Drug treatment of ADHD (Attention Deficit/Hyperactivity Disorder) in adults in Germany
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Health policy background
Attention-Deficit/Hyperactivity Disorder (ADHD) is a mental disorder which is characterized by 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. Yet, these symptoms can persist during 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 hyper-function. However, 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], Amphetamine Sulfate), norepinephrine uptake inhibitor (Atomoxetine [ATX]) and other anti-depressives (Bupropion, Venlafaxine) can be used. According to the guidelines for adult ADHD, the German Society for Psychiatry, Psychotherapy and Alternative Neural Medicine 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 medicinal 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, affective disorders and personality disorders.

Research questions

The effectiveness 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 clinical effectiveness of medical treatment of ADHD in adults are as follows:

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

Study questions regarding an economic evaluation are as follows:

1. What are the annual costs incurred for the medical 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 medical 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 medical treatment 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 was 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 (RCT), five meta-analyses, three economic studies and two studies relevant to the legal aspects of the HTA.

RCT

In all RCT, the treatment group receives medical 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 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 lawsuits, doctors prescribe medication less often for adult ADHS-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 medical treatment can reduce the signs of illness for ADHD patients so that symptoms such as lack of concentration can be improved.

The RCT 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 RCT, 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 medical 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 medical effectiveness of a therapy.

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