Eur Child Adolesc Psychiatry [Suppl 1]
13 : I/36–I/42 (2004) DOI 10.1007/s00787-004-1004-8

ORIGINAL CONTRIBUTION

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ADORE – Attention-Deficit Hyperactivity Disorder Observational Research in Europe

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Abstract *Background* Since there is little information about the naturalistic way of treatment in daily European practice, the Attention-Deficit Hyperactivity Disorder Observational Research in Europe (ADORE) project was designed as a prospective, non-interventional study of approximately 1,500 patients observed by approximately 300 investigators in various European regions. *Objective* The primary objective is the description of the relationship between treatment regimen prescribed and quality of life in ADHD patients over a two-year period. *Method* The naturalistic care provided and the outcomes (psychopathology, quality of life) are recorded at 7 data collection points. *Results* The present preliminary report provides data on the first 315 patients who were included in the study by the beginning of January 2004. The data provide an impression of the sample characteristics, the clinical diversity, and the effects of ADHD on school careers and social activities. Furthermore, treatment information dealing with the time both before and at baseline is given. *Conclusion* Even with this limited sample the negative effects on psychosocial development and quality of life in ADHD children are apparent.

Key words ADHD – children – naturalistic care – quality of life – Europe

Background

Throughout Europe the definition of ADHD varies both across the region and within countries. European literature reflects the use of both the ICD-10 definition of Hyperkinetic Disorder (HD), and the DSM-IV definition of ADHD. In addition certain countries may utilise a psychodynamic approach in lieu of formal criteria. Hence, diagnosis and perceptions of symptom severity are not consistent across the region [11].

Information on prevalence and incidence of ADHD in Europe is scarce and results are dependent on the definition utilised. However, although the published literature reports variable rates of prevalence, the majority of studies report rates within a 2 % – 5 % range (for years of age 6–16) when using the ICD-10 and DSM-IV diagnostic criteria, respectively. These rates are accepted by the ADHD medical community across Europe, and it is also accepted that ADHD is underdiagnosed and undertreated [1, 13, 14, 17].

Literature from the UK and the Netherlands indicate problems with ADHD assessment, low rates of referral and diagnosis [16, 19, 20] and scepticism regarding the disorder [8]. Females may also be underdiagnosed, as ADHD gender distribution is inconsistent across Europe. It is argued that females present less recognisable inattentive symptoms.

European sources reporting the intangible costs and consequences of ADHD are limited though some reports indicate that hyperactivity is a determinant of violence, aggression, defiant and disruptive behaviours,

stealing, shoplifting, joyriding and vandalism, offending, relationship problems (social functioning), and academic problems [3, 16].

Reported information from the US suggests that ADHD imposes a significant burden upon the patient, family and society. At present, European literature on ADHD outcomes is scarce, and does not establish the full burden of disease. In addition, there is no information (US or EU) in the naturalistic setting that accounts for the impact that treatment has upon ADHD burden of illness and Quality of Life (QoL). QoL in particular is an important area for both the patient and the family and has been assessed in clinical trials [21].

When ADHD is diagnosed, treatment guidelines suggest that pharmacotherapy is utilised across Europe as part of a multi-modal treatment package including parent training, family or school interventions and psychotherapy [4, 9, 18]. Treatment practices of ADHD across Europe are variable and are in the development stages. In some countries there is a reluctance to use available medication as first line therapy; whilst in others, treatment with available medication is often reserved for severe cases. European [2, 18] and country specific treatment guidelines [4, 9] have been published but treatment patterns in the European countries reviewed are still dependent on local medical culture and individual practices/experiences.

Rationale

It is apparent that there is an understanding of ADHD in the US, in European Academic Hospitals and European clinical trial results. However, there is a relative paucity of information in Europe and no information that describes the relationship between treatment regimen prescribed for ADHD and outcomes in the naturalistic setting. Clearly there is a need to assess long-term treatment patterns and patient outcomes in actual European practice settings.

To evaluate the relationship between treatment regimen and outcomes with ADHD in actual practice settings, an observational and naturalistic study design is required. In addition, to assess how ADHD symptoms are treated over a period of time in different settings, the study design is required to be longitudinal and to collect information from multiple centres and multiple countries. Likewise, there are many problems in diagnosing ADHD including:

- ADHD diagnostic criteria are open to subjective physician judgement of symptoms;
- High degree of comorbidities associated with ADHD;
- Physicians with different medical specialities diagnose ADHD;
- Scepticism of ADHD as a diagnosable and treatable disorder.

Research is needed to examine the relationship between diagnosis of ADHD, severity of ADHD symptoms and problems with the associated treatment regimen implemented.

Objectives

The primary objective of ADORE is to:

Describe the relationship between treatment regimen prescribed (no treatment, psychotherapy, pharmacotherapy and psychotherapy/pharmacotherapy combination) and QoL of ADHD, in actual practice, and in different countries over a two-year period with a total of 7 data collection points.

The secondary objectives of ADORE are to describe

- How treatment regimens are modified over a 2-year period;
- The relationship between diagnosis in actual practice and ratings of ADHD symptom severity;
- The relationship between treatment regimen and severity of ADHD symptoms and comorbidities; and
- The relationship between the treatment regimen prescribed and physicians with different medical specialities.

Design

The ADORE study is being conducted in a methodologically consistent fashion across ten European countries (see Table 1). The protocol and evaluation forms have been translated into eight languages and a dedicated research team is responsible for implementation of the study in each country. To ensure consistency and quality, there is a central, co-ordinating research team.

Within a 2-year, longitudinal, observational, naturalistic, multi-centre, multi-country study, diagnosis and associated choice of treatment regimen (treatment patterns) and the outcomes of this treatment decision in patients with ADHD symptoms will be studied. Approximately 300 physicians will observe approximately 1,500 patients across Europe. Each country will have a maximum patient-recruitment period of 6 months. Patients who are 6–18 years of age, have ADHD symptoms and have not been formally diagnosed with an ADHD syndrome in the past are suitable for inclusion. Patients suffering from mental retardation, autism, schizophrenia, and those who are simultaneously participating in studies that include treatment interventions and/or on investigational drug will be excluded from the study.

European Child & Adolescent Psychiatry, Vol. 13, Supplement 1 (2004)

Table 1 A summary of the design of the ADORE study

Type of study:	Observational, non-interventional	
Primary objectives	1. Describe the relationship between treatment regimen prescribed (no treatment, psychotherapy, pharmacotherapy and psychotherapy/pharmacotherapy combination) and Quality of Life of ADHD, in actual practice, and in different countries over a two-year period. 2. Describe how treatment regimens are modified over a 2-year period; 3. Describe the relationship between diagnosis in actual practice and ratings of ADHD (hyperactive/inattentive/impulsive) symptom severity; 4. Describe the relationship between treatment regimen and severity of hyperactive/inattentive/impulsive symptoms and comorbidities; 5. To describe the relationship between the treatment regimen prescribed and physicians with different medical specialities.	
Selection criteria	■ According to the participating psychiatrist, patients of 6–18 years of age, with ADHD (hyperactive/inattentive/impulsive) symptoms in the outpatient setting who have not been diagnosed previously with ADHD or a hyperactive/inattentive/impulsive syndrome in the past. ■ Patient consent ■ In the clinical judgement of the investigator the patient does not have mental retardation, autism or schizophrenia ■ Are simultaneously participating in a different study that includes a treatment intervention and/or an investigational drug	
Patients	No cohort specification	
Study investigators	Approximately 300 physicians from different medical specialties and treatment settings in the following countries: ■ Austria ■ France ■ Iceland ■ The Netherlands ■ Switzerland ■ Denmark ■ Germany ■ Italy ■ Norway ■ UK	
Methods	■ All patient care is at the discretion of the participating physician ■ Data collection will be conducted for a minimum of 24 months ■ Data collection points will be baseline assessment (T1), first return to the physician (T2), 3 months (T3), 6 months (T4) and then every 6 months thereafter (T5-T7)	
Measures	■ Demographics:	Age, gender, height, weight, diagnosis, family ADHD history, patient alcohol tobacco, substance, cannabis dependency/abuse/use
	■ Functioning:	Living conditions (information on the family), school, social relations
	■ Clinical status:	ADHD RS-IV, CGI severity, C-GAS, SDQ, single item questions on comorbidities and DSM-IV diagnosis
	■ Tolerability:	Sleep problems, decreased appetite, headaches, abdominal pain, changes in personality
	■ Treatment:	Pharmaco/psychotherapy name, dose/number of sessions
	■ Other treatment:	Educational interventions in school, speech therapy, occupational therapy, relaxational techniques, hypnosis, psychomotor/physiotherapy, EEG biofeedback, herb/homeopathy, diet
	■ Compliance:	Parent and psychiatrist report
	■ Contacts with police, social services:	Single items
	■ Bullying, truancy:	Single items
	■ Health-related quality of life:	CHIP – CE
	■ Medical resource use:	Contacts with primary care physician, accident and emergency rooms, referrals for therapy
	■ Costs:	Application of local unit cost standards to resource units
Sponsor	Eli Lilly and Company Limited	

Methods

Data collection

Data collection is conducted via a core data collection form (DCF) that is 12 pages long and takes approximately 30 minutes to complete. The DCF has been constructed to assess a broad range of variables while maintaining simplicity of use. Simplicity and brevity are pivotal in preserving the observational nature of the study; longer, more complicated assessment would increase the chances of altering the normal course of care. Table 1 shows the main areas evaluated in the study. Among the outcomes that will be assessed are QoL, social functioning, family environment, performance in school, behaviours, clinical status, treatment tolerability, and treatment satisfaction.

Symptom severity

The assessment of clinical severity in the ADORE study will be assessed at baseline using the ADHD rating scale-IV – Parent Version – Investigator completed (ADHD-RS-IV-Parent) [5] and the Children' Global Assessment Scale (C-GAS) [12]. In addition, at baseline 2 single item questions based on the DSM-IV criteria ask if the symptoms have been recognisable in two different environments, and if the symptoms are pervasive. Furthermore, symptom severity is assessed based upon clinical judgement throughout the study period with the use of the Clinical Global Impression – ADHD-Severity (CGI-ADHD-S) [7]. In addition, in selected countries a direct question asks if a formal ADHD, Hyperkinetic Disorder or "other" diagnosis had been made.

Comorbidity

Following the logic already employed in other psychiatric disorders, specific, single-item scales to assess the impact of comorbidities have been developed with a severity element. Diagnosis of ADHD (hyperactive/inattentive/impulsive) symptoms may be complicated by other comorbid problems as mentioned earlier. The incidence of a comorbid disorder may also be a determinant of symptom severity; hence ADORE will assess for these problems in single item questions. For comorbid problems where severity is a key determinant (Anxiety, Depression, Conduct Disorder, Oppositional Defiant Disorder), the investigator is requested to assess severity (if known) in single item questions similar to a Clinical Global Impression likert scale. For other problems (e.g., Tourette's syndrome or tics) the investigator is requested to simply state if the problem is present (if known) in single item questions. Psychopathology of patients is measured by the Strengths and Difficulties Questionnaire (SDQ) developed by Goodman [6]. The SDQ is a 25-item parent completed instrument that addresses both positive and negative behavioural attributes. Assessment of other health problems includes headaches, stomach ache, insomnia and changes in personality.

Treatment patterns and resource utilisation

The study documents the use of ADHD symptom related pharmacotherapy and concomitant medication, psychotherapy sessions, accident and emergency room visits, primary care physician visits, and any other diagnostic tests that the investigator conducts. From this information it will be possible to describe treatment patterns initiated by different physicians and for different levels of symptom severity. Local published costs will be applied to this resource utilisation to estimate the direct costs of treating patients with ADHD symptoms.

Quality of life (QoL)

QoL is assessed at baseline (T1), and at every subsequent data collection point (T2 – T7) using the Child Health and Illness Profile, Child Edition-Parent Reported Form (CHIP-CE) [10]. The CHIP-CE measures overall QoL and amongst other areas makes an assessment of patient mental health, self-esteem, general behaviour and involvement with family and peers.

Outcomes

To assess the broad impact of ADHD or hyperactive/inattentive/impulsive symptoms, information on a broad range of outcomes is assessed. These include behaviour in school, academic performance, social relationships, bullying, contact with social services, contact with law enforcement, and substance use and abuse.

Sample

For the present preliminary report a sample of the first 315 patients was used. These patients were enrolled in the ADORE project by the beginning of January, 2004 and came predominantly from the UK (37 %) and Austria (17 %) with the Netherlands (11 %), Denmark (5 %), Switzerland (3 %), and Germany (14 %) providing the rest of the sample. As expected, boys (89 %) grossly dominated over girls (11 %). Close to two-thirds lived together with both biological parents (68 %) and one-third was either the eldest (41 %) or youngest sibling (32 %). The mean age of the sample was 9.2 (SD = 2.6) years.

Findings

In the following, major findings will be described with regard to the various sections of the available data. Findings will be reported descriptively only due to the preliminary nature of the report. Only the most prominent findings for each category will be reported so that the percentages in each category do not necessarily sum up to 100 %.

DSM-IV *diagnostic criteria* were used most frequently (51 %) followed by ICD-10 criteria (23 %) or a combination of the two (9 %). The ADHD mean inattentiveness score was 19.4 (SD = 4.7), the mean hyperactivity/impulsivity score was 18.0 (SD = 5.6), and the mean overall score was 37.4 (SD = 9.0).

Comorbid disorder and problems were frequent and included oppositional defiant disorder, learning disorder, conduct disorder, anxiety, coordination problems, depression, and others listed in Table 2. No patients presented psychosis. Only two patients presented with tobacco dependency, while use/abuse of alcohol, cannabis, and/or tobacco amounted to only 1–6 %. Sleeping problems were relatively common (48 %) with nearly half of the affected children experiencing significant interference in well-being (20 %). The broad spectrum of co-existing problems is also reflected in the poor ratings of all scales of the SDQ compared to the English norms taken from the internet sdqinfo.com (Total difficulties: 21.3 vs. 8.4; Emotional symptoms: 4.1 vs. 1.9; Conduct problems: 4.9 vs. 1.6; Hyperactivity/Inattention: 8.5 vs. 3.5; Peer relationship problems: 3.9 vs. 1.5; Prosocial behaviour: 6.5 vs. 8.6).

School career and *social activities* were negatively affected in a sizeable proportion of the sample. Only 48 % were considered to be manageable in the classroom en-

European Child & Adolescent Psychiatry, Vol. 13, Supplement 1 (2004)

Table 2 Reported comorbid disorders and other health problems

	N	%
Anxiety	307	42
Asthma	310	11
Bipolar disorder	295	1
Conduct disorder	302	46
Coordination problems	300	31
Depression	307	29
Epilepsy	305	< 1
Learning disorder	286	55
Obsessive compulsive disorder	305	2
Oppositional defiant disorder	310	63
Psychosis	303	0
Tics	310	8
Tourette's syndrome	310	2

vironment, whereas 28 % experienced some exclusion from school lessons, 17 % were in a special education program, 4 % were requested to change to a special need school, and 5 % were suspended from school. The vast majority (83 %) of the sample was classified as having a worse academic performance than 60–100 % of children of the same age. Only 4 % were truant and of those involved in bullying 18 % were victims, 15 % were bullies and 7 % were both. Whereas 37 % had never been called for social activities in the past 4 weeks another 36 % had been called for more than 3 social activities in this period.

The section on *treatment information* revealed that (before baseline) 43 % of the sample had not received any treatment, whereas 33 % had received other types of therapies (not including pharmacotherapy or psychotherapy), 4 % had received pharmacotherapy and optionally other, 18 % had received psychotherapy and optionally other and 2 % had received the combination of the two (2 %) with the specific treatments allowing optionally also for a combination with other types of therapies. At baseline most patients received some form of pharmacotherapy (53 %) or psychotherapy (40 %). Again there was an option to prescribe these types of intervention with other therapies.

The distribution of prescribed drugs at baseline is shown in Table 3. Pharmacotherapy alone or in combination with other therapy was given to 22 % of the 6 to 9 years olds, 38 % of the 10 to 12 years olds, and 48 % of the 13 to 18 years olds. In contrast psychotherapy alone or in combination with other therapy was provided to 21 % of the 6 to 9 years olds, 17 % of the 10 to 12 years olds and 5 % of the 13 to 18 years olds. The respective figures for the combination of both interventions were 24 %, 23 %, and 17 %. As can be seen from Table 4 a sizeable proportion of subjects received other interventions than pharmaco- and/or psychotherapy.

Table 3 Pattern of prescribed drugs at baseline

	N*	%
Methylphenidate	165	81
Methylphenidate long acting	165	14
Dexamphethamine	165	1
SSRI	165	< 1
Other drug	165	4

* Only patients who were prescribed at least one pharmacotherapy at baseline were included

Table 4 Pattern of other therapies at baseline

	N*	%
Educational intervention in school	162	62
Speech therapy	162	15
Occupational therapy	162	15
Relaxational techniques	162	2
Psychomotor/psychotherapy	161	9
Herb/homeopathy	162	1
Diet (exclusion or supplement)	162	9
Other therapy	162	16

* Only patients who were prescribed at least one other therapy at baseline were included

Furthermore there is a series of indicators of *clinical severity* in the present study: There were < 12 % of patients who were considered to have been either normal, minimally ill or mildly ill as rated on the CGI for the past week. In contrast, 45 % were rated moderately ill, 35 % as being markedly ill, 8 % as being severely ill and < 1 % very severely ill. In 58 % of the patients first awareness of the ADHD problems occurred before the age of six years with a mean age of 5.3 (SD = 3.6) years. Treatment was first sought in the majority (64 %) at the age of 6–10 years, in 21 % at the age of 0–5 years, and in < 16 % beyond the age of 10 years.

The mean CGAS score was 46.8 (SD = 21.2) indicating that on average there was a moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area. Finally, the profile of the CHIP-CE is shown in Table 5 demonstrating that the present sample deviates significantly in the majority of domains from the standardization sample. Children with ADHD score significantly below the population norms with regard to the entire achievement domain, one out of three subdomains of the concept domain, two out of three subdomains of the resilience domain, the entire risk avoidance domain, and the entire satisfaction domain. In all these domains and subdomains children with ADHD show significantly poorer psychosocial functioning.

Table 5 Quality of Life profile as measured by the CHIP-CE (T-Scores and comparison with the mean of the standardisation sample; T = 50, SD = 10)

	N	Mean	SD	t	p
Achievement domain	309	4.0	0.6	−35.5	< 0.001
Academic performance subdomain	302	4.0	0.8	−33.2	< 0.001
Peer relation subdomain	314	4.0	0.6	−20.7	< 0.001
Comfort domain	314	4.3	0.4	−13.1	< 0.001
Physical comfort subdomain	314	4.3	0.5	−0.04	n. s.
Emotional comfort subdomain	315	4.1	0.6	−22.4	< 0.001
Restricted activity subdomain	312	4.6	0.6	1.30	n. s.
Resilience domain	315	4.2	0.4	−22.9	< 0.001
Family involvement subdomain	315	4.3	0.4	−13.9	< 0.001
Social problem-solving subdomain	311	4.0	0.7	−25.8	< 0.001
Physical activity subdomain	315	4.2	0.5	−2.6	0.01
Risk avoidance domain	315	4.4	0.5	−27.7	< 0.001
Individual risk avoidance subdomain	314	4.3	0.6	−17.7	< 0.001
Threats to achievement subdomain	315	4.5	0.5	−29.4	< 0.001
Satisfaction domain	314	4.3	0.4	−22.3	< 0.001
Satisfaction with health subdomain	315	4.2	0.4	−15.0	< 0.001
Satisfaction with self subdomain	313	4.4	0.6	−24.0	< 0.001

Comment

So where does the ADORE study fit into the scientific research of ADHD? As noted in the introduction of this paper, coordinated European research into ADHD is relatively scarce, and while anecdotal evidence suggests a significant burden upon the patient, family, education resources and overall society, research has not been fully assessed these to date, although European guidelines exist [15]. While ADORE will not answer all of these questions fully (indeed a number of studies are required to accomplish this), ADORE will go some way to provide more information in these areas and potentially document current beliefs. The question remains of why a naturalistic observational study would be suitable for assessing ADHD outcomes. The primary research question for ADORE is to longitudinally describe how in actual practice, the treatment regimen prescribed has an affect on QoL of ADHD, and how this is different from country to country. Design features required for such a study would be observational/naturalistic, longitudinal, large scale and pan European.

The ADORE study has been designed to answer questions about how people suffering from ADHD are actually treated and how treatment influences long-term outcomes including QoL, school and social functioning and family burden. The ADORE study was designed to maximize external validity while maintaining a high degree of internal validity. The intention with the ADORE study is to collect information from a sample representative of newly diagnosed/assessed European ADHD patients. However, since both the patients and investigators are not randomized and were free to participate, the sample is not representative in the purest form; nevertheless results will give a good idea of the situation. External validity is maximized by having open patient entry criteria. Hence, in the assessment of "actual practice", so the study enrolment criteria play a very important role. The aim for ADORE is to assess all ADHD patients; not just those who meet a particular score on a rating scale or are absent from comorbidities. Patients may be enrolled regardless of formal diagnosis, severity level or co-morbidity. External validity is also maximized through inclusion of patients from different countries, geographies, treatment settings (public, private) and regions (metropolitan and rural areas). Diagnosis and treatment decisions are completely separate from a decision to enter ADORE.

Internal validity should be maintained through the ADORE study design, comprehensiveness and size. The inclusion of only those patients who are newly diagnosed and not had a previous diagnosis will enable comparison of patients at a more or less common point in their episode of care. Furthermore, the large size of the ADORE study sample will allow stratification of treatment groups by prognostic variables (such as severity of symptoms and chronicity) either when differences are too large to control for statistically, common sense dictates, or when specific research questions focus on a specific patient type.

While there are always significant information gaps for any disorder and indeed worldwide for ADHD, the primary health outcomes information gaps in Europe are consistent information on epidemiology, treatment patterns, burden of illness and the impact of treatment on burden of illness. The ADORE study will provide information on the latter of these three areas. The ADORE project has been described with major objectives as outlined in the introduction. The overall goal of the project is to evaluate treatment regimen prescribed in different countries and how this impacts upon QoL of patients with ADHD symptoms. In addition, ADORE will assess diagnosis and symptom severity of patients and how this differs by the particular medical speciality and the subsequent treatment regimen prescribed. Based on these goals and the need to assess outcomes across a large and diverse sample, the study has been designed pragmatically with a measurement approach of breadth as opposed to specificity. Thus, selection of instruments was based heavily on considerations of simplicity and ease of use.

The project will not collect prevalence data and will not provide information on the number of undiagnosed and untreated subjects with ADHD symptoms. ADORE is a descriptive study and will be able to describe the treatment regimen prescribed and how this impacts QoL, and will allow us to gain an understanding of how

physicians with different medical specialities view a typical patient with ADHD symptoms and the associated treatment decision.

Despite these limitations and the preliminary findings of the present contribution based on about 20 % of the expected final sample there are some emerging findings of interest, mostly in line with the literature. The included children display not only sizeable ADHD problems but also a high rate of co-existing psychopathological and developmental problems, negatively affected school careers and social problems in a relatively large proportion of cases.

Due to the inclusion criteria of the study that precludes the consideration of previously diagnosed ADHD cases there is a high proportion of children in the present sample who did not receive specific and appropriate treatment before inclusion into the study. More specific treatments had been installed at baseline and it will be of interest how with increasing progress of this longitudinal study the indicators of clinical symptoms and severity and psychosocial impairment will change. The necessity of improvement is clearly indicated by the poor ratings of SDQ scales, Clinical Global Impressions (CGI-ADHD-S), the low children's Global Assessment Scale (C-GAS) of psychosocial functioning, and the relatively poor Child Health and Illness Profile (CHIP-CE) ratings in the majority of domains and subdomains of quality of life.

Clearly, the diversified methods, the large sample size, the longitudinal nature, and the multi-cultural origin of this pan-European study will allow more refined analyses in the future and allow definitive conclusions on the health status of ADHD children and its improvement.

Acknowledgements The ADORE Study Group would like to thank Stephen Ralston (UK), MJM Lorenzo (UK), Hans-Christoph Steinhausen (Switzerland), Aribert Rothenberger (Germany) and Manfred Döpfner (Germany) for their support while preparing the manuscript.

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