Eur Arch Psychiatry Clin Neurosci
DOI 10.1007/s00406-014-0542-4

REVIEW

Prediction of methylphenidate treatment outcome in adults with attention-deficit/hyperactivity disorder (ADHD)

Wolfgang Retz · Petra Retz-Junginger

Received: 29 August 2014 / Accepted: 7 September 2014

Abstract Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent mental disorder of childhood, which often persists in adulthood. Methylphenidate (MPH) is one of the most effective medications to treat ADHD, but also few adult patients show no sufficient response to this drug. In this paper, we give an overview regarding genetic, neuroimaging, clinical and other studies which have tried to reveal the reasons for non-response in adults with ADHD, based on a systematic literature search. Although MPH is a well-established treatment for adults with ADHD, research regarding the prediction of treatment outcome is still limited and has resulted in inconsistent findings. No reliable neurobiological markers of treatment response have been identified so far. Some findings from clinical studies suggest that comorbidity with substance use disorders and personality disorders has an impact on treatment course and outcome. As MPH is widely used in the treatment of adults with ADHD, much more work is needed regarding positive and negative predictors of long-term treatment outcome in order to optimize the pharmacological treatment of adult ADHD patients.

Keywords Adult ADHD · Prediction · Methylphenidate · Outcome · Response

W. Retz (✉)
Forensic Psychiatry and Psychotherapy, Department of Psychiatry and Psychotherapy, University Medical Center, 55131 Mainz, Germany
e-mail: wolfgang.retz@unimedizin-mainz.de

P. Retz-Junginger
Neurocenter, Saarland University Hospital, Homburg/Saar, Germany

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a frequent psychopathological disorder in childhood, with approximately 5.3 % of children and adolescents being affected [1]. In many of these cases, ADHD does not abate during adolescence, but can persist into adulthood as a full clinical picture or as a partial syndrome in 60 % of cases, with it becoming a chronic condition. A transnational prevalence of approximately 3.4 % has been shown in individuals aged 18–44 years [2]. Considering the high prevalence of ADHD in the adult population and the negative impact its symptoms may have on the different domains of a patient's life, it should be recognized as an important mental disorder requiring accurate identification and treatment.

The treatment of ADHD with stimulant medications, which include amphetamines and methylphenidate (MPH), was introduced in 1937 by Charles Bradley [3]. Methylphenidate is an indirect catecholamine agonist and was first synthesized 1944, and introduced into therapeutics in 1954. Beginning in the 1960s, it was used to treat children with ADHD. Until the 2000s, options in terms of stimulants were limited to immediate release (IR) and first-generation extended release (ER) formulations [4]. During the last decades, a series of randomized controlled MPH studies in adults with ADHD has demonstrated robust MPH treatment effects and a good tolerability of this drug [5]. Typical side effects of MPH include low appetite, headache, insomnia and weight loss, particularly in the initial phase of treatment. Also sympathomimetic effects on the cardiovascular system have to be considered, especially in patients with heart diseases and arterial hypertension.

It is important to recognize that MPH therapy not only improves the core symptoms of ADHD, namely

Published online: 18 September 2014

inattention, hyperactivity and impulsivity, but could also ameliorate the symptoms of emotional dysregulation and disorganization in adult ADHD patients. Decline of different measures of emotional dysregulation and disorganization in adults with ADHD has been shown as a result of methylphenidate treatment in several randomized placebo-controlled trials [6–9]. Moreover, positive effects of stimulants on a functional level and measures of quality of life have been reported [10]. Likewise, a significant effect of methylphenidate on social adjustment over a period of 1 year could be demonstrated [11]. Clinical and statistically significant improvement of social functioning together with amelioration of ADHD symptoms was also found in recent randomized trials with extended release MPH in adults with ADHD [12–14].

In several meta-analyses, moderate-to-high standardized effect sizes on the reduction in ADHD core symptoms were calculated from studies of appropriate design and methodological standards. In a first meta-analysis, Faraone et al. [15] included six trials with methylphenidate in adult ADHD. They found a mean effect size of 0.9 and no evidence of publication bias. Larger MPH effect sizes were associated with physician ratings of outcome and use of higher doses. An overall moderate effect size of 0.42 was reported from another meta-analytical approach of 16 studies with methylphenidate in adult ADHD patients [16]. In this analysis, no significant influence of mean daily dose on effect size and no publication bias were found. In a third meta-analysis, Mészáros et al. [17] analyzed the efficacy of pharmacological treatment of 1991 adults with ADHD from 11 stimulant and non-stimulant treatment trials. The effect size for stimulants was 0.67 and somewhat higher than that for non-stimulant medications, where an effect size of 0.59 was found. Similarly, in a meta-analysis of 19 treatment studies, a significant higher effect size was found for stimulants (0.73 for long-acting stimulants and 0.86 for short-acting stimulants) than for non-stimulants (0.39) [18]. In a multivariate meta-regression with 18 studies, Castells et al. [19] showed that methylphenidate had a moderate effect on ADHD symptoms compared with placebo in a dose-dependent fashion with effect sizes between 0.57 and 0.58. Regarding the large body of evidence, stimulants have become the standard medical treatment for ADHD in adults due to their favorable efficacy profiles and tolerability and have been recommended as one component of multimodal therapy by several evidence-based guidelines [20–22].

Another statistical method for the interpretation of the efficacy of treatment results of pharmacological treatment in randomized controlled trials (RCT) is the calculation of responder rates and the "number needed to treat" (NNT), which is the number of patients who need to be treated to achieve one response that cannot be attributed to a placebo effect. In an analysis of 19 trials with adults with ADHD, NNTs ranged from 2 to 3 for long-acting stimulants, from 2 to 4 for short-acting stimulants and from 2 to 5 for non-stimulants [18]. It can be assumed that stimulants are a highly effective treatment for ADHD in adult patients. However, it has also to be concluded that there are few patients, who have no sufficient benefit from these drugs. Moreover, it has to be considered that data from RCTs do not reflect treatment reality due to strict exclusion criteria like psychiatric and somatic comorbidities and treatment adherence, which might produce a selection bias in favor of the drug under investigation.

According to these limitations of treatment of ADHD in adult patients with MPH and other stimulants, it was the intention of this work to give an overview over the up-to-date knowledge regarding neurobiological and clinical factors which contribute to and therefore might help to predict the outcome of MPH treatment adult ADHD patients.

Procedure

A systematic MEDLINE search was conducted in order to identify studies regarding patient- and treatment-related variables that predict outcome of MPH treatment in adult ADHD patients. Search terms included ADHD, adult, treatment, clinical trial, prediction, outcome, response and comorbidity. In addition, published qualitative reviews and meta-analyses of the adult psychotherapy literature were accessed to find studies not located through MEDLINE. Only peer-reviewed articles were sought.

Results

General aspects of treatment prediction

Treatment of ADHD always takes place in a sensitive interaction between the patient, the physician and both basic and specific therapeutic approaches, which might include psychoeducation, coaching, behavioral psychotherapeutic and psychopharmacological treatment (Fig. 1). The outcome depends on several variables including the efficacy and tolerability of the drug, but also the competence of the physician and the patient́s adherence to the therapeutic approaches. Importantly, the different facets of therapy affect the outcome not independently, but strong interactions between patient, therapist, drug and environment have to be considered.

Potential patient-related factors that might influence treatment outcome include neurobiological, but also clinical variables (Table 1). For the therapeutic process, it

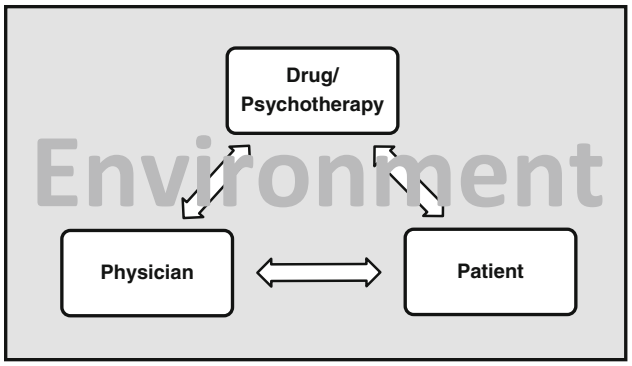

Fig. 1 Interaction of therapeutic approaches, patient- and physician-related factors and environment during the therapeutic process

Table 1 Potential patient-related predictors of treatment outcome

Neurobiological predictors	Clinical predictors
Genetic factors	Age/duration of ADHD
Neurochemical parameters	Severity of psychopathology
Neuronal correlates (MRI/fMRI, neurophysiology	Comorbidities (personality disorders, substance use disorders, depression)
Intelligence	Neurological status
Pharmacodynamics	Satisfaction with therapy/side effects
	Adherence to therapy
	Family and peer group of the patient

might be of importance to consider that neurobiological variables like genetic factors or intelligence are static parameters and cannot be changed, whereas clinical variables are dynamic factors and susceptible to modifications. For example, it is not possible to change genetic factor which contribute to the response to MPH, but integrating the spouse of the patient might be a significant intervention to improve the adherence to therapy and at least treatment outcome. Also the implementation of psychosocial support might help to keep a patient with ADHD in therapy and to improve overall efficacy.

Neurobiological predictors of treatment outcome

Potential neurobiological predictors of MPH treatment response comprise the use of neurochemical markers and correlates of neural activity observed with neuroimaging and neurophysiological techniques. Also pharmacogenomic studies have been performed in order to explain the variability of MPH response in individuals with ADHD. In contrast to the situation in children and adolescents, prediction of response to MPH by neurobiological parameters is generally not well studied in adult ADHD so far. Most studies have been performed with children and adolescents.

Neurochemical markers

In a huge number of studies, endogenous and exogenous chemical agents have been investigated regarding their impact on treatment outcome in ADHD patients. Recently, Scassellati et al. [23] used a meta-analytic approach to evaluate neurochemical markers in ADHD regarding diagnosis and treatment of ADHD. They identified and analyzed 210 studies of the main metabolites and metabolism enzymes of monoaminergic neurotransmission pathway; studies of environmental risk factors including heavy metals, chemical exposures, and nutritional factors, studies of the hypothalamic–pituitary–adrenal axis pathway and other neurochemical parameters. They found support for several peripheral biomarkers as being associated with ADHD both in diagnosis and in treatment efficacy, namely norepinephrine, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), monoamine oxidase, b-phenylethylamine and cortisol. These findings provide additional evidence to monoaminergic systems as well as hypothalamic–pituitary–adrenal axis being dysregulated in ADHD. However, they concluded that further studies are warranted to replicate these findings, to assess their specificity for ADHD and to quantify the degree to which they are sufficiently precise for the use as biomarkers for response to pharmacological treatment in clinical settings.

Pharmacogenetics

Genetic research has provided evidence to ADHD being highly heritable [24]. Candidate gene association studies, linkage analyses and genome-wide association studies (GWAS) have revealed a number of gene loci and susceptibility genes involved in adult ADHD and ADHD-related endophenotypes. Meta-analysis of linkage results has revealed one region that is significantly linked to ADHD on chromosome 16q [25]. Moreover, a huge number of association studies with genes regulating dopaminergic, noradrenergic and serotonergic neurotransmission support monoaminergic transporters and receptors being involved in ADHD pathophysiology [26–28], but these associations explain only a small amount of variance of ADHD symptoms. Candidate gene association studies have also provided new basic approaches regarding the neurobiology of ADHD [29, 30]. Although GWASs offer a powerful means to find genes that confer susceptibility to complex mental disorders, only few loci have been identified in such studies so far. However, beside improvement of study designs, also the development of innovative methods to study results from existing GWASs might help to identify new candidate genes [24, 31, 32]. Successful strategies to elucidate genetic mechanisms in the

pathophysiology of ADHD also include the investigation of gene x environment interactions [33, 34].

Pharmacogenetic and pharmacogenomic studies address inter-individual variability in the clinical response to pharmacological interventions. The potential of ADHD pharmacogenetics and pharmacogenomics for clinical application lies in predicting better medication choices, avoiding adverse effects, maximizing individual treatment outcomes and determining the most appropriate drug dosage. Regarding pharmacogenetic studies of ADHD treatment, an ongoing increase in the number of studies with different methodological strategies can be observed over the last years. In particular, a growing number of studies assessing gene–gene and gene–environment interactions, using genome-wide association approaches, have been conducted [35]. Also neurocognitive and neuroimaging endophenotypes are increasingly used in pharmacogenetic studies in order to elucidate the predictive value of genes regarding treatment effects. Much more genetic research in this field has been performed in children and adolescents than in adults ADHD subjects so far.

Numerous initial studies focusing on dopaminergic genes have described evidence of genetic factors influencing response to MPH [36, 37]. In particular, genetic variations of the dopamine transporter (DAT) have been widely investigated in adult ADHD, also regarding response to MPH treatment, but the results of the studies are very inconsistent. In a recent study, no support for an effect of several candidate genes including variants of dopaminergic and other genes in the pharmacogenetics of MPH among adults with ADHD was found [38]. Moreover, also a pharmacogenomic GWAS found no significant genome-wide associations between any gene and response to methylphenidate in a large sample of children with ADHD [39].

It can be assumed that efforts in pharmacogenetic studies of methylphenidate (MPH) response in patients with ADHD were yet not just fruitful and that the results from these investigations are inconsistent, especially among adults. The reasons for inconsistent findings seem to be manifold. On one hand, ADHD is a genetic heterogeneous disorder and also psychiatric comorbidities and environmental factors combined in different ways contribute to phenotypic heterogeneity of ADHD. On the other hand, also the heterogeneity in methodological strategies regarding the design of the study, response of treatment definition, the source of information, duration of treatment and dosing regimen might affect the results of these studies. It is also a relevant and still open question whether genes involved in ADHD and response to medication would be differentially expressed across the life cycle, which could explain inconsistent findings in different developmental stages.

It has to be concluded that no pharmacogenetic study has yet identified any gene with a strong impact in predicting response to MPH. Given the small and inconsistent effects of genetic variants studied so far, the variance of the treatment response explained by pharmacogenetic data does not seem to be substantial and does not justify genetic testing for treatment response.

Neuroimaging studies

The central objective of neuroimaging predictor studies is to identify common patterns of brain structure or activity in patients before treatment in relation to clinical response. In the best case, results from such studies could be generalized from the study group to an individual patient. It has been shown that this approach might be useful in the prediction of therapeutic response in patients with other psychiatric disorders, like depression and anxiety disorders [40]. Studies with adult ADHD patients are not available so far. In a naturalistic study with 107 children with ADHD, Shaw et al. [41] demonstrated that children with worse clinical outcome had a thinner left medial prefrontal cortex at baseline than children with the better outcome. Also smaller corpus callosum has been shown to be related to worse response to stimulant treatment [42]. Further analysis of this sample revealed that the stimulant responders had the smallest and symmetrical caudate volumes, as well as the smallest left anterior–superior cortex volumes, while the non-responders had reversed caudate asymmetry and the smallest retro-callosal parietal-occipital white matter volumes [43]. Also cerebellar structural anomalies have been reported to predict outcome to stimulant treatment. In a longitudinal case–control study with 36 children with ADHD, those with a worse clinical outcome exhibited smaller volumes of the right and left inferior posterior cerebellar lobes, which became progressively smaller during adolescence relative to ADHD subjects with a better outcome [44]. Although these studies have provided some promising findings, there is not enough evidence yet to use MRI as a clinical tool for the prediction of therapy response [45]. Moreover, due to significant developmental changes during brain maturation, one should be cautious to transfer findings from morphometric studies in children with ADHD to adult patients.

Neuronal activity has been investigated in functional imaging studies, including single-photon emission-computed tomography (SPECT) and positron emission tomography (PET) not only in order to elucidate the pathophysiology of ADHD, but also regarding the response to therapy. Radio-labeled ligands have been used mainly to study components of the dopaminergic system such as dopamine transporters (DAT) and dopamine D2 receptors as markers of treatment response to MPH.

According to the first study by Krause et al. [46], adult ADHD patients with high striatal DAT availability responded better to therapy with MPH than those with low DAT availability. La Fougere et al. [47] also hypothesized that the degree of DAT binding might be related to the response to MPH. Using SPECT, they compared striatal DAT binding in MPH responders and non-responders. Similar to the prior study, all except one ADHD patient presenting with high striatal DAT binding responded well to MPH therapy, while none of ADHD patients with lower DAT levels showed a significant improvement of ADHD symptoms. However, in another study with adult ADHD patients, no correlation between DAT binding and baseline symptom severity or with reduction in ADHD symptoms during open-label MPH treatment was found [48]. Also in a study with ADHD children, a good response to MPH was found in some patients with low DAT binding in the basal ganglia and some with higher DAT binding was shown, suggesting that outcome to MPH treatment is not directly associated with the density of DAT in basal brain areas [49]. According to these contradictory results, it seems not useful to use the DAT status in untreated ADHD patients as a predictor of response to MPH therapy.

Neuroimaging studies have also provided evidence that striatal dopamine D2 receptor availability might be predictive to MPH response [50]. In a small sample of children with ADHD, a negative correlation between D2 levels before treatment with the reduction in hyperactivity ratings, but not with response to attention-deficit scores, was detected. Data from adults with ADHD are not available.

Different patterns of regional cerebral blood flow (rCBF) in brain regions in responders and non-responders to MPH therapy have been reported by Cho et al. [51]. In a voxel-based investigation of rCBF using technetium-99m-hexamethylporphyleamineoxime (HMPAO) SPECT during resting state in a sample of children with ADHD, non-responders to MPH had higher rCBF in the left and right anterior, cingulate cortex, the left claustrum, and the right putamen, but lower rCBF was found in the right superior parietal lobule in non-responders to MPH relative to responders. Moreover, in a positron emission tomography (PET) study, whole-brain resting state rCBF volumes in unmedicated adult subjects with ADHD were correlated with improvement of ADHD scores after MPH medication [52]. Subjects with greater improvement in ADHD symptom ratings showed lower resting rCBF at baseline in the midbrain, posterior cerebellum and left middle frontal gyrus.

Clinical predictors

MPH dose and treatment adherence

Generally, controlled treatment trials offer the opportunity not only to test efficacy and tolerability of a drug, but also to analyze the impact of specific variables on treatment outcome. Regarding the influence of gender, age and cigarette smoking, the analysis of a multicenter RCT with extended release methylphenidate in adults with ADHD revealed no influence of these parameters on the response rates found in this study [13]. Data from this study also showed that higher doses of methylphenidate were associated with a greater reduction in ADHD symptoms. Evidence for a dose–response relationship comes also from meta-analyses of treatment studies [15, 19]. One meta-analysis of data from 18 RCTs in adults with ADHD indicated that efficacy could be increased by SMD 0.11–0.12 for every 10-mg increment of methylphenidate [19]. These results suggest that the use of low doses of methylphenidate might be predictive for only limited effects of MPH treatment in adults with ADHD.

The effectiveness of medication treatment outcome is also determined by how consistently and how long a patient follows the treatment regimen, which are behaviors described by the terms “adherence” and “persistence” [53]. Retrospective claim analyses from US managed care health plans have reported a mean treatment adherence of 43–58 % and a mean treatment persistence of 68–183 days for the treatment with MPH extended release and of 39–84 days for the treatment with MPH immediate release formulations [54, 55]. To date, descriptive data and knowledge of factors contributing to non-adherence and treatment discontinuation in adult ADHD are still limited and inconsistent [56, 57], although it has been shown that non-adherence is related to worse treatment outcome and course of the disorder [58]. Recently, Sobanski et al. [59] have identified patient-related factors associated with non-adherence in the sample of 241 adults with ADHD, who were involved in a 24-week RCT with extended release MPH. Factors contributing to non-adherence included young age (<25 years), education level lower than secondary education, lacking family history of ADHD, lower ADHD baseline severity, and lower self- and observer-rated medication efficacy. Factors associated with discontinuation of treatment included male gender, lower education level, lacking family history of ADHD, and lower self- and observer-rated medication efficacy. However, due to inconsistencies with other studies [58], the authors resumed that further prospective studies measuring adherence and persistence to treatment under naturalistic

conditions are needed to clarify which factors contribute to non-adherence and might therefore predictive for unfavorable treatment outcome.

Comorbidity

In clinical populations, the presence of ADHD with co-occurring psychiatric disorders is the rule, not the exception. During childhood and adolescence, learning disorders, tics, conduct disorders, nicotine and substance use disorders, including alcohol, are the most frequent comorbid conditions. Adults with ADHD often present with comorbid mood disorders, anxiety disorders, substance use disorders (SUD) and personality disorders, making both diagnosis and treatment of the different diseases a clinical challenge [60, 61]. The broad spectrum of comorbid conditions of people with ADHD should be scrutinized thoroughly because the comorbidities may influence the treatment process, as well as outcome. In children, it was found that the studies that have examined prediction have found only little evidence for comorbidity to impede treatment gains [62]. Although the clinical relevance of comorbidity for the treatment of adults with ADHD under naturalistic conditions is high, data regarding the impact of comorbid mental health problems on response to MPH treatment in older ADHD patients are rare.

A putative causal relationship between ADHD and SUD [63] has stimulated a number of studies to proof the hypothesis that treating ADHD could lead to an improvement of SUD outcomes in patients with coexisting ADHD and SUD. However, evidence of the efficacy of pharmacological treatment of co-occurring ADHD and SUD remained inconclusive. Some controlled clinical trials showed a reduction in ADHD symptoms and SUD outcomes, while others showed no benefit. In a recent meta-analysis of thirteen studies with a total of 1,271 patients, Cunill et al. [64] found a small-to-moderate reduction in ADHD symptoms, but no beneficial effect was observed either on drug abstinence or on treatment discontinuation. The effect size on ADHD symptoms, as shown by an odds ratio of 1.93 and a corresponding effect size (SMD) of 0.30, was about half of those observed in other studies in which SUD was an exclusion criterion [16, 19]. It has to be concluded from these findings that current SUD might limit the positive effects of pharmacological treatment in adult ADHD patients and may therefore serve as a negative predictor of treatment outcome, at least when no further psychotherapeutic and psychosocial interventions will be implemented into the therapeutic concept.

There are only few studies, which have focused on further comorbid conditions which are common in adults with ADHD. We found only two studies, which have evaluated the impact of comorbid personality disorders (PD) on the course and outcome of treatment of adults with ADHD. Robison et al. [65] have reanalyzed data from a randomized treatment trial with MPH in adult ADHD patients. They compared patients without PD with two further groups, one with one comorbid PD and one with two or more PDs and observed different treatment effects for these subgroups. They found that the responder rate in the group with two or more PDs treated with MPH was only 23 %, but 40 % and 66 % in the other two patient groups. Interestingly, in the group with two or more comorbid PDs, the response to placebo was higher than in the other two patient groups (responder rates 26 vs. 7 and 9 %, respectively) and did not differ from the response to MPH. The data suggest that comorbidity with complex disturbances in terms of a combination of different personality disorders has only a small chance to get benefit form a treatment with MPH under controlled conditions. In another study, Torgersen et al. [66] showed in a naturalistic sample that comorbid antisocial PD was a negative predictor for long-term treatment duration of adult ADHD patients with stimulants. As early termination might be associated with poor treatment response, the results of this study might indicate that antisocial PD predict unfavorable treatment outcome. With respect to studies, which show very good treatment effects in antisocials with ADHD within highly structured settings [67], it has to be assumed that the results from this naturalistic study are primarily a result of low treatment adherence in patients with a combination of ADHD and antisocial PD and not of inefficiency of MPH per se.

Discussion

As not all adult patients with ADHD respond sufficiently from treatment with methylphenidate, it was the aim to give an overview about the current knowledge regarding neurobiological and clinical predictors of MPH treatment outcome in adult ADHD. The identification of markers of treatment response might be useful, since they may guide the clinician as to which medication to prescribe. Moreover, knowledge about neurobiological markers of response to MPH treatment might also help to understand the neural mechanisms that underlie the pathophysiology of ADHD.

Systematic search of literature revealed only a very limited number of studies, which have been performed in adults with ADHD in order to identify relevant factors that predict MPH treatment outcome. Overall, the results from these studies are inconsistent and do not allow recommendations for the use of neurobiological markers for the prediction of treatment outcome. Although neuroimaging

studies in children and adolescents have revealed some promising findings, studies in adults are lacking and much more work should be done to establish more reliable neuroimaging markers of treatment response to MPH. However, some findings of patient- and treatment-related variables might be useful regarding clinical practice of treatment, like the quite robust finding of limited MPH treatment effects in adults with ADHD and comorbid unremitted SUD, or the positive dose–response relationship found in adult patients.

As a general limitation of studies, investigating the impact of several variables on treatment outcome is the absence of a generally accepted definition of response. Indeed, most studies use a 30 or 50 % decline of self- or expert-rated ADHD symptom scores for the definition of response. Moreover, it has to be mentioned that a lot of studies in this field used small sample sizes and open trial designs. On the other hand, some findings are secondary results from randomized clinical treatment trials, with narrow inclusion and exclusion criteria. It cannot be expected that results of these studies exactly reflect treatment reality. Also the duration of MPH treatment in RCTs is usually limited to several weeks, which might be too short in many cases to assess the real treatment outcome.

One should also bear in mind that ADHD is a developmental disorder and that findings from children and adolescents cannot be extrapolated to adult ADHD patients. Genes, for example, might be differentially expressed across the life cycle, the normal trajectory of brain development has to be taken into account regarding imaging studies, and also changes of the metabolism of neurotransmitters and metabolizing enzymes have to be considered when peripheral neurochemical markers are evaluated.

Conclusions

Based on the present evidence from studies, no neurobiological or clinical markers can be recommended as reliable markers for MPH treatment outcome in adult patients. However, it is an interesting question, why in most of adult patients with ADHD a beneficial effect of MPH can be observed, whereas some patients show no sufficient remission of symptoms. Knowledge about differences between responders and non-responders to MPH or other medications regarding genetic factors or neuronal activation measured with neuroimaging techniques might help to understand the heterogeneity of this disorder. Further research might therefore help to optimize treatment of adults with ADHD and to find new options for the treatment for patients who do not respond to MPH.

Conflict of interest WR is a member of the advisory board of Medice and has been invited speaker for Novartis. PRJ has no conflicts of interests to declare.

References

1. Polanczyk G, Rohde LA (2007) Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry 20:386–392
2. Fayyad J, De Graf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, De Girolamo G, Haro JM, Karam EG, Lara C, Lépine JP, Ormel J, Posada-Villa J, Zaslavsky AM, Jin R (2007) Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 190:402–409
3. Barkley RA, Fischer M, Smallish L, Fletcher K (2006) Young adult outcome of hyperactive children; adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry 45:92–202
4. Stein MA (2004) Innovations in attention-deficit/hyperactivity disorder pharmacotherapy: long-acting stimulant and nonstimulant treatments. Am J Manag Care 10:S89–S98
5. Retz W, Retz-Junginger P, Thome J, Rösler M (2011) Pharmacological treatment of adult ADHD in Europe. World J Biol Psychiatry 12(Suppl 1):89–94
6. Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK (2007) A double-blind, placebo-controlled, cross-over study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry 68:93–101
7. Rösler M, Fischer R, Ammer R, Ose C, Retz W (2009) A randomised, placebo-controlled, 24-week, study of low dose extended-release methylphenidate in adults with attentiondeficit/hyperactivity disorder. Eur Arch Psychiatry Clin Neurosci 259:120–129
8. Rösler M, Retz W, Fischer R, Ose C, Alm B, Deckert J, Philipsen A, Herpertz S, Ammer R (2010) Twenty-for-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. World J Biol Psychiatry 11:709–718
9. Marchant BK, Reimherr FW, Robison RJ, Olsen JL, Kondo DG (2011) Methylphenidate transdermal system in adult ADHD and impact on emotional and oppositional symptoms. J Atten Disord 15:295–304
10. Spencer TJ, Adler LA, Weisler RH, Youcha SH (2008) 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. J Clin Psychiatry 69:1437–1448
11. Wender PH, Reimherr FW, Marchant BK, Sanford ME, Czajkowski LA, Tomb DA (2011) A one year trial of methylphenidate in the treatment of ADHD. J Atten Disord 15:35–45
12. Huss M, Ginsberg Y, Tvedten T, Arngrim T, Philipsen A, Carter K, Chen CW, Kumar V (2014) Methylphenidate hydrochloride modified-release in adults with attention deficit hyperactivity disorder: a randomized double-blind placebo-controlled trial. Adv Ther 31:44–65
13. Retz W, Rösler M, Ose C, Scherag A, Alm B, Philipsen A, Fischer R, Ammer R (2012) Multiscale assessment of treatment efficacy in adults with ADHD: a randomized placebo-controlled, multi-centre study with extended-release methylphenidate. World J Biol Psychiatry 13:48–59
14. Rösler M, Ginsberg Y, Arngrim T, Adamou M, Niemelä A, Dejonkheere J, van Oene J, Schäuble B (2013) Correlation of symptomatic improvements with functional improvements and patient-reported outcomes in adults with attentiondeficit/

hyperactivity disorder treated with OROS methylphenidate. World J Biol Psychiatry 14:282–290
15. Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J (2004) Meta-analysis of the efficacy of methylphenidate for treating adult attentiondeficit/hyperactivity disorder. J Clin Psychopharmacol 24:24–39
16. Koesters M, Becker T, Kilian R, Fegert JM, Weinmann S (2009) Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. J Psychopharmacol 23:733–744
17. Mészáros A, Czobor P, Bálint S, Komlósi S, Simon V, Bitter I (2009) Pharmacotherapy of adult attention deficit hyperactivity disorder (ADHD): a meta-analysis. Int J Neuropsychopharmacol 12:1137–1147
18. Faraone SV, Glatt SJ (2010) A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry 71:754–763
19. Castells X, Ramos-Quiroga JA, Rigau D, Bosch R, Nogueira M, Vidal X, Casas M (2011) Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: a meta-regression analysis. CNS Drugs 25:157–169
20. Ebert D, Krause J, Roth-Sackenheim C, the DGPPN Expert Committee (2003) ADHD in adulthood—guidelines based on expert consensus with DGPPN support. Nervenarzt 74:939–946
21. 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, British Association for Psychopharmacology (2007) 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. J Psychopharmacol 21:10–41
22. National Institute for Health and Clinical Excellence (2008) Attention deficit hyperactivity disorder: pharmacological and psychological interventions in children, young people and adults. www.NICE.org.uk
23. Scassellati C, Bonvicini C, Faraone SV, Gennarelli M (2012) Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. J Am Acad Child Adolesc Psychiatry 51:1003–1019
24. Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, Mick E, Grevet EH, Johansson S, Haavik J, Lesch KP, Cormand B, Reif A; International Multicentre persistent ADHD Collaboration (2012) The genetics of attention deficit/hyperactivity disorder in adults, a review. Mol Psychiatry 17:960–987
25. Zhou K, Dempfle A, Arcos-Burgos M, Bakker SC, Banaschewski T, Biederman J, Buitelaar J, Castellanos FX, Doyle A, Ebstein RP, Ekholm J, Forabosco P, Franke B, Freitag C, Friedel S, Gill M, Hebebrand J, Hinney A, Jacob C, Lesch KP, Loo SK, Lopera F, McCracken JT, McGough JJ, Meyer J, Mick E, Miranda A, Muenke M, Mulas F, Nelson SF, Nguyen TT, Oades RD, Ogdie MN, Palacio JD, Pineda D, Reif A, Renner TJ, Roeyers H, Romanos M, Rothenberger A, Schäfer H, Sergeant J, Sinke RJ, Smalley SL, Sonuga-Barke E, Steinhausen HC, van der Meulen E, Walitza S, Warnke A, Lewis CM, Faraone SV, Asherson P (2008) Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147B:1392–1398
26. Retz W, Thome J, Blocher D, Baader M, Rösler M (2002) Association of attention deficit hyperactivity disorder-related psychopathology and personality traits with the serotonin transporter promoter region polymorphism. Neurosci Lett 319:133–136
27. Retz W, Rösler M, Kissling C, Wiemann S, Hünnerkopf R, Coogan A, Thome J, Freitag C (2008) Norepinephrine transporter and catecholamine-O-methyltransferase gene variants and attention-deficit/hyperactivity disorder symptoms in adults. J Neural Transm 115:323–329
28. de Azeredo LA, Rovaris DL, Mota NR, Polina ER, Marques FZ, Contini V, Vitola ES, Belmonte-de-Abreu P, Rohde LA, Grevet EH, Bau CH (2014) Further evidence for the association between a polymorphism in the promoter region of SLC6A3/DAT1 and ADHD: findings from a sample of adults. Eur Arch Psychiatry Clin Neurosci 264:401–408
29. Reif A, Jacob CP, Rujescu D, Herterich S, Lang S, Gutknecht L, Bähne CG, Strobel A, Freitag CM, Giegling I, Romanos M, Hartmann A, Rösler M, Renner TJ, Fallgatter AJ, Retz W, Ehlis AC, Lesch KP (2009) Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. Arch Gen Psychiatry 66:41–50
30. Weber H, Scholz CJ, Jacob CP, Heupel J, Kittel-Schneider S, Erhardt A, Hempel S, Schmidt B, Kiel T, Gessner A, Lesch KP, Reif A (2014) SPOCK3, a risk gene for adult ADHD and personality disorders. Eur Arch Psychiatry Clin Neurosci 264:409–421
31. Li Z, Chang SH, Zhang LY, Gao L, Wang J (2014) Molecular genetic studies of ADHD and its candidate genes: a review. Psychiatr Res 219:10–24
32. Lee HY, Song GG (2014) Genome-wide pathway analysis in attention-deficit/hyperactivity disorder. Neurol Sci 35:1189–1196
33. Retz W, Freitag CM, Retz-Junginger P, Wenzler D, Schneider M, Kissling C, Thome J, Rösler M (2008) A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: interaction with adverse childhood environment. Psychiatr Res 158:123–131
34. Getahun D, Rhoads GG, Demissie K, Lu SE, Quinn VP, Fassett MJ, Wing DA, Jacobsen SJ (2013) In utero exposure to ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. Pediatrics 131:e53–e61
35. Bruxel EM, Akutagava-Martins GC, Salatino-Oliveira A, Contini V, Kieling C, Hutz MH, Rohde LA (2014) ADHD pharmacogenetics across the life cycle: new findings and perspectives. Am J Med Genet B Neuropsychiatr Genet 165B:263–282
36. Froehlich TE, McGough JJ, Stein MA (2010) Progress and promise of attention-deficit hyperactivity disorder pharmacogenetics. CNS Drugs 24:99–117
37. Polanczyk G, Bigarella MP, Hutz MH, Rohde LA (2010) Pharmacogenetic approach for a better drug treatment in children. Curr Pharm Des 16:2462–2473
38. Contini V, Victor MM, Bertuzzi GP, Salgado CA, Picon FA, Grevet EH, Rohde LA, Belmonte-de-Abreu P, Bau CH (2012) No significant association between genetic variants in 7 candidate genes and response to methylphenidate treatment in adult patients with ADHD. J Clin Psychopharmacol 32:820–823
39. Mick E, Neale B, Middleton FA, McGough JJ, Faraone SV (2008) Genome-wide association study of response to methylphenidate in 187 children with attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147B:1412–1418
40. Evans KC, Dougherty DD, Pollack MH, Rauch SL (2006) Using neuroimaging to predict treatment response in mood and anxiety disorders. Ann Clin Psychiatry 18:33–42
41. Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, Giedd J, Castellanos FX, Rapoport J (2006) Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attentiondeficit/hyperactivity disorder. Arch Gen Psychiatry 63:540–549
42. Semrud-Clikeman M, Filipek PA, Biederman J, Steingard R, Kennedy D, Renshaw P, Bekken K (1994) Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psychiatry 33:875–881

43. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997) Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48:589–601
44. Mackie S, Shaw P, Lenroot R, Pierson R, Greenstein DK, Nugent TF 3rd, Sharp WS, Giedd JN, Rapoport JL (2007) Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. Am J Psychiatry 164:647–655
45. Skokauskas N, Hitoshi K, Shuji H, Frodl T (2013) Neuroimaging markers for the prediction of treatment response to Methylphenidate in ADHD. Eur J Paediatr Neurol 17:545–551
46. Krause J, la Fougere C, Krause KH, Ackenheil M, Dresel SH (2005) Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. Eur Arch Psychiatry Clin Neurosci 255:428–431
47. la Fougère C, Krause J, Krause KH, Josef Gildehaus F, Hacker M, Koch W, Hahn K, Tatsch K, Dresel S (2006) Value of 99mTc-TRODAT-1 SPECT to predict clinical response to methylphenidate treatment in adults with attention deficit hyperactivity disorder. Nucl Med Commun 27:733–737
48. van Dyck CH, Quinlan DM, Cretella LM, Staley JK, Malison RT, Baldwin RM, Seibyl JP, Innis RB (2002) Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. Am J Psychiatry 159:309–312
49. Cheon KA, Ryu YH, Kim YK, Namkoong K, Kim CH, Lee JD (2003) Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. Eur J Nucl Med Mol Imaging 30:306–311
50. Ilgin N, Senol S, Gucuyener K, Gokcora N, Sener S (2001) Is increased D2 receptor availability associated with response to stimulant medication in ADHD. Dev Med Child Neurol 43:755–760
51. Cho SC, Hwang JW, Kim BN, Lee HY, Kim HW, Lee JS, Shin MS, Lee DS (2007) The relationship between regional cerebral blood flow and response to methylphenidate in children with attention-deficit hyperactivity disorder: comparison between non-responders to methylphenidate and responders. J Psychiatr Res 41:459–465
52. Schweitzer JB, Lee DO, Hanford RB, Tagamets MA, Hoffman JM, Grafton ST, Kilts CD (2003) A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. Neuropsychopharmacology 28:967–973
53. Sabate E (2003) Adherence to long-term therapies: evidence for action. World Health Organisation, Geneva. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf
54. Hodgkins P, Sasane R, Christensen L, Harley C, Liu F (2001) Treatment outcomes with methylphenidate formulations among patients with ADHD: retrospective claims analysis of a managed care population. Curr Med Res Opin 27:53–62
55. Christensen L, Sasane R, Hodgkins P, Harley C, Tetali S (2010) Pharmacological treatment patterns among patients with attention-deficit/hyperactivity disorder: retrospective claims-based analysis of a managed care population. Curr Med Res Opin 26:977–989
56. Adler LD, Nierenberg AA (2010) Review of medication adherence in children and adults with ADHD. Postgrad Med 122:184–191
57. Caisley H, Mueller U (2012) Adherence to medication in adults with attention deficit hyperactivity disorder and pro re nata dosing of psychostimulants: a systematic review. Eur Psychiatry 27:343–349
58. Kooij JJ, Rösler M, Philipsen A, Wächter S, Dejonckheere J, van der Kolk A, van Agthoven M, Schäuble B (2013) Predictors and impact of non-adherence in adults with attention-deficit/hyperactivity disorder receiving OROS methylphenidate: results from a randomized, placebo-controlled trial. BMC Psychiatry 13:36
59. Sobanski E, Retz W, Fischer R, Ose C, Alm B, Hennig O, Rösler M (2014) Treatment adherence and persistence in adult ADHD: results from a twenty-four week controlled clinical trial with extended release methylphenidate. Eur Psychiatry 29:324–330
60. Miller TW, Nigg JT, Faraone SW (2007) Axis I and II comorbidity in adults with ADHD. J Abnorm Psychol 116:519–528
61. Sobanski E, Brüggemann D, Alm B, Kern S, Deschner M, Schubert T, Philipsen A, Rietschel M (2007) Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 257:371–377
62. Ollendick TH, Jarrett MA, Grills-Taquechel AE, Hovey LD, Wolff JC (2008) Comorbidity as a predictor and moderator of treatment outcome in youth with anxiety, affective, attention deficit/hyperactivity disorder, and oppositional/conduct disorders. Clin Psychol Rev 28:1447–1471
63. Wilens TE (2004) Attention-deficit/hyperactivity disorder and the substance use disorders: the nature of the relationship, subtypes at risk, and treatment issues. Psychiatr Clin North Am 27:283–301
64. Cunill R, Castells X, Tobias A, Capellà D (2014) Pharmacological treatment of attention deficit hyperactivity disorder with comorbid drug dependence. J Psychopharmacol. doi:10.1177/0269881114544777
65. Robison RJ, Reimherr FW, Gale PD, Marchant BK, Williams ED, Soni P, Halls C, Strong RE (2010) Personality disorders in ADHD Part 2: the effect of symptoms of personality disorder on response to treatment with OROS methylphenidate in adults with ADHD. Ann Clin Psychiatry 22:94–102
66. Torgersen T, Gjervan B, Nordahl HM, Rasmussen K (2012) Predictive factors for more than 3 years' duration of central stimulant treatment in adult attention-deficit/hyperactivity disorder: a retrospective, naturalistic study. J Clin Psychopharmacol 32:645–652
67. Ginsberg Y, Lindefors N (2012) Methylphenidate treatment of adult male prison inmates with attention-deficit hyperactivity disorder: randomised double-blind placebo-controlled trial with open-label extension. Br J Psychiatry 200:68–73