RESEARCH ARTICLE



Physician-reported treatment

outcomes for ADHD among children and adolescents in Europe

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- It is important to identify factors that may affect ADHD treatment effectiveness in real-world care.
- Clinicians should consider multimodal approaches to address core ADHD symptoms and functional impairments in the management of ADHD.
- Clinicians are aware that patient adherence to a medication treatment varies considerably with a range from 35 to 80%, and that this affects treatment outcomes.
- High levels of engagement and family involvement improve adherence, which, in turn, improves outcome.
- Poor symptom control (e.g., residual inattention or challenges with school performance) is more probable in nonadherent patients.
- There are still opportunities to implement improved treatment strategies and achieve better outcomes for patients with ADHD.
- Optimal treatment success, a new composite measure derived from measures of physician-reported symptom control and satisfaction with treatment, may be a helpful tool for comparing the effectiveness of treatment on outcomes in clinical practice.

SUMMARY Aims: The aim of this study was to describe associations between physician-reported patient characteristics, treatment modalities and assessed outcomes in children diagnosed with ADHD in six countries. **Methods:** Clinical records of ADHD patients were retrospectively reviewed by treating physicians. Patients had optimal treatment success (OTS) if the physician assessed them as having complete symptom control and was highly satisfied with treatment. **Results:** Out of the 708 patients, 505 (71.3%) were treatment adherent. OTS was reported in 28.1% of patients (33.7% adherent and 14.3% nonadherent; p < 0.0001). Among adherent patients, there was no association between treatment type and OTS. Multivariate logistic regression models suggest that patients achieving OTS were more likely to have fewer comorbidities and lower reported impairment levels for ADHD-associated symptoms/behaviors. **Conclusion:** Overall, OTS was low. Among adherent



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patients, those with more comorbidities/greater ADHD impairment achieved lower OTS. There was no difference between treatment modalities, suggesting that opportunities exist to develop improved ADHD treatments.

ADHD is a neurodevelopmental disorder commonly diagnosed in school-age children that often persists into adulthood [1,2]. Although diagnostic criteria for ADHD and efforts to detect or diagnose ADHD vary, the prevalence of ADHD is reported to be approximately 5–7% [3,4], an estimate that is consistent within individual European studies [5-7]. Core symptoms include hyperactivity, inattention and impulsivity. These core symptoms impact health-related quality of life, not only in daily activities of individuals but also in long-term achievement of academic goals, workforce productivity and social relationships [8]. Negative health-related quality of life consequences also extend to family members and manifest as depression, disrupted parent-child relationships, marital discord and parenting stress [8,9]. ADHD often coexists with other conditions, such as oppositional defiant disorder and conduct disorder, anxietyspectrum disorders, mood disorders, learning disabilities, motor and vocal tics and Tourette's syndrome [10,11].

Although the etiology of ADHD appears to be multifactorial [1,10,12], a key component appears to be dysregulation of the neurotransmitters dopamine and noradrenaline [13]. Given the limited understanding of the pathophysiology of ADHD, the complexity of the physical and behavioral needs of the affected children, and the inherent variation in the ability of each family to provide care, it follows that clinical management strategies may vary considerably. The ability to achieve optimal treatment outcomes, as demonstrated in clinical trials where patients with coexisting difficulties are usually excluded, may be diminished in real-world settings [14].

National and international guidelines have all recommended a multimodal approach to care [15], which allows for the use of behavioral intervention therapies, such as parent training, school intervention or child-focused supplemental treatment, either as a first-line approach or in combination with pharmacotherapy [16]. Although the evidence base supporting this strategy is mixed due to differences in study methodologies and patient populations [17], a multimodal approach allows clinicians to address both core ADHD symptoms and functional impairments of the patient [15]. The mainstays of pharmacologic treatment are stimulants, primarily methylphenidate and amphetamine classes [18,101]; methylphenidate is the only treatment widely available in the EU. Atomoxetine is a common nonstimulant therapy and the only nonstimulant currently approved in the EU [19]. In clinical trials, the efficacy of pharmacotherapy in ADHD is supported by a large amount of data [17]. However, there is a paucity of information on the effectiveness of ADHD medications in the real-world setting.

To date, reports regarding the effectiveness of ADHD treatment in observational settings suggest that there are many barriers to achieving optimal treatment goals, including failure to align the child's clinical severity with the appropriate provider type [20,21], infrequent follow-up visits [20,22], limited physician adherence to guidelines [23,24], regional variation in clinical guidelines [15], and limited patient and family adherence to medications and behavioral therapies (BTs) [16,19,25–27].

The proportion of patients that are classified as adherent to a medication regimen (i.e., taking the medications as prescribed) has varied considerably across studies, with an extensive review by Swanson citing adherence rates that range from 35 to 80% [27]. Much of this variation is due to differences in settings and study populations, methodologies and case definitions.

This wide variety of factors affecting ADHD treatment outcomes greatly impacts the ability to assess treatment effectiveness in observational settings. ADHD symptoms in those children who are adherent to their medications do improve in the long term [17]. However, there are very limited European population-based studies that have estimated the impact of ADHD treatment modalities on affected children in observational settings.

The purpose of the current study is to examine the association between treatment type and treatment success defined as 'physicianassessed symptoms control and satisfaction' in six European countries.

Methods Study design

This study was undertaken as part of a retrospective review of patient medical records by their treating physicians. Study participants included pediatricians, neuropediatricians, child and adolescent psychiatrists, and pediatric neurologists who treated patients with ADHD in six European countries (France, Germany, Italy, The Netherlands, Spain and the UK). Physicians were contacted using a list derived from nationally maintained physician directories in each country. Recruitment of patients continued until the target number of approximately 130 patients per country was met. Physicians were eligible for inclusion in the study if they were engaged in clinical practice for between 3 and 30 years of age and were responsible for making ADHD treatment decisions for their patients. Participating physicians identified up to five of their most recent patients who met the following criteria: received a diagnosis of ADHD between January 2004 and June 2007; were followed for at least 2 years after being diagnosed; received either pharmacologic treatment or BT, including child, parent or family BT, following the diagnosis; and were not enrolled in a clinical trial during the study period (Figure 1). Data regarding both physician and patient characteristics were collected retrospectively at the time of chart abstraction. Physicians were nominally compensated for their time.

Outcome variable

The binary outcome variable for this study, optimal treatment success (OTS), was created

using a combination of the physician's assessment of the patient's control of his/her ADHD symptoms (completely, moderately, poorly or not controlled) and the physician's level of satisfaction with the treatment (very satisfied, moderately satisfied, neither satisfied nor dissatisfied, moderately dissatisfied or very dissatisfied). Physician satisfaction and assessment of patients' ADHD symptom control with 'current' (at time of chart review) treatment were posed as two separate questions: how well controlled are ADHD symptoms for this patient with this current treatment? How would you define your level of overall satisfaction with this current treatment? As such, this outcome variable measures the physician's assessment of improvement in ADHD symptoms and their overall satisfaction with treatment. These questions were asked in general and were not conditional on treatment goal achievement or on resolution of symptoms or comorbid conditions, because these data were abstracted only once, at the time of diagnosis. Descriptive results from physician scoring of overall satisfaction with treatment demonstrated that physicians were moderately or very dissatisfied with treatment in only 3% of patients. Given the small numbers of patients in these groups, these levels of satisfaction were combined with the 'moderately satisfied' responses (55%) and compared with the 'very satisfied' level. Similarly, physicians reported that symptoms were not controlled



Figure 1. Study design.

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in <0.5% of patients and poorly controlled in 7%, and these responses were also combined with the 'moderately controlled' response group (62%) and compared with the 'completely controlled' group. The above dichotomization was supported by examining the distribution of ADHD symptoms/behaviors and comorbidities across each of the outcomes categorized into three levels (best, moderate or poor). This examination of the data confirmed that the moderate outcome group showed a greater similarity in distribution patterns to the poor outcome group than to the best outcome group, supporting the aggregation of the moderate and poor outcome response levels.

Given the high correlation (r = 0.82) between physician-reported satisfaction and physician ratings of symptom control, and in an effort to simplify the analysis and focus on the patients with the best outcomes, OTS was defined as the physician being 'very satisfied' with treatment and reporting 'complete symptom control'.

Explanatory variables

Treatment was categorized based on two different schemes: treatment modality and treatment type. Treatment modality included pharmacologic therapy only, BT only or both. Treatment type included all three modalities and was further refined by subclassifying the pharmacologic treatment group by medication classes: long-acting methylphenidate, short-acting (SA) methylphenidate, SA amphetamine, atomoxetine, other pharmacotherapy and multiple pharmacotherapies. The main explanatory variable was treatment type. Treatment characteristics included the number of therapy changes recorded on the patient's chart (up to five), the number of years of follow-up since diagnosis, the number of therapy changes per follow-up year and concomitant psychotropic medications. The study definition of initiating a new 'therapy' was the addition or discontinuation of an ADHD medication or BT. Dose titration was not counted as a new therapy. For this study, the analysis was based on the 'current' therapy (i.e., that being administered at the time of chart abstraction).

The following treatment goals were also reviewed and summarized (binary yes/no): improve concentration/functioning at school/work (i.e., improve inattention); control hyperactivity; control aggression; control impulsivity; increase self-esteem; reduce chances of substance abuse; enable patient to build relationships; enable patient to maintain relationships; improve behavior; reduce likelihood of being in trouble; reduce disruption at home; enable participation in activities outside of school; minimize chance of exclusion from school/work; improve family relationships; and other. Multiple responses regarding treatment goals were allowed per patient. Goals were grouped based on clinical considerations and empirical evidence (i.e., factor analysis) to reduce the number of categories. As treatment goals represent expectations from treatment and may be associated with physicianreported satisfaction with treatment and symptom control, the grouped goals were included as potential predictors. The factor labeled 'Restrain of inappropriate behavior' was the only factor extracted from the factor analysis and associated with the OTS outcome. It encompassed the following treatment goals: control aggression; reduce chances of substance abuse; reduce likelihood of being in trouble; and minimize chance of exclusion from school/work.

Clinical characteristics of patients with ADHD at the time of diagnosis included identification of the predominant ADHD symptoms/behaviors (i.e., inattention, hyperactivity, impulsivity, anger, irritability, active defiance, tendency to blame others, challenges with school performance, social problems when interacting with family/teachers/peers/ colleagues, difficulty making the right choices, inappropriate behavior and other symptoms/ behaviors). Each of these 12 symptoms/behaviors was scored by the physician with respect to 'ADHD impairment' using a scale from 1 to 10, with 1 being the lowest impairment and 10 being the highest impairment. Impairment scores were also aggregated by 'core' symptoms (i.e., inattention, hyperactivity and impulsivity) and the additional symptoms/behaviors (the other nine 'noncore' symptoms). These other noncore symptoms are well known to clinicians treating ADHD, as similar items are included in assessment tools often used among the schoolage ADHD population [28,102]. Other clinical characteristics used as explanatory variables included ADHD in the family (i.e., parent or sibling), comorbid diagnoses (i.e., depression, anxiety, aggression, oppositional defiance disorder, sleep disorder, Tourette's syndrome, bipolar disorder, schizophrenia, drug and alcohol abuse, and autism) and the total number of comorbid conditions present at diagnosis measured

as a continuous variable. Questions on clinical characteristics were asked independently of the treatment goals question described above.

Patient engagement with treatment and family involvement with treatment over the study period were each measured independently and continuously by the physician on a scale from 1 to 10, with 1 being 'no engagement/involvement' and 10 being 'strong engagement/involvement'.

A patient was considered adherent to pharmacotherapy when the physician reported that they believed patients were taking the medication at least 80% of the time on weekdays and 50% on weekends and holidays. Adherence was also defined for BT (i.e., 80% of scheduled sessions), and if BT did not take place on weekends or holidays, then only the weekday value was used for classification.

Statistical analyses

Descriptive analyses of patient characteristics and treatments were compared between adherent and nonadherent patients, and between patients with the poorest outcomes ('neither satisfied nor dissatisfied' or worse satisfaction and 'poorly controlled' or worse symptom control) and the rest to identify key differences between these groups. Patients with missing OTS or adherence data were excluded from analysis. As treatment outcomes and adherence were reported for the treatment taken at the time of chart review, patients who had discontinued treatment were missing these values and were excluded. Patients missing other covariates were only excluded from results affected by those missing values.

The main analysis of this study was limited to the subsample of adherent patients, both to improve interpretability and to estimate the maximum potential strength of the relationship between treatment type and OTS. Within the adherent subset, covariates were tested individually to assess the significance of their association with OTS using two-sample t-tests and χ^2 tests for continuous and categorical covariates, respectively. Logistic regression was used to examine the relationship between the binary OTS outcome and treatment type (exposure variable) among adherent patients, adjusted for other covariates that were significantly associated with OTS in bivariate tests. Covariates significantly associated with the outcome (p < 0.05) were included in a stepwise multiple logistic regression (p < 0.05 for entry and retain) to select a subset of simultaneously

significant covariates that predicted OTS. Odds ratios with 95% CIs were reported for the final selected model. As the objective was to assess the association of treatment type and treatment outcome, treatment type was retained in the model regardless of its significance. As there was just a single patient treated with SA amphetamine only and none with other pharmacotherapies, these treatment categories and the associated patient were removed from the sample prior to model estimation.

Finally, after the significant main effects were selected with the stepwise procedure, second-order terms (interactions and squared continuous covariates) were tested for the selected covariates. Only second-order terms that tested significant over and above the main effects were retained in the model for OTS. The Hosmer–Lemeshow goodness-of-fit test was used to assess the adequacy of the model and the c-statistic was used to evaluate the accuracy of prediction. The c-statistic ranges from 0.5 to 1, where c = 1 for a perfect model and c = 0.5 for a model demonstrating no better than random classification [29].

In modeling the relationship between treatment types and OTS, it is possible that some researchers might consider treatment adherence as an intermediate variable in the causal pathway, rather than as a variable warranting stratification. This possibility was tested in a sensitivity analysis of both adherent and nonadherent patients by modeling the relationship between ADHD treatment type and OTS with and without adherence as an independent variable in the model.

All reported tests were two sided at the $\alpha = 0.05$ significance level. Data were analyzed using SAS statistical software (Version 9.2, SAS Institute, Inc., NC, USA). This study complies with all US and International Conference on Harmonization human subjects ethics committee requirements and was approved by the Research Triangle Institute institutional review board.

Results

Data were collected by 337 physicians on 730 eligible patients. Of these 730 patients, 710 had adherence data and 708 also had treatment outcome data, thus comprising the final study population. The mean (standard deviation [SD]) age of all patients was 12.1 (2.6) years with a range from 6 to 17 years; 77.5% of patients were male. The number of patients (and

Table 1. Significant differences between the adherent and nonadherent patient groups.			
Patient characteristics	Adherent ⁺ (n = 505)	Nonadherent ⁺ (n = 203)	p-value
Comorbidity; n (%)			
Depression	28 (6)	32 (16)	<0.001*
Bipolar disorder	9 (2)	14 (7)	0.001*
OCD	19 (4)	19 (9)	0.005*
Drug abuse	6 (1)	8 (4)	0.031*
Mean (SD) number of comorbidities	2.58 (1.98)	3.07 (2.25)	0.005*
Predominant symptoms at diagnosis; n (%)		
Inattention	411 (81)	151 (74)	0.040*
Hyperactivity	357 (71)	126 (62)	0.032*
Challenges with school performance	376 (75)	129 (64)	0.004*
Mean (SD) predominant symptom impair	rment levels (scale 1–10)		
Inattention	7.90 (1.64)	7.60 (1.90)	0.037*
Tendency to blame others	4.62 (2.41)	5.43 (2.52)	<0.001*
Mean (SD) participation in ADHD treatme	ent (scale 1–10)		
Patient engagement [*]	6.64 (2.06)	5.71 (1.95)	<0.001*
Family involvement [§]	8.02 (1.54)	7.14 (1.98)	<0.001*
Treatment goals; n (%)			
Improve inattention	417 (82.6)	140 (69.0)	<0.001*
Reduce disruption at home	225 (44.6)	68 (33.5)	0.007*
[†] Percentages were calculated from the total number of	of patients per group ($n = 170$ fo	r OTS: n = 335 for non-OTS	

*Physician-rated extent of patient engagement in ADHD condition and treatment (1 = no engagement and 10 = strong engagement); n = 503 for the adherent group as two patients had missing values.

^sPhysician-rated involvement of family/caregiver in patient's ADHD condition and treatment (1 = no involvement and 10 = strong

involvement).

*Statistically significant result. OCD: Obsessive–compulsive disorder; SD: Standard deviation.

physicians) included in the sample by country were as follows: France 118 (50); Germany 137 (52); Italy 134 (73); The Netherlands 72 (55); Spain 132 (50); and the UK 137 (57).

Adherence versus nonadherence in the total sample

Differences between physician-perceived adherent and nonadherent patients are presented in Table 1 & Figure 2. Table 1 demonstrates that adherent patients had fewer comorbidities than nonadherent patients. The mean number of comorbidities was 2.6 for adherent patients compared with 3.1 for nonadherent patients (p = 0.005). Nonadherent patients were also more likely to have current symptoms of inattention (81 vs 74%; p = 0.040), hyperactivity (71 vs 62%; p = 0.032) and challenges with school performance (75 vs 64%; p = 0.004). On average, adherent patients had a higher level of engagement (6.6 vs 5.7; p < 0.001) and family involvement (8.0 vs 7.1; p < 0.001) with their treatment and were more likely to have treatment goals specifying improvement in inattentive symptoms (83 vs 69%; p < 0.001).

Figure 2 demonstrates that there were few differences in adherence rates for the various pharmacotherapies, with adherence for most medications averaging approximately 76%. For both adherent and nonadherent patients, methylphenidate was the most frequently used medication (69.0 and 64.1%, respectively). Approximately 12.0% of adherent and 9.1% of nonadherent patients used atomoxetine; similarly, 10.3 and 6.4% used multiple pharmacotherapies (data not shown). Approximately 50% of patients were on the same therapy over the entire study duration for a mean (SD) of 3.00 (1.04) years. The rest of the patients stayed on their last therapy for a mean (SD) of 1.95 (1.17) years. There was no significant difference in these mean treatment durations between treatment-adherent and -nonadherent patients.

Outcome distribution in the total sample

The rate of OTS was low in both the total population and the perceived adherent population. Overall, OTS was achieved in only 28.1% (199 out of 708) of all patients, and it was observed in 33.7% (170 out of 505) of adherent

patients and 14.3% (29 out of 203) of nonadherent patients (p < 0.0001) (Figure 3). Table 2 describes the unadjusted rates of adherence and OTS by treatment modality. Notably, the OTS rate was significantly lower for patients on BT only (13.8%). This corresponded with the lowest rate of adherence (56%), which was for patients on BT only. The best rate of OTS was observed for patients on pharmacotherapy alone (32.6%), where physician-reported satisfaction and symptom control were both 37%.

A subanalysis to compare 41 (5.8%) patients with poorest outcomes to the rest of the 667 patients with complete data was performed (Supplementary Table 1, see www.futuremedicine.com/doi/suppl/10.2217/NPY.13.76). The comparison revealed that patients with the poorest outcomes were significantly less adherent to treatment (43.9 vs 73.0%; p < 0.001), more prone to drug (9.8 vs 1.5%; p = 0.006) and alcohol (7.3 vs 1.2%; p = 0.021) abuse, had a higher rate of inappropriate behavior symptoms (68.3 vs 45.6%; p = 0.006), had higher average active defiance (7.0 vs 6.1; p = 0.025) and inappropriate behavior (7.0 vs 6.5; p = 0.036) impairment levels, higher average number of noncore symptoms (4.2 vs 3.4; p = 0.016), had lower average patient engagement (5.2 vs 6.5; p < 0.001) and family involvement (6.7 vs 7.8; p < 0.001), and a higher rate of BT-only treatment at the time of review (31.7 vs 10.0%; p < 0.001).

Subanalysis of perceived treatment-adherent patients

There were 505 patients whose physicians rated them as adherent and for whom data were reported (by 267 physicians). Physician specialties included pediatricians (36.3%), child/pediatric and adolescent psychiatrists (27.7%), psychiatrists treating children (22.5%), neuropediatricians treating children (22.6%). neuropediatricians treating children (2.6%). The mean (SD) age of adherent patients was 12.0 (2.5) years and 77.0% of patients were male. Among adherent patients, differences between those who did and did not have OTS are presented in **Table 3 & Figure 4**. OTS rates were lowest in Italy, France and the UK (19, 24 and 27%, respectively). There were no



Figure 2. Characteristics associated with adherence in all patients (n = 708). Other pharmacotherapies included medications other than MPH, amphetamine and atomoxetine. Adherence was defined as taking the medication at least 80% of the time on weekdays and 50% on weekends and holidays. Therapies (n) = number of therapies (as per study definition) recorded on the patient's chart.

BT: Behavioral therapy; LA: Long acting; MPH: Methylphenidate; Rx: Pharmacotherapy; SA: Short acting.



Figure 3. Optimal treatment success by adherence (n = 708). Optimal treatment success was defined as physician-reported complete symptom control and high satisfaction from treatment. Adherence was defined as taking the medication at least 80% of the time on weekdays and 50% on weekends and holidays. χ^2 p < 0.0001 comparing OTS in the adherent and nonadherent groups.

OTS: Optimal treatment success.

differences in age group, race or gender between those with and without OTS. However, patients with OTS had fewer comorbidities (2.0 vs 2.9; p < 0.001), were on average more engaged (7.6 vs 6.2; p < 0.001) and had more family involvement (8.5 vs 7.8; p < 0.001) compared with non-OTS patients. The presence of symptoms/behaviors of impulsivity, active defiance and anger at the time of ADHD diagnosis was significantly lower among OTS patients than non-OTS patients. Average impairment levels for individual ADHD symptoms/behaviors of impulsivity (6.6 vs 7.1; p = 0.018), anger (4.7 vs 5.8; p < 0.001), irritability (5.4 vs 6.0; p = 0.007), active defiance (5.6 vs 6.5; p < 0.001), social interaction problems (6.5 vs 7.3; p < 0.001) and inappropriate behavior (6.0 vs 6.8; p < 0.001), and for the total impairment score (67.7 vs 73.3; p < 0.001), were lower among patients with OTS. Patients with OTS were more likely to have a treatment goal to improve inattention (88.8 vs 79.4%; p = 0.009) and less likely to have a treatment goal to restrain inappropriate behavior (57.6 vs 68.1%; p = 0.024). There were no statistically significant associations between treatment type and OTS (p = 0.516) or between physician specialty and OTS (p = 0.164).

Adjusted odds ratios for OTS in adherent patients derived from the multivariate logistic regression model are described in Table 4. Treatment type was not a statistically significant predictor of OTS after adjustments (p = 0.872). The same model replacing treatment type with a three-level treatment modality resulted in similar odds ratios and significance levels for history of depression, inappropriate behavior impairment level, patient engagement level and country indicators, and a nonsignificant (p = 0.445) treatment modality effect on OTS [SHIRE PHARMACEUTI-CALS, DATA ON FILE]. Of note, the combined BT and pharmacotherapy treatment had the best effect on OTS after adjustment.

The odds of physicians reporting OTS were 4.1-fold lower for patients with a history of depression and 1.4-fold lower for patients with inappropriate behavior (per 1 SD increase in rating of inappropriate behavior). Conversely, the odds of OTS were 2.5-fold higher in more engaged patients (per 1 SD increase). The adjusted odds ratios for OTS varied among the European countries, with the highest odds found for The Netherlands and Germany.

The c-statistic for the logistic model was 0.77, indicating that, based on the covariate information provided, the model correctly classified OTS for 77% of the patients. The Hosmer–Lemeshow p-value was 0.244, demonstrating a good fit of the model. In addition, any changes in the effect estimate for treatment type estimated by the model when fitted to both adherent and nonadherent patients (n = 708) were assessed. The odds ratio estimates for the treatment type variable did not change significantly when adherence was retained or removed from the model (F-test p = 0.899),

Table 2. Rates of adherence and treatment outcomes overall and by treatment modality.					
Outcome	Total population; % (n = 708)	Pharmacotherapy only; % (n = 365)	BT only; % (n = 80)	Combination pharmacotherapy + BT; % (n = 263)	$\chi^2 p$ -value [†]
Adherence	71.3	75.9	56.3	69.6	0.0015
Symptom control	31.6	36.7	17.5	28.9	0.0018
Physician satisfaction	32.7	37.3	16.3	31.6	0.0012
Optimal treatment success	28.1	32.6	13.8	26.3	0.0022
[†] p-value to compare outcome rates BT: Behavioral therapy.	across treatment modalities.				

indicating that treatment adherence did not statistically function as a mediating variable [Shire Pharmaceuticals, Data on file].

Discussion

The study adds to the limited body of knowledge regarding the treatment outcomes of routine clinical care for children and adolescents with ADHD in Europe. Specifically, this study found that the country of reference and patient engagement levels were the strongest predictors of OTS, whereas inappropriate behavior levels and pre-existing depression markedly decreased the odds of achieving OTS. Noticeably, the type of ADHD treatment administered had no impact on treatment success in our models. In fact, the rate of overall physician-reported OTS for all patients in this sample was 28% (34% in adherent and 14% in nonadherent patients), which may indicate an unsatisfactory level of treatment effectiveness in this observational setting and a potential need for improved strategies in ADHD management.

The literature regarding treatment outcomes among patients with ADHD in observational

Table 3. Treatment type, patient characteristics and significant covariates for optimal t	reatment
success in adherent patients (n = 505).	

Patient characteristics	OTS ⁺ (n = 170)	Non-OTS ⁺ (n = 335)	p-value
Male; n (%)	126 (74)	263 (79)	0.266
Comorbidity; n (%)			
Anxiety	49 (29)	127 (38)	0.048*
Autism	3 (2)	20 (6)	0.040*
Depression	4 (2)	24 (7)	0.024*
Aggression	45 (27)	130 (39)	0.007*
Insomnia	33 (19)	104 (31)	0.006*
Learning disability	57 (34)	170 (51)	<0.001*
Epilepsy	0 (0)	9 (3)	0.032*
Mean (SD) number of comorbidities	2.0 (1.79)	2.9 (2.01)	<0.001*
Predominant symptoms at diagnosis; n (%))		
Impulsivity	102 (60)	236 (70)	0.021*
Anger	43 (25)	133 (40)	0.002*
Active defiance	62 (37)	156 (47)	0.036*
Mean (SD) predominant symptom impairm	nent levels (scale 1–10)		
Impulsivity	6.62 (2.57)	7.13 (2.17)	0.018*
Anger	4.74 (2.59)	5.77 (2.50)	<0.001*
Irritability	5.41 (2.54)	6.03 (2.36)	0.007*
Active defiance	5.57 (2.72)	6.47 (2.30)	<0.001*
Social interaction problems	6.45 (2.51)	7.25 (1.91)	<0.001*
Inappropriate behavior	5.95 (2.43)	6.82 (1.98)	<0.001*
Total (SD) ADHD impairment level (scale 12–120)	67.74 (17.56)	73.30 (14.52)	<0.001*
Mean (SD) participation in ADHD treatmen	it (scale 1–10)		
Patient engagement [*]	7.6 (1.60)	6.2 (2.10)	<0.001*
Family involvement [§]	8.5 (1.25)	7.8 (1.60)	<0.001*
Treatment goals; n (%)			
Improve inattention	151 (88.8)	266 (79.4)	0.009*
Restrain inappropriate behavior (factor)	98 (57.6)	228 (68.1)	0.024*
Therapy changes			
Mean (SD) number per follow-up year	0.53 (0.35)	0.62 (0.51)	0.034*
¹ Percentages were calculated from the total number of patients per group (n = 170 for OTS; n = 335 for non-OTS). ¹ Physician-rated extent of patient engagement in ADHD condition and treatment (1 = no engagement and 10 = strong engagement); n = 333 for the non-OTS group as two patients had missing values. ⁵ Physician-rated involvement of family/caregiver in patient's ADHD condition and treatment (1 = no involvement and 10 = strong involvement). *Statistically ciprificant result (noncignificant comorbidities symptoms impairments levels and treatment goals are not listed).			

*Statistically significant result (nonsignificant comorbidities, symptoms, impairments levels and treatment goals are not OTS: Optimal treatment success; SD: Standard deviation.



Figure 4. Characteristics associated with optimal treatment success among adherent patients (n = 505). Optimal treatment success was defined as physician-reported complete symptom control and high satisfaction from treatment. Other pharmacotherapies included medications other than MPH. amphetamine and atomoxetine.

 $^{\dagger}n = 410$ as race was not reported in France.

*n = 504 as one patient receiving pharmacotherapy only (SA amphetamines) was removed.
BT: Behavioral therapy; LA: Long acting; MPH: Methylphenidate; OTS: Optimal treatment success;
Rx: Pharmacotherapy; SA: Short acting.

settings is scarce, particularly literature examining the patient-, environmental- and treatment-level variables that may impact the rate of treatment success. Most of the available evidence refers to medication efficacy rates in clinical trials, where estimates are not wholly comparable with those that might occur in noncontrolled environments. Despite the fact that up to 80% of patients with ADHD have at least one comorbid disorder, such patients are usually excluded from clinical trials. One of the few effectiveness studies was commissioned by the NIH in the USA (the MTA study) and included 579 children with ADHD who were randomly assigned to controlled treatment groups (pharmacotherapy, BT or both) versus standard community care (real-world setting) [30]. Multiple ADHD symptoms were assessed by teachers and parents at baseline and after 14 months of treatment. Using a weighted average of mean group symptom scores for the three controlled treatment groups, the authors calculated teacher- and parent-rated changes in symptoms of inattention, hyperactivity/impulsivity and aggression/oppositional defiant disorder, and separately for social skills. Teacher-rated scores for inattention, hyperactivity/impulsivity and aggression/oppositional defiant disorder showed a 45-56% improvement in the controlled treatment groups compared with a 26-35% improvement in the standard community care group. Teacher-rated social skill scores improved by 38 and 21% in the controlled treatment and community care groups, respectively. Parent-rated scores showed slightly lower symptomatic improvement than teacher-rated scores with a similar pattern of lower improvement in the community care group. Social skills improvement rates were only 15.3 and 11.7% in the controlled treatment and community care groups, respectively. Overall, these results suggest an approximatly 40% symptomatic and 24-45% social skills loss of outcome improvement attributed to ADHD treatment in community care compared with controlled clinical trials.

More recent evidence suggests that communitybased physicians can achieve gains in ADHD symptom improvement comparable with that of the controlled treatment groups in the MTA study [31]. Within a formal study collaboration comprising 47 community practices, primary care providers and their staff were provided with didactic training sessions, ongoing report cards regarding adherence to evidence-based practices and the implementation of tools for tracking adherence to ADHD treatment guidelines, monitoring parent and teacher assessments of ADHD symptoms, and easing referrals [32]. In this ADHD study, rates of adoption of evidencebased treatment practices among physicians in the sample increased from 9 to 40% [32]. For 785 newly diagnosed children in the MTA study, large improvements in ADHD symptoms were noted in the first 3 months of stimulant care (parents' and teachers' Vanderbilt ADHD Rating Scales total symptom score Cohen's d effect size = 1.5) and appeared to stabilize over the following 9 months [31]. However, marginal improvement was noted in functional impairment (e.g., school performance), a result that is consistent with other studies [31,33,34]. A recent literature review of long-term outcomes in ADHD concluded that treatment of ADHD may improve long-term outcomes, including self-esteem, social function and academic performance, but usually not to the point of normalization [35].

This study describes the state of current child and adolescent ADHD treatment in a real-world setting in Europe with no formal interventions to improve community physician adherence to guidelines. The outcome measure we used consisted of physician-reported ADHD symptom control and satisfaction with treatment and did not directly include questions on symptom resolution or functional improvement. Our results show a relatively low effectiveness of ADHD treatment (28% physician-reported OTS), consistent with the results of the MTA study, which showed reduced effectiveness of treatment in a community setting in the USA. The ADHD collaborative study described above demonstrated that community interventions to improve physician adherence to evidence-based treatment guidelines can greatly improve response.

This study focused on treatment-adherent patients, where the intent was to study the relationship of treatment and OTS under conditions where treatment is administered as prescribed by the physician. This allowed us to obtain interpretable odds ratios for the treatment types, countries and patient characteristics associated with OTS. In addition, adherence was associated with many of the potential predictors of OTS (Table 1); therefore, a separate analysis for adherent patients appeared justified. As the main analysis was limited to the treatment-adherent patients, interpretation of these results should not be extrapolated to nonpersistent patients or nonadherent patients.

Table 4. Adjusted odds ratios of optimal treatment success from multip model (n = 502).	ole logistic regression
Covariate	Odds ratio (95% CI); c = 0.77 [†] ; p = 0.244 [‡]
History of depression	0.245 (0.089-0.673)
Patient engagement [§] (scale 1–10) – mean (SD): 6.4 (2.1)	2.527 (1.923-3.321)
Inappropriate behavior impairment level [§] (scale 1–10) – mean (SD): 6.6 (2.2)	0.736 (0.593–0.913)
Country (UK reference)	
France	1.143 (0.557–2.344)
Germany	2.666 (1.399–5.082)
Italy	1.964 (0.718–5.376)
The Netherlands	3.705 (1.688-8.133)
Spain	1.334 (0.662–2.691)
Treatment type (atomoxetine reference); not significant (p = 0.872)	
Pharmacotherapy only: SA MPH	1.083 (0.350–3.353)
Pharmacotherapy only: LA MPH	1.047 (0.414-2.644)
Multiple pharmacotherapies	0.863 (0.271-2.746)
BT only	0.629 (0.186–2.129)
Combination pharmacotherapy + BT	1.166 (0.464–2.934)
n = 502 as one patient receiving pharmacotherapy only (SA amphetamines) was removed and tw engagement values. ¹ A c-statistic of 1 indicates a perfect model and a c-statistic of 0.5 indicates the model is no better ¹ Hosmer–Lemeshow test. ⁹ Per 1 SD change in covariate. BT: Behavioral therapy, LA: Long acting; MPH: Methylphenidate; SA: Short acting; SD: Standard de	vo patients had missing r than random classification. viation.

Examination of the subgroup of adherent patients revealed that 55% were receiving pharmacotherapy only, 9% received BT only and 36% received a combination of both therapies. Pharmacotherapy was dominated by methvlphenidate (69% of all medications used), with negligible use of amphetamine. There were no demonstrable differences in OTS rates due to treatment type (i.e., medication, BT or combination) or by medication type. This study found a low OTS rate of only 34% and no difference in treatment success across treatment types. In addition, approximately 50% of patients were on the same therapy throughout the length of the chart review for an average duration of 2 years, and the rest stayed on their last therapy for an average of 3 years. These findings potentially suggest that there may be opportunities to implement improved strategies to achieve better outcomes in these patients. New strategies appear especially relevant for patients with comorbidities or with atypical symptoms.

Even within the adherent subgroup, OTS varied widely by country, raising another interesting finding that requires a deeper and more systematic analysis. This study was not designed to address the reasons for these differences and more research is needed to examine factors associated with variability of outcomes across countries. These results may be related to differences in physician training and practice settings across countries, national standards and insurance systems, treatment priorities and variability in other available resources, such as family and community support or supportive educational settings. Difference by country may be also related to ADHD diagnostic criteria variability across physician specialties and countries, and variability in ADHD drug availability by country. Differences may also reflect cultural differences in what are good and/or acceptable outcomes and how far treatments should be pushed for this condition.

There are several limitations to this study. While this was a considerably larger observational study relative to other published studies in the field [30–32], the generalizability of these results at the population or country level remains limited because of its reliance on a convenience sample that is not representative of physicians and patients. Given that we cannot report the usual metrics that provide a sense of how representative the sample was of physicians and patients used in this study (e.g., a defined sampling frame and estimate of nonresponse rate), reported prevalence and rates may be affected by selection bias and should be confirmed with other sources. However, although absolute levels of OTS and predictors may be limited by this uncertainty in the sampling source, the results obtained from odds ratios (generated by the logistic regression modeling) should be minimally affected.

This study also relied on physician-reported responses to treatment and adherence, as well as all other covariates used in our analysis, and no blinding was performed. Physician-reported responses may not be entirely consistent with the perception of the patients or their caregivers. Several studies have shown that parent-reported outcome assessments tend to be better compared with those of the physician even in the placebo arms [36-38]. Therefore, our results might be more conservative compared with a similar study with parent-reported outcomes. Furthermore, responses on OTS and other covariates may appear to be related, whereas if we had collected these data from various independent data sources, it is possible that correlations observed in this study would have been attenuated. Physician-reported adherence is likely to be an overestimation.

Information on ADHD diagnosis and presence of symptoms and comorbid conditions were retrieved from the charts. We did not require systematic criteria for diagnosis and conditions that may have standardized the data at the expense of greatly complicating the data collection process. The source of information might vary in the charts, and ADHD impact and symptom ratings can vary by informant. We did not collect data on the informant and did not account for this potential source of variation.

The OTS outcome measure was a new composite measure utilized for this study, and was derived from measures of physician-reported symptom control and satisfaction with treatment. Simplification of the analysis by focusing on the patients with the best outcomes conservatively estimated the rate of treatment success. However, the goal of ADHD management should be to strive for optimal results and not settle for intermediate outcomes. Examination of the data confirmed that the moderate outcome group also showed a greater similarity in distribution to the poor outcome group rather than to the best outcome group, supporting our definition of OTS.

The OTS outcome measure and the covariates examined have not been psychometrically validated. Therefore, there is no estimate of the variability attributed to test–retest discordance and

Physician-reported treatment outcomes for ADHD among children & adolescents in Europe **RESEARCH ARTICLE**

to differences in interpretation of satisfaction and symptom control. The results of this study should be confirmed by using more targeted sampling schemes, more comprehensive outcome measures with established validity and, where possible, obtaining the covariates information from independent data sources.

Conclusion & future perspective

This study provides insight regarding the effectiveness of ADHD management for school-age children in a real-world setting in Europe. The results suggest that OTS of ADHD appeared to be generally low and that effectiveness was improved in those who were treatment adherent. The adjusted results showed that increased numbers of comorbidities and symptomatology were negatively associated with OTS. Among treatment-adherent patients, there were no differences in OTS across treatment modalities, suggesting that opportunities exist for the improved use of current treatments and the development of new treatments for ADHD.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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