ACTUALIZACIÓN EN TRATAMIENTO DEL TDAH 2009-2010

Madrid, 22 de enero de 2011

Dra. Montse Pàmias

Servei de Psiquiatria Infantil. Corporació Sanitària Parc Taulí. Sabadell

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- Avances en tratamiento farmacológico:
  - Metilfenidato
  - Atomoxetina
  - Guanfacina
  - Dextroanfetamina

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METILFENIDATO

1. METILFENIDATO
FORMULACIÓN TRANSDÉRMICA

CMRO

Current Medical Research & Opinion Vol. 26, No. 1, 2010, 129–137

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doi:10.1185/03007990903437412

Article 5293/444102

Original article

Switching from oral extended-release methylphenidate to the methylphenidate transdermal system: continued attention-deficit/hyperactivity disorder symptom control and tolerability after abrupt conversion

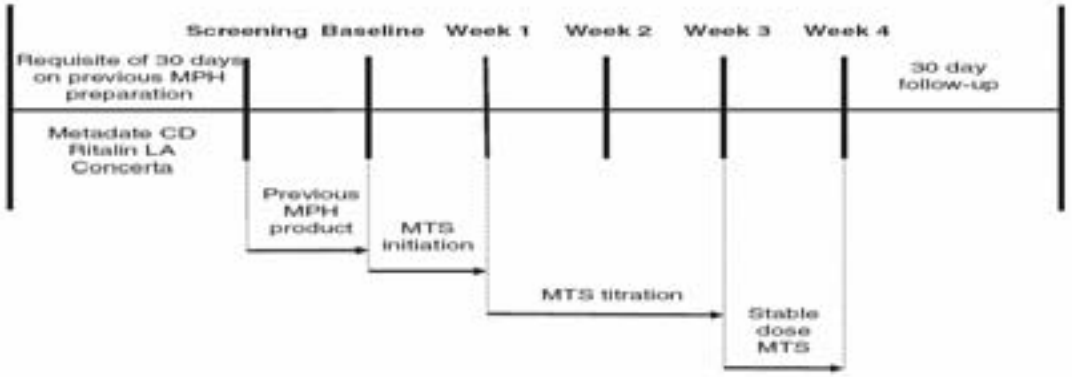


Figure 1. Abrupt conversion study design. Week 1 was the initial effectiveness evaluation point, which assessed the accuracy and feasibility of the dose-transition schedule. Week 4 was the primary effectiveness evaluation point, the last measured change in ADHD-Rating Scale-IV total score from baseline. MPH, methylphenidate; MTS, methylphenidate transdermal system.

Table 1. MTS dose-transition schedule.

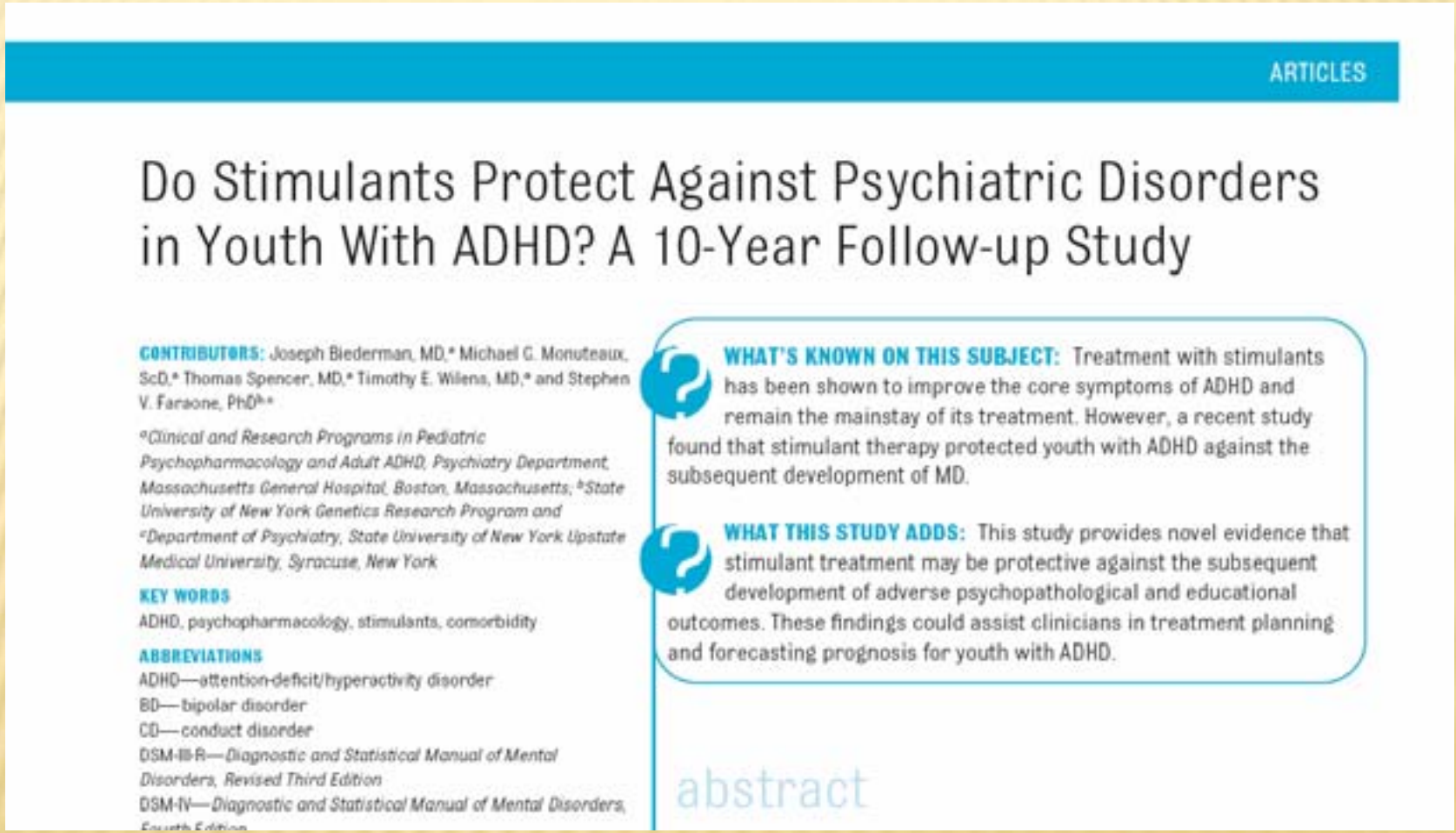
Previous dose, mg/day			Converted MTS dose, mg/9-hour wear time
Concerta	Ritalin LA	Metadate CD	
18	10 or 20	10 or 20	10
27	30	30	15
36	40	40	20
54	50	50	30

Table formulated by analyzing data provided in package inserts for the following: Concerta, Alza Corporation, Palo Alto, CA USA; Ritalin LA, Novartis AG, Basel, Switzerland; or Metadate CD, UCB Inc., Atlanta, GA, USA. MTS, methylphenidate transdermal system.

CONTROL DE SÍNTOMAS Y TOLERANCIA CON MTF TRANSDÉRMICO

- Sin cambios en respuesta clínica al cambio brusco al MTF transdérmico (ADHD- RS)
- Puede ser necesario un ajuste de dosis a la marcada como conversión
- Efectos secundarios similares al MTF oral, excepto algunas reacciones dérmicas locales

2. METILFENIDATO
TRATAMIENTO DE LA COMORBILIDAD



Do Stimulants Protect Against Psychiatric Disorders in Youth With ADHD? A 10-Year Follow-up Study

CONTRIBUTORS: Joseph Biederman, MD,[a] Michael G. Monuteaux, ScD,[a] Thomas Spencer, MD,[a] Timothy E. Wilens, MD,[a] and Stephen V. Faraone, PhD[b,a]

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KEY WORDS
ADHD, psychopharmacology, stimulants, comorbidity

ABBREVIATIONS
ADHD—attention-deficit/hyperactivity disorder
BD—bipolar disorder
CD—conduct disorder
DSM-III-R—*Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*
DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders,*

WHAT'S KNOWN ON THIS SUBJECT: Treatment with stimulants has been shown to improve the core symptoms of ADHD and remain the mainstay of its treatment. However, a recent study found that stimulant therapy protected youth with ADHD against the subsequent development of MD.

WHAT THIS STUDY ADDS: This study provides novel evidence that stimulant treatment may be protective against the subsequent development of adverse psychopathological and educational outcomes. These findings could assist clinicians in treatment planning and forecasting prognosis for youth with ADHD.

abstract

- Estudio follow up 10 años
- N 148 niños TDAH y 120 niños sin TDAH
- Edad diagnóstico 6-18 años
- 73% tratados con metilfenidato
- Edad media reevaluación 22 años
  - K-SDS
  - SCID
  - Entrevista clínica. Valoración académica

- RESULTADOS
- Pacientes en tratamiento con metilfenidato tenia menos posibilidades de presentar un trastorno de ansiedad o un trastorno de conducta y menor probabilidad de repetir curso que los pacientes sin tratamiento

TABLE 2 Cumulative Morbidity Risks and Hazard Ratios for Association Between Stimulant Treatment and Subsequent Psychiatric Comorbidity in Males With ADHD

Outcome	Age of Onset, Mean ± SD (Range), y	Events Before ADHD Onset, *n*[a]	Participants Used in Model, *n*	MR (95% CI)		Hazard Ratio	Test Statistic	*P*
				No Stimulant Therapy	Stimulant Therapy			
MD	8.0 ± 3.9 (2–16)	20	107	0.69 (0.55–0.82)	0.24 (0.15–0.37)	0.22	$\chi^2_1 = 19.7$	<.001
CD	10.8 ± 4.0 (3–18)	13	112	0.67 (0.53–0.81)	0.22 (0.14–0.34)	0.21	$\chi^2_1 = 21.4$	<.001
MA disorder	8.5 ± 6.0 (2–23)	18	108	0.60 (0.47–0.75)	0.07 (0.03–0.19)	0.15	$\chi^2_1 = 17.8$	<.001
ODD	7.4 ± 3.5 (2–18)	46	79	0.88 (0.78–0.95)	0.40 (0.25–0.58)	0.21	$\chi^2_1 = 19.9$	<.001
BD	11.4 ± 5.2 (3–18)	9	116	0.42 (0.27–0.61)	0.20 (0.12–0.32)	0.47	$\chi^2_1 = 3.5$	.063
Repeated grade	8.4 ± 4.0 (4–18)	2	122	0.63 (0.51–0.75)	0.26 (0.16–0.40)	0.25	$\chi^2_1 = 18.4$	<.001

MR indicates cumulative morbidity risk of disorder by age 21 as estimated by Kaplan-Meier failure function; MA, multiple (≥2) anxiety.
[a] Participants were excluded from given model.

Meta-Analysis: Treatment of Attention-Deficit/Hyperactivity Disorder in Children With Comorbid Tic Disorders

MICHAEL H. BLOCH, M.D., M.S., KAITLYN E. PANZA, B.A.,
ANGELI LANDEROS-WEISENBERGER, M.D., AND JAMES F. LECKMAN, M.D.

ABSTRACT

Objective: The Food and Drug Administration currently requires the package inserts of most psychostimulant medications to list the presence of a tic disorder as a contraindication to their use. Approximately half of children with Tourette's syndrome experience comorbid attention-deficit/hyperactivity disorder (ADHD). We sought to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette's syndrome and ADHD. **Method:** We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of medications in the treatment of ADHD in the children with comorbid tics. We used a random effects meta-analysis with standardized mean difference as our primary outcome to estimate the effect size of pharmaceutical agents in the treatment of ADHD symptoms and tics. **Results:** Our meta-analysis included nine studies involving 477 subjects. We assessed the efficacy of six medications—dextroamphetamine, methylphenidate, alpha-2 agonists (clonidine and guanfacine), desipramine, atomoxetine, and deprenyl. Methylphenidate, alpha-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with comorbid tics. Alpha-2 agonists and atomoxetine significantly improved comorbid tic symptoms. Although there was evidence that supratherapeutic doses of dextroamphetamine worsens tics, there was no evidence that methylphenidate worsened tic severity in the short term. **Conclusions:** Methylphenidate seems to offer the greatest and most immediate improvement of ADHD symptoms and does not seem to worsen tic symptoms. Alpha-2 agonists offer the best combined improvement in both tic and ADHD symptoms. Atomoxetine and desipramine offer additional evidence-based treatments of ADHD in children with comorbid tics. Supratherapeutic doses of dextroamphetamine should be avoided. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(9):884–893. **Key Words:** tic disorders, attention-deficit/hyperactivity disorder, methylphenidate, α2 adrenergic agonists, meta-analysis.

1. Metilfenidato, alfa agonistas, desimpramina y atomoxetina demostraron eficacia en mejorar síntomas de TDAH en niños con tics. MTF presentó mayor efecto en síntomas TDAH
2. Alfa agonistas y atomoxetina mejoraron tics. Alfa agonistas mejor combinación de mejora de tics y TDAH.
3. Dosis supraterapéuticas de dextroanfetamina emperoraron los tics, no hubo evidencia de que metilfenidato empeorora tics a corto plazo

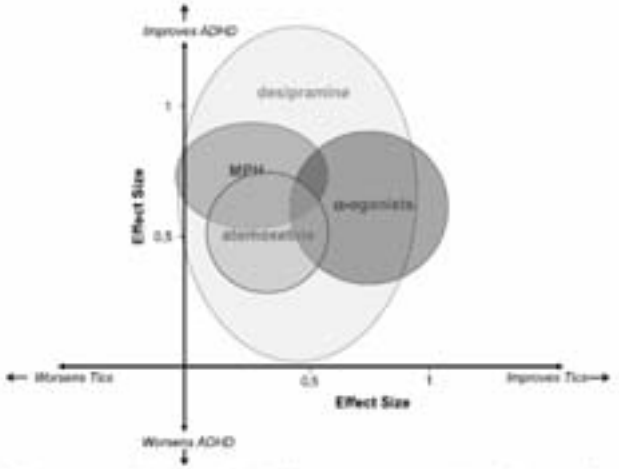

Fig. 3 Effect sizes of medications in treating AD/HD and tic disorders. Bubbles represent point estimate and 95% confidence interval for medications in terms of effect size (ES) in treating AD/HD and tic symptoms based on a meta-analysis of double-blind, placebo-controlled trials in children with AD/HD and comorbid tic disorders. Effect size estimates in treating AD/HD symptoms for pharmacological agents were methylphenidate (ES = 0.73; 95% CI 0.53–0.94), alpha-2 agonists (ES = 0.61; 95% CI 0.32–0.90), desipramine (ES = 0.80; 95% CI 0.02–0.91) and atomoxetine (ES = 0.51; 95% CI 0.27–0.74). Effect size estimates in treating tic symptoms for pharmacological agents were methylphenidate (ES = 0.26; 95% CI −0.03 to 0.58), alpha-2 agonists (ES = 0.74; 95% CI 0.44–1.04), desipramine (ES = 0.46; 95% CI −0.02 to 0.91), and atomoxetine (ES = 0.32; 95% CI 0.09–0.56). Superthreapeutic doses of dextroamphetamine moderately worsened tic symptoms (ES = −0.59; 95% CI −1.06 to −0.13) in a small crossover trial. These data are not depicted as there were no estimates for AD/HD improvement in this trial. The IDs for deprenyl, a monoamine oxidase B inhibitor, that is not available in the United States and did not demonstrate efficacy in the treatment of AD/HD or tics, is also not depicted in this figure. MAO-B = monoamine oxidase B; MPH = methylphenidate derivatives.

3. METILFENIDATO
ESTUDIOS DE EFICACIA

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Stimulant Drug Response in the Predominantly Inattentive and Combined Subtypes of Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: This study compared the methylphenidate (MPH) dose–response profiles of children with the Predominantly Inattentive (PI) and Combined (CB) subtypes of attention-deficit/hyperactivity disorder (ADHD). It is the first such study to enroll a sample comprised exclusively of children, all but one of whom had no prior exposure to ADHD medications.

Method: The design was a double-blind crossover with 1-week exposures to placebo and low, medium, and high, fixed, three times daily (t.i.d.) dosage regimens of immediate-release MPH, administered in random order. Parents and teachers completed weekly behavioral questionnaires (Conners, Swanson, Kotkin, Agler, M-Flynn and Pelham Scale [SKAMP]) and a child psychiatrist provided weekly ratings of symptom severity (ADHD Rating Scale [ADHD-RS]), side effects (Side Effects Rating Scale), and a Clinical Global Impressions-Severity (CGI-S). In addition, laboratory measures of vigilance (Continuous Performance Test [CPT]) and resistance to cognitive interference (Stroop) were administered weekly.

Results: Twenty-five children (15 CB, 10 PI), who met rigorous diagnostic criteria for their ADHD subtype, completed the study. Groups did not differ on demographic variables or severity at baseline. Behavioral questionnaires and clinical ratings indicated significant improvement on MPH for both subtypes but no differences in response profiles of the two groups. Drug effects were predominantly linear for both subtypes. Effects of MPH were significant for the CPT, but not the Stroop, instrument with no differences between ADHD subtypes.

Conclusions: Results support the clinical utility of MPH in the treatment of the PI subtype and provide no evidence of differences in response between the subtypes.

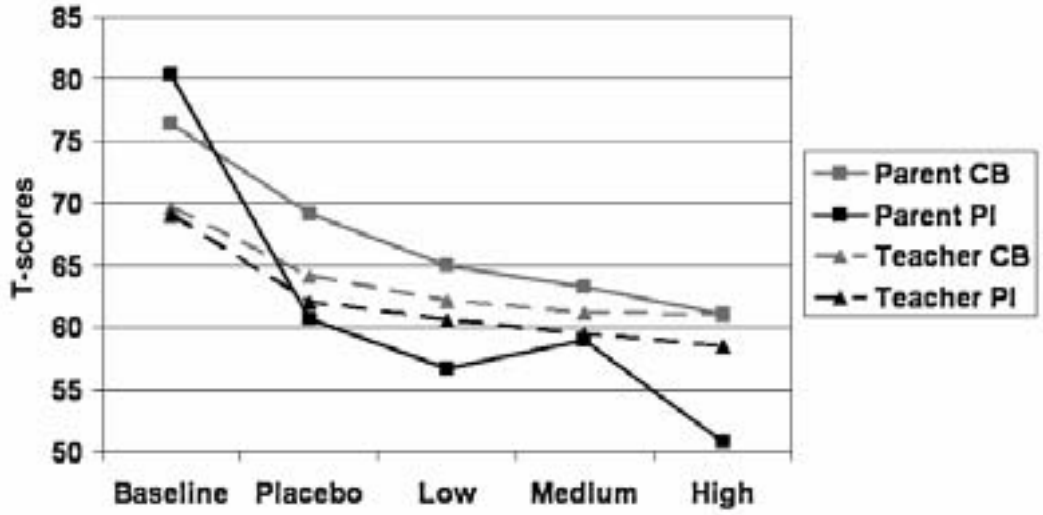

FIG. 1. Conners' Teacher and Parent DSM-IV Inattentive subscale scores as a function of methylphenidate treatment for the Combined and Inattentive subtypes. DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; CB = Combined; PI = Predominantly Inattentive.

Psychopharmacology (2010) 212:277–281
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ORIGINAL INVESTIGATION

Methylphenidate significantly improves declarative memory functioning of adults with ADHD

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Received: 1 April 2010 / Accepted: 5 July 2010 / Published online: 20 July 2010

Abstract *Conclusion* Methylphenidate improves declarative memory

Los déficits de memoria inmediata son disfuncionales en TDAH adultos no tratados
La memoria declarativa es la capacidad para almacenar y recuperar planes, ideas de la memoria

Estudio MTF/ placebo, 18 TDAH adultos respondedores

Resultados

En Worlk Learning Test :Test de memoria declarativa inmediata (1h) post tratamiento no diferencias significativas. Tampoco diferencias en tareas de reconocimiento

Test de memoria declarativa retrasada (3h) post tratamiento: cambios significativos

MTF mejora la memoria declarativa en pacientes adultos con TDAH

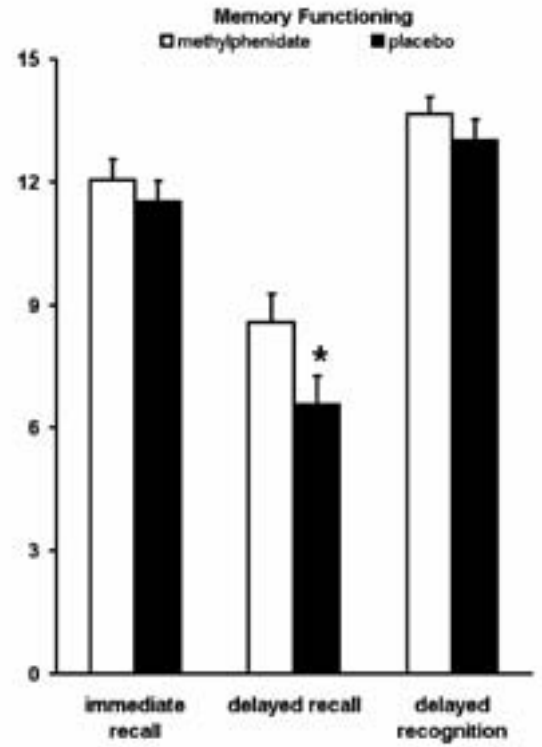

Fig. 1 Results of the Word Learning Test (WLT) Mean (SE) group score after intake of methylphenidate and placebo for immediate word recall, delayed word recall and recognition. * = $p<0.05$

Review

Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate

Katya Rubia*, Rozmin Halari, Anastasia Christakou and Eric Taylor

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We argue that impulsiveness is characterized by compromised timing functions such as premature motor timing, decreased tolerance to delays, poor temporal foresight and steeper temporal discounting. A model illustration for the association between impulsiveness and timing deficits is the impulsiveness disorder of attention-deficit hyperactivity disorder (ADHD). Children with ADHD have deficits in timing processes of several temporal domains and the neural substrates of these compromised timing functions are strikingly similar to the neuropathology of ADHD. We review our published and present novel functional magnetic resonance imaging data to demonstrate that ADHD children show dysfunctions in key timing regions of prefrontal, cingulate, striatal and cerebellar location during temporal processes of several time domains including time discrimination of milliseconds, motor timing to seconds and temporal discounting of longer time intervals. Given that impulsiveness, timing abnormalities and more specifically ADHD have been related to dopamine dysregulation, we tested for and demonstrated a normalization effect of all brain dysfunctions in ADHD children during time discrimination with the dopamine agonist and treatment of choice, methylphenidate. This review together with the new empirical findings demonstrates that neurocognitive dysfunctions in temporal processes are crucial to the impulsiveness disorder of ADHD and provides first evidence for normalization with a dopamine reuptake inhibitor.

Keywords: impulsiveness; timing; time perception; temporal discounting;

Table 2. Within-patients ANOVA differences in brain activation between the MPH and the placebo conditions during time discrimination versus order judgement. (BA, Brodman area; *N* voxels, number of voxels; Tal. co-ordinates, Talairach coordinates. *p*-value for ANCOVAs at $p<0.05$ for voxel activation and $p<0.006$ for cluster activation.)

brain region	BA	Tal. coordinates (*x*, *y*, *z*)	*N* voxels	cluster *p*-value
(*a*) *methylphenidate > placebo*				
L orbitofrontal/inferior frontal gyri/insula	47/45	−33, −11, −2	419	0.002
R medial prefrontal gyrus[a]	*46*	*40, 44, 9*	*38*	*0.02*
L anterior cingulated gyrus[a]	*32*	*−6, 37, 26*	*35*	*0.03*
R lateral cerebellum[a]		*14, −52, 46*	*30*	*0.05*
(*b*) *placebo > methylphenidate*				
R inferior/medial frontal gyri/insula	9/8/44	25, 15, 28	25	0.002
R superior frontal gyrus	8	18, 30, 49	14	0.003
R medial temporal lobe	22	29, −33, 7	23	0.002
R hippocampus, hippocampal gyrus	35	22, −15, −7	41	0.002
R putamen and globus pallidus	11	29, −11, 7	11	0.002

[a]Large three-dimensional clusters were broken into smaller two-dimensional clusters.

4. METILFENIDATO: EFECTOS SECUNDARIOS

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

A Naturalistic 10-Year Prospective Study of Height and Weight in Children with Attention-Deficit Hyperactivity Disorder Grown Up: Sex and Treatment Effects

Joseph Biederman, MD, Thomas J. Spencer, MD, Michael C. Monuteaux, ScD, and Stephen V. Faraone, PhD

Objective To assess the effect of attention-deficit/hyperactivity disorder (ADHD) and its treatment on growth outcomes in children followed into adulthood.

Study design Two identically designed, longitudinal, case-control studies of males and females with and without ADHD were combined; 124 and 137 control and subjects with ADHD, respectively, provided growth information at the 10- to 11-year follow-up. We used linear growth curve models to estimate the effect of time on change in height and whether this effect differed by sex and ADHD status. We also examined the effect of stimulant treatment on growth outcomes.

Results We found no evidence that ADHD was associated with trajectories of height over time or differences at follow-up in any growth outcomes. Similarly, we found no evidence that stimulant treatment was associated with differences in growth. However, among subjects with ADHD, major depression was associated with significantly larger weight in females and smaller height in males.

Conclusions Our results do not support an association between deficits in growth outcomes and either ADHD or psychostimulant treatment for ADHD. These findings extend the literature on this topic into young adulthood and should assist clinicians and parents in formulating treatment plans for children with ADHD. *(J Pediatr 2010;■ :■-■).*

- No se encontraron diferencias significativas en las trayectorias de altura o diferencias en ningún ítem de crecimiento

Table III. Growth outcomes of ADHD and control probands at follow-up, stratified by sex

Growth measure	Control probands	ADHD probands	Test statistic, *P* value
	Males*		
	n = 78	n = 68	
Height (cm)	179.0 ± 6.0	178.9 ± 7.7	t(145) = [illegible], P = .844
Age-corrected height (*z* score)	0.35 ± 0.8	0.27 ± 1.0	t(142) = -0.20, P = .844
Parent- and age-corrected height	0.02 ± 0.7	-0.03 ± 0.8	t(138) = -0.79, P = .43[illegible]
Weight (kg) (*z* score)	82.2 ± 15.6	81.8 ± 17.3	t(144) = -0.47, P = .638
Weight for age (*z* score)	0.80 ± 0.9	0.73 ± 0.9	t(141) = -0.57, P = .571
BMI for age (*z* score)	0.60 ± 0.9	0.55 ± 1.0	t(141) = -0.49, P = .628
	Females†		
	n = 59	n = 56	
Height (cm)	164.6 ± 6.5	166.4 ± 7.0	t(111) = 1.10, P = .275
Age-corrected height (*z* score)	0.20 ± 1.0	0.49 ± 1.1	t(111) = 1.12, P = .266
Parent- and age-corrected height (*z* score)	0.00 ± 0.9	0.29 ± 1.0	t(101) = 1.36, P = .178
Weight (kg)	67.5 ± 18.6	70.8 ± 18.3	t(111) = 0.51, P = .614
Weight for age (*z* score)	0.46 ± 1.1	0.70 ± 1.2	t(111) = 0.83, P = .411
BMI for age (*z* score)	0.38 ± 1.0	0.61 ± 0.9	t(111) = 0.70, P = .486

Values represent mean ± SD.
*Adjusted for social class, past GAF score, and ascertainment source.
†Adjusted for past GAF score.

- La presencia de TDAH y Depresión Mayor se asoció a mayor peso en chicas y menor talla en chicos
  - CHICAS
    - Mayor ingesta y menor ejercicio físico
    - Sobrepeso factor de riesgo para el desarrollo de depresión también en niñas TDAH
  - CHICOS
    - Población general (National Longitudinal Study of Adolescent Health) talla baja factor de riesgo de depresión en chicos entre 12 y 19 años

ORIGINAL ARTICLES

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Cardiovascular Effects of Longer-Term, High-Dose OROS Methylphenidate in Adolescents with Attention Deficit Hyperactivity Disorder

Paul Hammerness, MD, Timothy Wilens, MD, Eric Mick, ScD, Thomas Spencer, MD, Robert Doyle, MD, Michelle McCreary, BA, Judith Becker, MD, and Joseph Biederman, MD

Objective To examine the effects of high doses of extended-release methylphenidate (OROS MPH) on cardiovascular variables in adolescents with attention deficit hyperactivity disorder (ADHD).

Study design ECG indices plus systolic blood pressure (SBP), diastolic BP (DBP) and heart rate (HR) were assessed during an open-label study of OROS MPH in 114 adolescents with ADHD (doses up to 1.5 mg/kg/d). Cardiovascular parameters were assessed at 6 weeks and 6 months.

Results Small but statistically significant changes in DBP and HR were observed at 6 weeks, without further increases up to 6 months' follow-up. A small but statistically significant increase in SBP was observed over time. Twenty-nine percent of patients had isolated elevations in BP readings prior to study entry, and 14% had >3 consecutive visits at which elevated BP were observed during OROS MPH treatment. No clinically significant changes in ECG parameters were observed. No serious cardiovascular adverse events occurred.

Conclusions Treatment with relatively high doses of OROS MPH was associated with small but statistically significant mean increases in BP and HR, primarily during the first 6 weeks of treatment, without clinically meaningful changes in ECG. These observations are consistent with previous reports using lower doses. *(J Pediatr 2009;155:84-9)*.

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Table. Group differences in cardiac indices

	Baseline n = 114	Week 6 n = 114	3 Months n = 75	6 Months n = 57
Vital signs				
Systolic blood pressure (mm Hg)	112.8 ± 14.1	114.9 ± 12.5	115.4 ± 12.3	117.3 ± 13.6*
Diastolic blood pressure (mm Hg)	62.5 ± 9.0	65.4 ± 9.2*	63.3 ± 8.3†	63.8 ± 9.3
Heart rate (bpm)	81.7 ± 14.9	86.0 ± 14.1*	85.5 ± 14.0*	86.1 ± 12.5
ECG intervals (ms)				
PR interval	140.7 ± 16.6	137.6 ± 17.9	138.2 ± 16.6	137.9 ± 16.4
QRS interval	87.4 ± 9.6	86.6 ± 9.8	86.8 ± 10.3	87.5 ± 9.6
QT interval	380.2 ± 29.3	365.5 ± 28.3*	361.3 ± 25.5*	356.3 ± 24.3*,†
QTc interval	406.9 ± 13.4	408.5 ± 13.1	410.2 ± 14.9*	409.7 ± 12.6

*$P < .05$ vs baseline.
†$P < .05$ vs week 6.

1. El tratamiento con dosis altas de MTF oros, se asocia a pequeñas pero significativos incrementos de PA y FC durante los seis primeros meses de tratamiento.
2. Sin cambios clínicamente significativos en ECG

Changes in Emotions Related to Medication Used to Treat ADHD. Part II: Clinical Approaches

Journal of Attention Disorders
XX(X) 1–9

DOI: 10.1177/1087054710381232
http://jad.sagepub.com
SAGE

Robert L. Findling[1], Matthew Brams[2], Ann C. Childress[3], Frank A. López[4], Michael J. Manos[5], and Peter S. Jensen[6]

Posibles Causas de Cambios en EE en el Tratamiento del TDAH.

1.- Efecto directo del tratamiento
2.- Exacerbación de una comorbilidad enmascarada
3.- Interacciones Farmacológicas (no solo famacológicas, vitaminas, herbolarios …)
4.- Enfermedad Médica subyacente, (tiroides..)

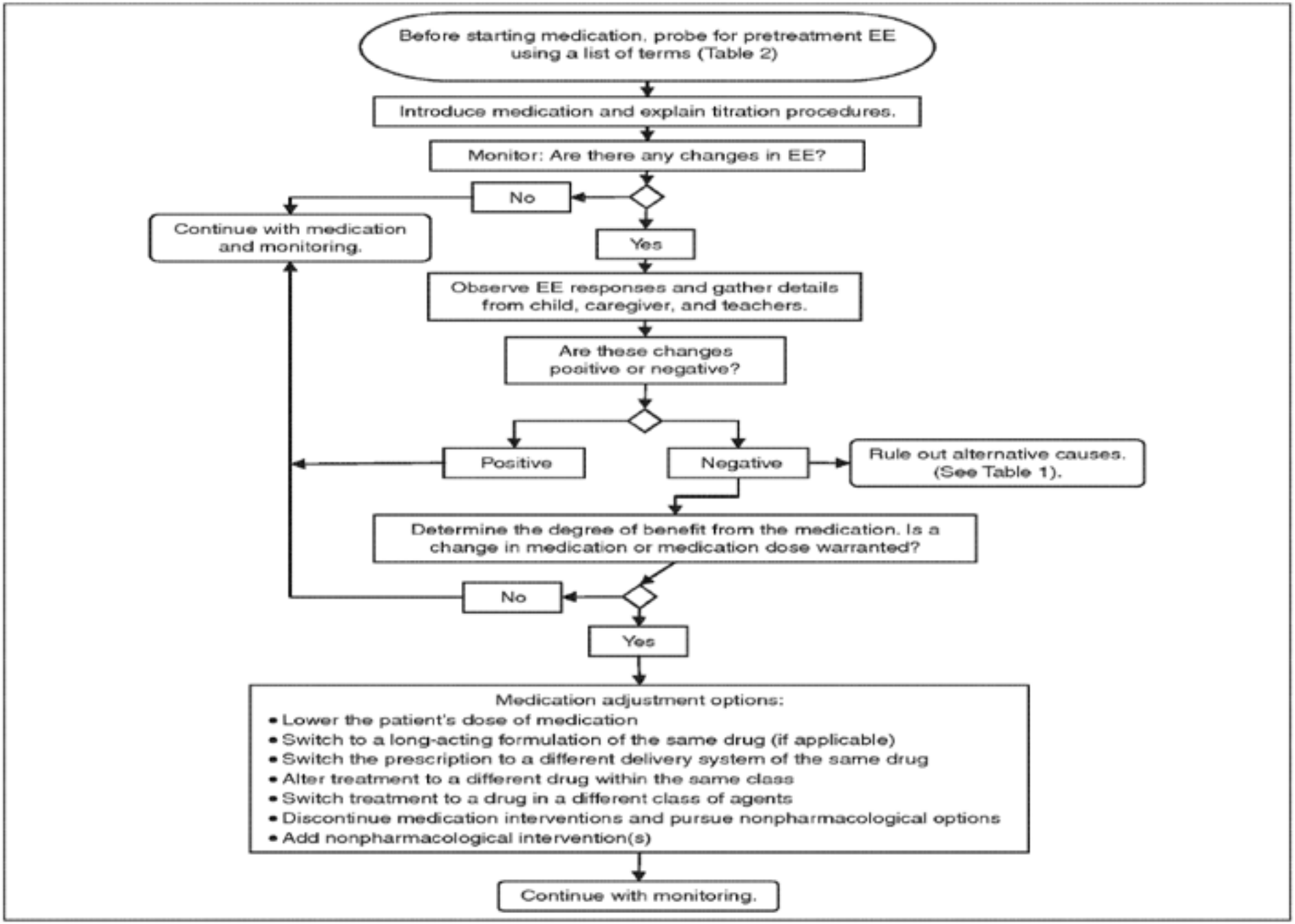

Figure 1. Practical approaches to address change in EE occurring with stimulant medication treatment for ADHD
EE = emotional expression.

5. METILFENIDATO
ADHERENCIA AL TRATAMIENTO

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 19, Number 6, 2009

Pp. 673–681
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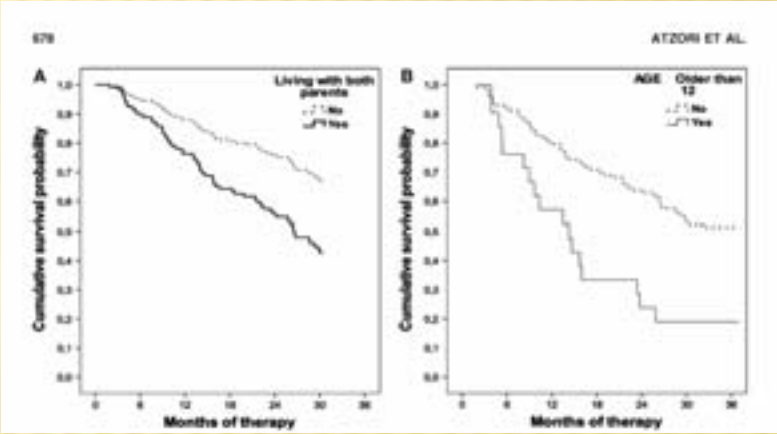
Predictive Factors for Persistent Use and Compliance of Immediate-Release Methylphenidate: A 36-Month Naturalistic Study

Paola Atzori, M.D.,[1] Tatiana Usala, M.D.,[1] Sara Carucci, M.D.,[1]
Fabrice Danjou, M.D.,[2] and Alessandro Zuddas, M.D.[1]

- N de 134, seguimiento mensual durante 36 m
- 4-16 años
- Conners y PICS –IV, WISC, CDI, MASC, para diagnóstico

- 46% en tratamiento
- 24% sin tratamiento por remisión funcional
- 30 % sin tratamiento por abandono

- Mantener tratamiento
  - Presencia de comorbilidad
  - Sexo femenino y menor edad
  - No vivir con familia nuclear
- Remisión
  - Ausencia de comorbilidad
  - Mayor edad
- Abandono
  - Mayor edad
  - TDAH subtipo hiperactividad



JOURNAL OF CHILD AND ADOLESCENT PSCYHOPHARMACOLOGY
Volume 19, Number 6, 2009

Pp. 691–698
DOI: 10.1089/cap.2009.0027

Measuring Methylphenidate Response in Attention-Deficit/Hyperactvity Disorder: How Are Laboratory Classroom-Based Measures Related to Parent Ratings?

Edmund J.S. Sonuga-Barke, Ph.D.,[1,2] David Coghill, M.D.,[3] Marc DeBacker, M.D.,[4] and James Swanson, Ph.D.[5]

Abstract

Background: Methylphenidate (MPH) is an efficacious and normally well-tolerated treatment for attention-deficit/hyperactivity disorder (ADHD). Although treatment effects are usually assessed using parent-rating scales, these can be supplemented by more objective methods. Here we examine the associations between ratings and one such method, assessments made across the day in the laboratory classroom.

Method: Comparison of Methylphenidates in the Analog Classroom Setting (COMACS) was made in a large ($n = 184$) placebo-controlled trial comparing Equasym XL®/Metadate CD®, Concerta®, and placebo (PLA) using a Laboratory School protocol. Therapeutic effects were measured using direct observation, scores on a simple math productivity task and parent ratings.

Results: Treatment effects were observed on all measures. Laboratory measures were correlated with each other, most strongly between Swanson, Kotkin, Agler, M-Flynn and Pelham Scale (SKAMP) inattention and Permanent Product Measure of Performance (PERMP). Parental ratings were correlated with classroom measures during the main morning period (1.5–4.5 hours after dosing) and to a lesser extent in the afternoon (6.0–7.5 hours after dosing), but not, by and large, immediately after dosing or in the evening. The morning correlations seemed stronger for female than for male participants.

Discussion: The results suggest that parental ratings and direct observations tap different aspects of MPH response and that both may be required for comprehensive assessment.

- Medidas objetivas de laboratorio
- Medidas clínicas de TDAH en laboratorio
- Medidas clínicas de TDAH en padres

- Niños inicio dosis baja,media, alta Concerta, Equasym or Metadate vs placebo
- Medidas en classe cada dia 7 , hasta 3 semanas
- Medidas padres dias 3 y 6

- Los efectos del tratamiento se objetivaron en todas las medidas
- Los datos de laboratorio de clase correlacionaron todos entre si y con las medidas de observación clínica
- Los resultados medidos por los padres correlacionaron con las de clase en el periodo de 1.5 a 4.5 horas post tratamiento y en el periodo final de 6 a 7.5 h

METILFENIDATO Y ATOMOXETINA

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Original Article

An Open Study of Adjunct OROS-Methylphenidate in Children and Adolescents Who Are Atomoxetine Partial Responders: I. Effectiveness

Timothy E. Wilens, M.D., Paul Hammerness, M.D., Linsey Utzinger, B.A., Mary Schillinger, B.A., Anna Georgiopoulous, M.D., Robert L. Doyle, M.D., MaryKate Martelon, M.P.H., and Kerry Brodziak, B.A.

Abstract

Objective: This study evaluated the effectiveness of adding OROS methylphenidate (MPH) to children who are partial responders to atomoxetine (ATMX) in the treatment of attention-deficit/hyperactivity disorder (ADHD).
Methods: This is a two-phase, 7-week, open study in children aged 6–17 years. Phase 1 initiated ATMX for a minimum of 4 weeks. Phase II entered partial responders to ATMX and added up to 54 mg of OROS MPH to their regimen. Subjects were assessed on multiple outcomes, including ADHD, executive functioning, and adverse effects. All analyses were intent to treat, with last observation carried forward.
Results: Fifty subjects who were partial responders to ATMX were treated with the combination therapy, with 41 subjects completing the entire protocol. There was a 40% reduction in their ADHD Rating Scale from the start of phase II through the end of study (from 21.14 ± 9.9 to 12.8 ± 9.7, $t = 6.5$, $p < 0.0001$). In addition, there was a clinically significant reduction in the Clinical Global Index of ADHD severity from moderate to mild: ADHD (start of phase II, 3.7; end of phase II, 2.7; 27%, $t = 6.5$, $p < 0.0001$), as well as improvements in executive functioning.
Conclusion: These results suggest that OROS MPH added to the regimen of partial responders to ATMX improves ADHD and executive functioning, necessitating further controlled trials.

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Original Article

An Open Study of Adjunct OROS-Methylphenidate in Children Who Are Atomoxetine Partial Responders: II. Tolerability and Pharmacokinetics

Paul Hammerness, M.D., Anna Georgiopoulos, M.D., Robert L. Doyle, M.D., Linsey Utzinger, B.A., Mary Schillinger, B.A., MaryKate Martelon, M.P.H., Kerry Brodziak, B.A., Joseph Biederman, M.D., and Timothy E. Wilens, M.D.

Abstract

Objective: The aim of this study was to evaluate the tolerability of adding OROS methylphenidate (MPH) to children who are partial responders to atomoxetine (ATMX) in the treatment of attention-deficit/hyperactivity disorder (ADHD).
Methods: This was a two-phase, 7-week, open study in children aged 6–17 years. Phase 1 initiated ATMX for a minimum of 4 weeks. Phase 2 entered partial responders to ATMX and added OROS MPH to their regimen. Safety was assessed using blood pressure and heart rate measurements, electrocardiogram readings, AEs, laboratories, and ATMX levels.
Results: Fifty subjects who were partial responders to ATMX received the combination therapy, with 41 subjects completing the entire protocol. As reported elsewhere (Wilens et al., 2009), OROS MPH added to partial responders of ATMX was accompanied by a 40% reduction in the ADHD rating scale score and improvements in executive functioning. However, the combination of ATMX plus OROS MPH was associated with greater rates of insomnia, irritability, and loss of appetite compared to ATMX alone. A small significant increase in diastolic blood pressure was observed during adjunctive OROS-MPH, with no clinically meaningful changes in electrocardiogram (ECG) parameters during the study. ATMX levels and liver function tests did not significantly change during the combination treatment.
Conclusion: Adjunct OROS MPH in ATMX partial responders yielded an additive adverse effect burden in this short-term study. Further controlled research with larger samples of children is warranted.

- Estudio abierto de 7 semanas (n 50 y 41)
  - Fase 1: 4 semanas con atomoxetina.
  - Fase 2: en respondedores parciales asociat MTF
- Reducción del 40 % ADHD RS en fase 2 vs inicio del estudio
- Reducción significativa en CGI
- Mejoría en funciones ejectivas

- En fase 2 (ATX +MTF) , incremento significativo de
  - Insomnio
  - Irritabilidad
  - Pérdida de apetito
  - Sin cambios significativos en parámetros ECG
  - No cambios significativos en niveles de ATX en asociación

ATOMOXETINA

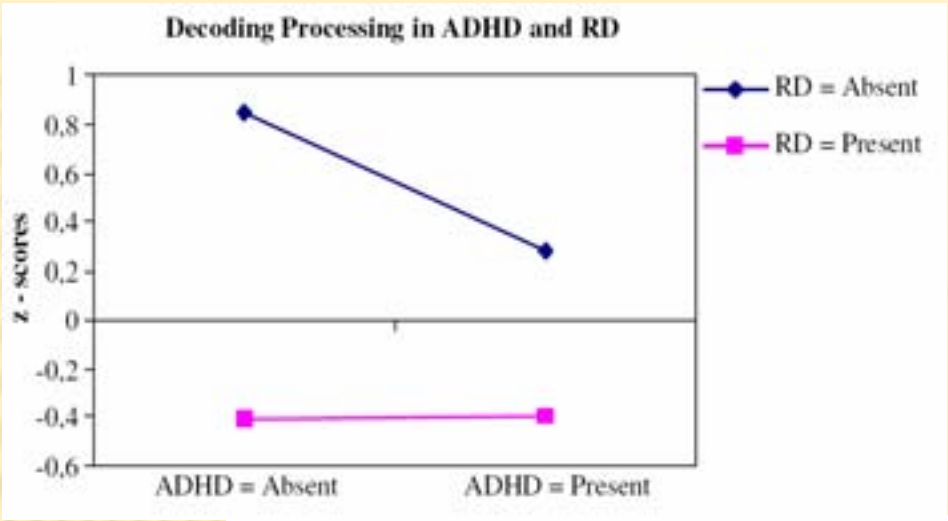
1. ATOMOXETINA

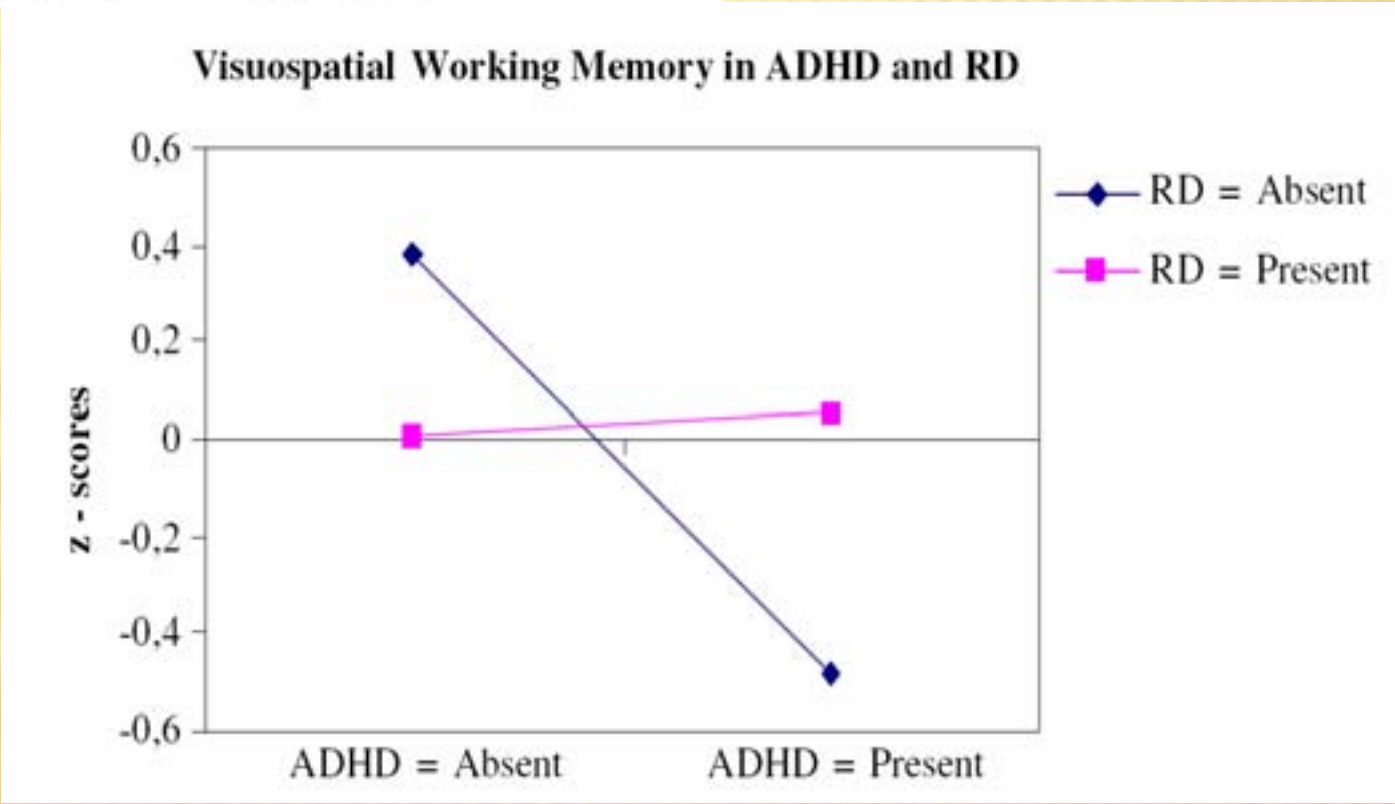
TDAH Y TRASTORNOS DE LECTOESCRITURA

Medidas neropsicológicas en los cuatro grupos del estudio

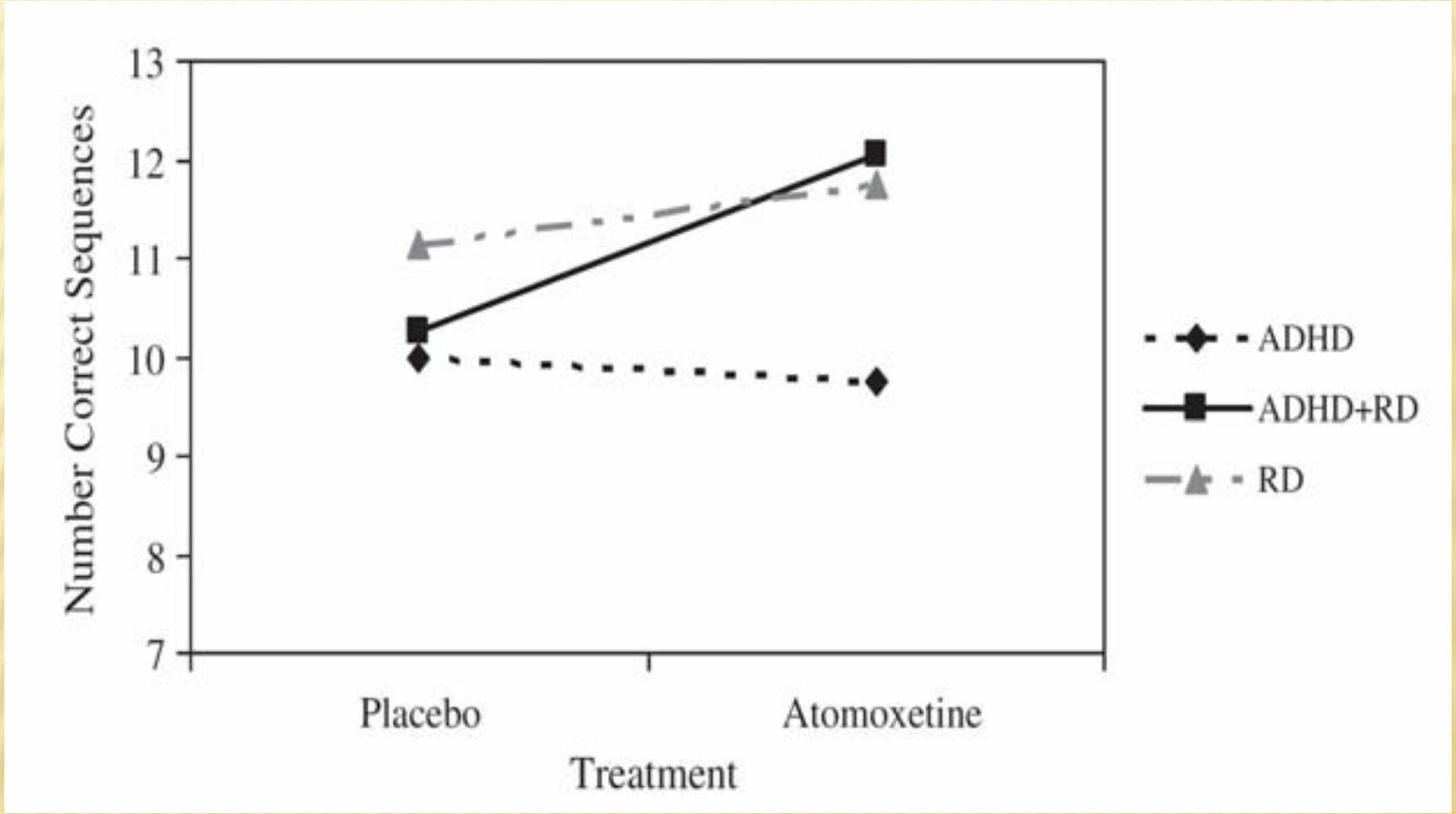
	ADHD $n=24$		ADHD+RD $n=29$		RD $n=41$		NC $n=26$	
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Stop Signal Paradigm								
SSRT	268.57	13.74	297.61	12.15	275.05	10.46	238.38	12.91
MRT	520.04	17.32	558.64	15.32	590.64	13.19	490.90	16.28
Omission Errors	2.22	0.91	5.01	0.81	3.23	0.69	0.31	0.86
Commission Errors	6.74	1.20	6.98	1.06	4.14	0.91	3.33	1.13
Corsi Block Tapping test								
WM Maximum Span	4.46	0.18	5.06	0.16	5.00	0.14	5.41	0.17
Lexical Decision[a]								
d′	2.68	0.17	1.99	0.15	2.38	0.13	3.16	0.16
MRT Valid Words	1092.25	70.70	1333.65	61.36	1304.02	51.67	868.78	64.19
MRT Pseudowords	1249.25	84.25	1575.60	73.12	1572.39	61.58	951.62	76.50

de Jong et al., Journal of Child and Adolescent Psychopharmacology, Volume 19, Number 6, 2009, 699-707





de Jong et al., **J Abnorm Child Psychol (2009) 37:1007–1017**



de Jong et al., Journal of Child and Adolescent Psychopharmacology, Volume 19, Number 6, 2009, 699-707

Resultados:

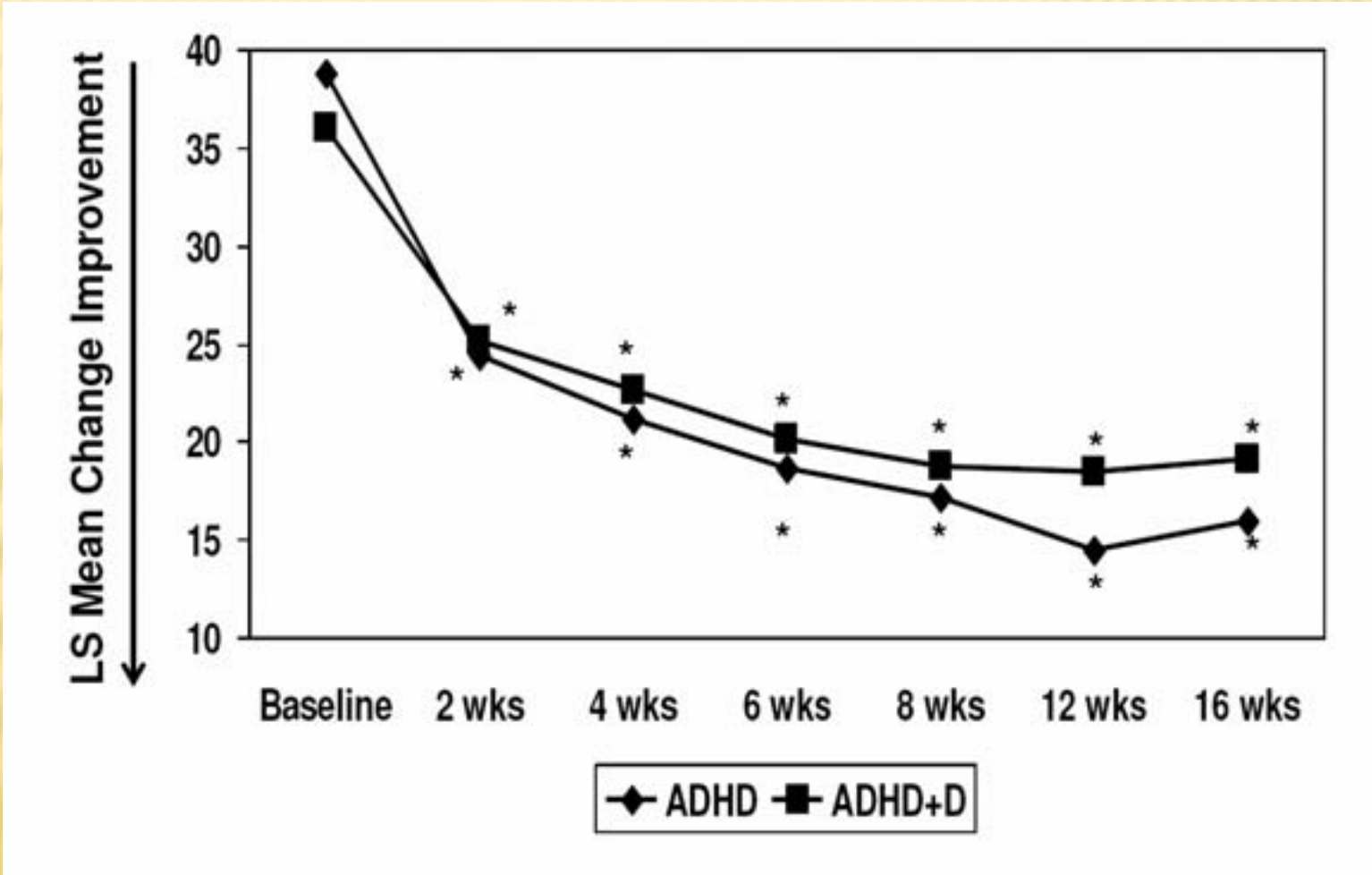
- Los niños con TDAH y TLE mostraron mejoras en la memoria de trabajo y mejoraron los déficits en inhibición en tratamiento con atomoxetina vs placebo.
- No se encontraron diferencias con atomoxetina vs placebo en pruebas de decisión en léxico.
- No se demostraron efectos de atomoxetina en los grupos de TDAH y TLE puros.

Conclusion:

Las diferencias neuropsicológicas junto con las diferencias en la respuesta a atomoxetina sugieren distintas vias de desarrollo en los casos de TDAH con TLE vs los casos de estas patologías sin comorbilidad.

Atomoxetina en el tratamiento de TDAH y Dislexia

ADHDRS-IV Total Scores Over 16 Weeks of Treatment



Summer ER, et al. Child and Adolescent Psychiatry and Mental Health 2009, 3:40

Atomoxetina en el tratamiento de TDAH y Dislexia

K-TEA Mean Baseline-to-Endpoint Scores

K-TEA Score, Mean (SE)	Group	Baseline	Endpoint	Change
Reading decoding standard	ADHD	94.3 (9.1)	100.2 (13.5)	3.9 (2.1)
	ADHD+D	80.2 (7.6)	84.8 (10.6)	5.6 (1.8)[a]
Reading decoding age equiv, mo	ADHD	137.7 (30.6)	158.1 (40.9)	17.8 (5.3)[a]
	ADHD+D	104.0 (12.2)	115.5 (22.2)	16.9 (5.7)[a]
Spelling standard	ADHD	90.2 (15.6)	93.0 (16.9)	3.2 (1.1)[a]
	ADHD+D	80.1 (8.6)	82.1 (10.0)	1.5 (1.0)
Spelling age equiv, mo	ADHD	132.6 (40.4)	140.6 (41.6)	9.7 (2.4)[a]
	ADHD+D	106.3 (18.9)	112.1 (25.7)	8.7 (2.2)[a]
Reading comprehension standard	ADHD	98.9 (14.0)	104.0 (15.2)	5.6 (2.0)[a]
	ADHD+D	81.6 (10.8)	89.3 (13.8)	9.8 (1.7)[a]
Reading comprehension age equiv, mo	ADHD	148.4 (41.0)	163.5 (43.8)	17.0 (5.7)[a]
	ADHD+D	106.5 (23.6)	124.8 (35.6)	26.0 (5.2)[a]
Reading composite standard	ADHD	96.6 (11.6)	102.6 (14.9)	4.5 (1.8)[a]
	ADHD+D	80.3 (8.6)	86.4 (11.4)	8.1 (1.6)[a]
Reading composite age equiv, mo	ADHD	144.3 (35.8)	161.9 (40.2)	17.2 (4.4)[a]
	ADHD+D	105.3 (16.6)	120.9 (26.5)	23.5 (4.3)[a]

Summer ER, et al. Child and Adolescent Psychiatry and Mental Health 2009, 3:40

Atomoxetina en el tratamiento de TDAH y Dislexia

WMTB-C Mean Standard and Component Baseline-to-Endpoint Scores

WMTB-C Score, Mean (SE)	Group	Baseline	Endpoint	Change
Phonological loop				
Component score	ADHD	92.4 (12.8)	95.5 (16.2)	1.5 (3.2)
	ADHD+D	90.8 (13.5)	96.7 (14.4)	4.8 (3.0)
Standard score	ADHD	376.0 (39.3)	386.4 (49.8)	5.2 (9.7)
	ADHD+D	365.5 (55.6)	385.5 (54.2)	20.2 (8.9)[a]
Central executive				
Component score	ADHD	87.8 (15.7)	97.5 (23.4)	8.4 (3.8)[a]
	ADHD+D	88.3 (13.3)	94.2 (14.5)	[illegible]
Standard Score	ADHD	268.1 (40.1)	292.8 (51.4)	24.3 (9.8)[a]
	ADHD+D	262.4 (45.7)	270.8 (44.8)	5.9 (9.1)
Visuo-spatial sketchpad				
Component score	ADHD	83.9 (16.9)	85.6 (13.1)	0.6 (4.3)
	ADHD+D	87.9 (17.5)	93.2 (20.1)	6.9 (4.1)
Standard score	ADHD	170.3 (33.9)	178.7 (35.1)	6.2 (9.1)
	ADHD+D	162.8 (47.0)	173.8 (50.7)	16.0 (8.5)

Summer ER, et al. Child and Adolescent Psychiatry and Mental Health 2009, 3:40

2. ATOMOXETINA
CALIDAD DE VIDA

REVIEW ARTICLE

CNS Drugs 2010; 24 (10): 843-866
1172-7047/10/0010-0843/$49.95/0

The Impact of Medications on Quality of Life in Attention-Deficit Hyperactivity Disorder

A Systematic Review

David Coghill

Centre for Neuroscience, Division of Medical Sciences, University of Dundee, Centre for Child Health, Dundee, UK

Coghill D. The impact of medications on quality of life in attention-deficit hyperactivity disorder: a systematic review. CNS Drugs. 2010 Oct 1;24(10):843-66.

Study (year)	Design	Measure	Rater	No. of patients	Duration
Methylphenidate (MPH)					
Pongwilairat et al.[28] (2005)	Naturalistic treatment (stimulant treated vs no medication)	PedsQL	Parent	17 stimulant-treated ADHD, 29 un-medicated ADHD	NA
Yang et al.[45] (2007)	Naturalistic treatment (MPH vs no medication)	CHQ	Parent	119 MPH-treated school-age children with ADHD, 129 healthy controls	NA
Flapper and Schoemaker[31] (2008)	Case-control followed by open-label trial (MPH)	DUX-25 TACQOL	Child, parent	23 ADHD + DCD, 23 healthy controls	4 wk
Manos et al.[65] (2009)	Open-label dose-optimized trial (MTS)	AIM-C	Parent	128 ADHD	8 wk
Bukstein et al.[66] (2009)	Open-label trial (switch from oral extended-release MPH to MTS)	AIM-C	Parent	164 ADHD	4 wk
Mixed amfetamine salts (MAS)					
Sallee et al.[67] (2004)	Open-label (MAS XR)	PedsQL	Parent	2968 ADHD	7 wk
Wigal et al.[68] (2005)	RCT (MAS XR vs ATX)	PedsQL	Parent	203 ADHD (102 MAS XR, 101 ATX)	3 wk

Coghill D. The impact of medications on quality of life in attention-deficit hyperactivity disorder: a systematic review. CNS Drugs. 2010 Oct 1;24(10):843-66.

Study (year)	Design	Measure	Rater	No. of patients	Duration
Atomoxetine (ATX)					
Matza et al.[40] (2004)	RCT (ATX vs placebo)	CHQ	Parent	297 ADHD	8 wk
Perwien et al.[69] (2004)	*Post hoc* analysis of three RCTs (ATX vs placebo)	CHQ	Parent	647 ADHD	8 wk × 2, 7 wk × 1
Newcorn et al.[43] (2005)	RCT (ATX vs placebo)	CHQ	Parent	293 ADHD, 39% with ODD	8 wk
Brown et al.[70] (2006)	RCT (ATX vs placebo)	CHQ	Parent	153 ADHD	7 wk
Perwien et al.[71] (2006)	Open-label trial; extension of RCTs (ATX)	CHQ	Parent	912 ADHD (312 completed long-term trial and included in outcome analyses)	24 mo
Biederman et al.[72] (2007)	*Post hoc* meta-analysis of RCTs (ATX vs placebo)	CHQ	Parent	196 ADHD only, 108 ADHD + ODD	NA
Cheng et al.[73] (2007)	Meta-regression analysis of RCTs (ATX vs placebo)	CHQ	Parent	1828 ADHD	NA

Coghill D. The impact of medications on quality of life in attention-deficit hyperactivity disorder: a systematic review. CNS Drugs. 2010 Oct 1;24(10):843-66.

Study (year)	Design	Measure	Rater	No. of patients	Duration
Atomoxetine (ATX)					
Prasad et al.[50] (2007)	Open-label trial (ATX vs standard clinical treatment)	CHIP-CE	Parent	201 ADHD (104 ATX, 97 standard clinical treatment)	10 wk
Wehmeier et al.[74] (2008)	Open-label trial (ATX)	GIPD	Child, parent, physician	262 ADHD	24 wk
Dittmann et al.[75] (2009)	Open-label trial (ATX)	GIPD	Young person, parent, physician	159 ADHD	24 wk
Escobar et al.[76] (2009)	RCT (ATX vs placebo)	CHIP-CE	Child, parent	151 ADHD	12 wk
Svanborg et al.[77] (2009)	RCT (ATX + psychoeducation vs placebo + psychoeducation)	CHIP-CE	Parent	99 ADHD	10 wk

Coghill D. The impact of medications on quality of life in attention-deficit hyperactivity disorder: a systematic review. CNS Drugs. 2010 Oct 1;24(10):843-66.

3. ATOMOXETINA

ESTUDIOS COSTE-EFICACIA

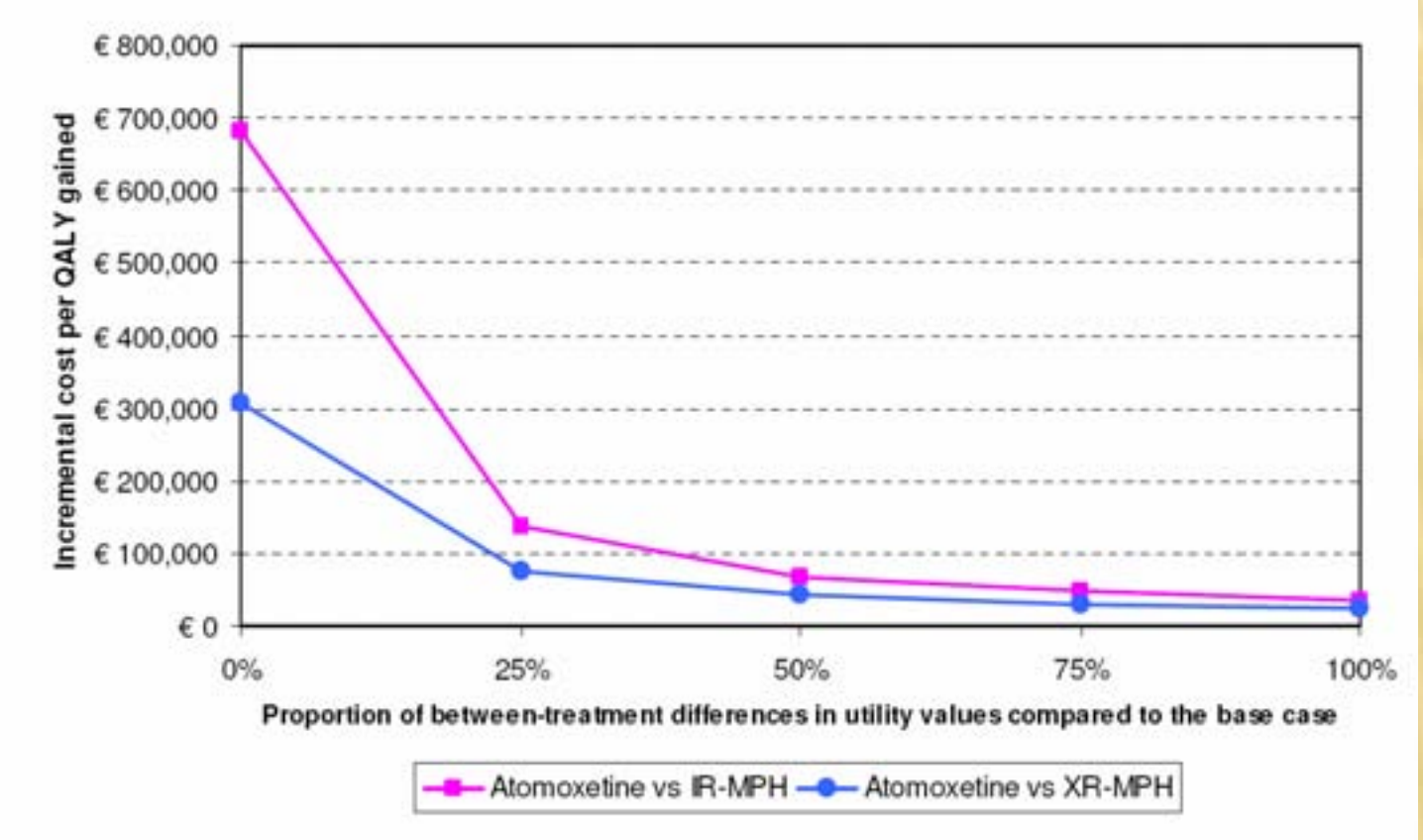
- QUALITY ADJUSTED LIFE YEAR
- Modelo económico con procesos de Markov. The UK economic model adaptado a España
- Modelos de población
  - Pacientes naives sin contraindicación a estimulantes, sin respuesta a estimulantes y con contraindicaciones a estimulantes
  - ATX respondedores/ no respondedores con /sin EF
  - MTF IR y MTF ER respondedores/ no respond. Con/sin EF
  - No tto F

Total costs, QALYs and incremental cost-effectiveness estimated in the economic model by patient population

Population	Cost per patient		QALYs per patient		Incremental cost per QALY gained
	ATX arm	Comparator arm	ATX arm	Comparator arm	
Population 1[a] (comparator: IR-MPH)	€ 1 047	€ 366	0.930	0.910	€ 34 308
Population 1[a] (comparator: XR-MPH)	€ 1 208	€ 902	0.933	0.920	€ 24 310
Population 2[b] (comparator: 'no medication')	€ 919	€ 0	0.919	0.880	€ 23 820
Population 3[c] (comparator: 'no medication')	€ 969	€ 0	0.922	0.880	€ 23 323

Hong J et al., BMC Psychiatry 2009, 9:15

THE ICERS OF ATOMOXETINE UNDER VARYING UTILITY VALUES USED IN THE MODEL IN POPULATION 1. METHYLPHENIDATE; QALY = QUALITY OF LIFE YEARS

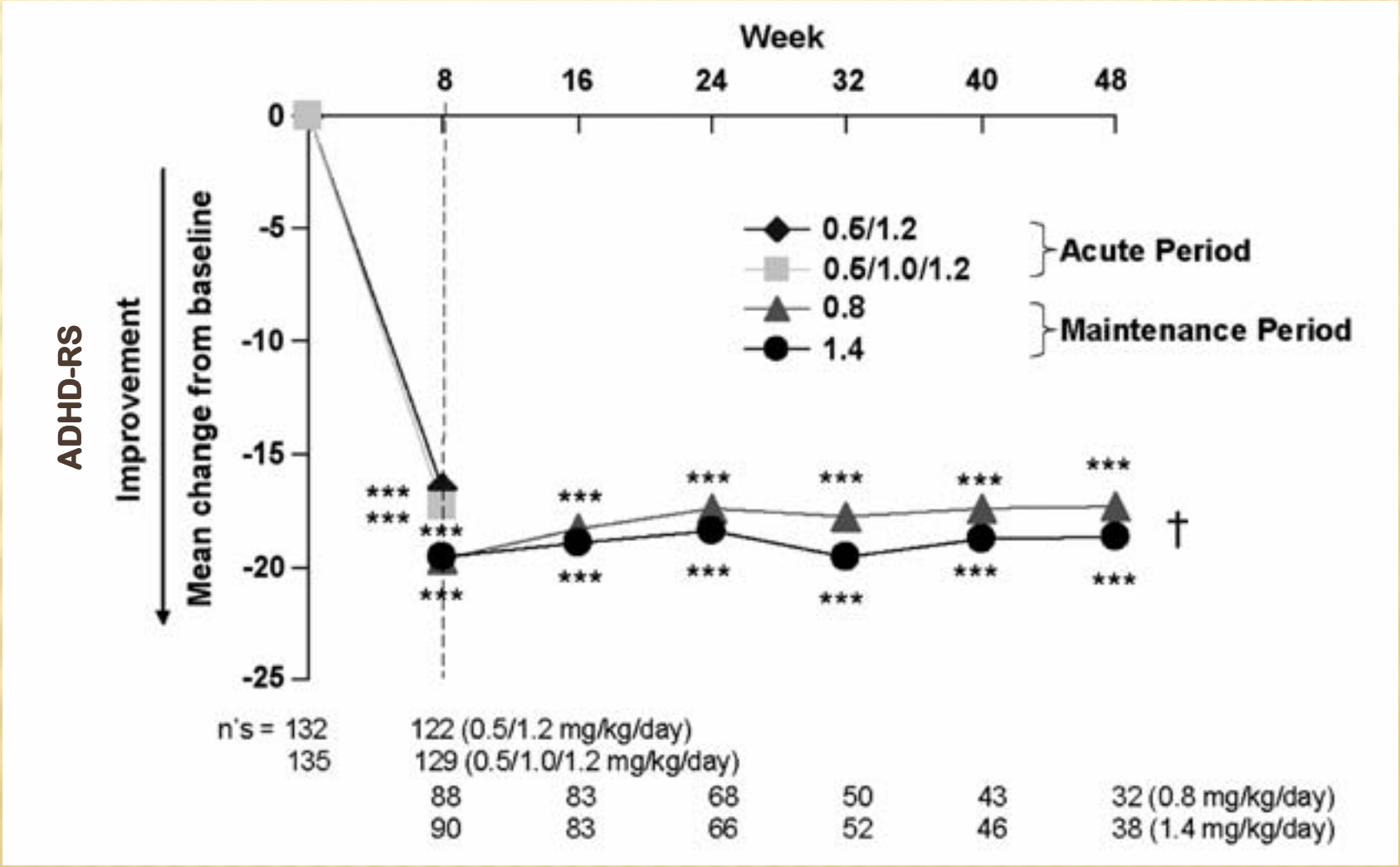


Abbreviations: IR-MPH = immediate-release methylphenidate; XR-MPH = extended-release

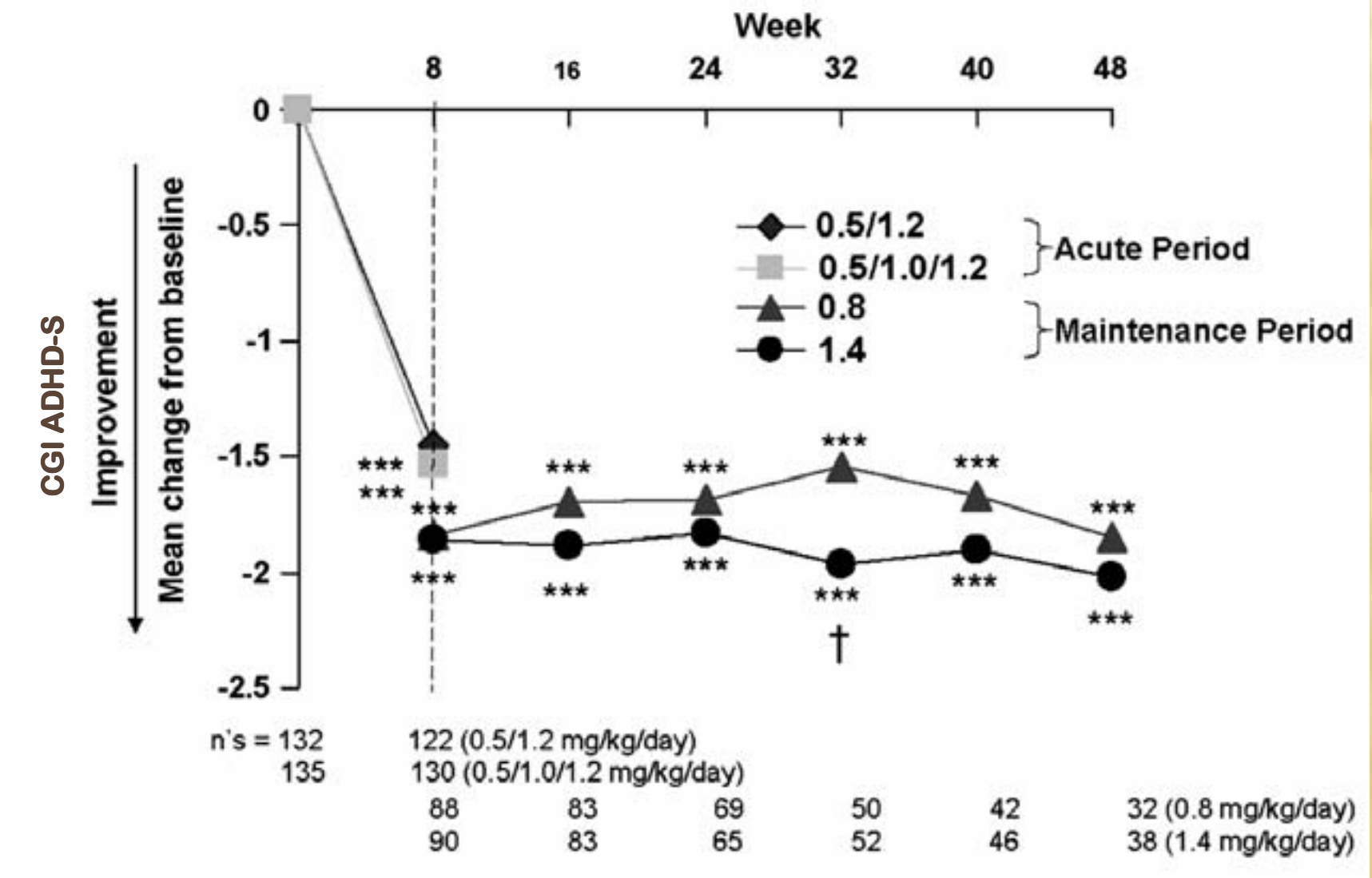
Hong J et al., BMC Psychiatry 2009, 9:15

3. ATOMOXETINA EFICACIA CLÍNICA
ESTUDIO ADOLESCENTES

Slow vs fast titration schedule

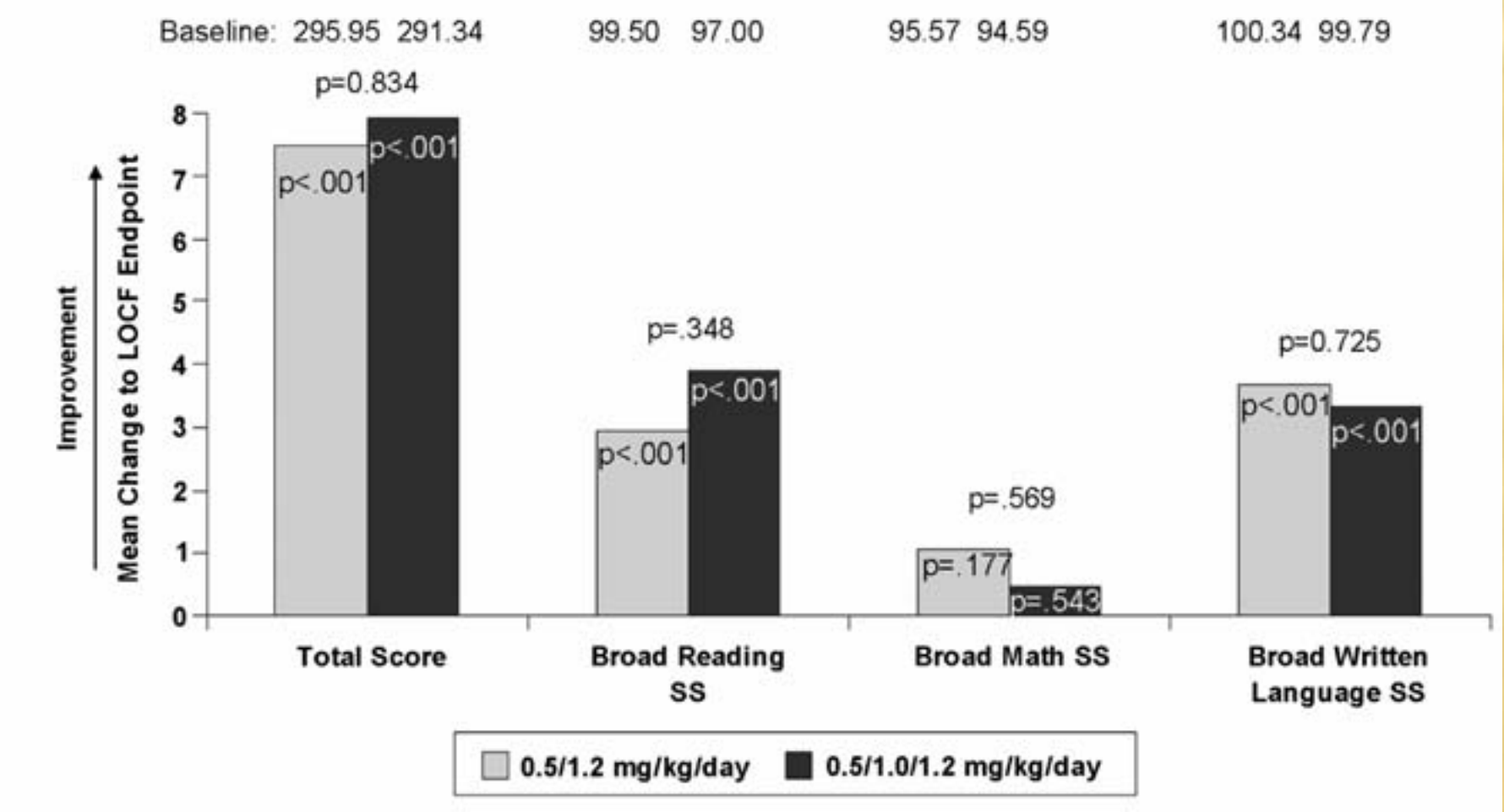


Wietecha et al., Journal Of Child And Adolescent Psychopharmacology Volume 19, Number 6, 2009



Wietecha et al., Journal Of Child And Adolescent Psychopharmacology Volume 19, Number 6, 2009

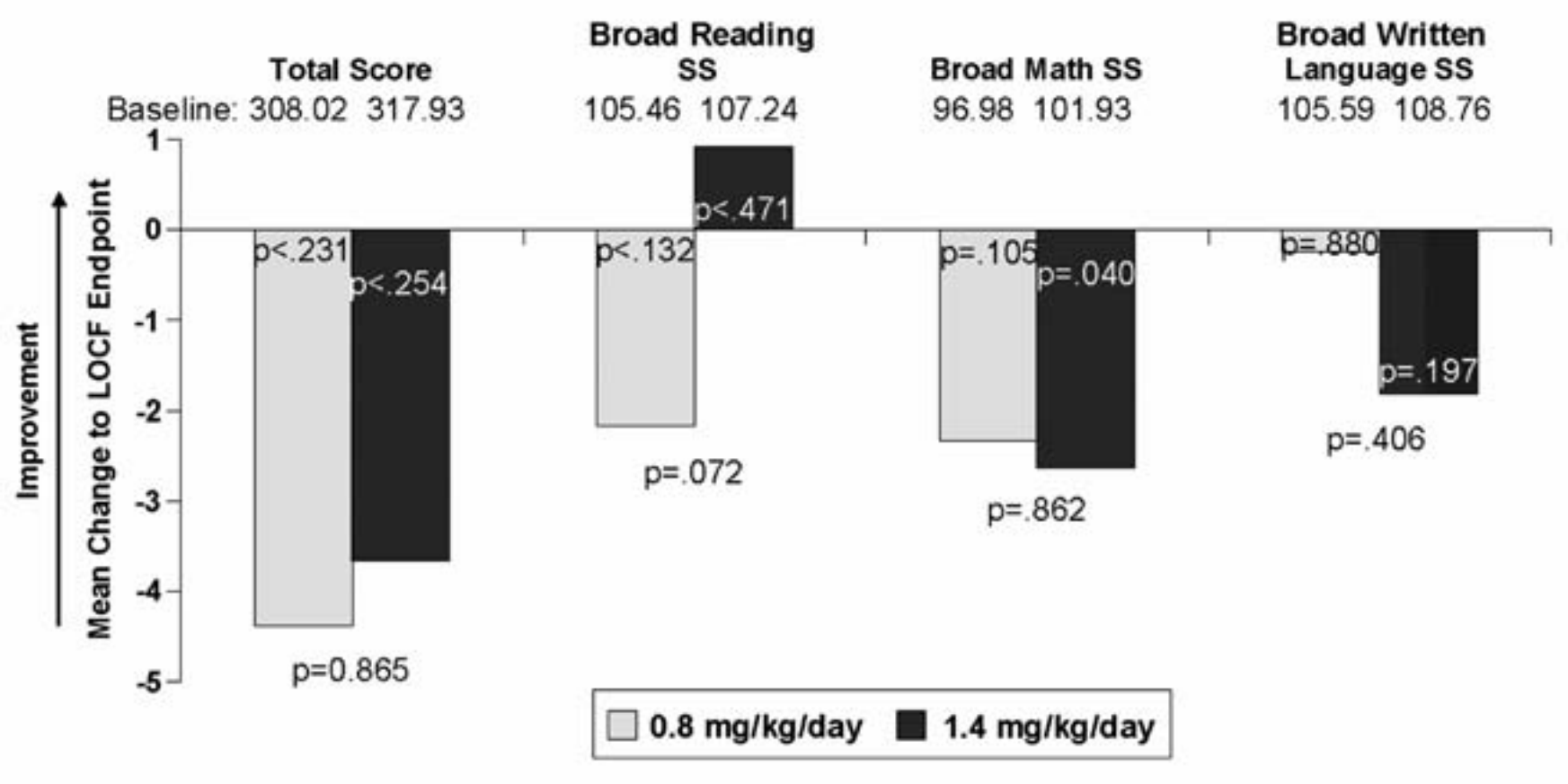
CAMBIOS PRODUCIDOS EN EL WOODCOCK JOHNSON III SCORES DURANTE LA FASE AGUDA DE 8 SEMANAS



SS=Standard score; LOCF=last observation carried forward

Wietecha et al., Journal Of Child And Adolescent Psychopharmacology Volume 19, Number 6, 2009

CAMBIOS PRODUCIDOS EN EL WOODCOCK JOHNSON III SCORES DURANTE LA FASEDE MANTENIMIENTO DE 40 SEMANAS



SS=Standard score; LOCF=last observation carried forward

Wietecha et al., Journal Of Child And Adolescent Psychopharmacology Volume 19, Number 6, 2009

DOSIS UNICA DE ATOMOXETINA : COMPARACIÓN TOMA MAÑANA VS NOCHE

10.1177/0009922809335321
http://clp.sagepub.com
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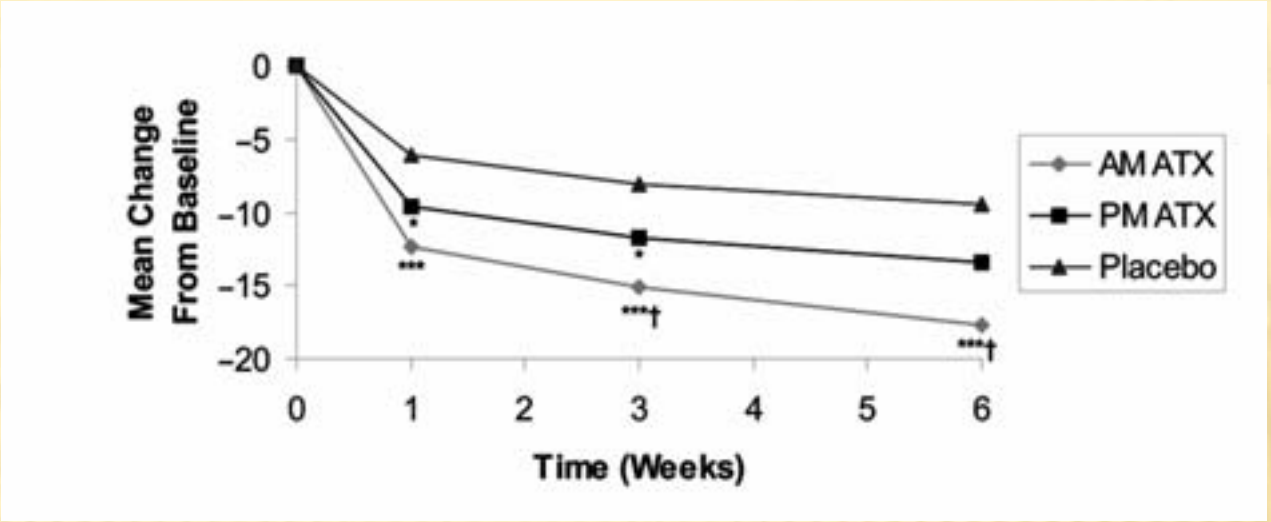
Once-Daily Atomoxetine for Treating Pediatric Attention-Deficit/Hyperactivity Disorder: Comparison of Morning and Evening Dosing

Stan L. Block, MD, Douglas Kelsey, MD, PhD, Daniel Coury, MD, Donald Lewis, MD, Humberto Quintana, MD, Virginia Sutton, PhD, Kory Schuh, PhD, Albert J. Allen, MD, PhD, and Calvin Sumner, MD

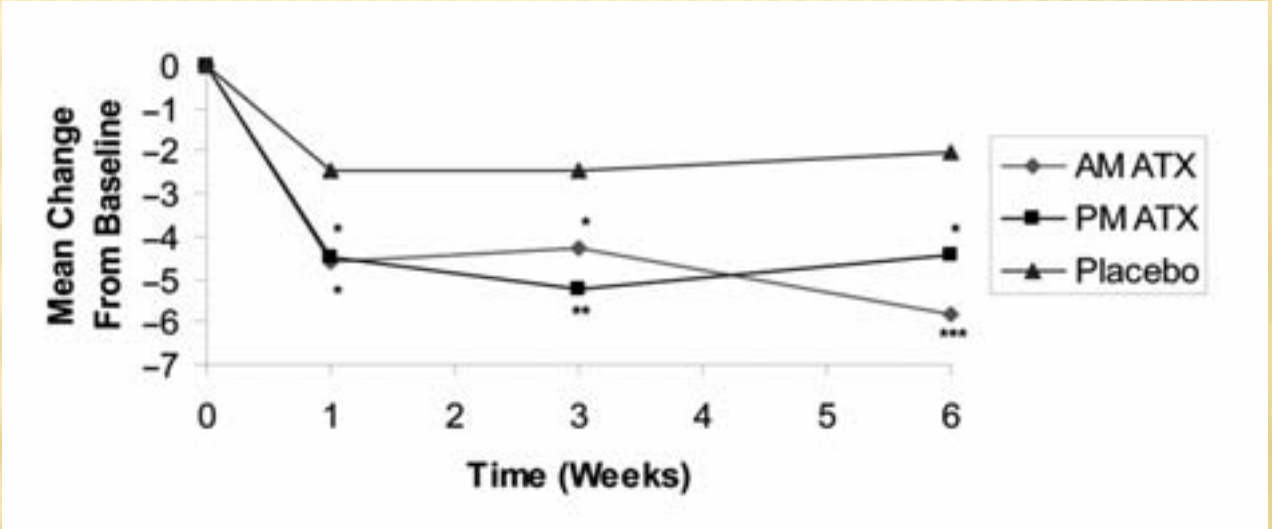
In this 3-arm, randomized, double-blind trial, once-daily morning-dosed atomoxetine, evening-dosed atomoxetine, and placebo were compared for treating pediatric attention-deficit/hyperactivity disorder (ADHD). Patients received morning atomoxetine/evening placebo (n = 102), morning placebo/evening atomoxetine (n = 93), or morning placebo/evening placebo (n = 93) for about 6 weeks. Core symptom efficacy was measured at weeks 0, 1, 3, and 6. Parent assessments of the child's home behaviors in the evening and early morning were collected daily during the first 2 weeks of treatment. Morning-dosed and evening-dosed atomoxetine significantly decreased core ADHD symptoms relative to placebo and produced symptom improvements that were measured up to 24 hours later. Morning dosing was superior to evening dosing on some efficacy measures. Evening dosing showed greater tolerability with significantly more patients receiving morning atomoxetine reporting at least 1 adverse event than those receiving evening atomoxetine.

Keywords: atomoxetine; ADHD; child; once-daily; duration of effect

ADHD-RS



CGI-ADHD-S



SS=Standard score; LOCF=last observation carried forward

Block SL et al., CLIN PEDIATR OnlineFirst, published on May 6, 2009

CMRO

Current Medical Research & Opinion Vol. 25, No. 11, 2009, 2745–2754

0300-7995
doi:10.1185/03007990903316152

Article 4941/431789

Brief report

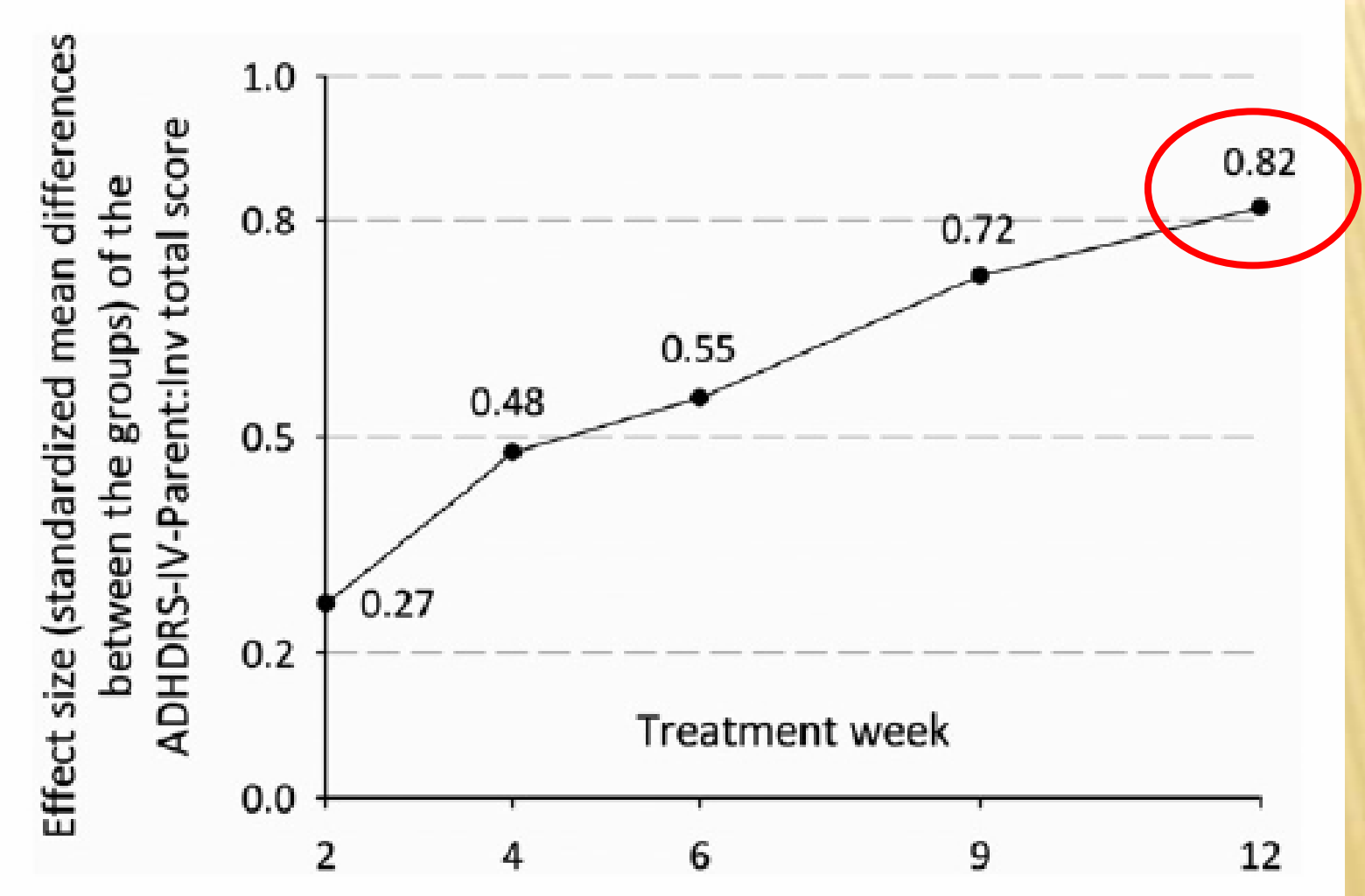
Evaluation of atomoxetine for first-line treatment of newly diagnosed, treatment-naïve children and adolescents with attention deficit/hyperactivity disorder

Alonso Montoya
Clinical Research, Lilly Research Laboratories, Alcobendas, Spain

Abstract

Objective:

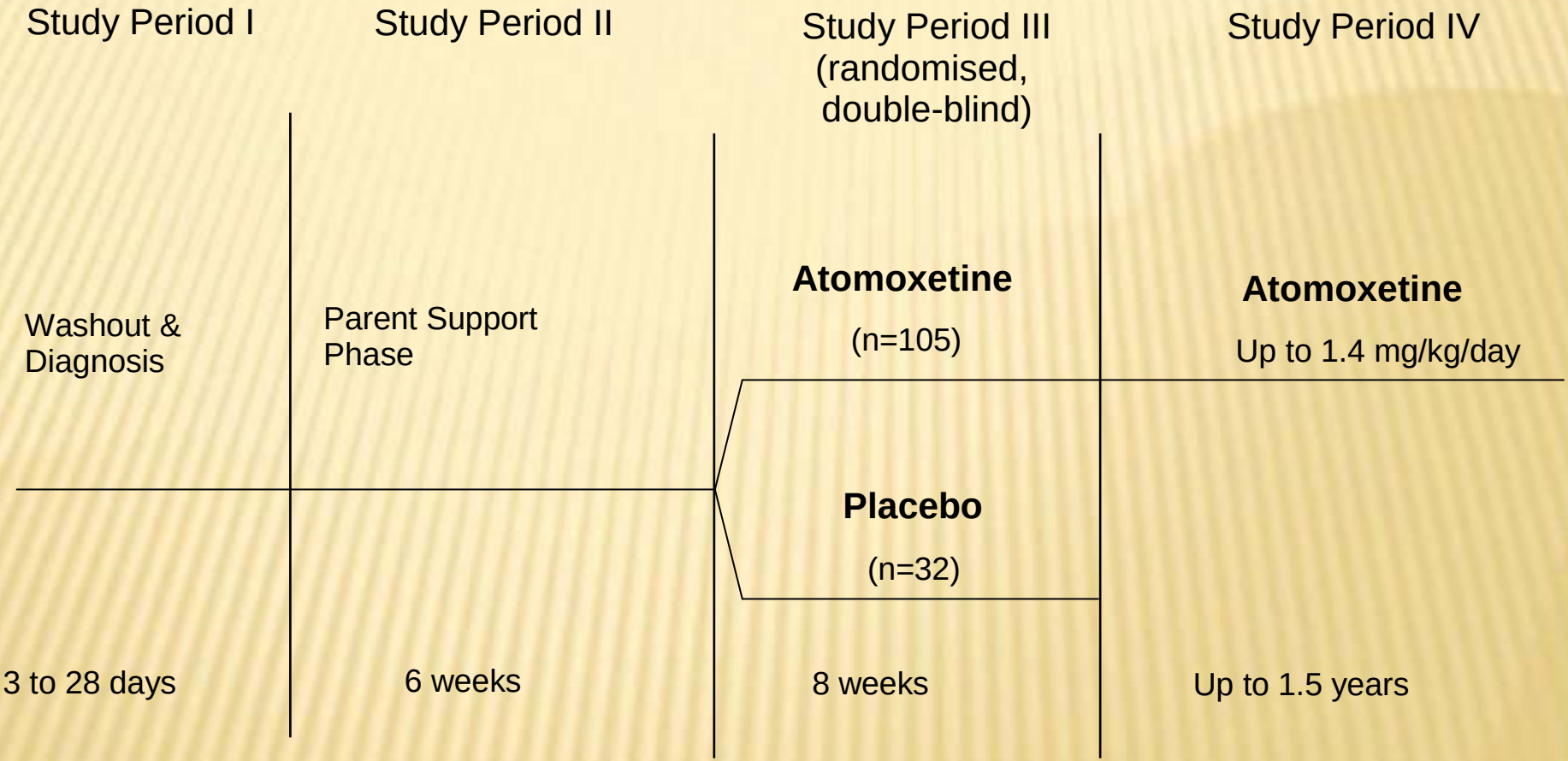
Tamaño del efecto de atomoxetina



Montoya A et al., Curr Med Res Opin. 2009 Nov;25(11):2745-54

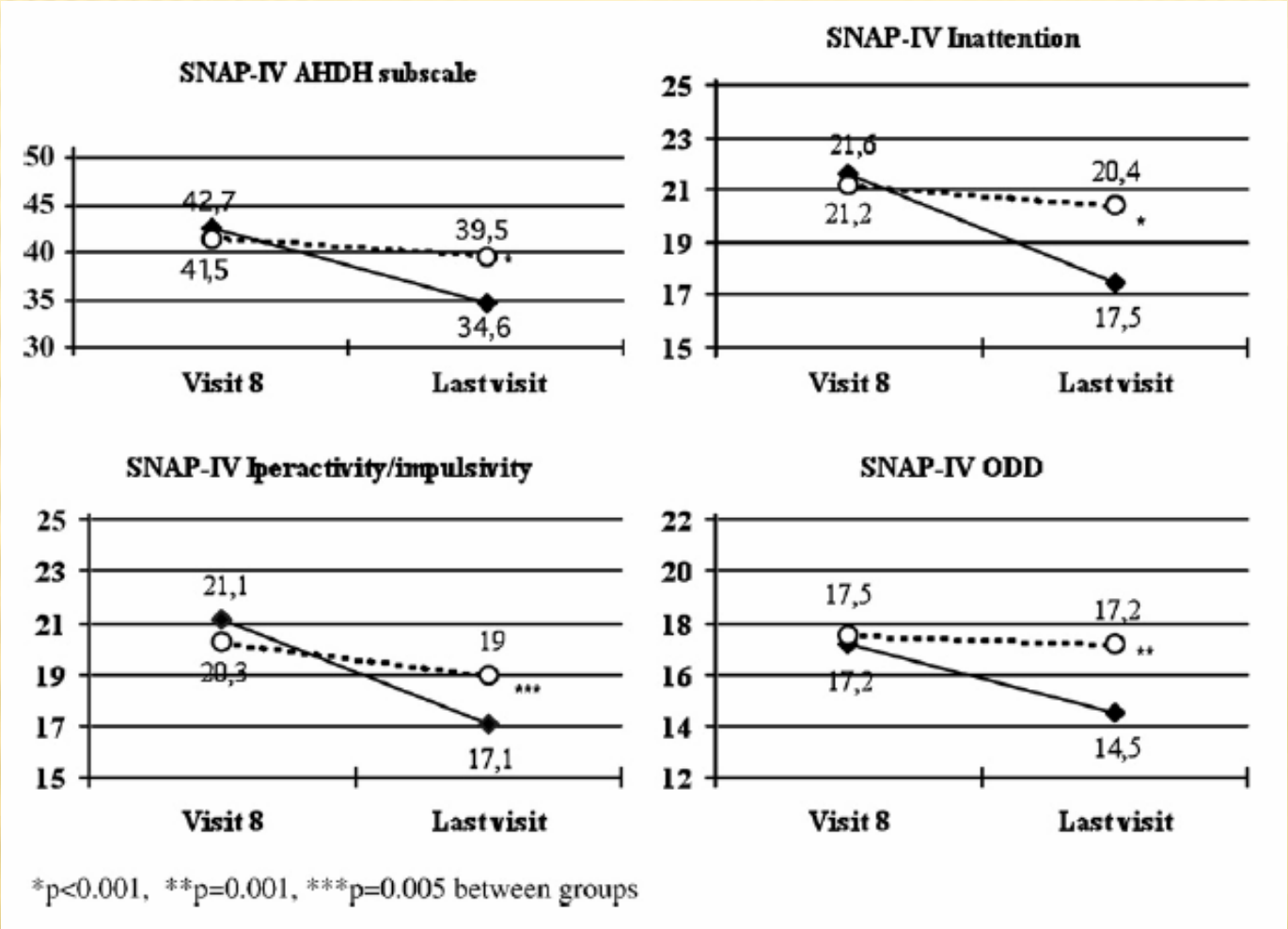
Atomoxetina en TDAH y TND

Italian Study



Dell'Agnello G, et Al. European Neuropsychopharmacology (2009) 19, 822–834

Atomoxetina en TDAH y TND



Placebo (n=32)

Atomoxetine (n=105)

Dell'Agnello G, et Al. European Neuropsychopharmacology (2009) 19, 822–834

Atomoxetina en TDAH y TND

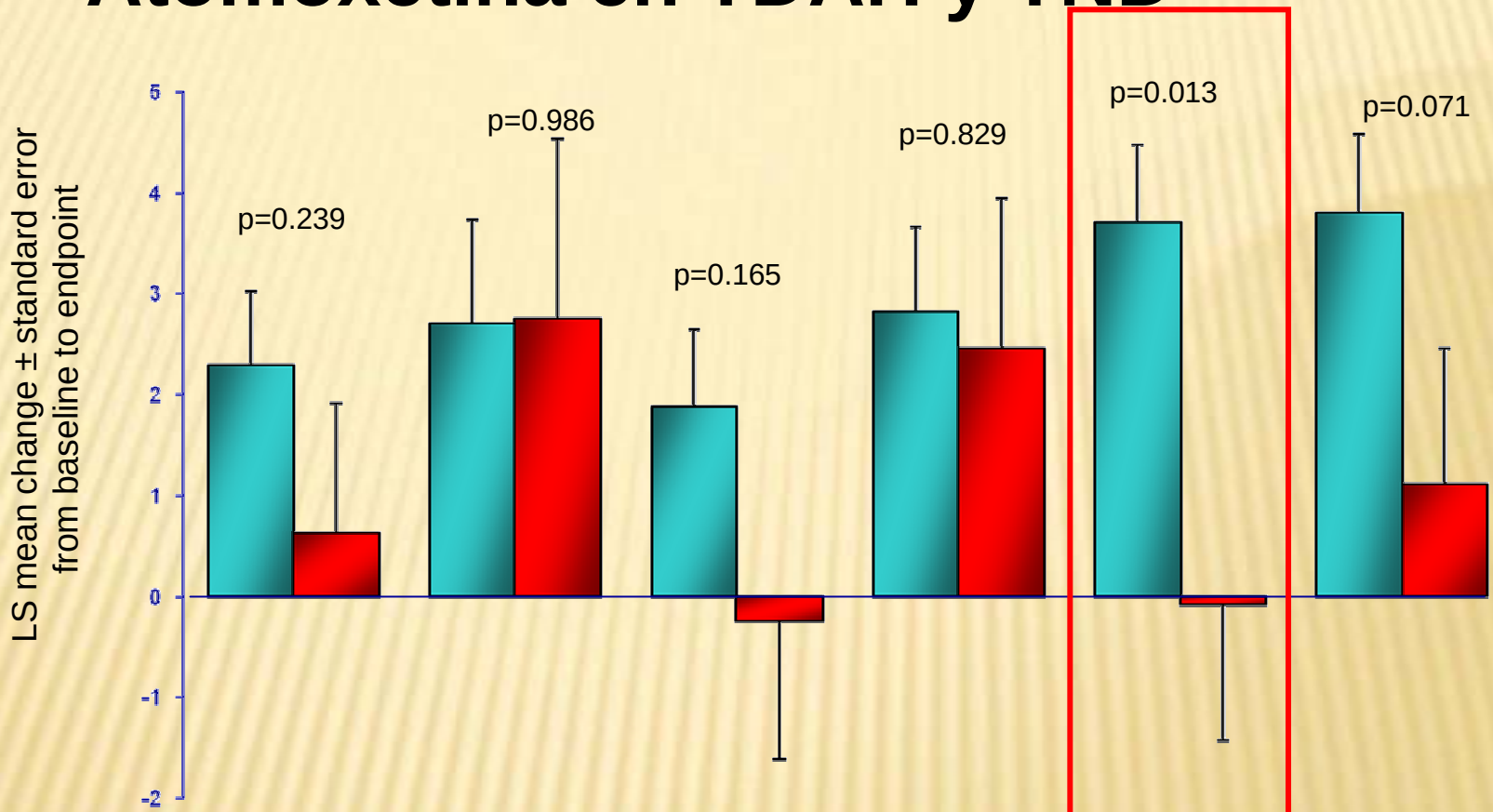
Table 3 Results of the CPRS-R:S and the CTRS-R:S in the randomised double blind phase.

Subscales	Atomoxetine		Placebo		*p* value
	Visit 8	Last visit	Visit 8	Last visit	
CPRS-R:S					
Oppositional	11.7±3.8	10.5±4.4	12.2±3.0	13.0±4.2	0.002
Cognitive problems	14.3±3.1	12.0±4.2	14.2±3.2	14.4±3.5	<0.001
Hyperactivity	12.0±3.8	9.8±4.4	12.0±4.0	11.3±4.6	0.022
ADHD index	28.2±4.9	23.1±7.1	28.4±5.2	28.3±5.6	<0.001
CTRS-R:S					
Oppositional	7.6±4.3	6.5±4.1	10.8±3.8	10.9±3.1	0.002
Cognitive problems	8.2±4.3	12.0±4.2	8.5±3.7	8.5±3.3	0.113
Hyperactivity	12.8±5.5	10.7±5.6	16.3±3.4	15.2±4.6	0.051
ADHD index	25.3±8.4	21.8±8.9	29.9±6.0	28.4±6.1	0.061
CGI-ADHD-S	5.1±0.8	4.5±1.0	5.1±0.9	5.2±1.0	<0.001

Values are means±standard deviation. *p* values refer to comparisons between groups in changes from visit 8 to the last visit.

Dell'Agnello G, et Al. European Neuropsychopharmacology (2009) 19, 822–834

Atomoxetina en TDAH y TND



Curatolo et al., ESCAP 2007. Florence, Italy

GUANFACINA

Receptores α 2

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 17, Number 4, 2007
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DOI: 10.1089/cap.2006.0098

Alpha-2 Adrenergic Receptor Agonists for the Treatment of Attention-Deficit/Hyperactivity Disorder: Emerging Concepts from New Data

Amy F. Arnsten, Ph.D.,[1] Lawrence Scahill, M.S.N., Ph.D.,[2] and Robert L. Findling, M.D.[3]

ABSTRACT

- Función del cortex prefrontal.
- Receptores alpha 2 postsinápticos en terminales NE.
- Tipos A, B (tálamo) , C
- Tambien acción presináptica
- Acción agonista adrenérgica en PFC relación con atención y función ejecutiva

Arnsten A, Scahill L, et al.(2007) Journal of Child and Adolescent Psychopharmacology, 17 (4)393-406

CLONIDINA

- Afinidad por receptores alpha 2 tipo A, B,C
- Mayor acción presináptica en receptores A y C en LC relacionada con la sedación
- Estudios RCT des de 1985
- Estudios asociado a MTF en TDAH, TDAH y Tourette des de 2000

GUANFACINA

- Afinidad por receptores alpha 2 tipo A
- Activa en circuitos PFC lateral y ventromedial
- Menor afinidad receptores I1 relacionada con menor hipotensión (x10) menor
- Indicado para el tratamiento de TDAH des de 2009 (FDA)

1.GUANFACINA
EFICACIA EN TDAH

ADIS DRUG PROFILE

Drugs 2010; 70 (13): 1693-1
0012-6667/10/0013-1693/$55.5

Guanfacine Extended-Release
In Attention Deficit Hyperactivity Disorder

Victoria J. Muir and *Caroline M. Perry*

Adis, a Wolters Kluwer Business, Auckland, New Zealand

Contents

- N 345, 6-17 años
- RCP, placebo vs GXR 2-3 -4 mg/dia
- Monoterapia
- ADHD RS, CPRS, CTRS, CGI
- 5 semanas


PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Randomized, Double-Blind, Placebo-Controlled Study of Guanfacine Extended Release in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

Joseph Biederman, Ross D. Melmed, Anil Patel, Keith McBurnett, Jennifer Konow, Andrew Lyne, Newton Scherer and for the SPD503 Study Group

Pediatrics 2008;121;e73-e84
DOI: 10.1542/peds.2006-3695

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.pediatrics.org/cgi/content/full/121/1/e73

TABLE 3 ADHD-RS-IV Scores: LS Mean and Placebo-Adjusted LS Mean End-Point Changes From Baseline in Hyperactivity/Impulsivity and Inattentiveness Subscales (ITT Population)

Parameter	Placebo	GXR		
		2 mg	3 mg	4 mg
Hyperactivity/impulsivity subscale				
LS mean	−3.51	−7.33	−7.32	−9.31
Placebo-adjusted LS mean	—	−3.82	−3.81	−5.80
P	—	.0002	.0002	<.0001
95% CI		−6.05 to −1.59	−6.03 to −1.58	−8.03 to −3.56
Inattentiveness subscale				
LS mean	−4.92	−8.7	−9.11	−9.44
Placebo-adjusted LS mean	—	−3.95	−4.19	−4.52
P	—	.0011	.0006	.0002
95% CI	—	−6.54 to −1.36	−6.78 to −1.60	−7.13 to −1.90

ERMAN et al

- Mejoria clínica estadísticamente significativa a las 5 semanas. Global y en subescalas

- Porcentaje de mejora con CGI con incremento en las ultimas semanas del estudio

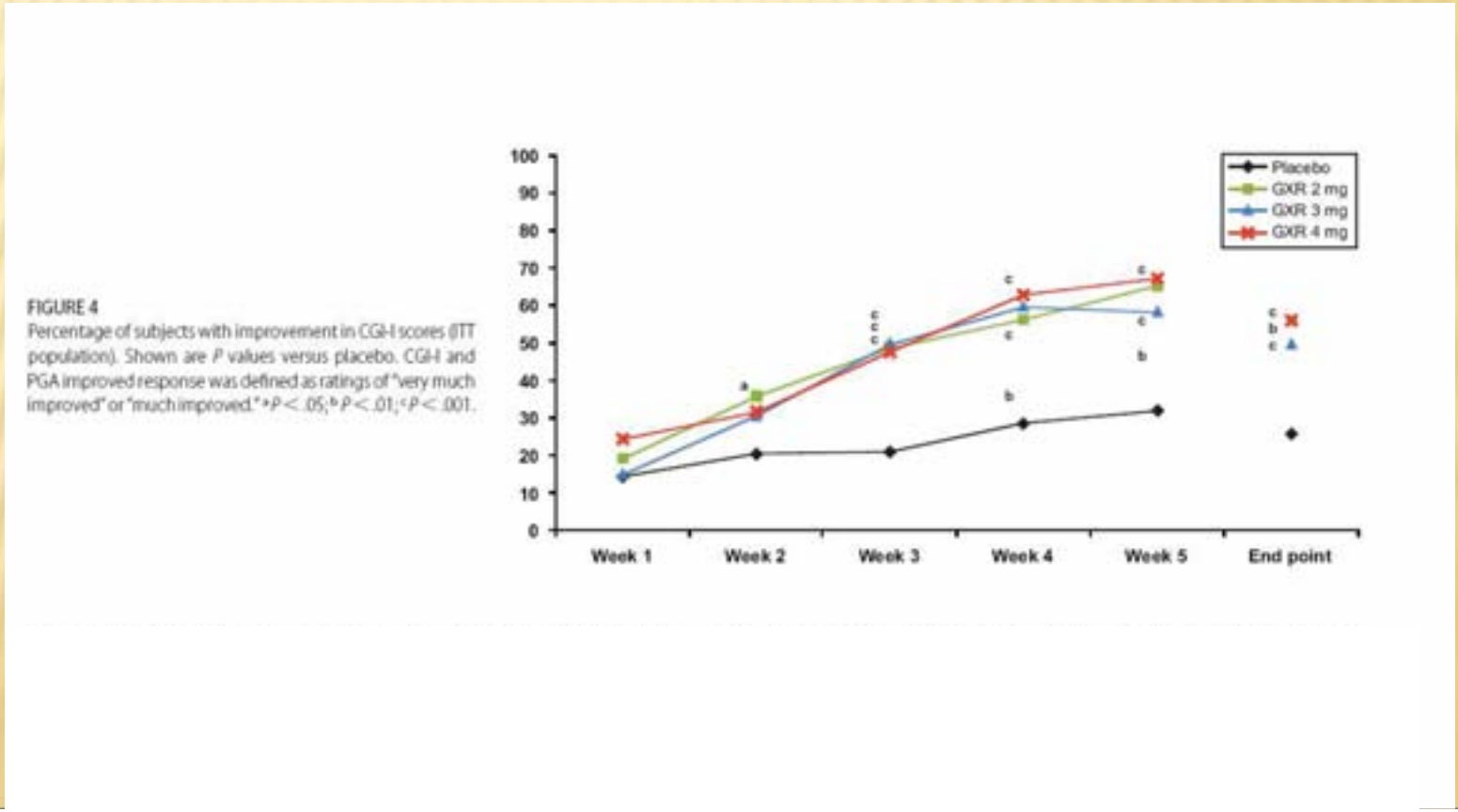


FIGURE 4
Percentage of subjects with improvement in CGI-I scores (ITT population). Shown are *P* values versus placebo. CGI-I and PGA improved response was defined as ratings of "very much improved" or "much improved." [a] $P < .05$; [b] $P < .01$; [c] $P < .001$.

Guanfacina: estudios de eficacia. Fase Aguda

Guanfacine Extended Release in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: A Placebo-Controlled Trial

FLOYD R. SALLEE, M.D., PH.D., JAMES McGOUGH, M.D., TIM WIGAL, PH.D., JESSICA DONAHUE, M.P.H., ANDREW LYNE, M.SC., C.STAT., AND JOSEPH BIEDERMAN, M.D., FOR THE SPD503 STUDY GROUP

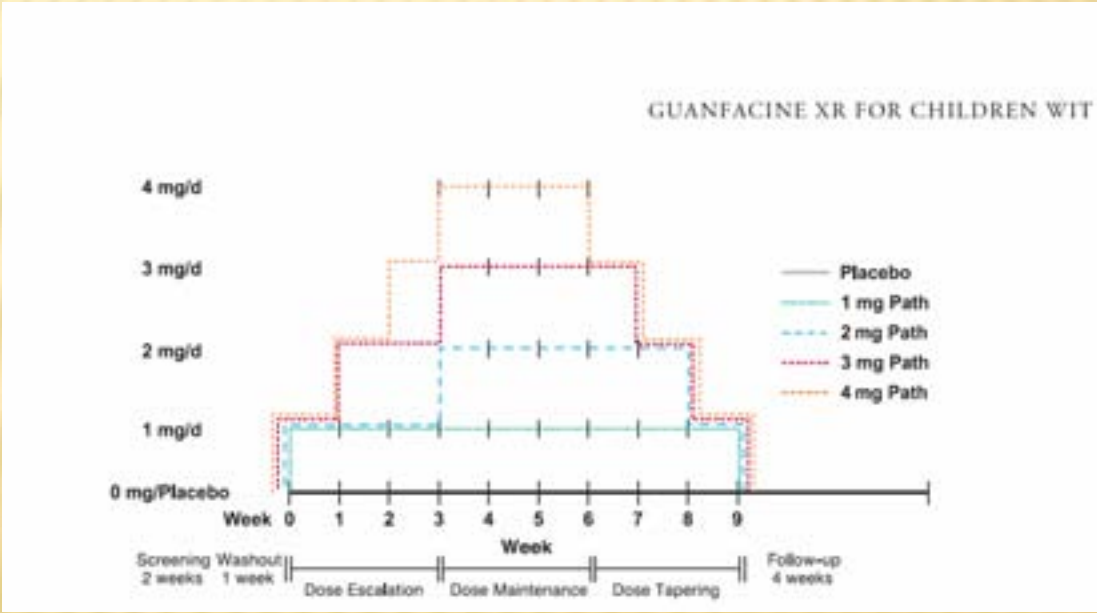
ABSTRACT

Objective: This study compared the efficacy of guanfacine extended release (GXR), a selective α_{2A}-adrenoceptor agonist, with placebo in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). **Method:** This double-blind, 9-week, dose-ranging, parallel-design, multicenter trial randomized 6- to 17-year-olds with ADHD to once-daily oral GXR in 1-, 2-, 3-, and 4-mg doses or placebo. Primary outcome was change in total ADHD Rating Scale-IV score from baseline to endpoint. Secondary outcomes included changes in scores of hyperactive/impulsive and inattentive subscales; clinician and parent ratings; duration of clinical effect; and safety measures. **Results:** Statistically significant reductions in ADHD Rating Scale-IV scores were observed from baseline to endpoint at all doses of GXR, with effect sizes ranging from 0.43 to 0.62. In subjects receiving GXR, mean heart rate and systolic and diastolic blood pressure decreased as the dose of GXR increased and then returned toward baseline during the dose-maintenance and dose-tapering phases of the trial. Most frequent treatment-emergent adverse events (≥5%) were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. Somnolence, sedation, and fatigue adverse events emerged within the first 2 weeks of dosing and generally resolved by study end. **Conclusions:** Guanfacine extended-release was effective in reducing symptoms of ADHD. Adverse events were mild to moderate, did not interfere with improvements in attention, and rarely led to discontinuation. *J. Am. Acad. Child Adolesc. Psychiatry*, 2009;48(2):155–165. **Key Words:** α_{2A}-adrenoceptor agonist, attention-deficit/hyperactivity disorder, ADHD, guanfacine, nonstimulant. Clinical trial registration information—Safety and Efficacy of SPD503 in Treating ADHD in Children and Adolescents Aged 6-17. URL: *http://clinicaltrials.gov*. Unique identifier: NCT00150618.

Guanfacina: estudios de eficacia. Fase Aguda

- RCT,multicéntrico, n: 324
- Cinco ramas: 1, 2, 3 ,4 mg/dia y placebo

  de 0.01mg/Kg/ dia a 0.17 mg/Kg/dia
- Medidas de eficacica: ADHD-RS, CPRS, CGI, EF



- Eficacia a todas las dosis de GXR
- Tamaño del efecto de 0.43 a 0.62

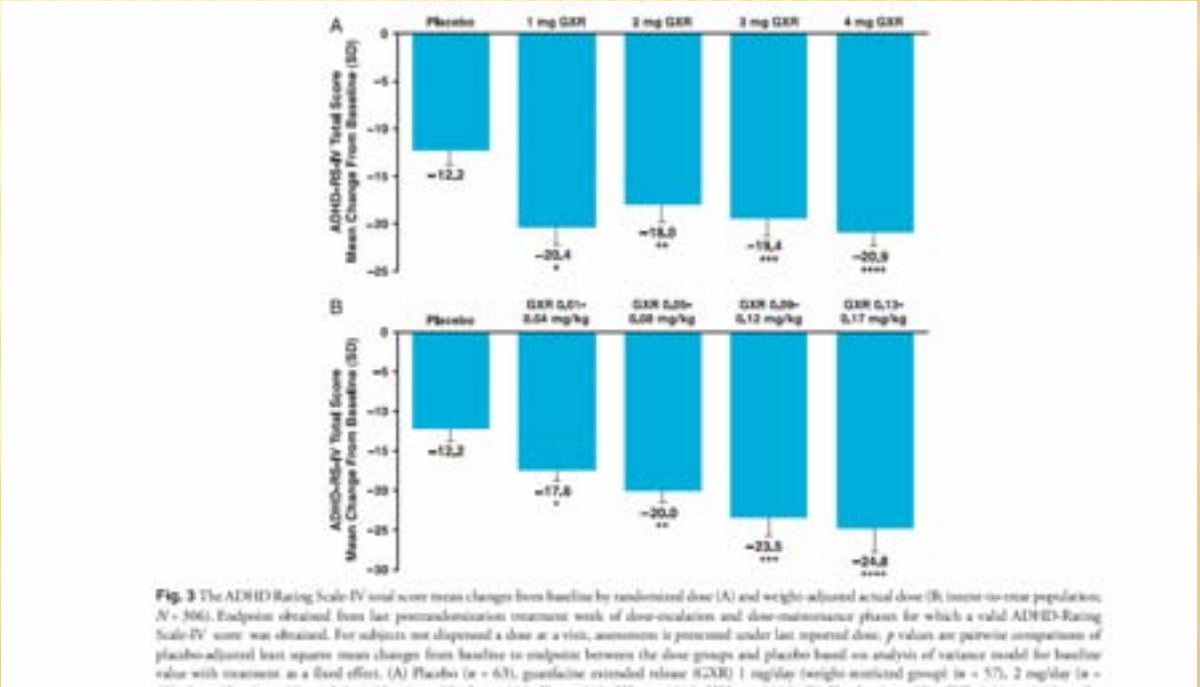
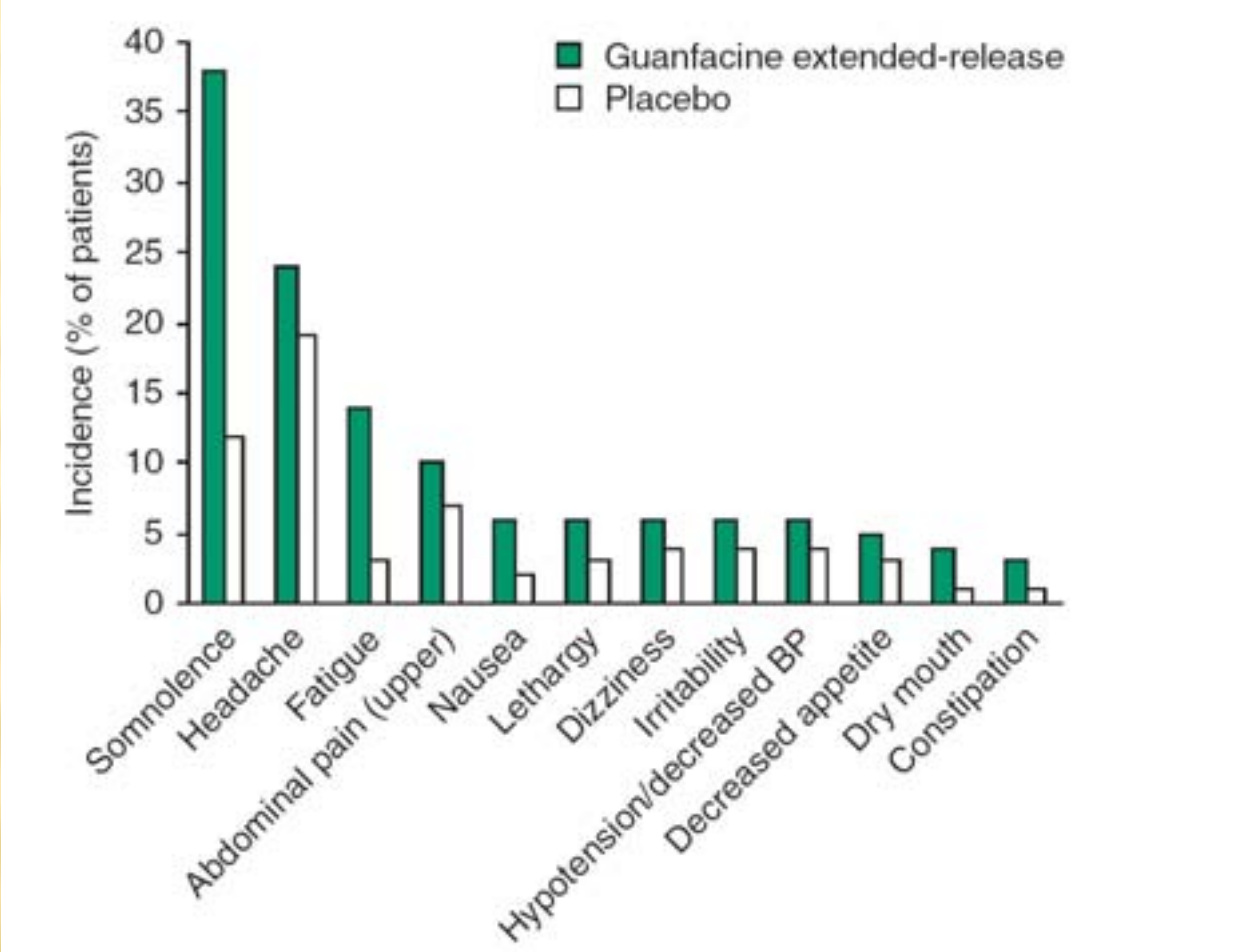


Fig. 3 The ADHD Rating Scale-IV total score mean changes from baseline by randomized dose (A) and weight-adjusted actual dose (B; intent-to-treat population; *N* = 306). Endpoint obtained from last postrandomization treatment week of dose-escalation and dose-maintenance phases for which a valid ADHD-Rating Scale-IV score was obtained. For subjects not dispensed a dose at a visit, assessment is presumed under last reported dose; *p* values are pairwise comparisons of placebo-adjusted least squares mean changes from baseline to endpoint between the dose groups and placebo based on analysis of variance model for baseline value with treatment as a fixed effect. (A) Placebo (*n* = 63), guanfacine extended release (GXR) 1 mg/day (weight-restricted group) (*n* = 57), 2 mg/day (*n* =

Guanfacina: efectos secundarios



Guanfacina: estudios de eficacia con psicoestiumulantes

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
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Original Article

Safety and Effectiveness of Coadministration of Guanfacine Extended Release and Psychostimulants in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Thomas J. Spencer, M.D.,[1] Michael Greenbaum, M.D.,[2] Lawrence D. Ginsberg, M.D.,[3] and William Rory Murphy, M.D.[4]

Abstract

Objective: The aim of this study was to evaluate the safety and effectiveness of guanfacine extended release (GXR) administered concomitantly with psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and suboptimal response to a psychostimulant alone.

Design and Methods: This was a multicenter, open-label, 9-week, dose-escalation study of 75 subjects with ADHD treated with methylphenidate (MPH) or amphetamine (AMP) alone for at least 1 month, yet with suboptimal control of ADHD symptoms. Sixty-three subjects (84.0%) completed the study. Patients received GXR in addition to their psychostimulant. Starting with 1 mg/day, GXR was increased weekly to the highest tolerated dose (1, 2, 3, or 4 mg/day), which was maintained through week 6. GXR was then titrated downward in 1-mg weekly decrements from week 7 through week 9. Psychostimulant treatment regimens were continued until at least week 7.

Main Outcome Measures: Safety assessments included adverse events (AEs), vital signs, physical examination, clinical laboratory tests, the Pediatric Daytime Sleepiness Scale, and the Pittsburgh Side Effects Rating Scale. Efficacy was assessed using the ADHD Rating Scale IV (ADHD-RS-IV), the Conners' Parent Rating Scale–Revised Short Form, Clinical Global Impressions, Parent Global Assessment, and Child Health Questionnaire–Parent Form.

Results: The most common treatment-related AEs were upper abdominal pain (25.3%), fatigue (24.0%), irritability (22.7%), headache (20.0%), and somnolence (18.7%). Most AEs were mild to moderate in severity. Investigator-rated AEs due to blood pressure decreases, heart rate, or electrocardiogram findings were infrequent. Mean changes from baseline (psychostimulant monotherapy just prior to receiving GXR) to endpoint in ADHD-RS-IV total score were statistically significant overall: −16.1 ($p < 0.0001$). Significant improvement in both subscales of the ADHD-RS-IV was observed. Improvement of symptoms was observed in a majority of subjects.

Conclusion: Coadministration of GXR and MPH or AMP was generally safe and associated with statistically significant and clinically meaningful ADHD symptom improvement in children and adolescents.

- Ef secundarios : dolor abdominal, fatiga, irritabilidad, cefalea (>20%)
- Efecto mantenido las 24 horas

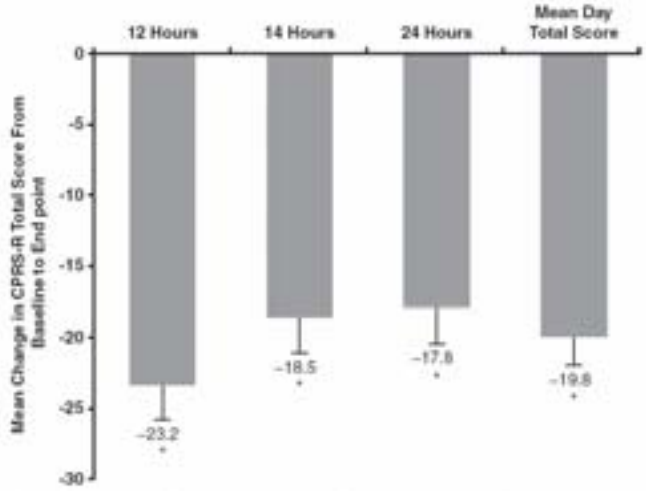

FIG. 2. Mean change in CPRS-R total score from baseline (psychostimulant alone) to end point (psychostimulant + GXR) (FAS). End point is the last postbaseline treatment week of the dose-titration and dose-maintenance phases (i.e., weeks 1–6 or days 1–42) for which a valid assessment was obtained. Mean day total scores were determined by averaging the total scores obtained at the three administrations. *$p < 0.0001$. CPRS-R = Conners' Parent Rating Scale–Revised Short Form; GXR = guanfacine extended release; FAS = full

- Respuesta significativa en ADHD RS total score a la semana 6 de tto combinado (p>0.0001)

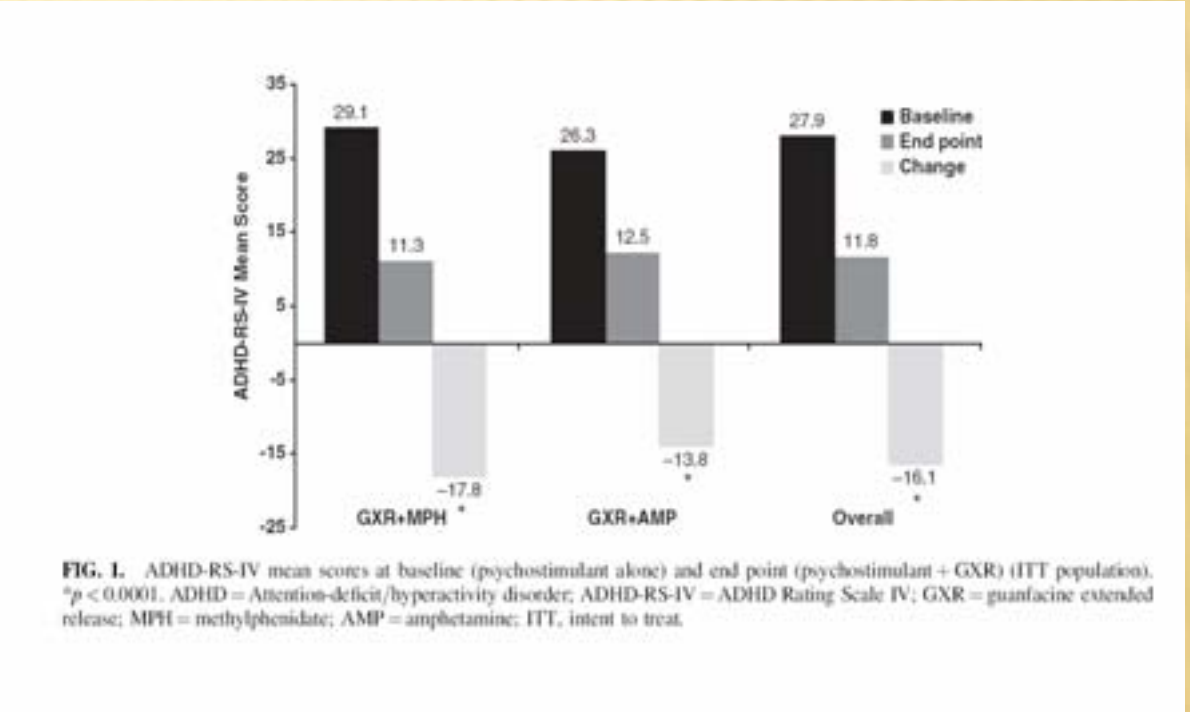

FIG. 1. ADHD-RS-IV mean scores at baseline (psychostimulant alone) and end point (psychostimulant + GXR) (ITT population). *$p < 0.0001$. ADHD = Attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV; GXR = guanfacine extended release; MPH = methylphenidate; AMP = amphetamine; ITT, intent to treat.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 19, Number 3, 2009

Pp. 215–226
DOI: 10.1089/cap.2008.0080

Long-Term Safety and Efficacy of Guanfacine Extended Release in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Floyd R. Sallee, M.D., Ph.D.,[1] Andrew Lyne, M.Sc., C.Stat.,[2] Timothy Wigal, Ph.D.,[3] and James J. McGough, M.D.[4]

Abstract

Objective: Short-term, controlled studies of extended-release guanfacine (GXR), a selective α_{2A}-adrenoreceptor agonist, demonstrate efficacy in treating attention-deficit/hyperactivity disorder (ADHD) symptoms as monotherapy. This 2-year open-label study was conducted to further assess the long-term safety and efficacy of GXR.

Methods: Study participants, aged 6–17 years with ADHD, had previously been exposed to GXR therapy alone or in combination with psychostimulants in one of two antecedent trials. In this study, doses were titrated to 1, 2, 3, or 4 mg/day of GXR alone or in combination with a psychostimulant. Safety and efficacy data collected at clinic visits over 24 months provided further evidence of the overall safety and efficacy of GXR for treating ADHD.

Results: The majority of adverse events (AEs) were mild to moderate, and few patients discontinued the study because of an AE. Efficacy measures demonstrated significant improvement beginning in the first month and lasting through the end of the 24-month treatment period. Throughout the entire 2-year study, 202 subjects (77.1%) discontinued and 60 (22.9%) completed the study.

Conclusions: Overall, these data support that GXR monotherapy is generally safe and effective for treating ADHD.

Sallee F et al.(2009) J. Child and Adolescent Psychopharmacology, 19(3):215-226

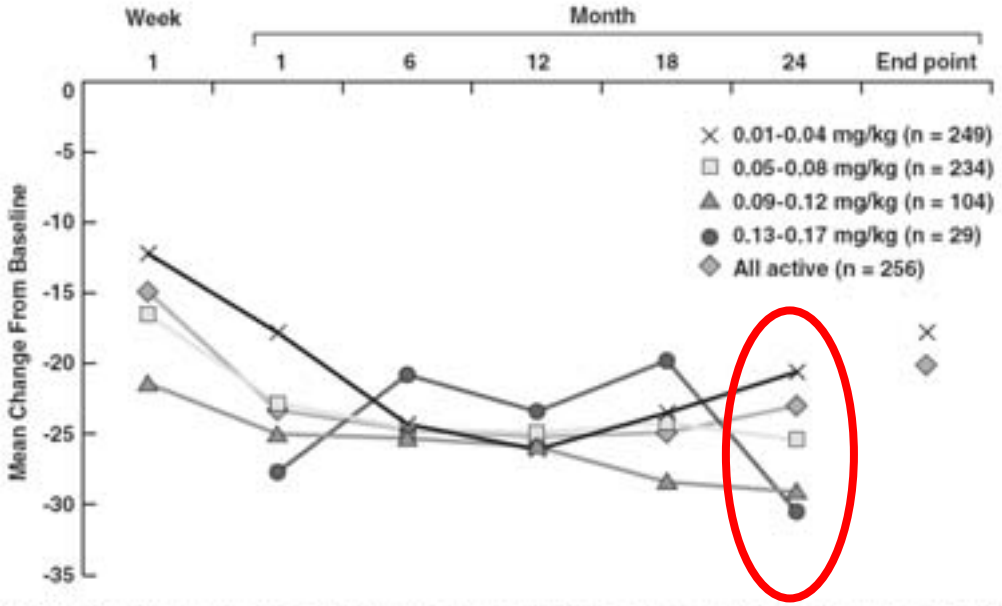

FIG. 5. ADHD-RS-IV total score by weight-adjusted actual dose (full analysis set). The earliest time point that included subjects in the 0.13- to 0.17-mg/kg dose group was the month 1 visit. At end point, mean ADHD-RS-IV total scores were significantly ($p < 0.001$) reduced from baseline in each weight-adjusted dose group. End point is the last valid ADHD-RS-IV total score obtained postbaseline and on treatment. ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV.

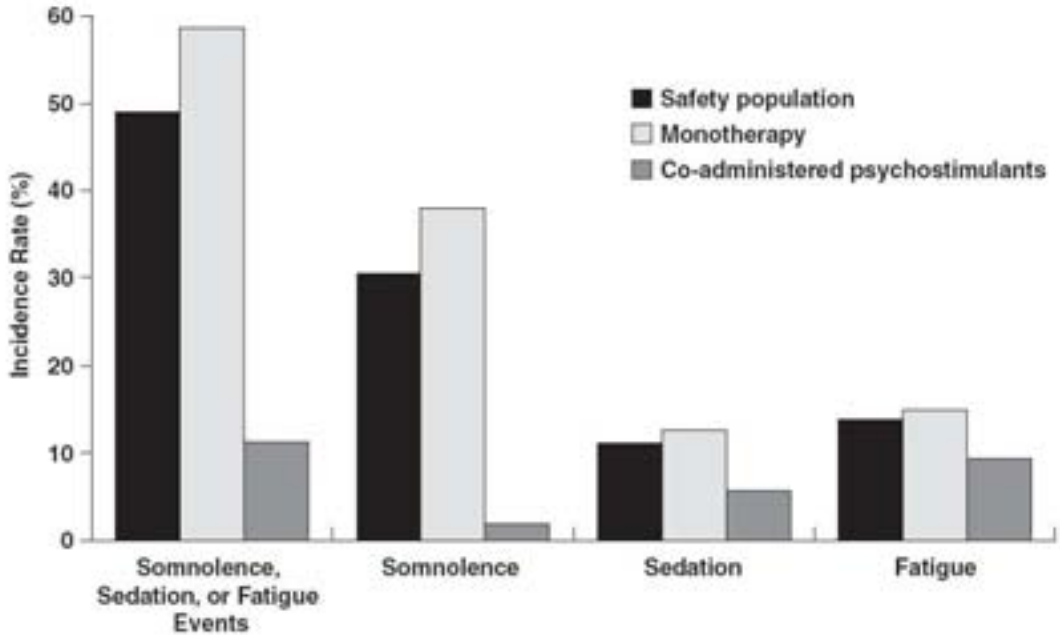

FIG. 3. Incidence of treatment-emergent somnolence, sedation, or fatigue events (safety population). Somnolence, sedation, or fatigue events were reported by 49% (127 of 259) of subjects in the safety population, 58.7% of subjects (121 of 206) administered monotherapy and 11.3% of subjects (6 of 53) administered guanfacine extended release with a psychostimulant.

2.GUANFACINA
TDAH Y TND

ORIGINAL RESEARCH ARTICLE

Effects of Guanfacine Extended Release on Oppositional Symptoms in Children Aged 6–12 Years with Attention-Deficit Hyperactivity Disorder and Oppositional Symptoms

A Randomized, Double-Blind, Placebo-Controlled Trial

Daniel F. Connor,[1] Robert L. Findling,[2] Scott H. Kollins,[3] Floyd Sallee,[4] Frank A. López,[5] Andrew Lyne[6] and Gerald Tremblay[7]

1 Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Connecticut School of Medicine, Farmington, Connecticut, USA
2 University Hospitals Case Medical Center, Cleveland, Ohio, USA
3 Duke University Medical Center, Durham, North Carolina, USA
4 Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio, USA
5 Children's Developmental Center, Winter Park, Florida, USA
6 Shire Pharmaceutical Development Ltd, Chineham, UK
7 Shire Development Inc., Wayne, Pennsylvania, USA

- 217 RCP GXR vs placebo
- 9 semanas
- Eficacia clínica global (ADHR-RS) p>0.001, tamaño del efecto de 0.59
- Reducción del ítem de oposicionismo de la CPRS, correlación con el total de 0.74
- Ef 2º: somnolencia

ADHD-RS IV

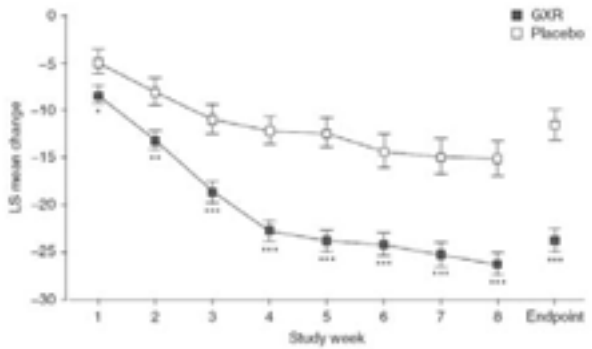

Fig. 3. Changes from baseline in Attention-Deficit Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) total score (full analysis set). Endpoint was defined, using the last observation carried forward method, as the last visit of the dose-optimization or dose-maintenance period (visits three to ten) at which a valid score was collected. This may represent different timepoints for different subjects. Least-square (LS) mean, effect size and p-value were based on type III sum of squares from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate. **GXR** = guanfacine extended release; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Problemas de conducta del CPRS

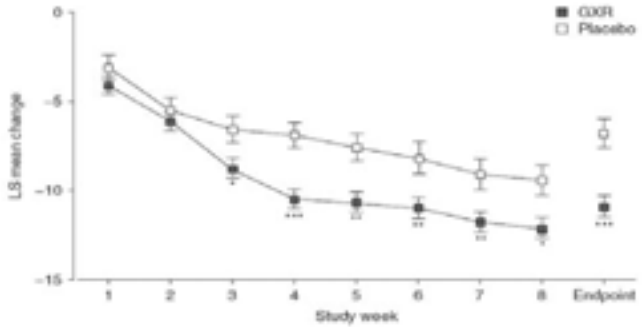

Fig. 2. Changes from baseline in oppositional subscale of the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L) score (full analysis set). Endpoint was defined, using the last observation carried forward method, as the last visit of the dose-optimization or dose-maintenance period (visits three to ten) at which a valid score was collected. This may represent different timepoints for different subjects. Least-square (LS) mean, effect size and p-value were based on type III sum of squares from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate. **GXR** = guanfacine extended release; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Connor D F, Findling R. et al.(2010) CNS Drugs 24 (9): 755- 768

L-DEXAMFETAMINA

1. L-DEXAMFETAMINA

ESTUDIOS DE FARMACOCINÉTICA

Neuropsychiatric Disease and Treatment

Dovepress

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ORIGINAL RESEARCH

Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
3 June 2010
Number of times this article has been viewed

Michael Pennick

Biosciences Department, Shire Pharmaceutical Development Ltd, Basingstoke, UK

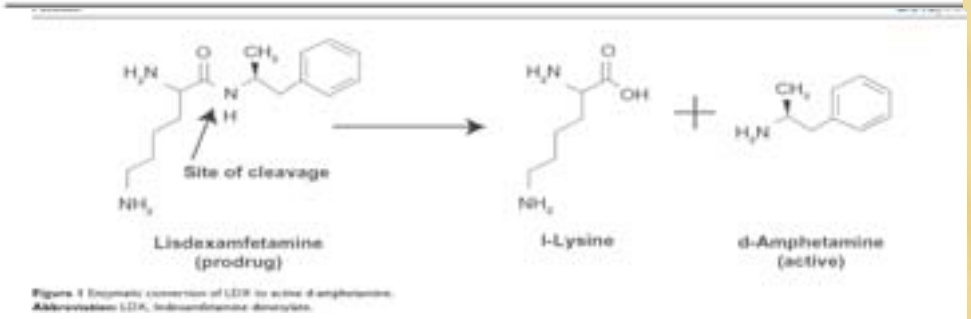

Figure 1 Enzymatic conversion of LDX to active d-amphetamine.
Abbreviation: LDX, lisdexamfetamine dimesylate.

Pennick M. et al.(2010) Neuropsychiatric Disease and Treatment (6):317-327

Absorción de LDS y dANFETAMINA: niveles plamàticos

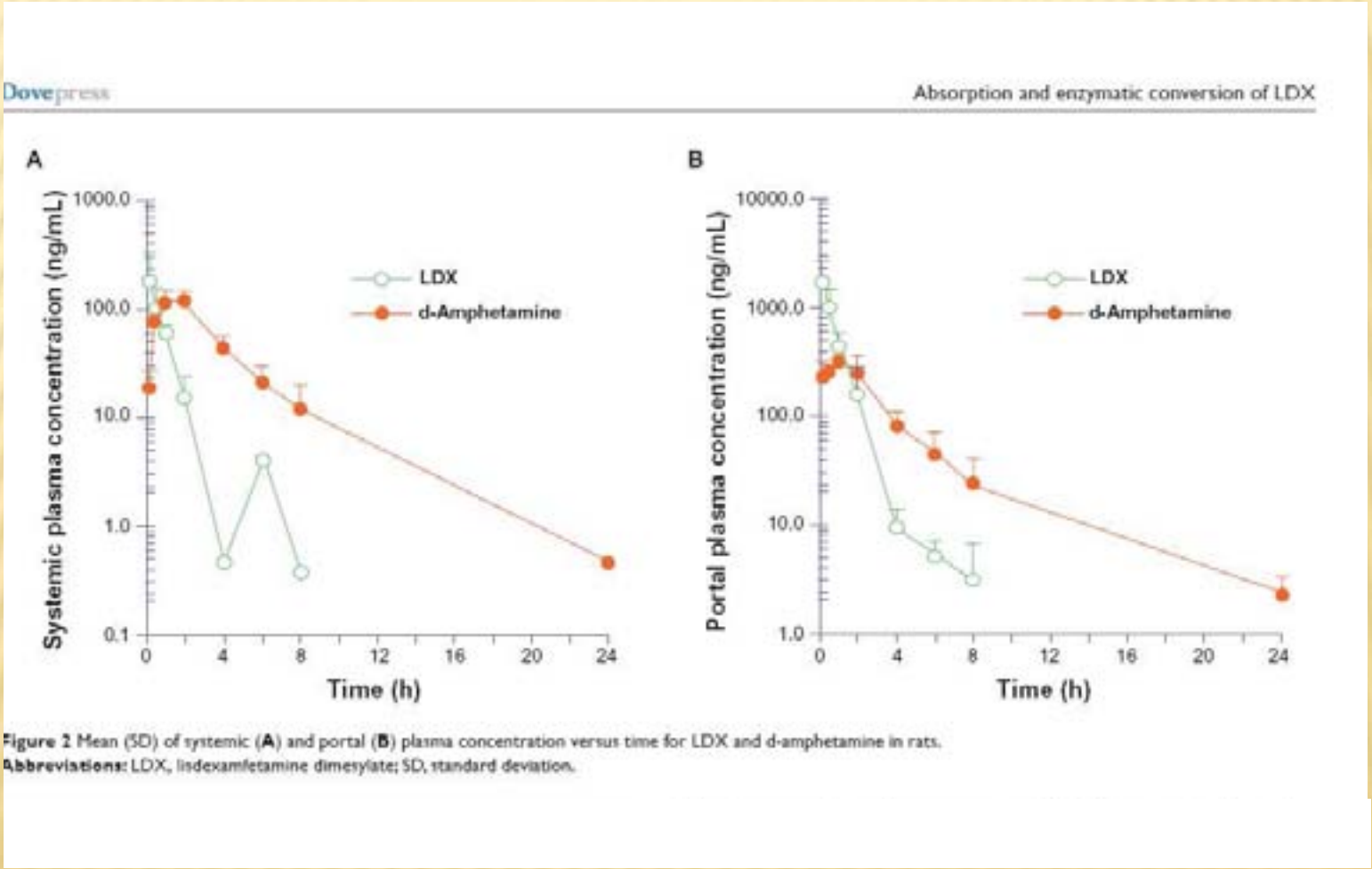

Figure 2 Mean (SD) of systemic (**A**) and portal (**B**) plasma concentration versus time for LDX and d-amphetamine in rats.
Abbreviations: LDX, lisdexamfetamine dimesylate; SD, standard deviation.

Absorción de LDS y dANFETAMINA: lugar de absorción

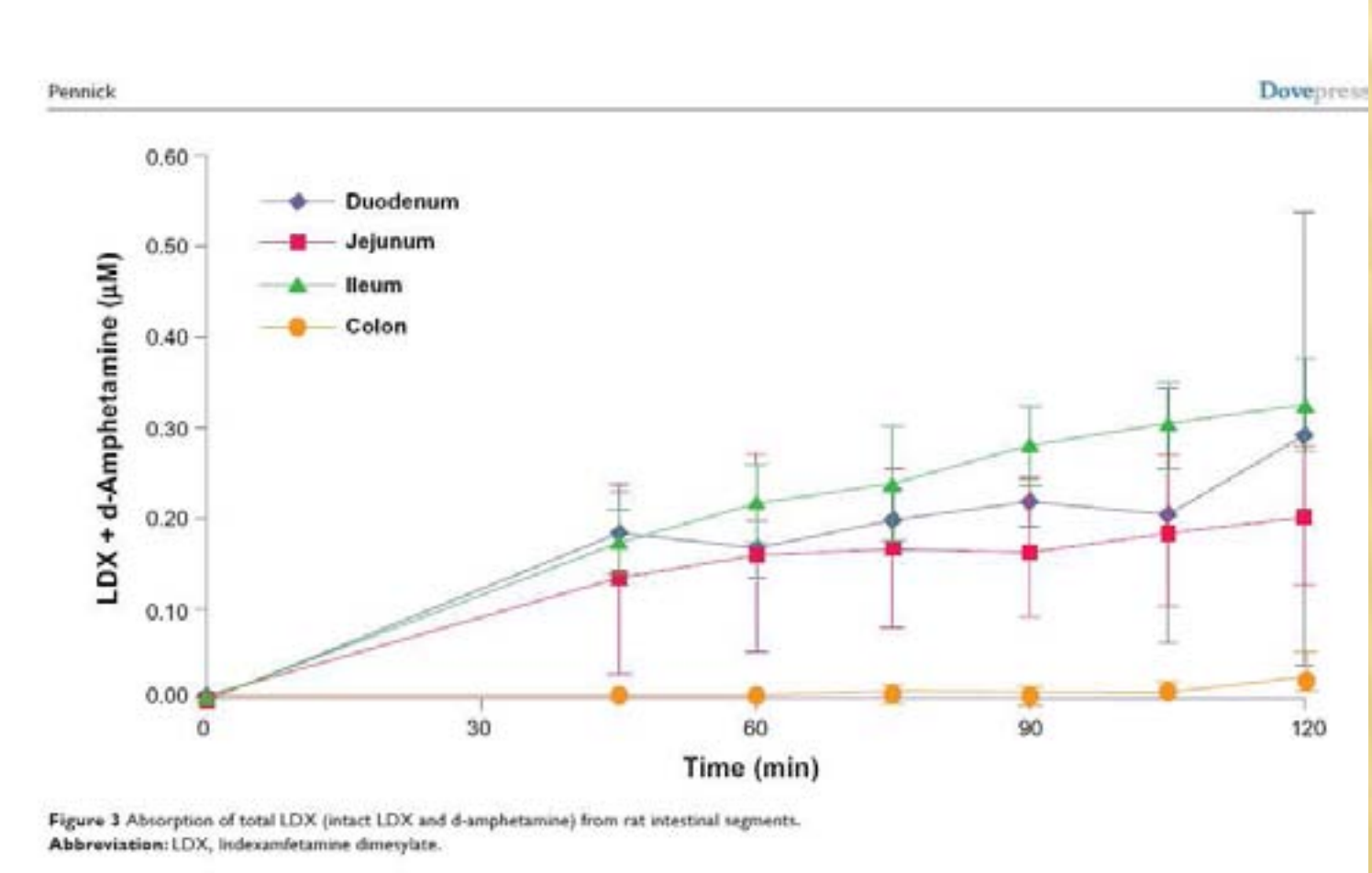

Figure 3 Absorption of total LDX (intact LDX and d-amphetamine) from rat intestinal segments.
Abbreviation: LDX, lisdexamfetamine dimesylate.

Absorción de LDS y dANFETAMINA: concentraciones tisulares

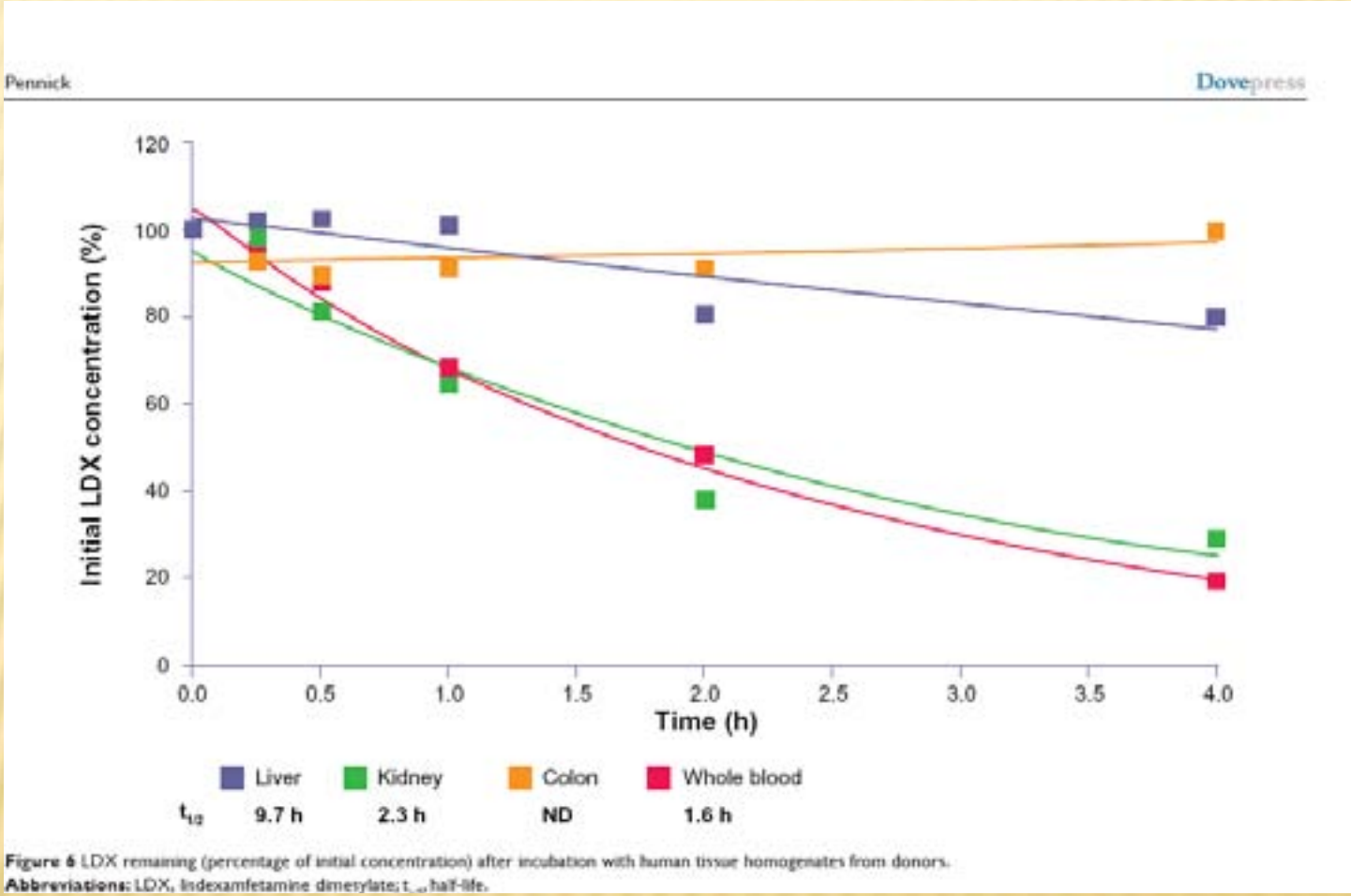

Figure 6 LDX remaining (percentage of initial concentration) after incubation with human tissue homogenates from donors.
Abbreviations: LDX, lisdexamfetamine dimesylate; $t_{1/2}$, half-life.

2.L-DEXAMFETAMINA

EFICACIA CLÍNICA: FUNCIONES EJECUTIVAS

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
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Pp. 649–662
DOI: 10.1089/cap.2008.0165

Effectiveness, Safety, and Tolerability of Lisdexamfetamine Dimesylate in Children With Attention-Deficit/Hyperactivity Disorder: An Open-Label, Dose-Optimization Study

Robert L. Findling, M.D.,[1] Lawrence D. Ginsberg, M.D.,[2] Rakesh Jain, M.D.,[3] and Joseph Gao, Ph.D.[4]

Abstract

Objective: The aim of this study was to assess the effectiveness and safety of lisdexamfetamine dimesylate (LDX) in children with attention-deficit/hyperactivity disorder (ADHD).

Method: This was a 7-week, open-label study evaluating 20, 30, 40, 50, 60, or 70 mg/day LDX in 318 children aged 6–12 years with ADHD. The ADHD Rating Scale IV (ADHD-RS-IV) was the primary efficacy assessment. Secondary measures included the Clinical Global Impressions–Improvement (CGI-I), Expression and Emotion Scale for Children (EESC), and Behavior Rating Inventory of Executive Function (BRIEF). Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, and electrocardiograms.

Results: At end point, mean (standard deviation [SD]) improvement from baseline in ADHD-RS-IV total score was 28.6 (10.9) ($p < 0.0001$). Most subjects (89.9%) were rated "improved" (i.e., CGI-I 1 or 2). Improvements from baseline were observed in the EESC total and subscale scores ($p \leq 0.0002$). LDX treatment resulted in significant improvement on the Global Executive Composite, Behavioral Regulation, and Metacognition indices of the BRIEF ($p < 0.0001$). TEAEs (incidences ≥10%) were decreased appetite, decreased weight, irritability, insomnia, headache, upper abdominal pain, and initial insomnia.

Conclusions: LDX was effective and generally well tolerated with a safety profile consistent with long-acting stimulant use. There was overall improvement in ADHD symptoms and executive function measures and no worsening of emotional expression measures.

Trial Registration: clinicaltrials.gov Identifier: NCT00500071.

m 318 pacientes
7 semanas
De 20-70 mg/dia

Medidas:
ADHD RS
CGI-I
EESC
BRIEF

Sg vitales, ECG
TEAEs

Findling R.. et al (2009) J. Child and Adolesc. Psychopharmacology 19(6):649-662

- ADHD RS significativo p< 0.001
- 89% mejoraban en ICG
- Mejoras en EESC total y subescalas p<0.0002

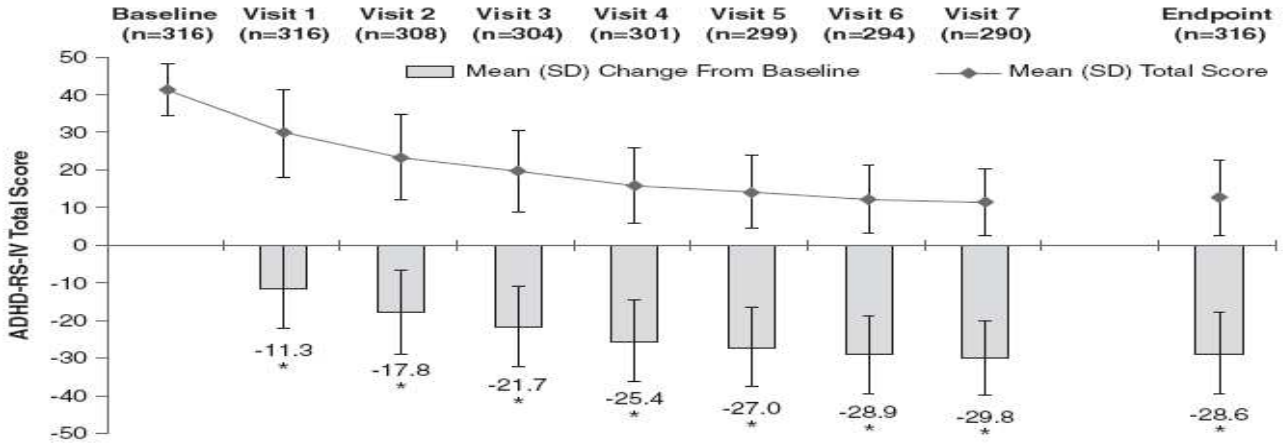
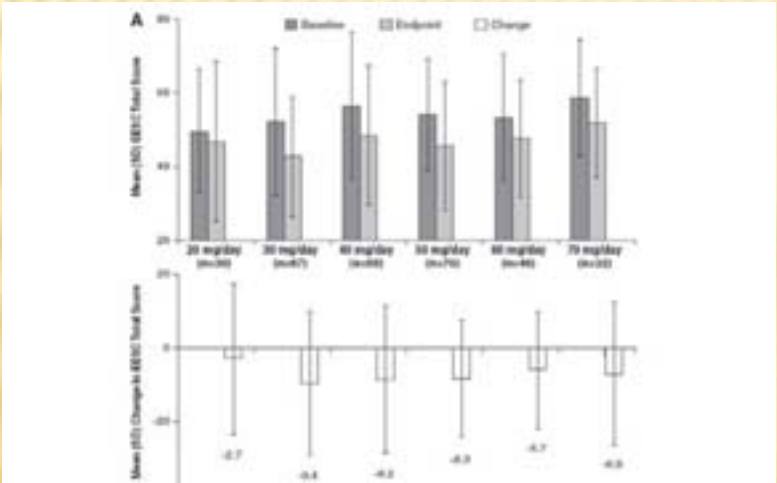
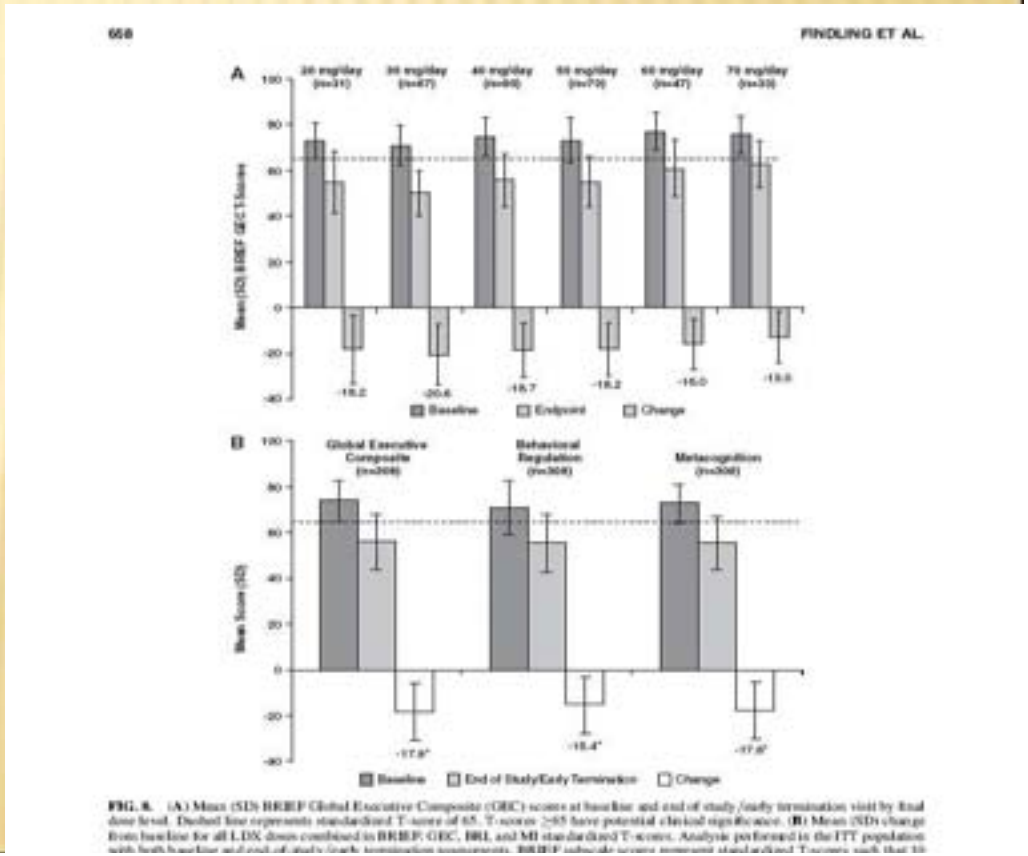


FIG. 3. ADHD-RS-IV total score by visit and at end point (ITT population). End point defined as the last valid score obtained after baseline. (*) $p < 0.0001$ by one-sample t-test. ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV; ITT = intention-to-treat; LDX = lisdexamfetamine dimesylate; LOCF = last observation carried forward; SD = standard deviation.

- Efectos secundarios en >10 %
  - Disminución apetito
  - Disminución de peso
  - Irritabilidad
  - Insomnio
  - Dolor abdominal

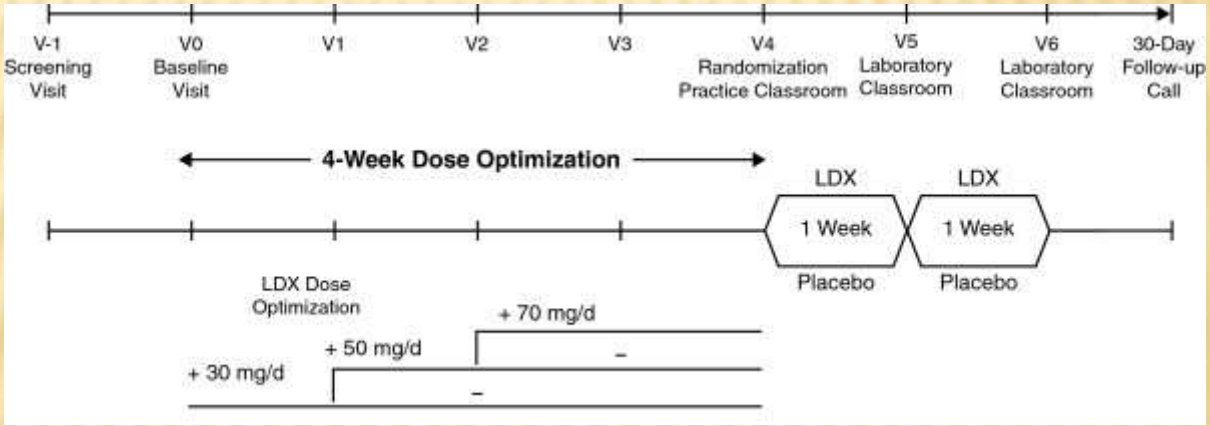
- BRIEF:mejoras significativas endpoint
  - Función ejecutiva global
  - Regulación de la conducta
  - Metacognición





3.L-DEXAMFETAMINA
OPINIÓN DE LOS PADRES

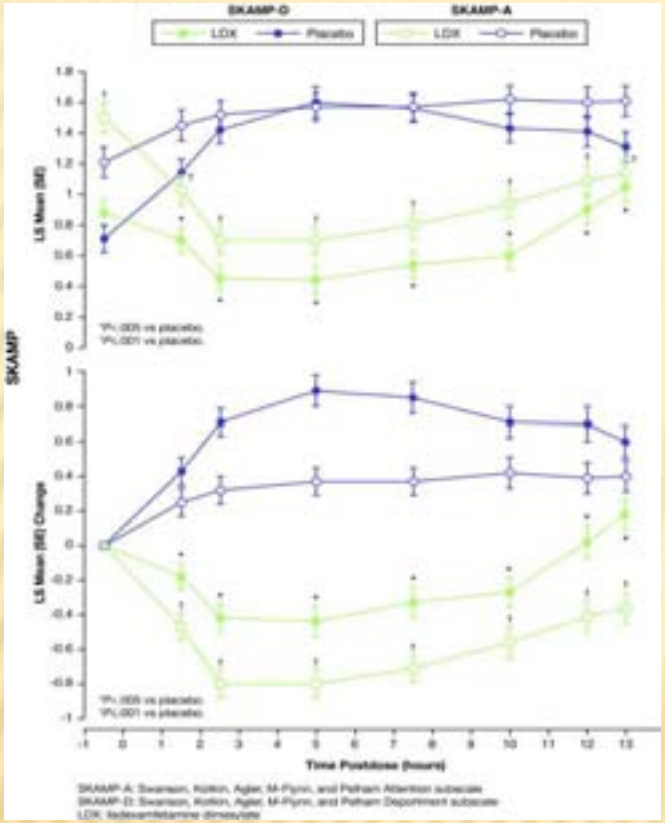
Laboratory school study, n 117
Fase abierta a dosis de 30-70 mg/dia y dp 2 formas cross over vs placebo una semana cada una
Medidas de eficacia: SKAMP (atención y conducta) PERMP: puntos horarios: 1.5, 2.5,5,7.5,10,12 y 13 h. Medidas seguridad

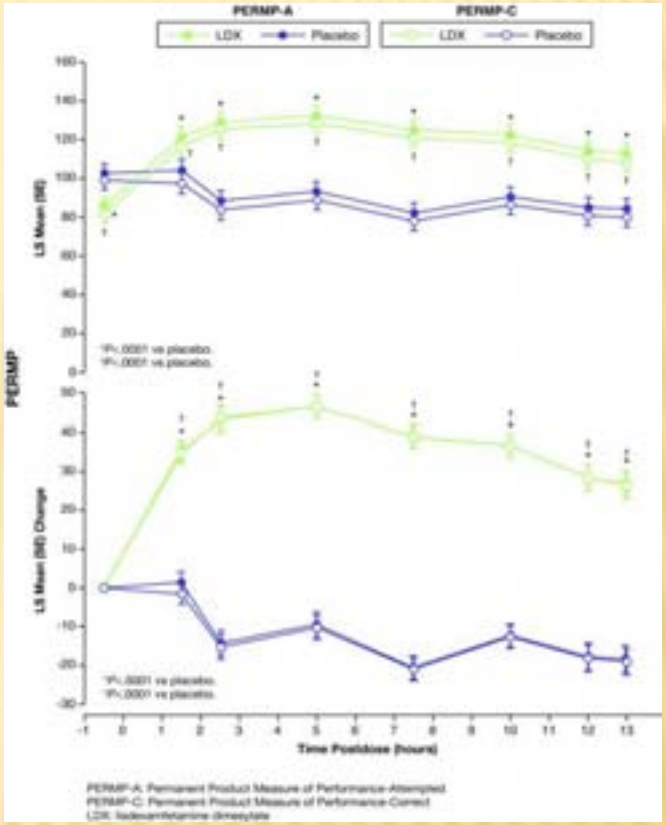


Wigal SB et al (2009) Child and Adolescent Psychiatry and Mental Health 3(17):1-15

3.L-DEXAMFETAMINA

estudio de laboratorio escolar

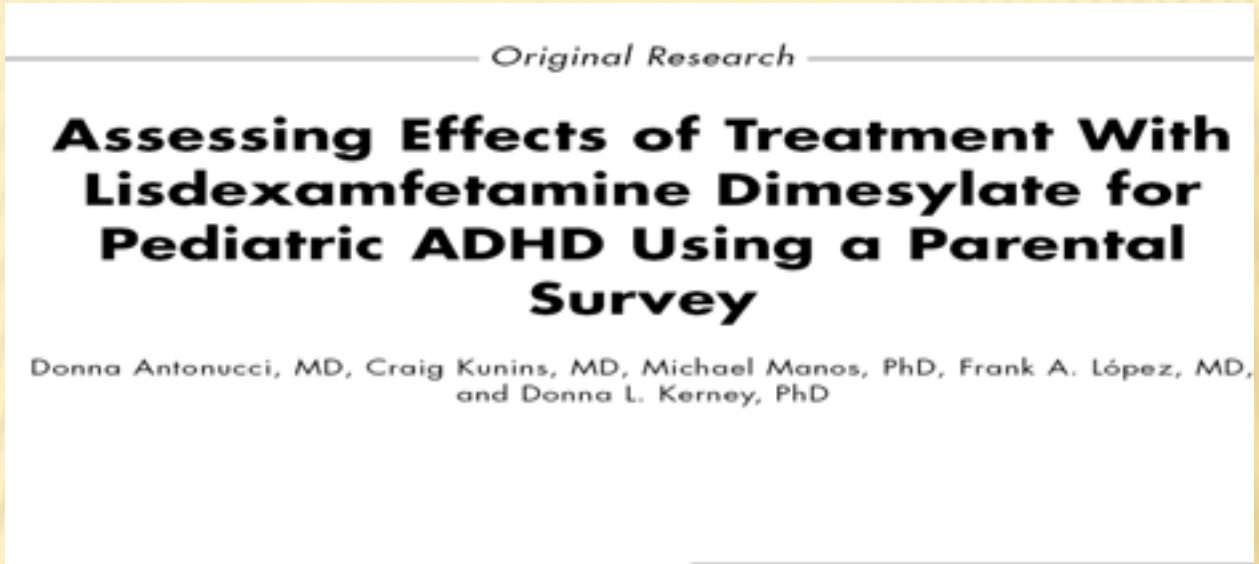




- LDX demostró eficacia en cada estadísticamente significativa en cada punto de mediada, de 1.5h a 13 h post dosis

Wigal SB et al (2009) Child and Adolescent Psychiatry and Mental Health 3(17):1-15

4.L-DEXAMFETAMINA
OPINIÓN DE LOS PADRES



Original Research

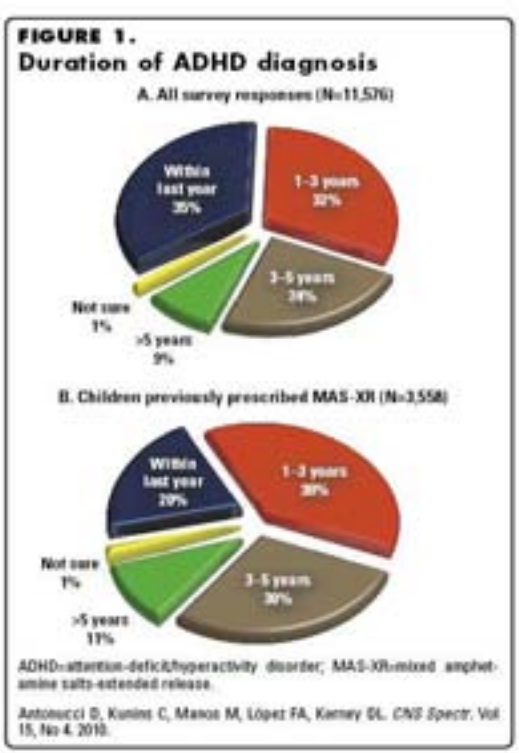
Assessing Effects of Treatment With Lisdexamfetamine Dimesylate for Pediatric ADHD Using a Parental Survey

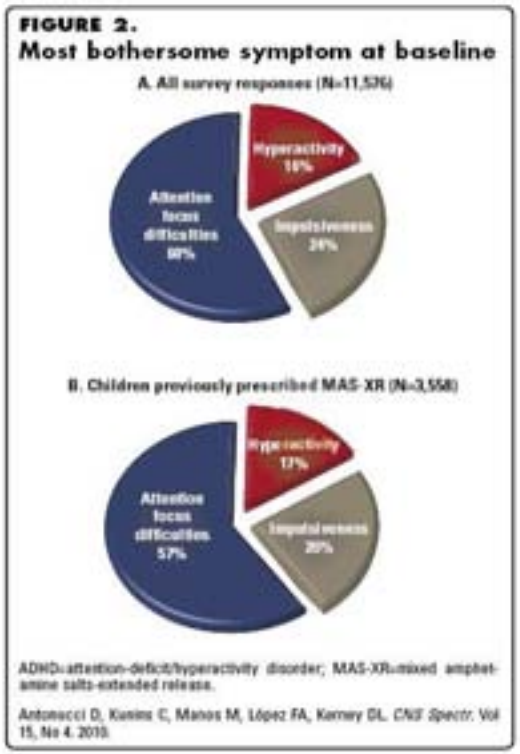
Donna Antonucci, MD, Craig Kunins, MD, Michael Manos, PhD, Frank A. López, MD, and Donna L. Kerney, PhD

- The vivance New Start Program. Encuesta telefónica previa, a las tres semanas y a los seis meses de iniciar tratamiento

Antonucci D et al (2010) CSN Spectr 15(4):248-256

- n 11.576 63% previamente en tratamiento con estimulantes, 5 % atomoxetina

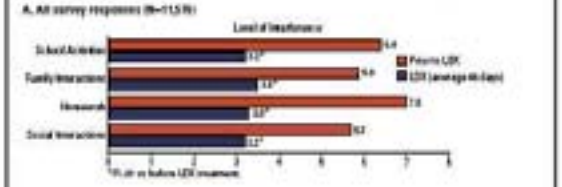


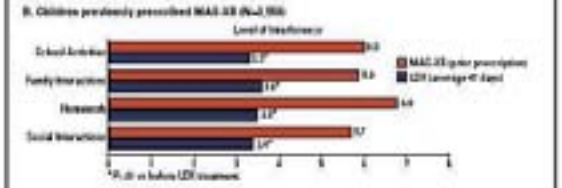


Diferencias significativas a 6m del tratamiento en nivel de interferencia

Actividades escolares
Relaciones en familia
Deberes
Relaciones sociales

FIGURE 4.
Interference of ADHD with activities, before and after LDX treatment





ADHD=attention-deficit/hyperactivity disorder; LDX=lisdexamfetamine dimesylate; MAS-XR=mixed amphetamine salts-extended release.

Antonuccci D, Kunins C, Manos M, López FA, Kerney DL. *CNS Spectr.* Vol 15, No 4. 2010.

Cambios en la frecuencia y severidad de síntomas de TDAH

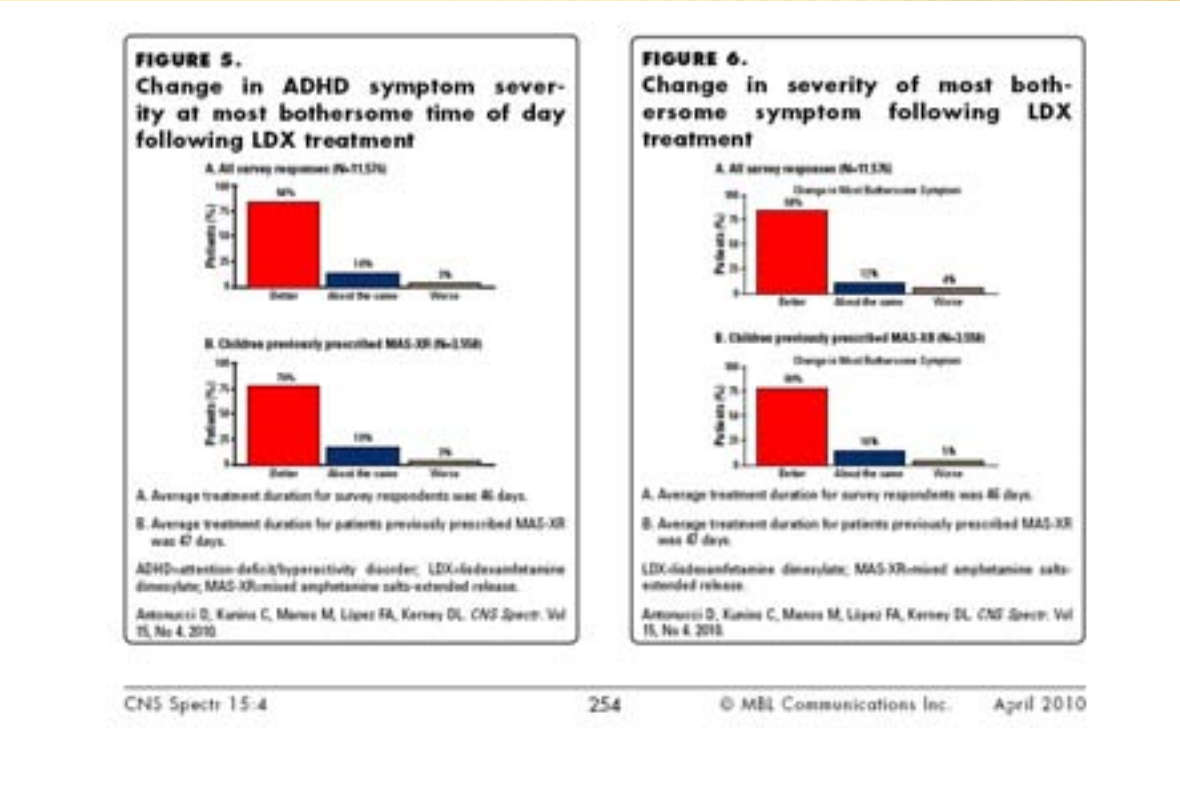


FIGURE 5.
Change in ADHD symptom severity at most bothersome time of day following LDX treatment

A. All survey responses (N=11,576)

B. Children previously prescribed MAS-XR (N=3,558)

A. Average treatment duration for survey respondents was 46 days.

B. Average treatment duration for patients previously prescribed MAS-XR was 47 days.

ADHD=attention-deficit/hyperactivity disorder; LDX=lisdexamfetamine dimesylate; MAS-XR=mixed amphetamine salts-extended release.

Antonuccio D, Kunins C, Manos M, López FA, Kerney DL. *CNS Spectr.* Vol 15, No 4. 2010.

FIGURE 6.
Change in severity of most bothersome symptom following LDX treatment

A. All survey responses (N=11,576)

B. Children previously prescribed MAS-XR (N=3,558)

A. Average treatment duration for survey respondents was 46 days.

B. Average treatment duration for patients previously prescribed MAS-XR was 47 days.

LDX=lisdexamfetamine dimesylate; MAS-XR=mixed amphetamine salts-extended release.

Antonuccio D, Kunins C, Manos M, López FA, Kerney DL. *CNS Spectr.* Vol 15, No 4. 2010.

4.L-DEXAMFETAMINA

EFECTOS SOBRE EL PESO, CRECIMIENTO Y SUEÑO

EFECTOS SOBRE EL USO DE SUSTANCIAS

Effects of Lisdexamfetamine Dimesylate Treatment for ADHD on Growth

Stephen V. Faraone, Ph.D., Thomas J. Spencer, M.D., Scott H. Kollins, Ph.D., Stephen J. Glatt, Ph.D.

Objective: To complete an exploratory uncontrolled study of the effects of lisdexamfetamine dimesylate (LDX) on growth of children treated for attention-deficit/hyperactivity disorder (ADHD). **Method:** Height, weight, and body mass index (BMI) from 281 children ages 6 to 13 years from longitudinal assessments up to 15 months were compared to norms from the Centers for Disease Control. **Results:** At study entry, children were taller and heavier than average. Growth delays were largest for weight and BMI, and there was a 13 percentile point decrease in height. Children continued to grow in terms of height while treated with LDX; we found no increase in raw weight or BMI during the study period. LDX treatment was significantly associated with diminished gains in height, weight, and BMI compared to levels that would be expected based on age-appropriate standards from the Centers for Disease Control. Growth delays were greatest for the heaviest and tallest children, for those who had not previously received stimulant therapy, and for those with a greater cumulative exposure to LDX. More work is needed to determine effects on ultimate adult height. **Conclusions:** Consistent with prior studies of stimulants, treatment with LDX leads to statistically significant reductions in expected height, weight, and BMI. Growth of patients with ADHD treated with LDX should be closely monitored and corrective action taken should growth delays be observed. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(1):24–32. Clinical trial registry information—Phase 3 Randomized Double-Blind Placebo-Controlled Study of NRP104 in Children Aged 6-12 With ADHD, URL: *http://www.clinicaltrials.gov*, unique identifier: NCT00556296; NRP104, Adderall XR or Placebo in Children Aged 6-12 Years with ADHD; URL: *http://www.clinicaltrials.gov*, unique identifier: NCT00557011. **Key Words:** attention-deficit/hyperactivity disorder, growth, lisdexamfetamine dimesylate, amphetamine, stimulants

Faraone S, Spencer T et al (2010) J.Am. Acad. Child and Adolesc. Psychiatry 49(1):24-32

TABLE 2 Growth Measurements

		Time of Endpoint Assessment			
	Baseline	≤6 mo	>6–12 mo	>12–15 mo	LOCF
A: Subjects with growth measurements available					
Weight	281	94	61	126	
Height	280	93	61	126	
BMI	280	93	61	126	
B: Mean growth z-scores at baseline and endpoint					
Weight	0.55	0.38	0.00	−0.12	0.07
Height	0.19	0.17	−0.04	0.15	0.11
BMI	0.62	0.35	0.03	−0.33	−0.03
C: Mean growth percentile scores at baseline and endpoint					
Weight	65	59	51	47	52
Height	55	53	50	54	53
BMI	67	59	51	43	50

Notes: A z-score of zero is the expected mean from the US population based on norms from the Centers for Disease Control. All subjects are included for the baseline column, but each subject is included in only one of the three endpoint assessment bins (the bin corresponding to their last observation). BMI = body mass index; LOCF = last observation carried forward.

Journal of Attention Disorders OnlineFirst, published on June 23, 2010 as doi:10.1177/1087054710371195

Effect of Lisdexamfetamine Dimesylate on Sleep in Children With ADHD

Journal of Attention Disorders
XX(X) 1–8

DOI: 10.1177/1087054710371195
http://jad.sagepub.com
SAGE

John M. Giblin[1] and Aaron L. Strobel[1]

Abstract

Objective: This study evaluated the potential effects of short-term treatment with lisdexamfetamine dimesylate (LDX) on both subjective and objective sleep characteristics in children aged 6 to 12 years ($n = 24$) with ADHD. **Method:** Polysomnography (PSG) and actigraph measures as well as assessments of subjective sleep parameters were examined in children before and after treatment with either LDX or placebo in a randomized, double-blind, single-center, parallel-group study. **Results:** There was no statistically significant increase in the primary endpoint of latency to persistent sleep (LPS) for the LDX-treated group compared to the placebo group. Secondary PSG or actigraph results generally supported primary endpoint results. Subjective sleep measure results indicated the possibility that responses are influenced by sleep hygiene counseling before and throughout the study. **Conclusions:** In this pilot sleep study in children with ADHD, LDX did not appear to contribute to any sleep disturbances as measured by both objective and subjective sleep parameters. The sample used in this study was small, and the multifarious nature of findings in this study warranted that the study conclusions be interpreted cautiously and that further study is required focusing on the influence of LDX on sleep in larger samples of ADHD children. (*J. of Att. Dis. 2010; XX(X) 1-XX*)

Keywords

ADHD, lisdexamfetamine dimesylate, LDX, sleep, polysomnography, Vyvanse

Giblin JM et al (2010) J. of Attention Disorders OnlineFirst 23: 1-8

- Estudio piloto de n 24
- Polisomnografia y parámetros relacionados con el sueño
- Niños con TDAH y tratamiento con LDX no mostraron alteraciones en las medidas de sueño objetivas ni subjetivas

Table 2. PSG Data—Mean Change from Baseline to Week 7 in Placebo-Treated and LDX-Treated Children

	Placebo[a]	LDX[b]	*p*-Value
LPS (min)	−0.29 ± 15.72	12.21 ± 43.61	.3520
Wake time after sleep onset (min)	−15.86 ± 55.26	−9.57 ± 42.89	.7974
Number of awakenings after sleep onset (#)	−0.57 ± 4.28	−4.64 ± 3.10	.0509
TST (min)	15.29 ± 41.57	−20.00 ± 60.61	.1366

Note: PSG = Polysomnography; LDX = lisdexamfetamine dimesylate; LPS = Latency to persistent sleep, TST = total sleep time.
a. *N* = 8.
b. *N* = 16.

Table 3. Actigraphy Data—Mean Change from Baseline to Week 7 in Placebo-Treated and LDX-Treated Children

Onset-Offset	Placebo[a]	LDX[b]
TST (min)	10.81 ± 87.63	20.84 ± 68.14
Sleep efficiency (self)	−4.88 ± 12.76	2.78 ± 5.98
Wake time after sleep onset (min)	32.30 ± 67.48	−12.47 ± 30.76

Note: LDX = lisdexamfetamine dimesylate; TST = total sleep time.
a. *N* = 7.
b. *N* = 12.

J Psychopharmacol OnlineFirst, published on March 27, 2009 as doi:10.1177/0269881109103113

Original Papers

Psychopha

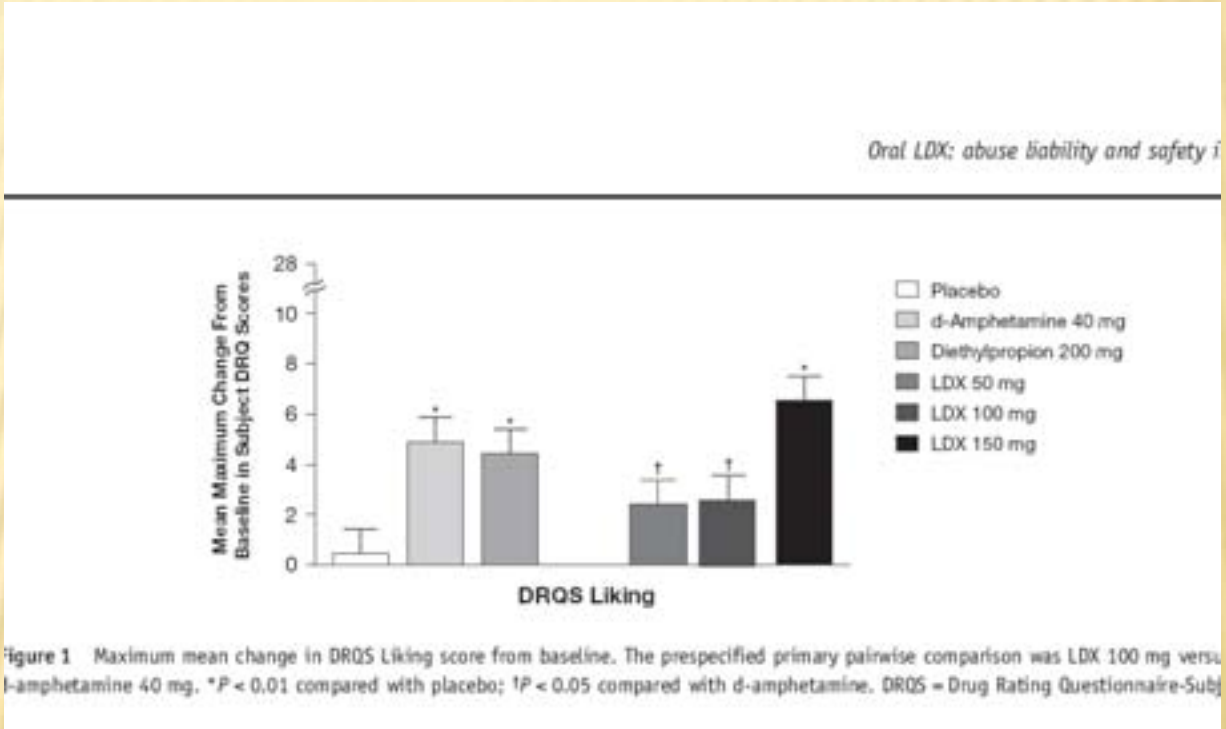
Abuse liability and safety of oral lisdexamfetamine dimesylate in individuals with a history of stimulant abuse

DR Jasinski *Department of Medicine, Johns Hopkins University, Baltimore, MD, USA.*
S Krishnan *Formerly of New River Pharmaceuticals, Inc., Wilmington, CA, USA.*

Abstract

- RCP 36 pacientes TDAH adultos con antecedentes de consumo de tóxicos
- Estudio de dosis única de
  - 50-100 (equivalente 40 DX)-150 LDX
  - 40 DX
  - 200 mg dietipropion

- Drug Rating Questionnaire-Subject Liking Scale
  - LDX diferencias significativas con placebo a dosis altas
  - Diferencias significativas de Dx40 vs LDX 100



Jasinski DR et al (2009) J. of Psychopharmacology 23(4):419-427

- ARCI
  - no diferencias singificativas entre LDX 100 y Dx40 mg

Table 3 Maximum mean change in ARCI scores from baseline ($N = 36$)

	Maximum mean change (standard error)					
	PBO	d-AMP 40 mg	DEP 200 mg	LDX 50 mg	LDX 100 mg	LDX 150 mg
ARCI subscale						
Euphoria scale (MBG)	0.8 (0.5)	4.1* (0.5)	3.0* (0.5)	1.8† (0.5)	3.1* (0.5)	4.5* (0.5)
Amphetamine scale (AS)	0.6 (0.3)	2.6* (0.3)	2.3* (0.3)	1.4† (0.3)	2.3* (0.3)	3.3* (0.3)
Stimulant scale (BG)	4.6 (0.3)	6.3* (0.3)	5.9* (0.3)	5.2† (0.3)	5.8* (0.3)	6.7* (0.3)
Dysphoria scale (LSD)	4.2 (0.2)	5.5* (0.2)	5.4* (0.2)	4.4† (0.2)	4.9*,† (0.2)	5.5* (0.2)
PCAG/Sedation scale	4.1 (0.2)	4.9* (0.2)	5.0* (0.2)	4.5 (0.2)	4.6 (0.2)	5.4* (0.2)

ARCI, Addiction Research Center Inventory; PBO, Placebo; d-AMP, d-amphetamine; DEP, Diethylpropion; LDX, Lisdexamfetamine dimesylate; MBG Morphine–Benzedrine group; BG, Benzedrine group; LSD, Lysergic acid diethylamide; PCAG, Phenobarbital-chlorpromazine-alcohol group.
*$P < 0.05$ vs PBO.
†$P < 0.05$ vs d-AMP 40 mg.

- Drug Rating Questionnaire Subject Feel Drug Effect significativamente menor en LDX 100 que DX40

Jasinski DR et al (2009) J. of Psychopharmacology 23(4):419-427

MUCHAS GRACIAS POR VUESTRA ATENCIÓN !!!