for crossover and parallel study design • Pooling of the strengths of effect using the DerSimonian & Laird estimator-based random-effect models • Heterogeneity test • Statistical significance of the heterogeneity is examined with the chi-square test • Visual presentation of the results using funnel and normal quantile plots • Performance of statistical test according to the method of Begg 1994 for uncovering publication bias and correction of the publication bias to incorporate unpublished results with presumably poorer results -> effect will be estimated more carefully
Assessed literature sources	
Overview	16 studies included Gualtieri et al. 1985, Kuperman et al. 2001, Levin et al. 2006, Levin et al. 2007, Mattes et al. 1984, Reimherr et al. 2007, Schubiner et al. 2007, Spencer et al. 1995, Spencer et al. 2005, Spencer et al. 2007, Tenenbaum et al. 2002, Wender et al 1985, Carpentier et al. 2005, Kooij et al. 2004, Bouffard et al. 2003, Jain et al. 2007

Kösters et al. 2009 – continued

Participant	Bouffard et al. 2003 • Number of randomised patients: 38 • Number of analysed patients: 30 • Average age: 34; drop-outs 21; 80 % male Carpentier et al. 2005: • Number of randomised patients: 25 • Number of analysed patients: 19 • Average age: 32, drop-outs 24; 88 % male Gualtieri et al. 1985: • Number of randomised patients: N. R. • Number of analysed patients: 19 • No further information Jain et al. 2007: • Number of randomised patients: 50 • Number of analysed patients: 39 • Average age: 38, drop-outs 22; 59 % male Kooij et al. 2004, average age (SD) 39; drop-outs: 0; 53 % male • Number of randomised patients: 45 • Number of analysed patients: 45 • Average age: 39, drop-outs 0; 53 % male Kuperman et al. 2001: • Number of randomised patients: 37 • Number of analysed patients: 8/11 • Average age: 31/32, drop-outs: No information Levin et al. 2006: • Number of randomised patients: 32/33 • Number of analysed patients: 31/32 • Average age: 40/39, drop-outs 34/24; 59/66 % male Levin et al. 2007: • Number of randomised patients: 53/53 • Number of analysed patients: 44/47 • Average age: 37/37, drop-outs 55/57; 83/83 % male Mattes et al. 1984: No information Reimherr et al. 2007: • Number of randomised patients: 47 • Number of analysed patients: 41 • Average age: 31, drop-outs 13; 66 % male Schubiner et al. 2007, Na(MPH/Pl) 24/24; Nb(MPH/Pl) 8/11; average age (SD) (MPH/Pl) 36/38; drop-outs 55/42; % male subjects (MPH/Pl) 88/92 Spencer et al. 1995: • Number of randomised patients: 25 • Number of analysed patients: 23 • Average age: 40, drop-outs 8; 44 % male Spencer et al. 2005: • Number of randomised patients: 104/42 • Number of analysed patients: 78/32 • Average age: 36/40, drop-outs 25/24; 60/55 % male Spencer et al. 2007: • Number of randomised patients: 168/53 • Number of analysed patients: 165/53 • Average age: 39/38, drop-outs 16/19; 60/51% male Tenenbaum et al. 2002: • Number of randomised patients: No information • Number of analysed patients: 24 • Average age: 42, drop-outs no information; 46 % male Wender et al 1985: • Number of randomised patients: N. R. • Number of analysed patients: 37 • Average age: 31, drop-outs: no information; 54 % male
Country	• The majority of studies (12) were performed in the USA. • 2 studies were performed in Canada • 2 studies were performed in the Netherlands

Kösters et al. 2009 – continued

Assessment of the studies after the intervention	Varying study durations (min. 5 days, max. 14 weeks) In 1 study (Spencer et al. 2007) treatment was administered only with dexmethylphenidate (study is only ruled out in the metaregression regarding the dose) In 15 of 16 studies the average daily dose is stated, (min. 20 mg daily, max. 82 mg daily), partially large differences
Target variables	ADHD symptom improvement
Results	
Methodological quality of the studies	No information
Results for the target criteria	Significant effect of the MPH treatment on the symptoms of ADHD in adults (d = 0.42; 95 % CI: 0.20-0.63) Significance varies in sensitivity analysis Heterogeneity of the studies: I^2 = 61 %, chi-square = 38.46, P < 0.001 Subgroup analysis Crossover/parallel design: • The strengths of effect in the two study designs (crossover: d = 0.44; 95 % CI: 0.27-0.60; parallel: d = 0.36; 95 % CI: -0.17-0.88) do not differ significantly from each other • Only the overall effect of the crossover studies differs significantly from the zero value • Heterogeneity in the parallel group studies (I^2 = 83 %) Subgroup analysis Self-/third-party assessment: • The strengths of effects in the two groups differ significantly from the zero value • No significant difference in the values between the self-assessment and the third-party assessment group (self-assessment d = 0.24; 95 % CI: 0.08-0.39; parallel: d = 0.46; 95 % CI: 0.2-0.72) • Homogeneity in the self-assessment group (I^2 = 0 %), heterogeneity in the third-party assessment group (I^2 = 83 %) Effect of the MPH dose on the strength of effect: Weighted regression analysis shows no significant effect of the average daily dose on the strength of effect (b = 0.008, p = 0.276) • No publication bias • Graphically not visible • No significant result of the Begg's rank test (p = 0.444) • Estimated variable is set to 144 Sensitivity analysis to examine the effect of the individual studies on the result: • Method: exclusion sensitivity plot • No study had a significant effect on the strength of effect Post hoc investigation of the effect of treatment duration on the strength of effect • No significant effect of the treatment duration on the strength of effect (b = -0.005, p = 0.242) Posthoc subgroup analysis ADHD patients with/without comorbidities
Authors' conclusions	Effectiveness of MPH compared with Pl, but not as strong as assumed so far
Comments	• Update of the metaanalysis of Faraone et al. • The problems of the publication bias especially with small samples and a high degree of heterogeneity is noted • CI of the calculation of the overall strength of effect in the two subgroup analyses (parallel/crossover, third-party/self-assessment) frequently includes 1 • No further explanations on the determination of the estimated variable • The strength of effect is only half the size of that of Faraone et al.

ADHD = Attention deficit/hyperactivity disorder. d = strength of effect. DSM-III = Diagnostic and Statistical Manual of Psychological Disorders, version 3. DSM-IV = Diagnostic and Statistical Manual of Psychological Disorders, version 4. ICD = International Classification of Diseases. n. i. = no information CI = Confidence interval. MPH = Methylphenidate. N. R. = Not relevant. Pl = Placebo. RCT = Randomised controlled trial. SD = Standard deviation.

Study description	Metaanalysis
Study type (assessed)	Metaanalysis with systematic literature search based on RCTs
Level of evidence (assessed)	Ia
Source	Meszaros A, Czobor P, Balint S et al. Pharmacotherapy of adult attention deficit hyperactivity disorder (ADHD): a meta-analysis. International Journal of Neuropsychopharmacology 2009.
Question/objective	Efficacy of drug treatment in adults with ADHD
Methods	
Literature search	• Search in MEDLINE using the PubMed search interface • Search period: 1994 to 2007 • Language: English • Check of the literature index for relevant publications • No supplementation by manual search
Inclusion and exclusion criteria: Study design	Inclusion: • Randomised, placebo-controlled, double-blind studies • Crossover studies estimate to what extent the data before the change of the therapy is useful for the analysis. Exclusion: • Pilot studies • Studies that relate to medications for which efficacy has not yet been tested.
Inclusion and exclusion criteria: Patients	Inclusion: Adult patients with ADHD
Inclusion and exclusion criteria: Intervention	Inclusion: • Intervention duration ≤ 12 weeks • Pharmacotherapy versus placebo
Inclusion and exclusion criteria: Target criteria	No information
Quality assessment of the studies	No information
Data extraction	Recording of the differences in the degree of severity of the symptoms of individual studies
Data analysis	• Calculation of the strength of effect according to Cohen • Cohen's d: Difference in the improvement of the trial and the controlgroups divided by the pooled standard deviation. • Effectiveness of the respective medication according to Cohen's d: small (< 0.3), medium (0.3-0.6) large (> 0.7) • The strengths of effects of the individual studies were combined using a random effects model into a shared, pooled effect estimator (placebo vs. intervention). The results were presented separately according to stimulants and non-stimulants. • Metaanalysis based on van Houwelingen et al.: linear regression model • DerSimonian & Laird estimator-based random effects model • Consideration of the publication bias based on funnel plots (Begg and Mazumdar)
Assessed literature sources	
Overview	12 studies (11 publications, 1 publication contains the analysis of 2 RCTs) Wilens et al. 1996, Wilens et al. 2001, Kuperman et al. 2001, Michelson et al. 2003, Spencer et al. 2005, Biederman et al. 2006, Weisler et al. 2006, Spencer et al. 2001, Spencer et al. 2001, Spencer et al. 2007, Adler et al. 2009
Participants	Number of patients in all studies N = 1991; N(PI) = 694; N(drug) = 1297 Average number per study: N(PI) = 57.8 (SD = 40.8); N(drug)[e] = 68.2 (SD = 41.9) Average age of the patients in years: N(PI) = 39.3 (SD = 16.5); N(drug = 37.7 (SD = 24.1) Average proportion of male patients: N(PI) = 58.6 %; N(drug) = 57.8 %
Country	No information

e N(PI) and N(drug) corrected.

Meszaros et al. 2009 – continued

Assessment of the studies after the intervention	The study period varies between 4 and 10 weeks. Active ingredients: desipramine (1 study), bupropion (3 studies), methylphenidate (3 studies), atomoxetine (1 study, 2 RCTs), amphetamine (3 studies), dexmethylphenidate (1 study) 1 study has a 3-armed design. 3 studies have a 4-armed design. 19 arms with medication 12 placebo arms
Target variables	Primary end points: ADHD rating scale: 5 studies CGI: 2 studies CAARS: 2 studies AISRS: 3 studies Secondary end points: CGI: 10 studies WURS: 1 study ADHD rating scale: 1 study AISRS: 1 study CAARS: 3 studies Q-LES-Q: 1 study
Results	
Methodological quality of the studies	No information
Results for the target criteria	• Pooled strengths of effect 0.65; 95 % CI (0.48-0.81); p < 0.0001 compared with a placebo Results for the stimulants: • Pooled strength of effect for stimulants assuming the lowest dosage in studies with variable dosage: 0.67; 95 % CI (0.36-0.97); p < 0.0001 in comparison with the placebo • Pooled strength of effect for stimulants assuming the highest dosage in studies with variable dosage: 0.69; p < 0.0001 in comparison with the placebo • The largest strengths of effects are achieved with MPH treatment in large study populations: 1.41; 95 % CI (1.02-1.80) • The second largest strength of effect is achieved with amphetamine treatment, but with a small study population: 1.05; 95 % CI (0.24-1.86) • The study by Spencer et al. 2007 with 3 different amphetamine dosages and a large study population achieves the greatest strength of effect with the largest dosing at 60 mg: 0.44; 95 % CI (0.08-0.81) • In the study by Adler et al. 2008 with 3 different lisdexamfetamine dosages, the greatest strength of effect is achieved with the highest dosage at 40 mg: 0.82; 95 % CI (0.43-1.21) Results, non-stimulants: • Pooled strength of effect, non-stimulants: 0.59; 95 % CI (0.37-0.81); p < 0.0001 compared with the placebo • Largest strength of effect (small study size): 1.73; 95 % CI (1.01-2.46) • The 3 studies with bupropion show a strength of effect of 0.66; 95% CI (0.02-1.29), 0.15; 95 % CI (-0.69-0.98) and 0.60; 95 % CI (0.29-0.92) • The two studies with atomoxetine have the largest study populations and have a strength of effect of 0.36; 95 % CI (0.12-0.60) and 0.38; 95 % CI (0.12-0.63)
Authors' conclusions	Pharmacotherapy is superior to the placebo
Comments	• Examination of the homogeneity of the studies is not described in the methods section • Sensitivity and subgroup analyses were not performed. • The 95 % CI covers the 1 in 5 studies. • The literature search was limited to MEDLINE • The selection of the random effect model was not justified. • The statistics and quality of the included studies were not described. • The review is not performed according to a standardised method (e.g. Cochrane) • No graph of the funnel plot

ADHD = Attention deficit/hyperactivity disorder. AISRS = Adult ADHD Investigator Symptom Rating Scale. CAARS = Conners Adult ADHA Rating Scale. CGI = Clinical Global Impression Scale. n.i. = no information. CI = Confidence interval MEDLINE = Medical Literature Analysis and Retrieval System Online (database). MPH = Methylphenidate. N = Number. Pl = Placebo. Q-LES-Q = Quality of life enjoyment and satisfaction questionnaire. RCT = Randomised controlled trial. WURS = Wender Utah Rating Scale.

Study description	Metaanalysis
Study type (proven)	Metaanalysis with systematic literature search based on RCTs
Level of evidence (proven)	Ia
Source	Peterson K, McDonagh MS, Fu R. Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. Psychopharmacology 2008; 197:1-11
Question/objective	Estimation of the relative advantages and disadvantages of competing drug treatments in adult patients with ADHD
Methods	
Literature search	• English-language publications (RCT) • Literature search in Cochrane Centre Register of Controlled Trials (1st quarter 2007), Cochrane Database of Systematic Reviews (1st quarter 2007), MEDLINE (1966 to 3rd week of March 2007). EMBASE (2nd quarter 2004), PsycINFO (1974 to 4th week of March 2007) • Search terms: methylphenidate, Concerta, Metadate, Methylin, Ritalin, dexmethylphenidate, Focalin, amphetamine, Adderall, dextroamphetamine, Dexedrine, atomoxetine, Strattera, Wellbutrin, bupropion, modafinil, Provigil, attention deficit disorder with hyperactivity, attention deficit disorder, attention deficit, ADHD • No restriction with respect to study duration or sample size • Check of the literature index for relevant publications • Drug information from drug producers were queried via DERP • All literature citations were imported in EndNote 9.0 • 2 independent reviewers decided on inclusion and exclusion
Inclusion and exclusion criteria: Study design	Inclusion: Randomised, placebo-controlled, double-blind study
Inclusion and exclusion criteria: Patients	Inclusion: Adult patients with ADHD
Inclusion and exclusion criteria: Intervention	Inclusion: • Stimulants with the active ingredients amphetamine, dextroamphetamine, modafinil • Non-stimulants with the active ingredients atomoxetine and bupropion
Inclusion and exclusion criteria: Target criteria	No information
Quality assessment of the studies	• Quality check of the studies by means of predefined criteria based on the criteria of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination • The internal validity of the studies is assessed by means of the following data: randomisation, concealment, blinding, comparability of the groups at the start of the study, drop-outs, crossover design, compliance with the terms of the study , lost-to-follow-up, ITT analysis
Data extraction	• 2 independent reviewers in the data extraction • Data extraction of the following criteria: study design, setting, characteristics of the population, exclusion criteria, intervention and comparative intervention, number of screened patients, included patients, lost-to-follow-up, methods of the end point assessment, results of the end points, ITT analysis
Data analysis	• End points for the assessment of effectiveness: Incidence of the clinical response and change of the ADHD symptoms from baseline to the end of the study • Grouping of the studies in 4 categories according to active ingredients • For all endpoints, the data of the placebo-controlled studies are pooled for each active ingredient to calculate the RR with a 95% CI. • For the sensitivity analysis, the risk differences are calculated for all results. • Check of the heterogeneity of the study using Cochran's Q-Test • Performance of the metaanalysis with the random effects model • Chi-square independence test for examining the RR for clinical response of the patients to ADHD medications (divided into medication groups) vs. placebo • Chi-square independence test for examining the RR between medication groups • Presentation of these results in a funnel plot • Subgroup analysis for patients with medication abuse

Peterson et al. 2008 – continued

Data analysis *(continued)*	• Subgroup analysis regarding target criterion; sensitivity analysis with studies on medication abuse • Subgroup analysis regarding type of questioning (investigative/self-reporting); sensitivity analysis with studies on medication abuse • Egger's test and funnel plot for identification of a publication bias • Regression model for link between dependency status and medication type • Pooled RR for ADHD medications vs placebo, chi-square independence test for the characteristic expressions of medication/placebo and side effects, where one medication is explicitly listed (atomoxetine), but the others are combined in groups • All analyses are performed with Stata V9.0
Assessed literature sources	
Overview	• 22 included studies (21 publications, publication of Michelson et al. 2003 contains 2 studies) • Biedermann 2006, Michelson (I) 2003, Michelson (II) 2003, Carpentier 2005, Kooij 2004, Levin 2001, Levin 2006, Levin 2007, Paterson 1999, Schubiner 2002, Spencer 1995, Spencer 1998, Spencer 2001, Spencer 2005, Spencer 2007, Reimherr 2005, Reimherr 2007, Weisler 2006, Wilens 2001, Wilens 2005, Weiss 2006, Wender 1985,
Participants	• Different study sizes (N(min) = 22; N(max) = 280) • Proportion of male participants in all studies: 59 % • Average age over all studies: 38 years • Only 41 % of the studies report the ethnic composition of the study population: mostly white, with predominance of the combined ADHD type • Most common ADHD subtype: combined subtype • Most common comorbidities: Anxiety disorders
Country	No information
Dosing	No information
Assessment of the studies after the intervention	• Follow-up fluctuates between 2 and 13 weeks • Active ingredients: Atomoxetine (2 studies), tomoxetine (1 study), bupropion (3 studies), dextroamphetamine (2 studies), MPH (11 studies), mixed amphetamine (2 studies), dexmethylphenidate (1 study) • Classification of the medication in groups (atomoxine, long-acting forms of bupropion, fast-acting stimulants, long-acting stimulants)
Target variables	End points: • ADHD-RS: 11 studies • WRAADS: 2 studies • GSI: 1 study • CGI-I-ADHD: 1 study • CGI: 3 studies • Physician's Global Rating Scale: 1 study • AISRS: 1 study • Physician-rated moderate improvement: 1 study • No information: 3 studies
Results	
Methodological quality of the studies	Consistent study quality over all included studies: • Study design insufficiently described • Too little information on randomisation and the method blinding allocation • Only a few studies state performing an ITT analysis • Exclusion criteria are often not reported • In all studies double blinding • 15 studies in the parallel design (14 publications) • 7 studies in crossover design • A small bias must be assumed in crossover studies due to the carry-over effect.
Results for the target criteria	• The RR for clinical response in ADHD medications vs. placebo is more probable for medication across all medication groups; RR = 4.32 for fast-acting stimulants (95 % CI 3.03-6.16); RR = 1.87 in slow-acting forms of bupropion (95 % CI 1.36-2.58); RR = 1.35 in slow-acting stimulants (95 % CI 0.997-1.84) • The indirect comparison of the RR in the medicated groups shows significant differences (chi-square = 24.15, p = 0.0001), the fast-acting stimulants being superior to the other medication groups.

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Results for the the target criteria *(continued)*	• A lesser clinical response of patients, who practice medication abuse than in other patients (RRR = 0.53; 95 % CI 0.38-0.74); immediate discontinuation of MPH was effective in the treatment of ADHD symptoms (RR = 2.72; 95 % CI 1.36-5.42), no effectiveness with delayed elimination (RR = 0.83; 95 % CI 0.60-1.14) • ADHD medications were less effective compared with the placebo for the target criterion "30% or greater reduction in the ADHD-RS Total Score" than the specification for other target criteria (RRR = 0.65; 95 % CI 0.44-0.96); no significant result with inclusion of studies with substance-abusing patients • Greater effectiveness of the ADHD medication in questioning, compared with self-assessment (RRR = 1.72; 95 % CI 1.20-2.45); no significant result with inclusion of medication-abusing patients • Egger's test and funnel plot do not identify a publication bias • Chi-square independence test on pooled RR • RR for sleep disorders is significantly higher with the ADHD medication than with the placebo group (chi-square = 2.62; p = 0.45), no differences within the groups • RR for loss of appetite is significantly higher in the ADHD medication group (atomoxetine, fast-acting and slow-acting stimulants) than in the placebo group (chi-square = 0.78; p = 0.68); here the RR for slow-acting stimulants is significantly greater than for fast-acting stimulants (RRR = 4.14; 95 % CI 1.41;12.11) and atomoxetine; no data for loss of appetite in studies with slow-acting bupropion • Risks in a treatment discontinuation adjusted for treatment duration are not significantly higher in the ADHD medication group than in the placebo group (chi-square = 2.08; p = 0.5559)
Authors' conclusions	MPH is superior to placebo therapy.
Comments	• First indirect comparative metaanalysis of competing ADHD medications vs. placebo • A study with scientific, occupational, social and legal end points was not found • In many studies, the ADHD type was not reported • The absence of a publication bias is doubted due to the small number of studies • The included studies contain no information regarding sudden death

ADHD = Attention deficit/hyperactivity disorder. ADHD-RS = ADHD Rating Scale. AISRS = Adult ADHD Investigator Symptom Rating Scale. CGI = Clinical Global Impression Scale. CGI-I-ADHD = Clinical Global Impression Improvement Scale ADHD. DERP = Drug Effectiveness Review Project. EMBASE = Experta Medica Database. GSI = Global Severity Index. ITT = Intention-to-treat. n. i. = no information. CI = Confidence interval. MEDLINE = Medical Literature Analysis and Retrieval System Online (database). MPH = Methylphenidate. N = Number. RCT = Randomised controlled trial. RR = Relative risk. RRR = Relative risk reduction. WRAADS = Wender Reimherr ADHD Scale.

Study description	Systematic review
Study type (assessed)	Systematic review
Level of evidence (assessed)	Ia
Source	Verbeeck W, Tuinier S, Bekkering GE. Antidepressants in the treatment of adult attention-deficit hyperacitvity disorder: a systematic review. Advances in Therapy 2009; 26(2): 170-184.
Question/objective	To determine the effect[f] of antidepressants in the treatment of adults with ADHD
Methods	
Literature search	• Databases: Cochrane Library (Central), PubMed, PsycINFO • Supplementation by manual search • Search terms: antidepressants, lithium, attention deficit disorder with hyperactivity, attention deficit disorder, ADHD • The search was performed August 2008 • Language: English
Inclusion and exclusion criteria: Study design	Inclusion: Controlled studies Exclusion: No information

f "To determine the" is interpolated, according to the source it should just start with "The efficacy…".

Veerbeck et al. 2009 – continued

Inclusion and exclusion criteria: Patients	Inclusion: Adults Exclusion: No information
Inclusion and exclusion criteria: Intervention	Inclusion: Antidepressants and lithium placebo Exclusion: No information
Inclusion and exclusion criteria: Target criteria	No information
Quality assessment of the studies	Quality assessment of the RCTs: • Does the randomisation use an accepted procedure? • Is the allocation blinded? • Is this a double-blinded study? • Are the groups comparable at the start of the study? • Will an ITT analysis be performed, e.g. are all randomised patients included in the final analysis? Each question can be answered with a "yes", a "no" or "?".
Data extraction	• Data are extracted by 2 reviewers • Data that is extracted from the RCTs: • Study design, patient characteristics, exclusion criteria, type and duration of the intervention, number of screened patients, number of patients lost-to-follow-up, diagnostic criteria, methods of the end point assessment, results of the effectiveness and the end points • Data from unrandomised studies will only be discussed.
Data analysis	• Data of individual RCTs are pooled, if possible. • For this purpose the difference of the end points between intervention and placebo is calculated for each study. • Input of the differences in a random effect model. The approach is based on the Cochrane Collaboration • For graphic illustration, the results of the metaanalysis are presented as a forest plot.
Assessed literature sources	
Overview	• 8 RCTs: 5 studies with Bp 1 study with LIT 1 study with PAR 1 study with despiramine • Included RCTs: Wilens et al. 1996, Kuperman et al. 2001, Wilens et al. 2001, Dorrego et al. 2002, Wilens et al. 2005, Reimherr et al. 2005, Levin et al. 2006, Weiss et al. 2006.
Participants	• The number of screened participants ranges from 32 to 526 patients in total. • 2 studies (Wilens et al. 2005 and Reimherr et al. 2005) do not provide a number.
Country	No information
Dosing	Average dosing in the individual studies • Despiramine: 147 mg • Bp: 300 mg, 2-times 200 mg, 393 mg, 298 mg, max. 400 mg • LIT: 0.68 mg/l • PAR: 40 mg daily • Despiramine: max. 20 mg twice daily.
Assessment of the studies after the intervention	No information
Target variables	Primary and secondary end points • CGI • ADHD-RS • HAM-D, HAM-A • Beck Scale • CGI-I • Neuropsychological tests

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Target variables *(continued)*	• CAARS • Irritability Scale • CAARS-S:S • CAARS-O:S • WRAADS • Urine toxicology • CGI-I-ADHD • CGI-I-Int • ADHD-RS
Results	
Methodological quality of the studies	• The standardised randomisation is unclear in all studies, likewise the concealment • All studies are blinded • The groups of all studies are comparable at the start of the study. • 6 studies perform a "true" ITT analysis • Most studies have clinical and methodological weaknesses (e.g. exclusion of patients with comorbidities, no description of the randomisation) • Most studies contain no assessment of the ADHD symptoms, e.g. of spouses or family members • The duration of the studies is set too short. • The dosing of the studies is mostly suboptimal. • The influence of the industry is unclear, but is mostly not analysed in this review.
Results for the target criteria	Results for the RCTs • Wilens et al. 1996: p = 0.0001 (CGI-I and ADHD-RS) • Kuperman et al. 2001: p = 0.14 (CGI); p = 0.69 (ADHD-RS) • Wilens et al. 2001: p = 0.007 (CGI); p = 0.02 (ADHD-RS) • Dorrego et al. 2002: 95 % CI -12% to 34 % difference between LIT and MPH • Wilens et al. 2005: p = 0.03 (CGI); p = 0.004 (ADHD-RS) • Reimherr et al. 2005: p = 0.14 • Levin et al. 2006: p = 0.42 • Weiss et al. 2006: p = 0.001 (CGI-I); p = 0.003 • All studies with Bp use the CGI-I scale. This data will be entered in a Random Effects Model Pooled OR = 2.42 95 % CI (1.09-5.36) • Patients with a bupropion treatment are 2.4-times more likely to achieve an improvement of the clinical end points compared with patients in a placebo treatment. Results of the open studies: • Bp can be useful as an active ingredient of 2nd choice for ADHD without complication and should be used in ADHD with comorbid unipolar depressions or bipolar disorders, substance abuse or patients who wish to stop smoking. • Tricyclic antidepressants: Can be administered in combination therapy with stimulants. • Monoaminoxidase inhibitors: not suitable in the treatment of ADHD. • Selective serotonin re-uptake inhibitors: show no effectiveness in the treatment of ADHD
Authors' conclusions	There is further need for research since only a few studies have been performed on the use of antidepressants in adults with ADHD. Only treatment with Bp shows an average strength of effect, but it is still lower than for stimulants.
Comments	• No heterogeneity tests • No subgroup and sensitivity analyses • Qualitative assessment very brief and not profound • Methodological description of the metaanalysis not extensive • No justification of why the Random Effects Model was used

ADHD = Attention deficit/hyperactivity disorder. ADHD-RS = ADHD Rating Scale. Bp = Bupropion. CAARS = Conners Adult ADHA Rating Scale. CAARS = Conners Adult ADHA Rating Scale/Self-rated. CAARS-O = Conners Adult ADHA Rating Scale/Observer-rated. CGI = Clinical Global Impression Scale. CGI-I = Clinical Global Impression Improvement scale. HAM-A = Hamilton Scale for Anxiety Disorders. HAM-D = Hamilton Scale for Depression. ITT = Intention-to-treat. n. i. = no information. CI = Confidence interval. LIT = Lithium. OR = Odds Ratio. PAR = Paroxetine. RCT = Randomised controlled trial. WRAADS = Wender Reimherr ADHD Scale.

9.6.3 Economic studies

Study description	Metaanalysis, economic study, review
Study type (assessed)	Systematic review
Level of evidence (assessed)	N. R.
Source	Matza, LS, Paramore C, Prasad M. A review of the economic burden of ADHS. Cost Effectiveness and Ressource Allocation 2005; 3 (5):1-9
Question/objective	Assessment and summary of the literature regarding economic costs of ADHD and possible economic benefit in the treatment of this disease
Methodology	
Literature search	Search in MEDLINE Keywords: "ADHD" (also written out and individual word components), "cost", "costs", "economic", "economics" Direct contact with the authors to view conference presentations or as yet un-published articles 22 relevant studies were included (published original studies, economic assessments, unpublished conference presentations)
Inclusion and exclusion criteria: Study design	n. i.
Inclusion and exclusion criteria: Patients	n. i.
Inclusion and exclusion criteria: Intervention	n. i.
Inclusion and exclusion criteria: Target criteria	Exclusion: ADHD studies that contain no costs
Quality assessment of the studies	No information
Data extraction	No information
Data analysis	The health costs of the studies originate from 1987-1998 Updating of the costs and adjustment to 2004 in US-dollars, based on the proportion for medical costs in the consumer price index Cost data sources: • Private insurances (Guevara et al. 2001, Swensen et al. 2003, Swensen et al. 2004) • Agencies for health services (Mandell et al. 2003, Kelleher et al. 2001) • Private insurances and agencies for healthcare services (Burd et al. 2003, Leibson et al. 2001) • National representative household polls (Chan et al. 2002) • Literature and expert opinions (Marchetti et al. 2001) Cost types: • Direct medical costs • Listing of various additional costs ○ Additional costs for affected families ○ Costs due to increased criminality ○ Costs due to comorbidities ○ Costs due to accidents ○ Loss of work costs ○ Cost effectiveness of treatments of ADHD symptoms
Assessed literature citations	
Overview	Birnbaum et al. 2005, Burd et al. 2003, Chan et al. 2002, Guevara et al. 2001, Kelleher et al. 2001, Leibson et al. 2001, Leslie et al. 2001, Mandell et al. 2003, Marchetti et al. 2001, Secnik et al. 2005, Swensen et al. 2003, Swensen et al. 2004, Gilmore & Milne 2001, Novartis data on file (2000; referred to in Lord & Paisley 2000), Zupanic et al. 1998
Participants	Birnbaum et al. 2005: • ADHD patients: N = 1,219, ages between 7-44 years, • Their families: N = 3,692, ages below 65 • Matched control without ADHD: N = 121 • Matched controls of the families N = 3,692 • Matching with regard to age, sex, occupational status, geographical location, address (and again occupational status)

Matza et al. 2005 – continued

Participants *(continued)*	Secnik et al. 2005: • Ages between 18-64 • ADHD patients: N = 2,252 • Controls performed (regarding sex, age, statistical cluster areas, type of insurance coverage) without ADHD: N = 2,252 Swensen et al. 2004: • Ages between 0-64 years • ADHD patients: N = 1,308 • Controls performed (regarding sex, age, location and occupational status) without ADHD: N = 1,308
Country	Mostly the USA
Inclusion of baseline, titration, assessment and phase-out phase	N. R.
Assessment of the studies after the intervention	N. R.
Target variables	Annual medical costs for adults and children with ADHD
Results	
Methodological quality of the studies	Not assessed
Results for the target criteria	The annual medical costs for adults with ADHD are significantly higher than those in the matched control groups Individual results of the studies Birnbaum et al. 2005: • Examination of the additional costs due to ADHD (= cost difference between the ADHD patients and the control group) • Annual average direct additional costs of the ADHD treatment: 674 US-dollars (girls) and 745 US-dollars (boys); in total additional costs 0.53 billion US-dollars (girls) and 1.06 billion US-dollars (boys); 412 US-dollars (women) and 529 US-dollars (men); total additional costs 0.13 billion US-dollars (women) and 0.40 billion US-dollars (men); • Other average annual direct additional treatment costs: 865 US-dollars (girls) and 990 US-dollars (boys); total additional costs 0.80 billion US-dollars (girls) and 2.0 billion US-dollars (boys); 2,609 US-dollars (women) and 3,022 US-dollars (men); total additional costs 0.67 billion US-dollars (women) and 1.46 billion US-dollars (men) Secnik et al. 2005: • Adults with ADHD (effect of the comorbidities is controlled) cause higher outpatient costs (3,009 US-dollars vs. 1,491 US-dollars), higher inpatient costs (1,259 US-dollars vs. 514 US-dollars), higher costs for pharmaceuticals (1,673 US-dollars vs. 1,008 US-dollars) and higher annual total treatment costs (5,651 US-dollars vs. 2,771 US-dollars) as the matched controls without ADHD Swensen et al. 2003: Average annual direct treatment cost for the ADHD group: 2,046 US-dollars (SD = 3,474 US-dollars) vs. 703 US-dollars (SD = 2,215 US-dollars) for the matched control group without ADHD ($p < 0.0001$) Swensen et al. 2004: • Average annual direct treatment cost for children with ADHD: 1,747 US-dollars vs. 577 US-dollars for the matched control group without ADHD ($p < 0.05$) • Average annual direct treatment cost for adolescents with ADHD: 2,230 US-dollars vs. 783 US-dollars for the matched control group without ADHD ($p < 0.05$) • Average annual direct treatment cost for adults with ADHD: 4,929 US-dollars 1,473 US-dollars for the matched control group without ADHD ($p < 0.05$) Gilmore and Milne 2001: Costs per gained QALY in MPH treatment vs. no treatment vary from 15,509 US-dollars to 19,281 US-dollars when considering short- and medium-term effects with MPH. In sensitivity analyses, the costs per gained QALY vary from 9,850 US-dollars to 9,101 US-ollars Novartis data on file (2000; referred to in Lord et Paisley 2000): Costs per gained QALY in MPH treatment vs. no treatment are 27,766 US-dollars

Matza et al. 2005 – continued

Results for the the target criteria *(continued)*	More additional costs • Additional costs of affected families: Swensen et al. 2003: Families, whose members are affected by ADHD, are sick 1.6-times more often, cause direct per capita medical costs that are twice as high (2,740 US-dollars vs. 1,365 US-dollars), cause higher indirect costs (illness and absence times 888 US-dollars vs. 551 US-dollars); Birnbaum et al. 2005: estimated 6.78 billion US-dollars in additional costs for members of families with children who are afflicted with ADHD: estimated 12.10 billion US-dollars additional costs for members of families with adults who are afflicted with ADHD • Costs due to increased criminality: Swensen et al. 2001: Average total costs due to criminal actions are clearly higher for ADHD patients than for controls (12,868 US-dollars vs. 498 US-dollars): Costs due to accidents • Swensen et al. 2004: The accident-specific costs for adults are significantly higher for ADHD patients than in the control group (642 US-dollars vs. 194 US-dollars) • Absence from work costs: Birnbaum et al. 2005: Costs of absence from work for women: 1.20 billion US-dollars; costs of absence from work for men: 2.26 billion US-dollars • Costs due to comorbidities: Burd et al. 2003: annual costs per patient rise annually (358 US-dollars for depression conditions, 258 US-dollars for "contrariness" disorder, 541 US-dollars for bipolar disorder, 488 US-dollars for disturbed social behaviour, 499 US-dollars for states of anxiety, 868 US-dollars for non-dependent use of medication, 198 US-dollars for ticks, 247 US-dollars for personality disorders, 630 US-dollars for respiratory path illnesses, 670 US-dollars for acute sinusitis, 972 US-dollars for general injures, 507 US-dollars for allergies
Authors' conclusions	High costs of ADHD
Comments	• Only search in MEDLINE • Many different cost sources • Collection of different cost variables in the studies • No precise country-specific information regarding study population • In Gilmore et Milne 2001, Novartis data on file (2000; referred to by Lord et Paisley 2000), in Zupanic et al. 1998 there is no information on the study population • It is not evident which studies were ruled out • It is not clear how the differing data were integrated into a total result

ADHD = Attention deficit/hyperactivity disorder. ICER = Incremental cost effectiveness ratio. MEDLINE = Medical Literature Analysis and Retrieval System Online (database). MPH = Methylphenidate. N = Number. N. R. = Not relevant. n. i. = no information. QALY = Quality-adjusted life year. SA = Sensitivity analysis. SD = Standard deviation.

Study description	Economic study
Study type (assessed)	Cost data collection, retrospective case control study
Level of evidence (assessed)	N. R.
Source	Secnik K, Swensen A, Lage MJ. Comorbidities and costs of adult patients diagnosted with attention-deficit hyperactivity disorder. Pharmacooeconomics 2005; 3(1): 93-102.
Question/objective	Examination of the prevalence of the comorbidities, the consumption of resources, the direct medical costs and the costs for loss of work in adults with ADHD
Country/currency	USA; US-dollars
Perspective	n. i.
Analysis type	• Investigation of the homogeneity of the ADHD studies with the control group regarding comorbidities and use of medical services is performed by means of the chi-square test and the T-statistic. • The differences between the two groups regarding absences from work were examined by means of the covariance analysis (ANCOVA). • Cost estimates by means of protocolled values of the costs as dependent variables and demographic properties and comorbidities as independent variables; back transformation of the log values by using an estimator ($p \leq 0.05$) • Statistical calculation using Statistical Analysis System 8.1
Cycle length	1 year
Intervention arms	Persons with ADHD

Secnik et al. 2005 – continued

Validation of the model	N. R.
Target variables	• Direct and indirect costs • Direct costs: Outpatient and inpatient costs, prescription medications; prices adjusted to the base year 2001 according to the consumer index for health expenses • Indirect costs: Indirect costs are defined as costs arising due to disease-related absences (determined using company-specific absence rates, sick pay and work compensation payments) • Pricing: company-specific absenteeism rate: 240 US-dollars/day, sickness pay and work compensation payments 144 US-dollars/day
Study population	• Employees of one of the 6 Fortune 200 companies (the companies with the highest revenues in the world, almost exclusively listed on the stock exchange) • Total sample N(total) = 4,504 • N = 2,292 in the ADHD group • N = 2,252 in the control group • Adjustment ratio 1 : 1, adjustment rate: 98.25% • Sex: M: 1,608, F: 2,898 • Age groups: N = 1,980 for ≥ 18 and < 25; N = 564 for ≥ 25 and < 35; N = 1,016 for ≥ 35 and < 45; N = 784 for ≥ 45 and < 55; N = 160 for ≥ 55 and < 65 • Regions: North East: 890; North: 1,272; South: 1,782; West: 550; unknown: 10 • Insurance type: comprehensive insurance coverage: 248; HMO: 234; POS: 1,220; PPO: 368; POS with per capita flat rate: 2,434 • Partial sample for loss of work: • N = 362 employees in the ADHD group • N = 354 employees in the control group • Adjustment ratio 1 : 1, adjustment rate: 97.79 %
Clinical data	No information
Cost data	• Prevalence of the comorbidities in %: Accident/injury ADHD group: 2.04 %, control group: 1.51% (p-value: 0.18), asthma: ADHD group: 4.71 %, control group: 2.89 % (p-value: < 0.01), anxiety states: ADHD group: 13.77 %, control group: 3.46 % (p-value: < 0.01), bipolar disorders: ADHD group: 4.48 %, control group: 0.58 % (p-value: < 0.01), depression: ADHD group: 17.10 %, control group: 2.93 % (p-value: < 0.01), drug or alcohol abuse: ADHD group: 5.11 %, control group: 1.87% (p-value: < 0.01), antisocial personality disorders: ADHD group: 0.31 %, control group: 0 % (p-value: < 0.01), bed wetting: ADHD group: 0.18 %, control group: 0.13% (p-value: 0.71), oppositional disorder: ADHD groups: 0.53 %, control group 0.04 % (p-value: < 0.01), social phobia: ADHD group: 0.04 %, control group: 0 % (p-value: 0.32), irritable bowel syndrome: ADHD group: 0.93 %, control group: 0.71 % (p-value: 0.41) • Medication: Anxiolytics: ADHD group: 10.75 %, control group: 3.46 %: (p-value: < 0.01); antidepressant: ADHD group: 41.30 %, control group: 8.97 %: (p-value: < 0.01); methylphenidate, dexamphetamine, amphetamine-dex-amphetamine or bupropion: ADHD group 62.39 %; in this group 11.46 % receive anxiolytics in addition and 42.3 % an antidepressant in addition. In 35.9 % of the ADHD patients who have an antidepressant prescribed, a depression was not diagnosed • Use of medical services: (outpatient) psychiatrist: ADHD groups: 27.53 %, control group: 2.22% (p-value: < 0.01), psychologist: ADHD group: 16.03 %, control group: 1.38 % (p-value: < 0.01), general physician: ADHD group: 57.77 %, control group: 51.20% (p-value: < 0.01), rehabilitation facilities: ADHD group: 0.09 %, control group: 0 % (p-value: 0.16). ADHD group: 1.33 %, control group: 0.27 % (p-value: < 0.01), (inpatient) emergency admission: ADHD group: 14.34%, control group: 10.26 % (p-value: < 0.01), frequency of the admission: ADHD group: (0, 1, 2, 3) 93.29 %, 5.24 %, 1.02 %, 0.45 %, control group: (0, 1, 2, 3) 95.91%, 3.55 %, 0.40 %, 0.14% (p-value: < 0.01)

Secnik et al. 2005 – continued

Cost data *(continued)*	• Annual costs: 1) direct costs: outpatient costs: ADHD group: 3,009 US-dollars, control group: 1,492 US-dollars (p-value: < 0.01), inpatient costs ADHD group: 1,259 US-dollars, control group: 514 US-dollars (p-value: < 0.01), prescription medications: ADHD group: 5,651 US-dollars, control group: 277 US-dollars (p-value: < 0.01), marginal costs associated with ADHD: 2,881 US-dollars 2) indirect costs: no significant difference in the official days of absence, but employees with ADHD are more often absent from work unexcused (4.33 days vs. 1.13 days; p-value: < 0.01); no difference in the absences results from a calculation of lost days regarding sick pay and work compensation payments; employees with ADHD are absent more often than employees in the control group (43.03 days vs. 29.34 days; p-value: 0.03) 3) Total costs for employees with ADHD are significantly higher than for those in the control group (11,816 US-dollars vs. 8,024 US-dollars; p-value < 0.01); these are composed of significantly higher direct costs (5,532 US-dollars vs. 3,185 US-dollars; p-value: 0.04) and the significantly higher indirect costs (7,044 US-dollars vs. 5,214 US-dollars; p-value: < 0.01); direct costs: outpatient costs 3,258 US-dollars vs. 2,119 US-dollars; p-values: < 0.01); inpatient costs, prescription medications (1,904 US-dollars vs. 1,187 US-dollars; p-values: < 0.01); no significant difference in inpatient costs (723 US-dollars vs. 344 US-dollars; p-value: 0.2); indirect costs: Costs due to absences are significantly higher in the ADHD group (4,240 US-dollars vs. 3,357 US-dollars; p-value: < 0.01), also significant difference in the costs that result from sick pay (413 US-dollars vs. 210 US-dollars; p-value: < 0.01) and work compensation payments (2,339 US-dollars vs. 1,123 US-dollars; p-values: < 0.01)
SA	None
Estimators for effectiveness	N. R.
Estimators for costs – base case	N. R.
IKER – base case	N. R.
SA	N. R.
Authors' conclusions	• Patients with ADHD more frequently have comorbidities (especially psychological disorders), use more medical services and have significantly higher direct medical costs • Subgroup analysis of employees shows that employees with ADHD cause significantly higher costs regarding loss of work • In 35.9 % of ADHD patients, who have had an antidepressant prescribed, a depression was not diagnosed • 11.5 % of ADHD patients who receive an ADHD medication also have an anxiolytic prescribed although this combination cannot be recommended • ADHD patients are more frequently treated by specialists than the control group • ADHD patients are more commonly treated in the emergency room and are sent more often to the emergency room for treatment • ADHD patients are more often absent from work
Comments	According to the authors, unexcused absences are also due to the personality structure of ADHD patients.

ADHD = Attention deficit/hyperactivity disorder. ANCOVA = Covariance analysis. HMO = Health maintenance organisation. ICER = Incremental cost effectiveness ratio. n. i. = no information. N = Number. N. R. = Not relevant. POS = Point of service. PPO = Preferred Provider Organisation. SA = Sensitivity analysis SD = Standard deviation.

Study description	Economic study
Study type (assessed)	N. R.
Level of evidence (assessed)	N. R.
Source	Wu E, Birnbaum HG, Zhang HF et al. Health care costs of Adult treatment for attention-deficit/hyperactivity disorder who received alternative drugs. Journal of Managed Care Pharmacy 2007; 13(7): 561-569.
Question/objective	Comparison of the treatment costs and the overall health costs in adults with ADHD who start a therapy with OROS-MPH, MAS-XR or atomoxines
Country/currency	USA, US-dollars

Wu et al. 2007 – continued

Perspective	n. i.
Analysis type	Cost comparison calculation, cost/cost calculation, descriptive cost analysis
Cycle length	Cost recording for 6 months after start of the therapy
Intervention arms	• OROS-MPH • MAS-XR • Atomoxetine
Validation of the model	• Comparison of averages (study group characteristics) by means of a T-test • Homogeneity test (frequency distribution) by means of the chi-square test • GLM (linear models) for cost comparison in the intervention arms, adjusted for demographic characteristics, abuse of medication, depression and the Charlson comorbidity index (combines 17 comorbidities)
Target variables	Total direct treatment costs plus costs for medications and only medical costs
Study population	• 4,569 patients between 18 and 64 years, average age: 37 years • Patient characteristics include age, sex, region, selected comorbidities (medication abuse and depression/anxiety disorders and the Charlson comorbidity • 43 % of the sample are female • In 3 % diagnosed medication abuse • In 26 % a depression or anxiety disorder was diagnosed in the previous 6 months • Inclusion criteria: At least 1 diagnosis according to ADD/ADHD At least 1 prescription for OROS-MPH, MAS-XR atomoxetine, that was identified according to the National Drug Code Insured for the previous 6 months and in the 6 months after start of the therapy, therapy-free time
Clinical data	• 1,452 patients (31.8 %) received OROS-MPH for an average therapy duration of 99 days • 1,554 patients (34.0 %) received MAS-XR for an average therapy duration of 128 days • 1,563 patients (34.2 %) received atomoxetine for an average therapy duration of 86 days
Cost data	Data collection from 1999 to 2004 The costs were measured in the amount of money according to the treatment plan of the manufacturer, not by the invoice amount Patient copayments and deductibles were excluded The costs include inpatient and outpatient services • ADHD medication costs: OROS-MPH: 246 US-dollars/282 US-dollars; MAS-XR: 275 US-dollars/322 US-dollars; atomoxetine: 325 US-dollars/392 US-dollars • Total costs for medications: OROS-MPH 246 US-dollars/282 US-dollars; MAS-XR: 490 US-dollars/748 US-dollars; atomoxetine: to 282 US-dollars • Inpatient accommodation: OROS-MPH 449 US-dollars/747 US-dollars; MAS-XR: 490 US-dollars; atomoxetine: 626 US-dollars/959 US-dollars • Inpatient treatment costs: OROS-MPH 0 US-dollars/139 US-dollars; MAS-XR: 0 US-dollars/261 US-dollars; atomoxetine: 0 US-dollars/334 US-dollars • Medical outpatient costs: OROS-MPH 403 US-dollars/1,112 US-dollars; MAS-XR: 418 US-dollars/1,161 US-dollars; atomoxetine: 431 US-dollars/ 1,247 US-dollars • Costs for psychotherapy OROS-MPH: 0 US-dollars/132 US-dollars; MAS-XR: 0 US-dollars/122 US-dollars; atomoxetine: 0 US-dollars/106 US-dollars • Total treatment costs OROS-MPH: 404 US-dollars/1,251 US-dollars; MAS-XR: 421 US-dollars/1,422 US-dollars; atomoxetine: 432 US-dollars/1,581 US-dollars • Total treatment and medication costs OROS-MPH: 1,062 US-dollars/2,008 US-dollars; MAS-XR: 1,080 US-dollars/2,169 US-dollars; atomoxetine: 1,271 US-dollars/2,540 US-dollars • The costs were adjusted by means of the consumer price index for medical care to the inflation rate for 2004 in US-dollars Descriptive cost analysis • 6-month average costs for OROS-MPH 2,008 US-dollars (SD: 3,231 US-dollars, average: 1,062 US-dollars)

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Cost data *(continued)*	• 6-month average costs for MAS-XR 2,169 US-dollars (SD: 4,828, average: 1,080 US-dollars) • 6-month average costs for atomoxetine 2,540 US-dollars (SD: 4,269 US-dollars, average: 1,271 US-dollars) • Total costs inpatient: 52% of the total costs • Medication costs: 38 % of the total costs (OROS-MPH 282 US-dollars; SD: 215 US-dollars, average: 246 US-dollars¸ MAS-XR 322 US-dollars, SD: 250 US-dollars, average: 275 US-dollars, atomoxetine 392 (SD: 298 US-dollars, average: 325 US-dollars) • Outpatient hospital costs: 7 % of the total costs (OROS-MPH average: 139 US-dollars¸ MAS-XR average: 261 US-dollars, atomoxetine average: 334 US-dollars) • Multivariate regression: risk-adjusted illness costs for OROS-MPH are less by 156 US-dollars (8.0 %) than for MAS-XR and by 226 US-dollars than for atomoxetine
SA	No
Estimators of effectiveness	None
Estimators of costs – base case	None
ICER – base case	None
SA	None
Authors' conclusions	Adult patients with ADHD (medication dependency, depression and the Charlson comorbidity index included), who were treated with OROS-MPH have on average, over a period of 6 months after the start of therapy, fewer medical costs, total and medical costs, than ADHD patients who were treated with MAS-XR or atomoxetine.
Comments	No explanation why the GLM is used with a logistic function Weak points (given by the authors): • Observation period too short • Severity of the course of the illness not recorded • No clean differentiation of ADD and ADHD, since ICD-9-Codes 314.00 and 314.01 were included • No specific data for the illness costs specifically only for ADD/ADHD; therefore, general illness and hospital costs are used Imprecise cost descriptions No information on effectiveness (no strength of effect):

ADD = Attention deficit disorder. ADHD = Attention deficit/hyperactivity disorder. GLM = General linear model. ICD-9 = International Classification of Illnesses, version 9. ICER = Incremental cost effectiveness ratio. MAS-XR = Mixed amphetamine salts extended release. MPH = Methylphenidate. N = Number. N. R. = Not relevant. n. i. = no information. OROS-MPH = Osmotic-controlled release delivery system MPH. SA = Sensitivity analysis. SD = Standard deviation.

9.7 Check-lists of the excluded studies

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**							
Report No.:								
Title:	Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder							
Authors:	Adler LA, Goodman DW, Kollins SH et al.							
Source:	J Clin Psychiatry 2008; 69: 1364-1373							
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐				
		Case series: ☐		Other: ☐				

Class	**A Selection of the study participants**	**Yes**	**No**	**?**
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐

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	B Allocation and study participation	Yes	No	?
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence of "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Functional Outcomes in the treatment of adults with adhd
Authors:	Adler LA, Spencer TJ, Levine LR et al.
Source:	Journal of Attention Disorders 2008; 11(6): 720-727

Document type	RCT:	☒	Cohort study:	☐	Case control study:	☐	Longitudinal study: ☐
			Case series:	☐			Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☒
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☐	☐	☒
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☒	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Adler et al. 2008b – continued

	G Statistical analysis	Yes	No	?
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**					
Report No.:						
Title:	Once-Daily atomoxetine for adult attention-deficit/hyperactivity disorder. A 6-month, double-blind trial					
Authors:	Adler LA, Spencer T, Brown TE et al.					
Source:	Journal of Clinical Psychopharmacology 2009; 29(1): 44-50					
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study:		☐
		Case series: ☐		Other:		☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☒	☐	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐

Adler et al. 2009b – continued

	F Drop-outs	Yes	No	?
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**						
Report No.:							
Title:	A pilot study of the effects of Atomoxetine on driving performance in adults with adhd						
Authors:	Barkley RA, Nderson DL, Kruesi M						
Source:	Journal of Attention Disorders 2007; 10(3): 306-316						
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐			
		Case series: ☐		Other: ☐			

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☐

Barkley et al. 2007 – continued

	E Outcome measurement	Yes	No	?
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☒	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder
Authors:	Biederman J, Mick E, Surman C et al.
Source:	Biol Psychiatry 2006; 59: 829-835

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☒	☐	☐
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐

Biederman et al. 2006 – continued

	D Study administration	Yes	No	?
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**						
Report No.:							
Title:	Attention-deficit/hyperactivity disorder and substance use disorder						
Authors:	Carpentier PJ, de Jong C, Dijksta B et al.						
Source:	Addiction 2005; 100: 1868-1874						
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐			
		Case series: ☐		Other: ☐			

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☐	☒	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☐	☐	☒
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒

Carpentier et al. 2005 – continued

	C Intervention and exposure	Yes	No	?
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☒	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, are they significant?	☐	☐	☐
QB	5. If differences were found, are they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**			
Report No.:				
Title:	Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder			
Authors:	Chamberlain SR, del Campo N, Dowson J et al.			
Source:	Biol Psychiatry 2007; 62: 977-984			
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐

Chamberlain et al. 2007 – continued

	B Allocation and study participation	**Yes**	**No**	**?**
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☐	☒
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis	**Yes**	**No**	**?**
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	A randomized, double-blind, crossover study of methylphenidate and lithium in adults with attention-deficit/hyperactivity disorder: preliminary findings
Authors:	Dorrego MF, Canevaro L, Kuzis G
Source:	J Neuropsychiatry Clin Neurosci 2002; 14(3): 289-295

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☐	☒	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☒	☐	☐
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☐	☒	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☒
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Dorrego et al. 2002 – continued

	G Statistical analysis	Yes	No	?
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Bupropion SR v. Methylphenidate vs. Placebo for Attention Deficit Hyperactivity Disorder in Adults
Authors:	Kuperman S, Perry PJ, Gaffney GR et al.
Source:	Annals of Clinical Psychiatry 2001; 13(3): 129-134

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☒	☐	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐

Kuperman et al. 2001 – continued

	F Drop-outs	Yes	No	?
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Treatment of methadone-maintained patients with adult adhs: double-blind comparison of methylphenidate, bupropion and placebo
Authors:	Levin FR, Evans SM, Brooks DJ et al.
Source:	Drug and Alcohol Dependence 2006; 8: 137-148

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☐	☒	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒

Levin et al. 2006 – continued

	E Outcome measurement	Yes	No	?
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Treatment of cocaine dependent treatment seekers with adult ADHS: double-blind comparison of methylphenidate and placebo
Authors:	Levin FR, Evans SM, Brooks DJ, Garawi F
Source:	Drug and Alcohol Dependence 2007; 87(1): 20-29
Document type	RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. For cohort studies: Were the study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐

Levin et al. 2007 – continued

	D Study administration	Yes	No	?
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**					
Report No.:						
Title:	A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with adhd with assessment of oppositional and emotional dimensions of the disorder					
Authors:	Reimherr FW, Williams ED, Strong RE et al.					
Source:	J Clin Psychiatry 2007; 68: 93-101					
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐		
		Case series: ☐		Other: ☐		

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒

Reimherr et al. 2007 – continued

	C Intervention and exposure	Yes	No	?
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☐	☐	☒
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Double-blind placebo-controlled trial of Methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence
Authors:	Schubiner H, Saules KK, Arfken CL et al.
Source:	Experimental and Clinical Psychopharmacology 2002; 10(3): 286-294

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐

Schubiner et al. 2002 – continued

	B Allocation and study participation	Yes	No	?
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☒	☐	☐
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☒	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder
Authors:	Spencer T, Biederman J, Wilens T et al.
Source:	Arch Gen Psychiatry 2001; 58: 775-782

Document type RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐
Case series: ☐ Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Spencer et al. 2001 – continued

	G Statistical analysis	Yes	No	?
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒ Reason: no description of the case number estimate and randomisation				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**					
Report No.:						
Title:	A large, double-blind, randomized clinical trial of methylphenidat in the treatment of adults with attention-deficit/hyperactivity disorder					
Authors:	Spencer T, Biederman J, Wilens T et al.					
Source:	Biol Psychiatry 2005; 57: 456-463					
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐		
		Case series: ☐		Other: ☐		

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☒	☐	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐

Spencer et al. 2005 – continued

	F Drop-outs	Yes	No	?
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☒	☐
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐

Final evaluation: This publication will be: included ☐ excluded ☒

Reason: The study exhibits methodological deficiencies in its implementation; no description of the sample size calculation and randomisation; in the MPH intervention group, there are 2.5 times as many subjects as in the placebo group, without reasons being given

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder
Authors:	Spencer TJ, Adler LA, McGough JJ et al.
Source:	Biol Psychiatry 2007; 61: 1380-1387

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In the cohort studies: Were known/possible confounders considered at the start of the study?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐

Spencer et al. 2007 – continued

	D Study administration	Yes	No	?
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒ Reason: No description of the sample size calculation and randomisation				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**			
Report No.:				
Title:	Attention-deficit/hyperactivity disorder-specific quality of life with triple-bead mixed amphetamine salts (spd465) in adults: results of a randomized, double-blind, placebo-controlled study			
Authors:	Spencer TJ, Landgraf JM, Adler LA et al.			
Source:	J Clin Psychiatry 2008; 69: 1766-1775			
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒

Spencer et al. 2008a – continued

	C Intervention and exposure	Yes	No	?
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐

Final evaluation: This publication will be: included ☐ excluded ☒

Reason: no sample size calculation

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Triple-bead mixed amphetamine salts (spd465), a novel, enhanced extended-release amphetamine formulation for the treatment of adults with adhd: a randomized, double-blind, multicenter, placebo-controlled study
Authors:	Spencer TJ, Adler LA, Weisler RH
Source:	J Clin Psychiatry 2008; 69: 1437-1448

Document type RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐

Case series: ☐ Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined.	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐

Spencer et al. 2008b – continued

	B Allocation and study participation	Yes	No	?
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☒	☐	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☒	☐	☐
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Comparing guanfacine and dextroamphetamine for treatment of adult attention-deficit/hyper-activity disorder
Authors:	Taylor FB, Russo J
Source:	J Clin Psychopharmacol 2001; 21(2): 223-228

Document type RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐
Case series: ☐ Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☒	☐	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Taylor et al. 2001 – continued

	G Statistical analysis	Yes	No	?
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐

Final evaluation: This publication will be: included ☐ excluded ☒

Reason: The study has severe qualitative weaknesses (no description of the randomisation and case number calculation; no description of the drop-outs; no assurance of compliance

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**			
Report No.:				
Title:	An experimental comparison of Pycnogenol and methylphenidate in adults with attention-deficit/ hyperactivity disorder (ADHD)			
Authors:	Tenenbaum S, Paull JC, Sparrow EP et al.			
Source:	Journal of Attention Disorders 2002; 6(2): 49-60			
Document type	RCT: ☒ Cohort study: ☐ Case control study: ☐ Longitudinal study: ☐			
	Case series: ☐ Other: ☐			
Class	**A Selection of the study participants**	**Yes**	**No**	**?**
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☐	☒
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☒	☐	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☒
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐

Tenenbaum et al. 2002 – continued

	F Drop-outs	Yes	No	?
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☐	☒
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☐	☒
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒ Reason: no information on randomisation and sample size calculation; low case number; short therapy phases				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**						
Report No.:							
Title:	Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder						
Authors:	Turner DC, Clark L, Dowson J et al.						
Source:	Biol Psychiatry 2004; 55: 1031-1040						
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐			
		Case series: ☐		Other: ☐			

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined.	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒

Turner et al. 2004 – continued

	E Outcome measurement	Yes	No	?
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**						
Report No.:							
Title:	Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder						
Authors:	Turner DC, Blackwell AD, Dowson JH et al.						
Source:	Psychopharmacology 2005; 178: 286-295						
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐			
		Case series: ☐		Other: ☐			

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐

Turner et al. 2005 – continued

	D Study administration	Yes	No	?
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☐	☐	☒
QA	2. Were the outcomes recorded in a valid and reliable manner?	☐	☐	☒
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☐	☒	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒ Reason: very small sample number; no description of the sample size calculation and randomisation				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Methylphenidate significantly improves driving performance of adults with attention-deficit hyperactivity disorder: a randomized crossover trial
Authors:	Verster JC, Bekker EM, de Ross M
Source:	Journal of Psychopharmacology 2008; 22(3): 230-237

Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐
		Case series: ☐		Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☒	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☐	☐	☒
QB	3. Was the selection randomised in a standardised process?	☒	☐	☐
QC	4. Was the randomisation blind?	☒	☐	☐
QA	5. Were known/possible confounders considered at the start of the study?	☐	☐	☒

Verster et al. 2008 – continued

	C Intervention and exposure	Yes	No	?
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☐	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☒	☐	☐
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☒	☐	☐
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☐	☒	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☒	☐	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐

Final evaluation: This publication will be: included ☐ excluded ☒

Reason: The selected randomisation procedure does not appear suitable in light of the small case number. The small case number can result in distortions of the results. The calculated case number of 30 was not achieved.

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**						
Report No.:							
Title:	Bupropion xl in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study						
Authors:	Wilens TE, Haight BR, Horrigan JP et al.						
Source:	Biol Psychiatry 2005; 57: 793-801						
Document type	RCT: ☒	Cohort study: ☐	Case control study: ☐	Longitudinal study: ☐			
		Case series: ☐		Other: ☐			

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐

Wilens et al. 2005 – continued

	B Allocation and study participation	Yes	No	?
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☐	☐	☒
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☒	☐	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☐	☒
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis ?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐
	G Statistical analysis			
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☐	☒	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☐	☒	☐
Final evaluation: This publication will be: included ☐ excluded ☒				

Check-list:	**Primary studies (RCTs/case control studies/cohort studies/longitudinal studies/ case series)**
Report No.:	
Title:	Atomoxetine treatment of adults with adhd and comorbid alcohol use disorders
Authors:	Wilens TE, Lenard AA, Weiss MD et al.
Source:	Drug and Alcohol Dependence 2008; 96: 145-154

Document type	RCT:	☒	Cohort study:	☐	Case control study:	☐	Longitudinal study: ☐
			Case series:	☐			Other: ☐

Class	A Selection of the study participants	Yes	No	?
QA	1. Are the inclusion and exclusion criteria of the study sufficiently/unambiguously defined?	☒	☐	☐
QA	2. Were the inclusion/exclusion criteria determined before the start of the intervention?	☒	☐	☐
QA	3. Was the disease status validly and reliably recorded?	☒	☐	☐
QBI	4. Have the diagnostic criteria of the disease been described?	☒	☐	☐
QB	5. Is the study population/exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6. In cohort studies: Were study groups observed simultaneously?	☐	☐	☐
	B Allocation and study participation			
QA	1. Are the exposed persons/cases and unexposed persons/controls from a similar basic totality?	☒	☐	☐
QA	2. Are the intervention/exposed and control/unexposed groups comparable at the start of the study?	☒	☐	☐
QB	3. Was the selection randomised in a standardised process?	☐	☐	☒
QC	4. Was the randomisation blind?	☐	☐	☒
QA	5. Were known/possible confounders considered at the start of the study?	☐	☒	☐
	C Intervention and exposure			
QA	1. Were intervention and exposure recorded in a valid, reliable and identical manner?	☒	☐	☐
QB	2. Were intervention/control groups with the exception of the intervention treated in the same manner?	☒	☐	☐
QB	3. If deviating therapies were present, were these recorded in a valid and reliable manner?	☐	☐	☐
QA	4. For RCTs: Were placebos used for the control groups?	☒	☐	☐
QA	5. For RCTs: Was it documented how the placebos were administered?	☐	☒	☐
	D Study administration			
QB	1. Is there evidence for "overmatching"?	☐	☒	☐
QB	2. In multicentre studies, were the diagnostic and therapeutic methods as well as the outcome measurement identical in the participating centres?	☒	☐	☐
QA	3. Was it ensured that the study participants did not switch between the intervention and control group?	☐	☐	☒
	E Outcome measurement			
I	1. Were patient-proximate outcome parameters used?	☒	☐	☐
QA	2. Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3. Was the outcome measurement blinded?	☐	☐	☒
QC	4. In case series: Was the distribution of prognostic factors sufficiently recorded?	☐	☐	☐
	F Drop-outs			
QA	1. Was the response rate in the intervention/control groups sufficiently high; or in cohort studies: Was it possible to follow a sufficiently large part of the cohort for the entire study period?	☐	☐	☒
QA	2. Were reasons listed for the study participants dropping out?	☒	☐	☐
QB	3. Were the outcomes of the drop-outs described and included in the analysis?	☒	☐	☐
QB	4. If differences were found, were they significant?	☐	☐	☐
QB	5. If differences were found, were they relevant?	☐	☐	☐

Wilens et al. 2008a – continued

	G Statistical analysis	Yes	No	?
QA	1. Are the described analytical methods correct and the information for a flawless analysis sufficient?	☒	☐	☐
	2. Were confidence intervals stated for averages and significance tests?	☐	☒	☐
QB	3. Are the results presented in graphic form and were the values underlying the graphics stated?	☒	☐	☐
Final evaluation: This publication will be: included ☐ excluded ☒ Reason: no information on sample size calculation and randomisation, high drop-out rate				

The systematic evaluation of medical procedures and methods, *Health Technology Assessment* (HTA), is an integrated part of health politics by now. HTA was established as an effective instrument for the assurance of quality and efficiency in the German health care system.

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