R. Escobar[1]
C. Soutullo[2]
J. San Sebastián[3]
E. Fernández[1]
I. Julián[1]
F. Lahortiga[2]

Atomoxetine safety and efficacy in children with attention deficit/hyperactivity disorder (ADHD): initial phase of 10-week treatment in a relapse prevention study with a Spanish sample

[1] Lilly Research Laboratories
Medical Department
Alcobendas (Madrid)

[2] Psychiatry and Medical Psychology Department
Clínica Universitaria
Universidad de Navarra
Pamplona

[3] Child Psychiatry Unit
Hospital Ramón y Cajal
Madrid

Introduction. Attention-deficit/hyperactivity disorder (ADHD) appears to be associated to problems with regulation of cortical dopaminergic/noradrenergic function. The purpose of this work is to present efficacy and safety data from 10-week open label treatment with atomoxetine, a highly selective norepinephrine reuptake inhibitor, in a Spanish sample of children and adolescents with ADHD participating in a double-blinded, placebo-controlled, multinational study on relapse prevention.

Patients and methods. Sub-analysis of data in 36 children and adolescents aged 6 to 15 years, with diagnosis of ADHD (DSM-IV) included in Spain, receiving open-label treatment with atomoxetine for 10 weeks and assessed using ADHD-RS, CGI-ADHD-S, CPRS-R:S, CTRS-R:S y CHQ-PF50.

Results. After 10 weeks of treatment with atomoxetine, statistically significant reductions in ADHD-RS, CGI-ADHD-S, CPRS-R:S and CTRS-R:S scores were obtained in both subtypes; 87.5 % of inattentive patients and 82.14 % of patients with combined subtype were responders. No recurrences were observed. No serious adverse event-driven discontinuations occurred, and no statistically significant changes in blood pressure, but a mild increase in heart rate ($p < 0.0001$) were observed.

Conclusions. In general, atomoxetine was well tolerated and effective in the open phase in Spanish patients, both for inattentive and combined subtypes. Atomoxetine appearsas a non-stimulant therapeutic alternative for the treatment of ADHD.

Key words:
Attention-deficit/hyperactivity disorder. Atomoxetine. Safety. Efficacy.

Actas Esp Psiquiatr 2004;32(1):26-32

Correspondence:
Rodrigo Escobar Giraldo
Lilly, S.A.
Departamento Médico
Av. de la Industria, 30
28108 Alcobendas (Madrid). Spain
e-mail: escobar_rodrigo@lilly.com

Seguridad y eficacia de la atomoxetina en niños con trastorno por déficit de atención/hiperactividad (TDAH): fase inicial durante 10 semanas en estudio de prevención de recaídas en una muestra española

Introducción. El trastorno por déficit de atención/hiperactividad (TDAH) parece estar asociado con problemas de regulación de la función dopaminérgica/noradrenérgica cortical. El propósito del presente trabajo es presentar los datos de eficacia y seguridad del tratamiento abierto durante 10 semanas con atomoxetina, un inhibidor altamente específico de la recaptación de noradrenalina, en una muestra española de niños y adolescentes con TDAH que participan en un estudio multinacional, doble ciego, controlado con placebo de prevención de recaídas.

Pacientes y métodos. Subanálisis de los datos de 36 niños y adolescentes de 6 a 15 años diagnosticados de TDAH (DSM-IV) incluidos en España tratados durante 10 semanas de forma abierta con atomoxetina y valorados mediante las escalas ADHD-RS, CGI-ADHD-S, CPRS-R:S, CTRS-R:S y CHQ-PF50.

Resultados. Tras 10 semanas de tratamiento con atomoxetina se produjo una reducción estadísticamente significativa en las escalas ADHD-RS, CGI-ADHD-S, CPRS-R:S y CTRS-R:S en ambos subtipos, respondiendo el 87,5 % de los pacientes del subtipo déficit de atención y el 82,14 % de los pacientes del subtipo combinado. No se produjeron recaídas. No se produjeron abandonos debidos a acontecimientos adversos graves ni se detectaron cambios estadísticamente significativos en la presión arterial, aunque sí un ligero aumento en la frecuencia cardíaca ($p < 0,0001$).

Conclusiones. En general, atomoxetina fue bien tolerada y se mostró efectiva en la fase abierta en los pacientes de la muestra española, tanto en el subtipo déficit de atención como combinado. La atomoxetina parece mostrarse como una alternativa terapéutica no estimulante para el tratamiento de la TDAH.

Palabras clave:
Trastorno por déficit de atención con hiperactividad. Atomoxetina. Seguridad. Eficacia.

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a psychiatric disorder that is usually seen in childhood, affecting 3 % to 10 % of school aged children and frequently continues in adult life[1,2]. ADHD prevalence data are not homogeneous and the differences not only depend on the use of different diagnostic criteria (DSM-IV or ICD-10) but also on the way the diagnosis is made: with clinical evaluations (the most reliable form) or with ques-tionnaire to the parents, professors or parents and professors. Specifically in Spain, different studies estimate ADHD prevalence at 4 %-6 % in children from 6 to 15 years[3], 14.4 % (3.5) in 8 year old children, 5.3 % (2.1) in 11 year old children, 3 % (1.9) in 15 year old children[4] and from 3.6 % to 8 % in 10 year old children[5,6]. The impact of this disorder is important since it is frequently associated with school/work, family and social functioning difficulties[7] and with the development of comorbid psychiatric disorders[8]. In addition, recent studies state that ADHD children generate a total medical cost and medical resource use that is more than twice that of children having the same age without ADHD[9].

ADHD diagnosis is based on a strict clinical history and direct observation by parents, professors and clinicians. At present, there is still no pathognomonic biological or psychological marker of the disease10. DSM-IV characterizes this disorder as a «persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development». To diagnose ADHD according to DSM-IV criteria, five criteria should be fulfilled: *a)* presence of six symptoms of inattention or six symptoms of hyperactivity-impusivity that is maladaptive and inconsistent with developmental level; *b)* presence of some inattentive or hyperactive-impulsive symptoms that caused impairments before 7 years of age; *c)* presence of some impairments caused by symptoms in two or more settings; *d)* evidence of clinically significant impairment in social, academic or occupational activity, and *e)* differential diagnosis of other medical or psychiatric disorders. Three main subtypes of ADHD have been described: predominantly inattentive, predominantly hyperactive-impulsive and combined inattentive/hyperactive-impulsive. Although its etiology is unknown, ADHD seems to be associated with cortical dopaminergic and noradrenergic function problems[11].

ADHD treatment should be aimed at symptom improvement. In a recently performed study, it was demonstrated the pharmacological intervention was associated to better results than psychosocial interventions that did not include medication[12]. Among the psychosocial intervention, psychostimulants (methylphenidate, dextroamphetamine, etc.) have been the drugs of choice for many years, however, they may have abuse risk, they are effective only for 4 to 12 hours and they may produce variations in mood state, sleep disorders or increase in tic severity. In addition, 10 %-30 % of the patients are treatment resistant. Alternative treatments, such as bupropion, pemoline, modafinil, tricyclic antidepressants as well as alpha-2 noradrenergic agonists, have been studied[13,14].

Atomoxetine, a highly selective noradrenaline reuptake inhibitor was approved in the United States of America by the Food and Drug Administration (FDA) for the treatment of ADHD in children, adolescents and adults and is presently still being studied as treatment for ADHD. Several previous placebo controlled studies have demonstrated its efficacy in ADHD in children, adolescents and adults[15-17]. Comparable efficacy to that of methylphenidate[18] and a good safety and tolerability profile19 have been observed, the side effects fundamentally observed being appetite loss with resulting weight loss and mild increases of blood pressure and heart rate, without detecting effects on the cardiac conduction.

The purpose of this present study is to present efficacy and safety data of a ten week open treatment phase with atomoxetine in a Spanish sample of children and adolescents with ADHD who participate in a multinational study of relapse prevention.

METHODS

A double blind, placebo controlled multicentric study in 14 countries on the prevention of relapses in children who fulfill the DSM-IV ADHD criteria has recently end-ed. The present study shows the results of the initial ten week period of open study with atomoxetine in a sample of patients included in Spain (University Clinic, University of Navarra in Pamplona and Hospital Ramón y Cajal in Madrid).

Patients

This study's sample included children and adolescents whose ages ranged from 6 to 15 years who fulfilled DSM-IV ADHD criteria and reached a minimum score of 1.5 standard deviation above that expected for age and gender, according to the ADHD version assessment scale of the parents administered by the investigator (ADHD-RS)[20]. The diagnosis was confirmed through a clinical interview and semistructured diagnostic interview: Kiddie's schedule for affective disorders and schizophrenia for school aged children - present and lifetime version (K-SADS-PL)[21], that includes a module for ADHD. The main exclusion criteria were weight under 20 kg, background of bipolar, psychotic or convulsive disorder, hypertension, substance abuse, serious medical diseases and pregnancy or breast-feeding period. This study was approved by the Institutional Review Boards corresponding to each study center and was carried out according to the ethical principles of the Declaration of Helsinki and good clinical practice guidelines. Once the study was explained to the patient and to his/her parents or legal representative, written informed consent was obtained from the parent or legal representative and the agree-ment of the

patient before inclusion in the study. After, a copy of the informed consent was sent to the Public Attorney.

Study design

After an evaluation and drug wash-out period, the patients were included in an initial 10 week open treatment period with atomoxetine, during which the dose was gradually increased for the first 4 weeks from 0.5 mg/kg/day to a maximum of 1.8 mg/kg/day, based on efficacy and tolerability assessed by the investigator. At the end of this period, treatment responding patients, appropriate to be randomized in the study relapse prevention period, were identified.

Study evaluations

The main efficacy endpoints were the ADHD-RS scale evaluated by the investigator, an 18 item scale in which each item corresponds to one of the 18 ADHD criteria symptoms of the DSM-IV, based on an interview with one of the parents (each item is scored on a 0 to 3 scale, so that the maximum score is 54, a higher score indicating greater severity); and the clinical global impression ADHD severity scale (CGI-ADHD-S)[22], a clinical evaluation of severity of ADHD symptoms, according to his/her experience with this type of patients, of a single item score on a 1 to 7 scale (1: normal; 7: extremely ill). Secondary endpoints included, among others, inattention and hyperactivity-impulsivity subscales of the ADHD-RS scale; the Conners' parent rating scale-revised: short form (CPRS-R:S) and the Conners' teacher rating scale-revised: short form (CTRS-R:S)[23], two 27 item and 28 item scales, respectively, in which the parents or teacher assess the behavior problems related with ADHD in the corresponding setting; and the child health questionnaire (CHQ-PF50)[24] a 50 item instrument constructed to measure physical and psychosocial well-being in children of 5 years or more. Safety was evaluated by collection of adverse events through open questions, measurement of vital signs, electrocardiogram and laboratory tests.

Statistical analysis

A subanalysis of the initial 10 week period data of open treatment with atomoxetine in the patients included in Spain was carried out with descriptive statistics and comparisons between the baseline and final values (Student's *t* test or Wilcoxon non-parametric test), with last observation carried forward (LOCF) for the absent data.

RESULTS

The Spanish sample was made up of 36 children and adolescents from 6 to 15 years, whose demographic and baseline characteristics are described in table 1. Most of the patients presented combined ADHD subtype. A total of 35.7 % of them presented oppositional defiant disorder and 67.9 % had received previous treatment with stimulants.

Efficacy results are shown in table 2 and figures 1 and 2. After 10 weeks of open treatment with atomoxetine, there was a statistically significant decrease in the total group of the ADHD-RS scale total score from 42.2 ± 6.3 to 15.5 ± 10.9 ($p < 0.0001$) and in the inattention sub-scale scores from 21.8 ± 2.6 to 8.3 ± 5.2 ($p < 0.0001$) and hyperactivity/impulsivity from 20.2 ± 5.7 to 7.2 ± 6.4 ($p < 0.0001$). The same occurred in the attention deficit subtype and combined subtype patients. A statistically significant decrease was also observed in the CGI-ADHD-S scale score in both ADHD subtypes. In addition, at 10 weeks of treatment, statistically significant differences were observed in the ADHD index scores of the CPRS-R:S and CTRS-R:S scales, in all the patients and in each disease subtype (except in the CTRS-R:S scale for attention deficit subtype patients). Considering responders as those patients who reach a CGI-ADHD-S ≤ 2 score and who show a decrease of at least 25 % on the ADHD-RS scale in regards to the baseline value during the last two consecutive visits, 83.3 % of the patients showed response at 10 weeks of treatment (87.5 % of the patients having the attention deficit subtype and 82.14 % of those with the combined subtype). In addition, no relapses occurred during the first 10 weeks of the treatment.

Table 1 Demographic and baseline characteristics of the patients

Characteristics	Atomoxetine (n = 36)
Gender [n (%)]	
Male	32 (88.9)
Female	4 (11.1)
Age (mean [SD])	10.4 (2.2)
Onset age (mean [SD])	4.6 (1.5)
Intelligence quiotient (mean [SD])	104.8 (16.5)
ADHD subtype (n [%])	
Inttentive	8 (22.2)
Hyperactive/impulsive	—
Combined	22 (77.8)
Presence of oppositional defiant disorder (n [%])	10 (27.8)
Inattentive	—
Combined	10 (35.7)
Previous treatment with stimulants (n [%])	20 (55.6)
Inattentive	1 (12.5)
Combined	19 (67.9)

SD: standard deviation.

Table 2 Efficacy results

	N	Basaline (mean [SD])	Final (mean [SD])	Change (mean [SD])	p
Total ADHS-RS	36	42.19 (6.34)	15.47 (10.90)	−26.72 (11.02)	< 0.0001
Inattentive	8	33.63 (3.07)	13.88 (11.98)	−19.75 (10.70)	0.0133
Combined	28	44.64 (4.66)	15.93 (10.77)	−28.71 (10.45)	< 0.0001
ADHD-RS inattention subscale	36	21.83 (2.60)	8.25 (5.22)	−13.78 (5.47)	< 0.0001
Inattentive	8	22.00 (2.51)	9.5 (5.15)	−12.50 (6.30)	0.0032
Combined	28	22.04 (2.66)	7.89 (5.27)	−14.14 (5.28)	< 0.0001
ADHD-RS hyperactive/impulsitivity	36	20.17 (5.66)	7.22 (6.41)	−12.94 (6.55)	< 0.0001
Inattentive	8	11.63 (3.85)	4.38 (7.21)	−7.25 (5.01)	0.0128
Combined	28	22.61 (3.14)	8.04 (6.06)	−14.57 (6.06)	< 0.0001
CGI-ADHD-S	36	5.22 (0.48)	2.47 (1.30)	−2.75 (1.36)	<0.0001
Inattentive	8	5.00 (0.00)	2.38 (1.06)	−2.63 (1.06)	0.0008
Combined	28	5.29 (0.53)	2.50 (1.37)	−2.79 (1.45)	< 0.0001
CPRS-R:S	34	57.53 (12.07)	35.56 (15.44)	−22.26 (15.55)	< 0.0001
Inattentive	7	45.88 (11.09)	26.71 (9.60)	−18.29 (17.95)	0.0077
Combined	27	60.86 (10.26)	37.85 (15.96)	−23.30 (15.07)	< 0.0001
CTRS-R:S	27	39.15 (15.17)	32.39 (14.42)	−4.96 (10.76)	0.0391
Inattentive	8	38.13 (11.84)	34.25 (10.01)	−3.88 (5.74)	0.6737
Combined	19	39.46 (16.25)	31.65 (16.02)	−5.42 (12.39)	0.0407

ADHD-RS: version assessment scale of the parents admnistered by the investigator; CGI-ADHD-S: clinical global impression-ADHD; CPRS-R:S: Conners parent rating scale-revised: short form; CTRS-R:S: Conners teacher rating scale-revised: short version; SD: standard deviation; p: p value of change between baseline and final value (Wilcoxon).

Regarding the health results measured with the CHQ-PF50 presented in table 3, improvements were observed in the psychosocial group, the behavior and mental health items showing statistically significant increases.

In regards to safety, there were no drop-outs due to serious adverse events during the first 10 weeks of open treatment with atomoxetine. A mild statistically significant increase was detected in heart rate, while the changes

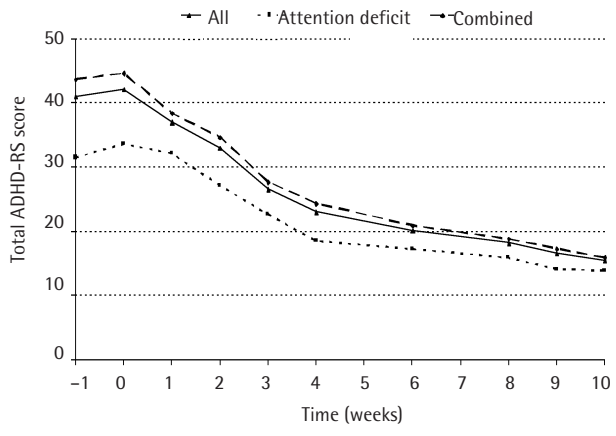

Figure 1 *Evolution of mean scores on the ADHD-RS scale by disease subtypes.*

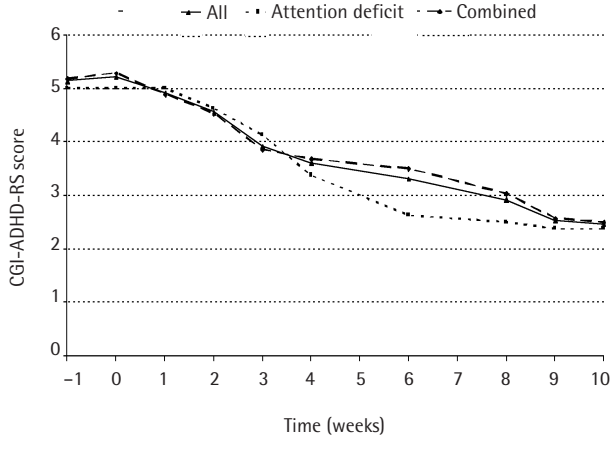

Figure 2 *Evolution of the mean scores on the CGI-ADHS-S scale by disease subtype.*

Table 3 Health results derived from the Child Health Questionnaire (CHQ-PF50)

	N	Baseline (mean [SD])	Final (mean [SD])	Change (mean [SD])	p
Physical group	33	57.5 (6.1)	55.8 (6.5)	−1.3 (8.0)	0.3280
Physical functioning	34	98.5 (4.9)	98.9 (3.6)	0.5 (4.2)	0.9915
General health	33	76.6 (12.9)	77.8 (11.7)	1.2 (16.0)	0.7370
Role-physical	34	88.9 (24.9)	92.2 (18.0)	3.9 (23.9)	0.9396
Pain	34	81.1 (21.1)	81.1 (20.2)	−0.9 (27.2)	0.8868
Psychosocial group	33	33.3 (7.9)	39.1 (9.7)	6.6 (10.0)	0.0076
Self esteem	34	63.9 (20.0)	71.1 (19.8)	7.6 (17.9)	0.1610
Behavior	34	41.7 (13.5)	56.5 (15.6)	14.9 (14.5)	0.0002
Family activities	34	54.6 (23.4)	63.2 (24.7)	9.7 (17.3)	0.0804
Mental health	34	52.8 (13.1)	62.4 (15.4)	9.6 (16.8)	0.0096
Parental impact-emotional	34	42.1 (18.6)	43.0 (18.0)	1.1 (23.4)	0.8634
Parenteral impact-time	33	86.0 (13.8)	86.6 (17.5)	2.0 (14.8)	0.5694
Role-social	34	73.8 (29.5)	81.7 (22.5)	8.8 (29.7)	0.2727

SD: standard deviation; p: p value of change between baseline and final value (Wilcoxon). Greater scores indicate better quality of life.

observed in systolic and diastolic blood pressure were not significant (table 4). The most frequent adverse events (frequency (10 %) were appetite loss (30.6 %, mild in all the cases except one that was moderate), headache (16.7 %; mostly mild with a 1 to 2 day duration), pharyngitis (16.7 %), tachycardia (13.9 %; mild in all the cases and this stopped during the follow-up), vomiting (11.1 %; mild in all the cases and with a 1 to 4 day duration) and oppositional behaviors (11.1 %).

CONCLUSIONS

The results of this present study are coherent with those previously published, since they provide evidence that atomoxetine is effective, reducing ADHD symptoms and producing functional improvement in children and adolescents. The high percentage of responding patients (83.3 %) shows that the effects of atomoxetine were clinically important, although due to the absence of active comparator, it was not possible to determine if the magnitude of the results is totally attributable to the treatment and if it would be similar to the presently available drugs for ADHD. Although the sample size is quite limited, above all in attention deficit subtype patients, it has also been possible to observe atomoxetine efficacy in the two ADHD subtypes present in this study, attention deficit and combined.

An interesting aspect of this study, which is also described by other authors[18], is the use of a semistructured interview of the parents administered by the investigator to assess the ADHD symptoms course in addition to direct reports by pa-

Table 4 Vital signs

	N	Baseline (mean [SD])	Final (mean [SD])	Change (mean [SD])	IC 95%	p
Systolic blood pressure (mmHg)	36	118.5 (14.9)	117.3 (14.5)	−0.6 (14.0)	(−5.7. 4.4)	0.8025*
Diastolic blood pressure (mmHg)	36	73.4 (14.5)	75.3 (12.4)	2.3 (13.7)	(−2.7. 7.3)	0.3516*
Heart rate (lpm)	36	70.6 (8.5)	83.2 (12.0)	13.2 (10.9)	(9.3. 17.1)	< 0.0001**

SD: standard deviation; 95 % CI: 95 % confidence interval of change between baseline and final value; p: p value of change between baseline and final value (*Student's *t* and ** Wilcoxon).

rents and professors. This instrument (ADHD-RS) has demonstrated psychometric properties, so that it is considered adequate as a main efficacy endpoint. In addition, an instrument administered by the investigator guarantees that the patients are evaluated coherently by an experienced clinician who can place the symptom severity within the adequate clinical context and integrate the data of different domains in a single evaluation. In any event, parent and teacher reports in this case have also observed improvement of the patients both in the family as well as school setting. This improve-ment has been greater in the parents' evaluations than in those of the teachers. Some authors[15] have observed in multicentric studies that the evaluations performed by the teachers are not satisfactory due to lack of consistency between the baseline and final values, probably due to the fact that multiple schools and teachers are involved and because of the existence of different attitudes related to participation, so that the evaluations of the parents may be more reliable than those of the teachers.

Previous data have demonstrated that ADHD is not a benign disease and has an important impact on social and family as well as school functioning. Little data exist that demonstrate that satisfactory drug treatment and reduction of ADHD symptoms lead to improvement in the functional results. In the present study, the data derived from the Child Health Questionnaire suggest that atomoxetine is associated not only with an improvement in psychopathological symptoms characteristics of the disease but also in other psychosocial aspects, even during this acute treatment phase. If the changes determining this improvement persist in time, treatment could be beneficial in the long term in children and their families, in addition to producing immediate reduction of the symptoms.

This study's data show that atomoxetine was well tolerated, no drop-out due to adverse events being observed. In general, the adverse events pattern and effects on vital signs were consistent with that expected for a drug associated with increase in noradrenergic tone. However, no statistically significant changes were observed in blood pressure, and, even though a significant increase was detected in pulse, the magnitude of this change was small and it is unlikely that it represents a clinically important finding. In any event, it would be interesting to investigate it more carefully in future studies. Although appetite loss was mild in all the cases except one, its effects on weight may be important during chronic treatment. The long term results of the study that is presently underway will provide greater information on this aspect.

Interpretation of the results of this study is limited due to several factors. In the first place, it is an open study in which there is no active or placebo comparator, so that it is not possible to rule out the possibility of influences in the results due to the patient's or investigator's expectations. In addition, the study used a gradual dose titration design based on efficacy assessed by the investigator, which made it impossible to assess the onset of the treatment effects. In addition, the data provide evidence of acute efficacy, but not on the long term treatment value once the patients have reached a satisfactory initial response. Finally, as it is a subanalysis of a sample of patients included in Spain who are participating in a long term multinational study of relapse prevention, the sample size is very reduced. However, it is likely that the complete study data, with a much greater number of patients and follow-up, will add new data on the efficacy and safety of atomoxetine regarding its role in relapse prevention in ADHD patients.

In summary, the data of this study show additional evidence of atomoxetine efficacy and safety in children and adolescents with ADHD and that satisfactory treatment with atomoxetine is associated to symptomatic and functional improvement. In addition, as it is not an amphetaminic derivative, it is unlikely that atomoxetine has abuse risk. Thus, atomoxetine seems to be shown as a ther-apeutic alternative to psychostimulants for ADHD treatment.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington: American Psychiatric Association, 2000.
2. American Academy of Pediatrics, Committee on Quality Improvement and Subcommittee on ADHD. Clinical practice guideline: diagnosis and evaluation of the child with ADHD. Pediatrics 2000;105:1158-70.
3. Benjumea Pino P, Mojarro Práxedes MD. Trastornos hipercinéticos: estudio epidemiológico en doble fase de una población sevillana. An Psiquiatría 1993;9:606-311.
4. Gómez-Beneyto M, Bonet A, Catalá MA, Puche E, Vila V. Prevalence of mental disorders among children in Valencia, Spain. Acta Psichiatr Scan 1994;89:352-7.
5. Andrés MA, Catalá MA, Gómez Beneyto M. Prevalence, comorbidity, risk factors and service utilisation of disruptive behaviour disorders in a community sample of children in Valencia (Spain). Soc Psychiatry Psychiatr Epidemiol 1999;34: 175-9.
6. Andrés-Carrasco MA, Catalá MA, Gómez-Beneyto M. Estudio de la prevalencia del TDAH en niños de 10 años residentes en el municipio de Valencia. Actas Luso-Esp Neurol Psiquiatr 1995; 23:184-8.
7. Murphy KR, Barkley RA. Prevalence of ADHD symptoms in adult licensed drivers. J Attent Disord 1996;1(3):147-61.
8. Biederman J, Baldessarini RJ, Wright V, Knee D, Harmatz JS. A double-blind placebo-controlled study of desipramine in the treatment of ADD: I. Efficacy. J Am Acad Child Adolesc Psychiatry 1989;28(5):777-84.
9. Leibson CL, Katusic SK, Barbaresi WJ, Ranson J, O'Brien PC. Use and costs of medical care for children and adolescents with and without ADHD. JAMA 2001;285:60-6.
10. Curran S, Taylor EA. Attention-deficit hyperactivity disorder: biological causes and treatments. Curr Opin Psychia-try 2000; 13:397-402.

11. Zametkin AJ, Rapoport J. Neurobiology of attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry 1987; 8:145-60.
12. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1999;56(12):1073-86.
13. Soutullo C. Diagnóstico y tratamiento farmacológico del trastorno por déficit de atención e hiperactividad. Med Clin 2003; 120(6):222-6.
14. Spencer TJ, Biederman J, Wilens TE, Faraone SV. Novel treatments for attention-deficit/hyperactivity disorder in children. J Clin Psychiatry 2002;63(12):16-22.
15. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. and the Atomoxetine ADHD Study Group. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics 2001;108(5):E83-91.
16. Heillgenstein J, Spencer T, Faries DE, Biederman J, Kratochvil CJ, Conners CK. Efficacy of atomoxetine vs placebo in pediatric outpatients with ADHD. Scientific Proceedings of the 47th Annual Meeting of the American Academy of Child and Adolescent Psychiatry. New York, 2001.
17. Michelson D, Adler L, Spencer T, Reimherr FW, West SA, Allen AJ, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry 2003;15;53(2): 112-20.
18. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, et al. Atomoxetine and methyl-phenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry 2002; 41(7):776-84.
19. Wernicke JF, Kratochvil CJ. Safety profile of atomoxetine in the treatment of children and adolescents with ADHD. J Clin Psychiatry 2002;63(Suppl. 12):50-5.
20. Du Paul GJ, Anastopoulos AD, Power TJ, Reid R, Ikeda MJ, McGoey KE. Parent ratings of attention-deficit/hyperactivity disorder symptoms: factor structure and normative data. J Psychopathol Behav Assess 1983;20:83-102.
21. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7):980-8.
22. National Institutes of Mental Health. Psychopharmacol Bull 1985;21(4):839-43.
23. Conners CK. Conners' rating scales-revised, technical manual. Toronto: Multi-Health Systems Inc., 1997.
24. Landgraf JM, Abetz L, Ware JE. The CHQ user's manual. 3.ª ed. Boston: The Health Institute. New England Medical Center, 1996.