Until the late 1990s, attention deficit hyperactivity disorder (ADHD) was often regarded in the German speaking countries as a disorder that fades away in late adolescence. However, it has recently become clear from numerous studies that core symptoms of ADHD persist into adulthood in a substantial subgroup of patients.

**Methods**: Selective review of relevant literature in Medline, up to September 2007.

**Results**: The prevalence of ADHD in adulthood is estimated at about 2%. Core symptoms include attention deficit in the presence of understimulation, chronic restlessness, impulsivity, disorganized behaviour, and disorders of affect regulation. The extent of psychosocial impairment depends on symptom severity, psychiatric comorbidity (such as addiction or depression), and psychosocial support. As in childhood, ADHD in adulthood is a clinical diagnosis. Genetic factors probably play a key role in primary ADHD. Treatment should include psychotherapy and medical treatment.

**Discussion**: ADHD in adulthood is commoner than for example bipolar disorder or schizophrenia. It may be regarded as a risk factor for the development of other psychiatric conditions. Highly effective treatment is possible not only in childhood but also in adulthood. The problem of off-label use of psychotropic medication in adults limits treatment in adult ADHD.

**Key words**: ADHD, adulthood, diagnosis, treatment, methylphenidate
Problem is that the criteria are defined on a child-specific "residual type" in 1980. As with the ICD-10, one symptom into adulthood was already defined as according to the DSM-IV diagnostic system of the American Psychiatric Association, persistence of the diagnosis nor its exclusion (8). Neuropsychological tests

According to the guidelines (4), an examination based on psychological tests, for example of attention performance, working memory and impulse control, may contribute to confirming the diagnosis. An individual diagnosis, however, cannot be made on the basis of a test value. When interpreting the results it should be remembered that adults with ADHD can even achieve very good results if interested and stimulated, although they may be suffering from relevant restrictions in daily life.
Somatic exclusion diagnosis
A medical and neurological examination must be performed and a medicine and illicit drug abuse history should be taken for exclusion and differential diagnostic purposes. The guidelines applied in the German speaking countries recommend thyroid function tests and electroencephalography (EEG) (4).

Comorbidities
The high rate of comorbid disorders (80%) and psychosocial consequences is particularly significant in adult psychiatry and psychotherapy (1). Depression (40% to 60%), anxiety disorders (20% to 60%) and addictive diseases (50% to 60%) are among the commonest comorbidities (8). The prevalence rates of ADHD among drug dependent persons and the prison population are significantly higher compared to the general population and run at about 25%. ADHD is thus a considerable risk factor for further psychiatric morbidities (box 2).

At the same time, some comorbidities are also differential diagnoses, such as depressive disorder with its impairments of concentration. However, it can be distinguished from ADHD based on its usually phasic course.

Differential diagnosis from borderline personality disorder (BPD) can be particularly difficult due to the high overlap of clinical symptoms – such as impulsivity and emotional lability – and comorbidity. BPD is frequently dominated clinically by states of tension followed by self harm, chronic suicidal ideation and possible symptoms of posttraumatic stress disorder.

The results of the Nordbaden childhood study (9) and our own clinical observations in adults have shown that somatic diseases such as allergies and arterial hypertension are frequent comorbidities.

Neurobiology and differential diagnosis
The exact cause of ADHD remains unknown. Most experts agree, however, that ADHD is not a single clinical disorder but rather represents a group of etiologically heterogeneous entities which share a group of core symptoms.

Numerous genetic studies have shown that children of parents with ADHD can also suffer more frequently from ADHD themselves. Parents and siblings of affected patients have a two to eight-fold risk of developing ADHD symptoms (10). A metaanalysis of six twin studies revealed that 80% of the variance of the clinical symptoms can be explained in terms of genetic factors. Adopted siblings of ADHD children have a lower risk than biological siblings, and biological siblings perform more poorly than adopted siblings in neuropsychological tests of sustained attention (10). All these findings point to an important role of genetic factors in the etiology of ADHD symptoms.

Many cerebral imaging studies have demonstrated both structural as well as neurochemical and functional abnormalities in ADHD patients. For example, reductions in total brain volume, prefrontal brain (especially right-sided), basal ganglia (especially the caudate nucleus) and the cerebellum (especially the vermis) have been reported (10–13). Neurochemical abnormalities in various areas of the brain have also been reported (14). The good efficacy of adrenergic and dopaminergic substances point to an important role of these systems in the pathogenesis of ADHD. Abnormalities have also been demonstrated for the cerebral dopamine transporter and pre-synaptic dopamine decarboxylase activity in PET and SPECT studies (15). However, these findings have not so far been robustly replicated, and the individual measured values do not reliably differentiate between healthy and sick persons but only become significant in the group mean.

A further risk factor is chronic intrauterine nicotine exposure (10), which is associated with a 2 to 2.7-fold elevated risk for the later development of ADHD (e1). Other factors such as certain diets, lead exposure, sugar and food additives or metabolic diseases such as cryptopyrroluria are also contentiously debated as possible causes of ADHD (10). A recently published study provided support for the hypothesis that certain food additives are associated with the development of hyperactive symptoms later in life (e2). The authors are however unaware of any data that could conclusively resolve these controversies as regards the other factors mentioned.

Chronic familial conflicts, reduced familial cohesion and confrontation with parental (especially maternal) psychopathology are more often observed in families with ADHD sufferers compared to control families (13). For example, depending on the extent of the psychosocial handicap (Rutter’s indicator [RI] 1–4), the odds ratio for children from psychosocially handicapped families for developing an attention deficit hyperactivity disorder increases to values of 7.4 (for RI 1) to 41.7 (for RI 4) (e3). Odds ratios > 1 indicate an increased risk.

When thinking about the causes of ADHD it is important to distinguish the elements causality (etiolo-
gy), mechanisms of action (pathogenesis) and clinical picture (syndrome) from each other. The capacity of attention control, impulse control and affect regulation are pathogenically closely associated with the fronto-striato-thalamo-frontal feedback loop systems. However, these are distributed cerebral neuronal networks. Their function may be disturbed at various sites for various reasons, for example due to lesions of greatly varying origin such as perinatal asphyxia, encephalitis, metabolic disorder, intoxication and febrile seizure.

Lesions at various sites in the brain can thereby lead to a similar clinical deficit if an identical feedback loop system is affected somewhere along its course. This means that it is no longer possible to reliably deduce the site of a functional lesion and even less the cause of a disorder, on the basis of the clinical presentation. The function of these feedback loops, however, may also be systematically compromised, i.e. independently of individual lesions, due to functional disorders of the adrenergic or dopaminergic system. Because of the genetic component and the good efficacy of dopaminergic and adrenergic substances on the core symptom of attention control, it may readily be assumed that the adrenergic and dopamine systems play a central pathogenic role at least in a large subgroup of ADHD patients.

Against this background, there is much that argues in favor of distinguishing between a primary and a secondary attention deficit hyperactivity disorder from the etiologic perspective. A positive familial history and lacking evidence of mild cerebral dysfunctions then point to primary ADHD. Birth complications, inflammatory brain diseases, intoxications, head traumas or possibly a familial history of convulsive disorder would rather suggest secondary ADHD (table 1).

### Treatment

The guidelines (4) recommend treatment if, in the presence of a definite clinical diagnosis of ADHD, at least one area of life is severely impaired or two areas of life are slightly impaired (box 3).

Treatment should – as in childhood and adolescence – consist of a combination of pharmacotherapy and psychotherapy. A rationale should be provided for monotherapy. If comorbid disorders such as depression or addiction dominate the clinical picture, they should be treated first, for instance with antidepressant medication, detoxification and withdrawal treatment. After treating the comorbid disorder, the extent of ADHD related impairment should be reassessed.
Pharmacotherapy
In contrast to child and adolescent psychiatry, no medication has yet (as at October 2007) been approved in Germany for the management of adult ADHD (off-label use) (box 4).

Stimulant therapy
According to the German guidelines, the first-line medication is methylphenidate. Its prescription is subject to the provisions of the German Narcotics Prescription Act. The available meta-analyses rate the efficacy of methylphenidate as very good (16). The dosage and choice of product – for example as a sustained release formulation – depend on the patient’s needs and therapeutic response (17). The Federal Institute for Drugs and Medical Devices recommends a dose range similar to that for pediatric use of 0.5 to 1.0 mg/kg body weight (BW) daily, although in some studies better efficacy was achieved with higher dosages up to 1.4 mg/kg BW daily. In daily clinical practice, however, it has been found that lower dosages are often sufficient for long-term therapy, especially since many adults aspire to achieve a reduction but not complete suppression of the symptoms.

Medical contraindications (box 5) for methylphenidate include untreated arterial hypertension and cardiac arrhythmias. Before starting medication, electrocardiography (ECG) and measurement of blood pressure and pulse are recommended. These parameters should be monitored in all patients receiving methylphenidate treatment since patients without arterial hypertension may also experience a mild increase in blood pressure and pulse rate. Monitoring of body weight is also recommended because loss of appetite is a common undesirable effect. Methylphenidate should not be prescribed during pregnancy and lactation.

Abuse potential of methylphenidate
Oral use as directed in the therapeutic dose range is not generally associated with an increased dependence potential (18), although some cases of abuse involving intranasal or intravenous use have been documented. The sustained release formulations have an even lower abuse potential because of the slower rate of drug influx.

Comorbid addictions are usually treated initially with alternative therapy options such as noradrenergic substances like atomoxetine.

However, patients with dependence diseases can also be treated with stimulants under controlled conditions, i.e. with regular negative substance abuse screening.

Atomoxetine and other substances
If methylphenidate is ineffective or if the patient has contraindications or comorbidities such as depression or anxiety disorders, frequently used alternative medications include atomoxetine or antidepressants such as venlafaxine, reboxetine and desipramine. As regards significant efficacy in adult ADHD, however, so far only the selective noradrenaline reuptake inhibitor atomoxetine has been evaluated – also in larger studies – in comparison to placebo (19, 20). Atomoxetine is approved for the treatment of adult ADHD if it was already prescribed before the patient was 18 years old. Atomoxetine is also associated with mild increases in blood pressure and resting pulse as well as palpitations. The target dose is 1.2 mg/kg BW. Treatment should be in progress for 3 to 4 weeks before performing a maximal efficacy assessment. Comparative studies on the efficacy of methylphenidate and atomoxetine are still lacking. Other active agents such as modafinil, bupropion and nicotine patch are under investigation but usually in small case numbers and over only a few weeks.

Duration of treatment
Adult ADHD usually exhibits a chronic course and therefore requires long-term medication. In most cases, symptoms reappear after terminating medication.

BOX 3
Multimodal therapy – guideline based

- No need for treatment based on the diagnosis
- Treatment only if – conclusively because of ADHD – there are marked impairments in one life area, slight impairments in several life areas or symptoms of pathological significance
- Methylphenidate is the first-line medication
- Psychotherapy: apply disorder-specific elements
- Combination of medication and psychotherapy, rationale to be provided for monotherapies
- Therapy should always be guided by comorbid disorders, if present
- Further studies, especially long-term studies, are needed.

BOX 4
Off-label use in adult ADHD

Off label use as defined by the German Federal Social Court (Bundessozialgericht) is applicable in adult ADHD when

- quality of life is permanently impaired due to severe ADHD
- no other, approved medications are available
- the database shows that there is a reasonable expectation of therapeutic success

(Point 1 is to be clarified in the individual case, Points 2 and 3 are applicable for adult ADHD)
The treatment of adult patients in clinical practice is impeded at present by the lack of an approved medication.

Conflict of Interest Statement
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Psychotherapy
Since the psychosocial consequences such as job loss and/or interrupted relationships are frequently predominant features in adult ADHD and these aspects cannot be influenced directly by medical therapy, psychotherapeutic interventions are also recommended. The group and individual psychotherapy concepts evaluated so far are based on cognitive-behavioral and/or dialectic-behavioral therapy and show positive results (21–24). Both patients without medication and patients who still have residual symptoms after ADHD specific medication derive benefits. Psychotherapy can reduce the severity of ADHD and provide an improvement in commonly associated symptoms such as depression and anxiety and in self esteem. Initial evidence suggests that combination therapy comprising pharmacologic and psychotherapeutic components may be superior to medication alone (25). However, no study has yet evaluated the efficacy of psychotherapy compared to ADHD specific medication on a randomized, blind basis. The Federal Ministry for Education and Research is therefore sponsoring a large, randomized, multicenter study to further evaluate structured psychotherapy compared to one-to-one psychiatric interview (clinical management) in combination with methylphenidate or placebo.

Conclusions
Adult ADHD is a disorder that can be validly diagnosed and which, as in pediatric and adolescent psychiatry, can be treated medicinally and with psychotherapy with positive results. Further scientific research into the long-term course of this condition and the efficacy and tolerability of different therapeutic strategies is necessary.

BOX 5
Contraindications for the prescription of methylphenidate

Absolute contraindications for methylphenidate:
- Pregnancy and lactation
- Untreated arterial hypertension
- Cardiac tachyarrhythmias
- Coronary heart disease
- Arterial occlusive disease
- Cerebral ischaeas
- Schizophrenia
- Medicine and/or illicit drug dependence

Relative contraindications for methylphenidate:
- Tic disorders and Tourette’s syndrome (deterioration possible)
- Anxiety disorders (exacerbation possible)
- Epilepsies (prescription only under sufficient anticonvulsive protection)
- Bipolar disorders (prescription only with reliable phase prophylaxis)
- Anorexia nervosa


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