ORIGINAL RESEARCH

Predictors and consequences of adherence to the treatment of pediatric patients with attention-deficit/hyperactivity disorder in Central Europe and East Asia

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Purpose: To assess baseline predictors and consequences of medication non-adherence in the treatment of pediatric patients with attention-deficit/hyperactivity disorder (ADHD) from Central Europe and East Asia.

Patients and methods: Data for this post-hoc analysis were taken from a 1-year prospective, observational study that included a total of 1,068 newly-diagnosed pediatric patients with ADHD symptoms from Central Europe and East Asia. Medication adherence during the week prior to each visit was assessed by treating physicians using a 5-point Likert scale, and then dichotomized into either adherent or non-adherent. Clinical severity was measured by the Clinical Global Impressions-ADHD-Severity (CGI-ADHD) scale and the Child Symptom Inventory-4 (CSI-4) Checklist. Health-Related Quality of Life (HRQoL) was measured using the Child Health and Illness Profile-Child Edition (CHIP-CE). Regression analyses were used to assess baseline predictors of overall adherence during follow-up, and the impact of time-varying adherence on subsequent outcomes: response (defined as a decrease of at least 1 point in CGI), changes in CGI-ADHD, CSI-4, and the five dimensions of CHIP-CE.

Results: Of the 860 patients analyzed, 64.5% (71.6% in Central Europe and 55.5% in East Asia) were rated as adherent and 35.5% as non-adherent during follow-up. Being from East Asia was found to be a strong predictor of non-adherence. In East Asia, a family history of ADHD and parental emotional distress were associated with non-adherence, while having no other children living at home was associated with non-adherence in Central Europe as well as in the overall sample. Non-adherence was associated with poorer response and less improvement on CGI-ADHD and CSI-4, but not on CHIP-CE.

Conclusion: Non-adherence to medication is common in the treatment of ADHD, particularly in East Asia. Non-adherence was associated with poorer response and less improvement in clinical severity. A limitation of this study is that medication adherence was assessed by the treating clinician using a single item question.

Keywords: ADHD, non-adherence, response, effectiveness, Asia, Central Europe

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent mental disorders in childhood and adolescence, affecting 6% to 8% of this population worldwide.[1,2] It is characterized by the core symptoms of hyperactivity, impulsivity, and inattention,[3] and is now recognized as a lifelong, chronic disorder that can extend into adulthood either as the full condition or in partial remission.[4] In the absence of early and appropriate treatment, the disorder may also result in long-term negative consequences, such as

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low educational achievement, occupational or interpersonal difficulties/failures, as well as an increased risk of substance abuse, crime, and accidental injury.[5–10]

A multi-disciplinary approach is often recommended for the management of ADHD, in which pharmacotherapy can be an integral part when remedial measures alone prove insufficient.[11] Both stimulants and non-stimulant medications have been proven to be effective in the treatment of ADHD, providing that patients adhere to the prescribed regimen.[11–14] A recent review of adherence studies, however, showed a high level of medication non-adherence among children/adolescents with ADHD.[15] The prevalence of medication non-adherence was reported to range from 13.2% to 64%, depending on the clinical setting, definition and assessment of adherence, duration of study, and characteristics of the study population. Although the consequences of medication non-adherence have been poorly documented in ADHD, limited evidence from the US shows the negative impact of non-adherence on clinical and functional outcomes. Charach et al assessed the impact of adherence on outcomes in 79 patients with ADHD, who were followed up for 5 years after completing a 12-month randomized controlled trial (RCT) of methylphenidate in the US.[16] The study showed greater improvement in teacher-reported symptoms among adherent patients, compared to non-adherent patients or those off medication. Similarly, Marcus and Durkin also found an association between adherence to stimulants and higher academic grades, using Medicaid claims data and academic administrative records in Philadelphia (US).[17] Further research is warranted to examine whether these findings are replicated in other clinical and cultural settings, and if so, to what extent. Furthermore, a greater understanding of the factors associated with non-adherence to ADHD medications is needed so that any avoidable risk factors can be identified and managed using appropriate interventions.

A variety of predictors of medication non-adherence in ADHD have been reported previously. These include frequent daily dosing,[18–21] male gender,[21,22] older age,[18,20,21,23–25] ethnic minorities,[25,26] lower childhood IQ,[26–28] lower self-control,[27] later onset of ADHD,[20] poor family support,[19] family history of ADHD,[20] maternal psychological distress,[18] greater[20,27,28] or lower symptom severity,[24,25] concomitant medications,[21] comorbid conditions, such as oppositional or defiant behavior,[19,24] adverse effects,[20] and privacy issues.[5,18,19,29] This evidence is again mostly from the US and Canada. The exceptions are two Taiwanese retrospective studies conducted by Gau et al.[18,20] The authors earlier examined the extent and predictors of poor adherence to immediate-release

methylphenidate (IR-MPH) among 307 pediatric patients with ADHD who had been receiving IR-MPH in Taiwan.[18] Approximately, one in four patients (25.7%) was found to have poor adherence. Frequent daily dosing and older age were found to be the main predictors of poor adherence to IR-MPH. Poor adherence was also associated with maternal psychological distress, indifferent parenting, maternal overprotection/control, poor family support, less interaction with parents, and more problems at home. Later, Gau et al conducted a similar study and reported a greater rate of poor adherence (39.5%).[20] Factors associated with poor adherence were older age, a family history of ADHD, later onset of ADHD, higher parental educational level, multi-dose administration, and more severe ADHD-related symptoms. While the study did not examine the impact of non-adherence to ADHD medications, the authors suggested that poor adherence may be an important reason for sub-optimal outcomes in the treatment of ADHD in the region.

Using data from a 1-year large, prospective, observational study involving 1,068 newly-diagnosed pediatric patients with ADHD symptoms from Central Europe and East Asia, this post-hoc analysis explored predictors of medication non-adherence in the treatment of ADHD, and examined the impact of non-adherence on clinical severity and health-related quality of life (HRQoL) measures during 12 months of treatment and follow-up in a naturalistic outpatient setting in Central Europe and East Asia.

Material and methods
Study design and patient sample
This was a 12-month, international, prospective, non-interventional, observational study, primarily designed to examine treatment patterns and health outcomes in the treatment of newly-diagnosed pediatric patients with ADHD symptoms in actual clinical practice. From October 2005 to July 2006, 58 psychiatrists and pediatricians enrolled a total of 1,068 pediatric patients from eight countries across Central Europe and East Asia (People's Republic of China, the Czech Republic, Hungary, Romania, Slovakia, South Korea, Taiwan, and Turkey). This study followed the ethical standards of responsible local committees and regulations of the participating countries, and was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice (GCP) where applicable to a study of this nature. Ethical Review Board (ERB) approval was obtained as required for observational studies wherever required by local law. The parents/guardians of all patients provided written informed

consent, and patients provided assent. Further details on the study design have been provided elsewhere.[30–33]

Child and adolescent outpatients aged 6–17 years could participate in the study if they presented within the normal course of care with ADHD symptoms, and had not been previously diagnosed with, or treated for, ADHD. The diagnosis of ADHD symptoms was made by an investigator using standard diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders,* 4th ed; text revision [DSM-IV-TR][34] or the ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines [ICD-10]).[35] That is, in the clinical judgment of the investigator, participating patients were required to have hyperactive/inattentive/impulsive symptoms/problems associated with ADHD described by DSM-IV-TR, or hyperkinetic conduct disorder according the ICD-10 at baseline. The study excluded those patients who had severe mental retardation (unable to attend school due to mental disability), epilepsy or schizophrenia, or were participating in a different study that included a treatment intervention and/or investigational drug.

Data collection for the study occurred during visits within the normal course of care. The routine outpatient visit at which patients were enrolled served as the time for baseline data collection. Subsequent data collection was targeted at 1-month after the baseline visit and then every 3 months (3, 6, 9, and 12 months) since the baseline visit. Patient demographics and clinical history were recorded at the baseline assessment. Clinical severity of ADHD symptoms was assessed by treating physicians at each visit using the Clinical Global Impressions-ADHD-Severity (CGI-ADHD) scale[36] and the Category A of the Child Symptom Inventory-4 Parent Checklist (CSI-4).[37] The CSI-4 is made up of 18 items related to ADHD symptoms (9 each for the ADHD-inattentive type [ADHD-I] and the ADHD-hyper/impulsive type [ADHD-HI]) that are each rated on a scale from 0 (never) to 3 (very often) in terms of symptom frequency. In the present analysis, the physician-rated version, of which CSI-4 scores were recorded by the treating physicians in consultation with parents, was used after converting them to norm-referenced standardized CSI-4 scores using US-based population norms. HRQoL was assessed using the Parent Report Form of the Child Health and Illness Profile-Child Edition (CHIP-CE).[38] The CHIP-CE is a validated generic HRQoL measure, developed in the US and Spain. The Parent Report Form assesses the health of the child from the perspective of their parents on five domains (Satisfaction, Comfort, Resilience, Risk Avoidance, and Achievement),

which themselves are made up of 12 different subdomains. Similarly, norm-referenced standardized CHIP-CE T-scores were derived for each of the five domains using US-based population norms. Higher scores indicate better health.

Patients could be prescribed any treatment regimen by the treating physician for the treatment of their ADHD symptoms. Treatment decisions were made solely at the discretion of the physician, patient, or parent/guardian, and were independent of study participation. In actual practice, patients could receive no treatment, psychotherapy, pharmacotherapy, a combination of psychotherapy and pharmacotherapy, or other treatments. The most commonly prescribed medication at baseline was methylphenidate (45.5% [n = 486/1,068] in the total sample; 69.0% [n = 486/704] in patients who were prescribed at least one medication). Psychotherapy included formal sessions of psychoeducation and counseling, cognitive behavioral therapy, family therapy or psychodynamic therapy, which were conducted by a certified healthcare provider at a regular frequency for an acceptable length of time. Other treatments included educational interventions, speech therapy, occupational therapy, herbal therapy/homeopathy, informal hypnosis, psychomotor/physiotherapy, electroencephalogram (EEG) biofeedback, diet exclusion, diet supplementation, and relaxation techniques.

Adherence

Adherence to ADHD medications during the week prior to each follow-up evaluation was assessed by the treating physician using information obtained during the interview, and categorized into one of the six groups: prescribed medication was taken (1) never, (2) occasionally, (3) some of the time, (4) most of the time, (5) always, and (6) not applicable (ie, no medication). Patients were then re-categorized into two groups at each post-baseline visit: non-adherent (groups 1, 2 and 3), and adherent (groups 4 and 5). Overall adherence/non-adherence was further defined to examine baseline predictors of adherence during follow-up: patients, who were categorized as non-adherent on one or more post-baseline evaluations, were subsequently considered to be non-adherent during the follow-up period; otherwise, patients were considered to be adherent during follow-up.

Measures of the consequences of non-adherence

The consequences of medication non-adherence were examined by assessing the association between non-adherence/adherence status (as a time-varying variable) and the following outcomes measured at a next visit: response,

change in symptom severity, and change in HRQoL. Response was defined as a decrease of at least one point in the CGI-ADHD. Change in clinical severity was measured using the CGI-ADHD and the CSI-4, while change in HRQoL was measured using each of the five domains of the CHIP-CE. Changes in clinical severity or HRQoL were measured since baseline, except for those visits where patients experienced worsening symptoms compared with a previous visit. For these visits, changes in clinical severity or HRQoL were measured since the previous visit in order to better capture the detrimental impact of non-adherence on the subsequent outcomes. A similar logic was also applied to response. If a patient achieved at least one score reduction in the CGI-ADHD since baseline and did not experience worsening symptoms compared to a previous visit, the patient was considered to have achieved response at the visit. Otherwise, the patient was considered not to have achieved response.

Statistical analysis

The present analysis included those patients who were prescribed a medication either at baseline and/or during follow-up (n = 860). Baseline characteristics of the two groups of patients by adherence status during follow-up were summarized using descriptive statistics (mean, standard deviation, percentage).

Logistic regression analysis was performed to identify baseline predictors of overall adherence during follow-up. The model included age, gender, age at first symptoms, region (Central Europe; East Asia), birth problems, a family history of ADHD, and a CGI-ADHD score. The model also included the following variables but only if they appeared to be significant at $P < 0.1$ in univariate analyses: body mass index (BMI) (kg/m^2), having other children living at home, mother having paid employment, father having paid employment, emotional health problems of parents/guardians due to their children's behavioral problems, having been truant in the past 4 weeks, having been involved in bullying (as a bully) in the past 4 weeks, having primary care visits for behavioral problems in the past 4 weeks, having been invited to social activities in the past 4 weeks, and a CSI-4 score.

Generalized estimating equation (GEE) regression models with exchangeable correlation structure were employed to analyze the consequences of non-adherence on response, and changes in clinical severity and HRQoL, controlling for patient demographics and visits. The models included the same covariates as listed above, plus visits and adherence as a time-varying covariate. The variable included here was

not overall adherence during follow-up but adherence at the visit before the outcome was assessed.

All analyses were repeated for each region (ie, Central Europe and East Asia, respectively). In addition, sensitivity analyses were carried out by including a subset of patients, (1) who initiated pharmacotherapy at baseline (75.1%, n = 646); and (2) who were considered to be ADHD cases at baseline (85.1%, n = 732). An ADHD case was defined as the number of counts for "often" and "very often" in the nine questions for ADHD-I greater than or equal to six and/or that in the nine questions for ADHD-HI ≥6.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 860 patients, who initiated pharmacotherapy either at baseline and/or during follow-up, were included in this analysis (n = 485 for Central Europe, and n = 375 for East Asia). Approximately three-quarters of these patients (75.1%, n = 646) initiated pharmacotherapy with/without psychotherapy at baseline. Of the remaining 214 patients, 86 patients initiated either psychotherapy (n = 45) or other treatment (n = 41), and 128 patients had no treatment documented at baseline.

More than one in three patients (35.5%, n = 305) were considered to be non-adherent during follow-up. In East Asia, almost half of the patients (44.5%, n = 167) were considered to be non-adherent during follow-up, which was much higher than the rate of overall non-adherence in Central Europe (28.5%, n = 138, $P < 0.001$). Table 1 summarizes the baseline patient characteristics by adherence status during follow-up. A higher percentage of patients who were non-adherent during follow-up were living in East Asia, had a higher BMI, had no other children living at home, and had parents/guardians experiencing emotional difficulties due to their child's behavioral problems.

Predictors of non-adherence/adherence during follow-up

Table 2 shows the results of logistic regression, which examined the predictors of non-adherence to ADHD medication during follow-up. Patients living in East Asia were more likely to be non-adherent during follow-up, compared with those in Central Europe (odds ratio [OR] = 0.55; 95% confidence interval [CI] = 0.36, 0.84; $P = 0.005$). Among patients living in East Asia, a family history of ADHD (OR = 0.57, 95% CI = 0.33, 0.96; $P = 0.036$), and parental emotional

Table 1 Baseline patient characteristics by adherence status during follow-up

Baseline characteristic	Non-adherent during follow-up (n = 305)	Adherent during follow-up (n = 555)
Age, mean (SD)	9.29 (2.67)	8.98 (2.48)
Male	83.83%	80.37%
Age at first symptoms, mean (SD)	5.51 (2.32)	5.45 (2.41)
Being from East Asia (versus Central Europe)*	54.75%	37.48%
BMI (kg/m²), mean (SD)*	18.71 (3.79)	18.13 (3.62)
Birth problems	28.81%	28.22%
Family history of ADHD	48.79%	48.36%
Having other children living at home*	48.45%	63.41%
CGI-ADHD, mean (SD)	4.58 (0.96)	4.50 (1.00)
CSI-4 category A (standardized), mean (SD)	76.10 (10.57)	76.50 (10.65)
Paid employment (mother)	72.91%	68.27%
Paid employment (father)	90.97%	87.27%
Parental emotional distress due to their children's behavioral problems*	57.97%	45.16%
Being truant in the past 4 weeks	9.89%	7.63%
Being involved in bullying (as a bully) in the past 4 weeks	22.85%	22.98%
Primary care visit in the past 4 weeks for behavioral problems	15.00%	12.92%
Being invited to social activity in the past 4 weeks	60.14%	54.98%

Notes: Data were presented as percentage or mean (standard deviation) as appropriate. *Significant at $P < 0.05$.
Abbreviations: BMI, body mass index; ADHD, attention-deficit/hyperactivity disorder; CGI-ADHD, Clinical Global Impressions-ADHD-Severity; CSI-4, Child Symptom Inventory-4 Parent Checklist; SD, standard deviation.

Table 2 Association between overall adherence during follow-up and baseline patient characteristics

Variables	OR[a]	OR 95% CI	P-value
Age	0.993	0.918, 1.075	0.8703
Year at first symptoms	0.954	0.876, 1.040	0.2856
Male	0.709	0.438, 1.149	0.1629
Being from East Asia (versus Central Europe)*	0.549	0.361, 0.836	0.0051
Having birth problems	1.286	0.862, 1.919	0.2179
Family history of ADHD	0.806	0.545, 1.192	0.2802
Being involved in bullying (as a bully)	0.773	0.497, 1.203	0.2547
CGI-ADHD	1.057	0.876, 1.275	0.5650
BMI	0.957	0.908, 1.008	0.0972
Having other children living at home*	1.658	1.124, 2.446	0.0108
Parental emotional problems	0.818	0.554, 1.209	0.3139

Notes: *Significant at $P < 0.05$. [a]OR >1 indicates a positive association with overall adherence.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CGI-ADHD, Clinical Global Impressions-ADHD-Severity; CI, confidence interval; OR, odds ratio.

problems (OR = 0.50; 95% CI = 0.29, 0.87; $P = 0.014$) were associated with non-adherence, while having no other children living at home was associated with non-adherence in Central Europe (OR = 1.93; 95% CI = 1.06, 3.50; $P = 0.030$) as well as in the overall sample (OR = 1.66; 95% CI = 1.12, 2.45; $P = 0.011$).

Consequences of non-adherence/ adherence

Table 3 summarizes the associations between adherence to ADHD medications and subsequent outcomes during follow-up, adjusted for baseline patient characteristics. The models included adherence as a time-varying covariate: each outcome was related to the adherence rating of the previous assessment visit. Compared to non-adherent patients, adherent patients were more likely to achieve response during follow-up (OR = 1.52; 95% CI = 1.14, 2.02; $P = 0.004$). In addition, they had greater improvement in symptom severity, measured using the CGI-ADHD (estimate = −0.35; 95% CI = −0.51, −0.20; $P < 0.001$) and the CSI-4 (−2.98; 95% CI = −4.79, −1.17; $P = 0.001$). However, there were no significant differences in any of the domains of the CHIP-CE between adherent and non-adherent patients, although the directions of the estimates indicated greater improvement in all dimensions of the CHIP-CE in adherent patients. The results remained largely consistent when the analyses were conducted on (1) patients living in East Asia and Central Europe, respectively, (2) patients defined as ADHD cases, and

Table 3 Summary of associations between adherence to ADHD medication and subsequent outcomes during follow-up

Outcomes	OR	95% CI	P-value
Response[a]	1.516	1.140, 2.017	0.0042
	Estimates	**95% CI**	**P-value**
Change in clinical severity[b]			
CGI-ADHD	−0.353	−0.506, −0.200	<0.001
CSI-4 A category	−2.980	−4.787, −1.172	0.0012
Change in CHIP-CE five domains[c]			
Satisfaction	1.507	−0.011, 3.025	0.0517
Comfort	0.988	−0.590, 2.565	0.2198
Risk avoidance	0.958	−0.592, 2.507	0.2257
Resilience	1.213	−0.223, 2.649	0.0977
Achievement	0.192	−1.096, 1.479	0.7705

Notes: [a]OR >1 indicates a higher odds of achieving response in adherent patients; [b]estimate <0 indicates greater improvement in clinical severity among adherent patients; [c]estimate >0 indicates greater improvement in health-related quality of life (CHIP-CE) among adherent patients.
Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; OR, odds ratio; CI, confidence interval; CGI-ADHD, Clinical Global Impressions-ADHD-Severity; CSI-4, Child Symptom Inventory-4 Parent Checklist; CHIP-CE, Child Health and Illness Profile-Child Edition.

(3) patients who initiated pharmacotherapy at baseline (data not shown).

Discussion

The results of this large 1-year observational study revealed a high prevalence of medication non-adherence (35.5%) during the treatment of newly-diagnosed children and adolescents with ADHD symptoms in Central Europe and East Asia. In particular, almost half of the patients from East Asia (44.5%) were found to be non-adherent during follow-up. This was significantly higher than the rate of overall medication non-adherence found in Central Europe (28.5%). More importantly, our findings confirmed the negative impact of non-adherence on achieving response and symptom improvement. A family history of ADHD, parental psychological distress, and having no other children living at home were identified as potential risk factors of medication non-adherence in Central Europe and/or East Asia.

Whilst the rate of medication non-adherence in our study (35.5%) was within the range reported in other studies, our rate for East Asia (44.5%) was slightly higher than those reported in two Taiwanese retrospective studies, which are the only studies that have assessed the level of non-adherence to ADHD medication in this region.[18,20] Gau et al examined the extent and predictors of poor adherence to IR-MPH among 307 pediatric patients with ADHD who had been receiving IR-MPH in Taiwan.[18] Poor adherence was defined as maternal reports of a child missing more than 14 days of any dose of IR-MPH on a daily basis during the previous month. Approximately, one in four patients (25.7%) was found to have poor adherence. Later, they conducted a similar study that involved a total of 607 pediatric patients with ADHD in Taiwan.[20] Poor adherence to IR-MPH was defined as missing one or more doses on a school day on two or more days per week during the previous four weeks. The rate of poor adherence was reported to be 39.5%. Although these rates are slightly lower than ours, this may not be surprising since our definition of overall medication non-adherence was based on a longer time frame (ie, up to 12 months) than theirs (ie, maternal reports of a child missing pills during the previous month). Nevertheless, these studies also confirm that non-adherence to medication is common in the treatment of school-aged children with ADHD in East Asia.

It is, however, not clear why non-adherence to ADHD medication is more prevalent in East Asia compared to Central Europe. It should be highlighted that this was not all explained by differences in baseline patient characteristics between the two regions. A recent study, based on the opinions and feedback of international leaders in developmental psychopathology research, revealed a great deal of variation in ADHD diagnosis rates and treatment practices across and within countries.[39] This study also demonstrated how social context including historical, cultural, and economic factors greatly influences perceptions, diagnosis, and treatment of ADHD. For example, the following are salient characteristics of diagnosis and treatment patterns in the People's Republic of China, which are crucial in understanding the current treatment practices and outcomes of ADHD in that country: high acceptance of herbal treatments (Traditional Chinese medicines), high levels of stigma attached to mental illness, a lack of training in the treatment of ADHD among medical and mental health professionals, and strong controls on potentially addictive medications such as stimulants.[39] Indeed, the Shanghai Health Bureau and relevant insurance regulations in the People's Republic of China mandate that any methylphenidate prescriptions be given for a maximum of only 2 weeks, and thus frequent follow-up is necessary for further prescriptions.[39] Such stringent guidelines can curtail the use of medication for the treatment of ADHD, and also discourage a long-term treatment if it incurs extra out-of-pocket payments due to frequent office visits required.

In addition, many parents of children/adolescents with ADHD in East Asia tend to take personal responsibility for their children's behavioral problems and have negative attitudes towards the use of medications for ADHD on cultural grounds, as indicated in a recent literature review, although the review focused mainly on parents and teachers of school-aged children with ADHD in South Korea and the US.[40] The review also highlighted that South Korean parents tended to be more concerned about their children's academic performance, rather than behavioral problems, while US parents tended to be more concerned about their children's behavioral problems mainly due to reduced independence and autonomy of their children, which are important values in that culture. It also reported that the use of medications was more accepted by parents in the US because of their tendency to believe that the medications can improve their children's behavioral problems. This observation may also explain the association between parental psychological distress and medication non-adherence found in our study (for East Asia) and similarly in Gau et al's.[18] Parents who suffer from psychological distress due to their children's behavioral problems are more likely to be those who also take heavy responsibility for their children's problems and make excessive parental involvements. It is possible that these types of parents are more skeptical about the benefits

of drug treatment for ADHD, and also more concerned about adverse effects, potentially leading to high levels of medication non-adherence in their affected children.

Another predictor of non-adherence identified among East Asian patients was a family history of ADHD, which is again consistent with the study by Gau et al.[12] Although the reason for this association is still unclear, Gau et al speculated that this relationship may be suggestive of decreased organization and monitoring of medication compliance in the context of familiar ADHD traits. Further research is clearly required to confirm this relationship and explore the underlying mechanism.

Parental psychological distress and a family history of ADHD were, however, not associated with medication non-adherence in Central Europe and in the overall sample. Instead, having no other children living at home was associated with non-adherence in both cases. This association may imply that parents in such family have less time to provide other behavioral interventions at home for their children with ADHD, thereby being more reliant on pharmacologic treatment. Alternatively, more children could mean more conflicts within the family, which can increase the need to control behavioral problems of children with ADHD. We also cannot exclude the possibility that the other children living at home act as additional caregivers who can help remind patients to take their medication. Notably, this association was not found in a subset of East Asian patients, possibly because many families in East Asia have an only child, especially in the People's Republic of China due to the government's one child policy. In addition, it should be noted that our study did not show the association between medication non-adherence and other risk factors previously identified, such as older age[18,20,21,23–25] and male gender,[21,22] although the directions of the associations were consistent with previous studies. Moreover, important predictors of non-adherence previously identified, such as frequent daily dosing, were not included, as these parameters were not assessed. Further research, preferably culturally-sensitive, is warranted to better identify risk factors of medication non-adherence for optimal treatment outcomes in ADHD.

Our study also demonstrated the negative impact of medication non-adherence on achieving response and symptom improvement in the treatment of newly-diagnosed pediatric patients with ADHD symptoms in Central Europe and East Asia. This finding was consistent with previous studies showing similar impacts of non-adherence in ADHD.[16,24] Charach et al assessed the impact of adherence on outcomes in 79 patients with ADHD, who were followed up for 5 years

after completing a 12-month RCT of methylphenidate in the US.[16] The study showed greater improvement in teacher-reported symptoms among adherent patients, compared to non-adherent patients or those off medication. Using data from a 13-week RCT with methylphenidate conducted in Europe, Kooij et al also showed that non-adherence is a significant predictor of reduced response to treatment, although the study focused on the adult ADHD population.[4] Our study, however, did not find a significant association between adherence and improvement in HRQoL, although the associations with all five domains of the CHIP-CE (Satisfaction, Comfort, Resilience, Risk Avoidance, and Achievement) were in the expected directions. While there is no study that specifically looked at the impact of non-adherence on HRQoL in ADHD, Marcus and Durkin demonstrated an association between adherence to stimulants and higher academic grades among school-aged children with ADHD in the US, using Medicaid claims data and academic administrative records in Philadelphia.[17] Taken together, more efforts should be made to improve communication with patients and their parents/caregivers about the importance of medication adherence as an effective strategy to achieve optimal treatment outcomes.

There are several limitations that should be taken into account when interpreting these results. First, this study was originally not designed to assess medication adherence in ADHD but other treatment outcomes and patterns. These results can, therefore, only be considered as secondary analyses. Second, although this observational study included more than one thousand patients (n = 860 in this current analysis), they may not be representative of the pediatric patients with ADHD in Central Europe and East Asia. Third, the patients included in our study were those with ADHD symptoms, not ADHD cases. The sensitivity analyses, which included patients with ADHD cases using the CSI-4 cut-off points (85%), provided consistent results, however. Fourth, assessment of adherence was based on physician clinical judgment only, rather than with an objective measure of adherence, such as pill counts. Therefore, the rate of non-adherence may have been underestimated, and thereby the impact of non-adherence as well (ie, the difference in clinical outcomes between adherent patients and non-adherent patients). In addition, patients and their families had to be willing to participate in this relatively long-term follow-up study, implying that they could be more compliant to the treatment regimen than a representative clinical sample. Fifth, although our study demonstrated the negative impact of medication non-adherence on clinical outcomes, it has been suggested that physician assessment of adherence

may be influenced by the clinical state of the patient; that is, physicians assume that patients who are doing better in terms of symptoms are taking more of their medication than patients who are not doing so well.[41] Finally, given the observational design, the associations found in our study do not imply causal relationships.

Conclusion

Despite these limitations, the present study highlights a high level of medication non-adherence in the treatment of ADHD, particularly in East Asia. Being from East Asia, amongst other clinical and demographic factors, was found to be the strongest predictor of medication non-adherence. A family history of ADHD and parental psychological distress were found to contribute to the high level of medication non-adherence in this region, whereas having no other children living at home was identified as a risk factor of medication non-adherence in Central Europe. Our findings also emphasize the importance of adherence to ADHD medication in achieving response and symptom improvement. If treatment outcomes are considered to be suboptimal, clinicians should consider not only inadequate effectiveness or adverse effects but also poor adherence to medication. They should also pay particular attention to those patients who have a higher chance of non-adherence, and if possible, implement strategies, preferably culturally sensitive ones, to address modifiable risk factors associated with medication non-adherence. Furthermore, more efforts should be made for more effective communication with patients and their parents/caregivers to discuss the benefits and risks of drug treatment and the importance of medication adherence.

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