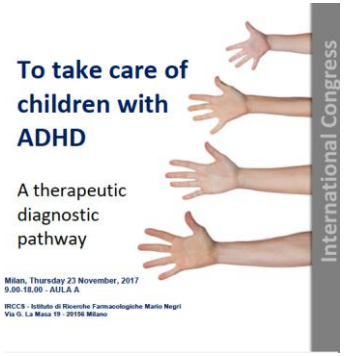

The Clinical Global Impression score: a widely used instrument in psychiatry

A discussion of Benedetto Vitiello presentation

Alessandro Zuddas

Child & Adolescent Neuropsychiatry

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Member of Data Safety Monitory Boards

Otsuka, Lundbek,

European rules for approval of new ADHD medications

The EMA has developed the only formal guideline on ADHD clinical trial design – *Guideline on clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder*[1]

- Recommendations include:
  - Three-arm studies (inclusion of an active comparator)
  - Both *symptomatic* and *functional* efficacy outcomes
  - Measures of clinical response
  - Monitoring of treatment-emergent adverse events (TEAEs), vital signs, ECG parameters and suicidal ideation and behaviours
  - Evidence of the *maintenance of effect* which may be assessed via randomized withdrawal design

1. EMA, 2010. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095686.pdf (Accessed 17 January 2014)

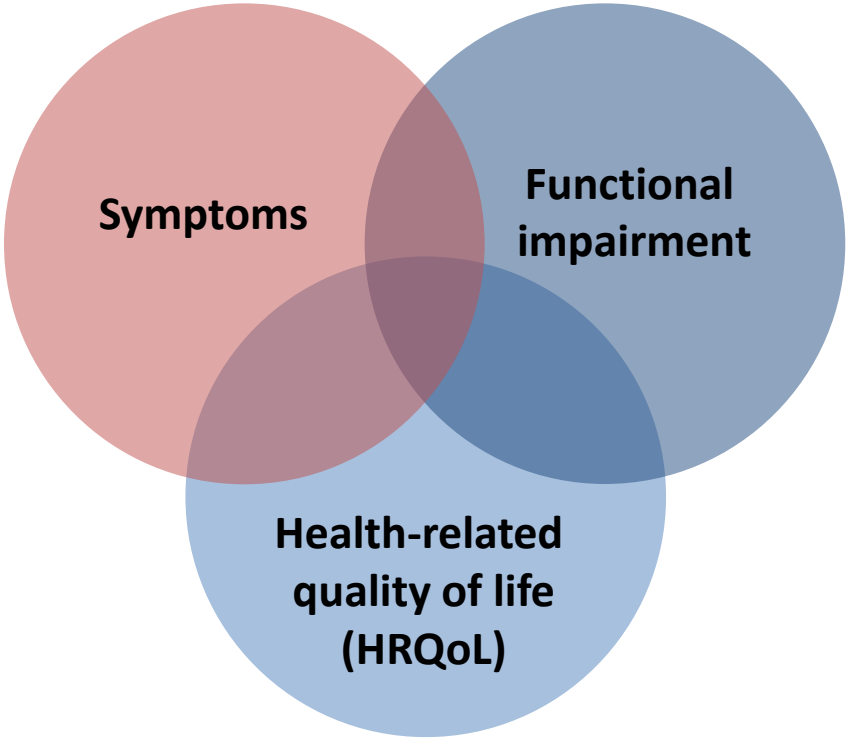
ADHD, attention-deficit/hyperactivity disorder; EMA, European Medicines Agency

The effects of ADHD on an individual's life extend beyond symptoms

Subject of next presentation (by César Soutullo)

Defined in diagnostic criteria

- Hyperactivity/ impulsivity
- Inattention



Also required for diagnosis

- Social
- Academic
- Occupational

The impact of disease on an individual's quality of life in multiple domains

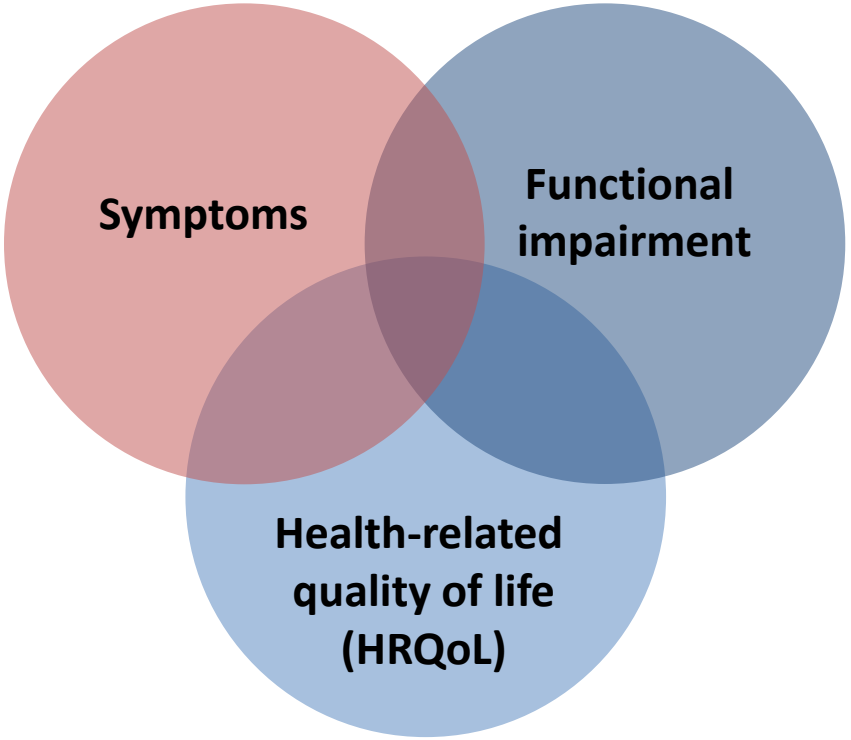
Coghill D *Eur Neuropsychopharmacol* 2011;21:571-83.

The effects of ADHD on an individual's life extend beyond symptoms

Defined in diagnostic criteria

- Hyperactivity/ impulsivity
- Inattention

Symptoms do not capture the range of outcomes and impact of ADHD



Also required for diagnosis

- Social
- Academic
- Occupational

Impact of behaviour on daily life is the major motivation for seeking treatment

The impact of disease on an individual's quality of life in multiple domains

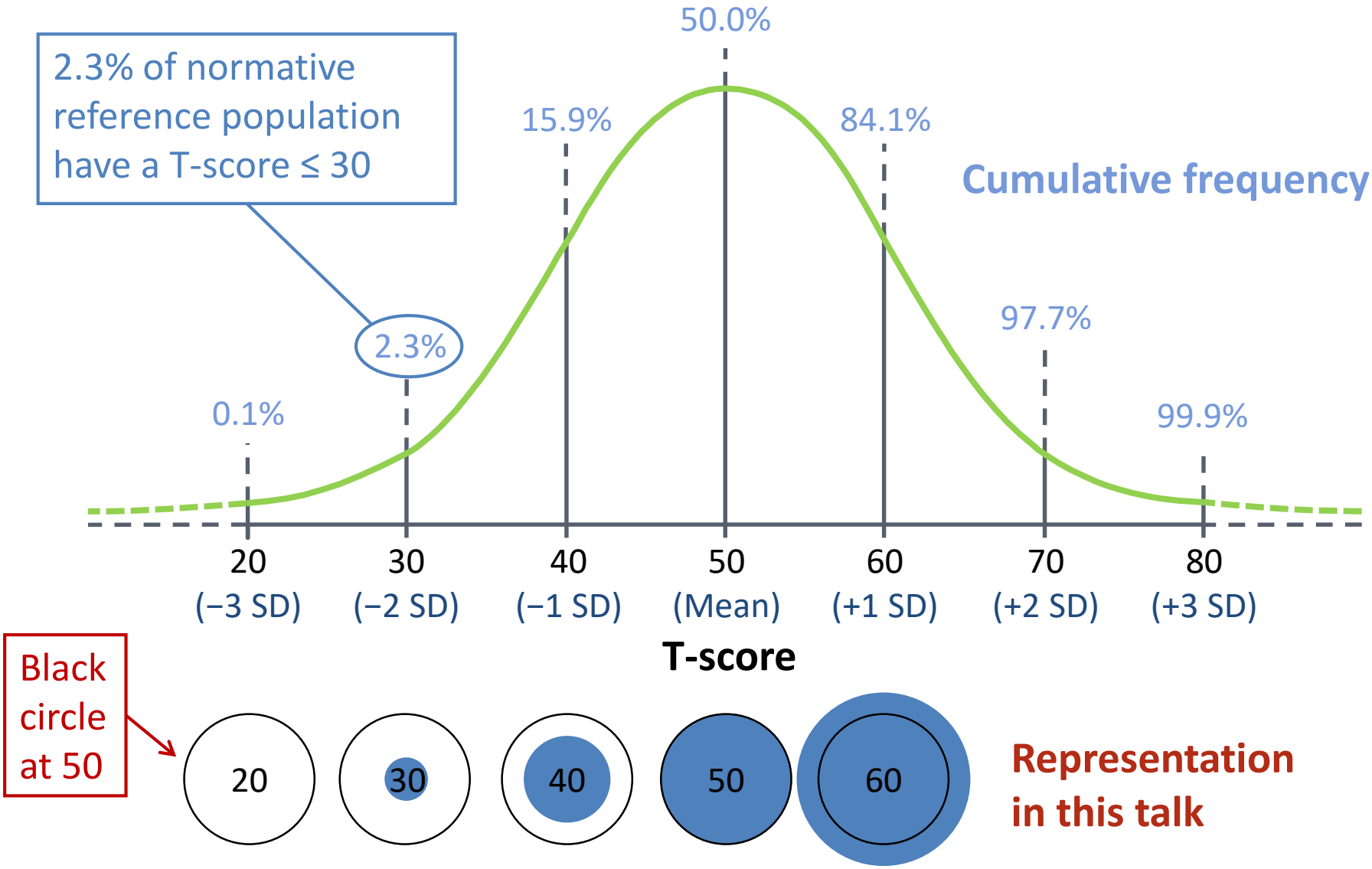
Coghill D *Eur Neuropsychopharmacol* 2011;21:571-83.

Child Health and Illness Profile – Child Edition: Parent Report Form (CHIP-CE:PRF)

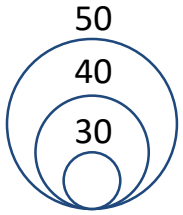
- Questionnaire (76 items) completed by parents
- Five domains and 12 associated subdomains

Domain (number of items)	Subdomains (number of items)		
Achievement (10)	Academic Performance (5)	Peer Relations (5)	
Risk Avoidance (14)	Individual Risk Avoidance (4)	Threats to Achievement (10)	
Resilience (19)	Family Involvement (8)	Physical Activity (6)	Social Problem-Solving (5)
Satisfaction (11)	Satisfaction with Health (7)	Satisfaction with Self (4)	
Comfort (22)	Physical Comfort (9)	Emotional Comfort (9)	Restricted Activity (4)

Interpreting T-scores: normal distribution, mean = 50 and standard deviation (SD) = 10



Pretreatment mean domain T-scores in three ADHD study populations and controls



	LDX EU Studies n=262	ADORE Study n=1477	Pooled ATX studies n=793	Diabetes Coghill & Hodgkins ECAP 2016	Control Coghill & Hodgkins ECAP 2016
Achievement	30.2	30.2	30.5	49.7	48.6
Risk Avoidance	32.3	29.9	30.2	50.0	50.5
Resilience	36.8	36.0	36.0	45.3	44.6
Satisfaction	35.5	32.8	34.4	45.5	42.8
Comfort	44.5	42.5	43.7	50.8	53.5

No statistical comparisons between these studies have been performed

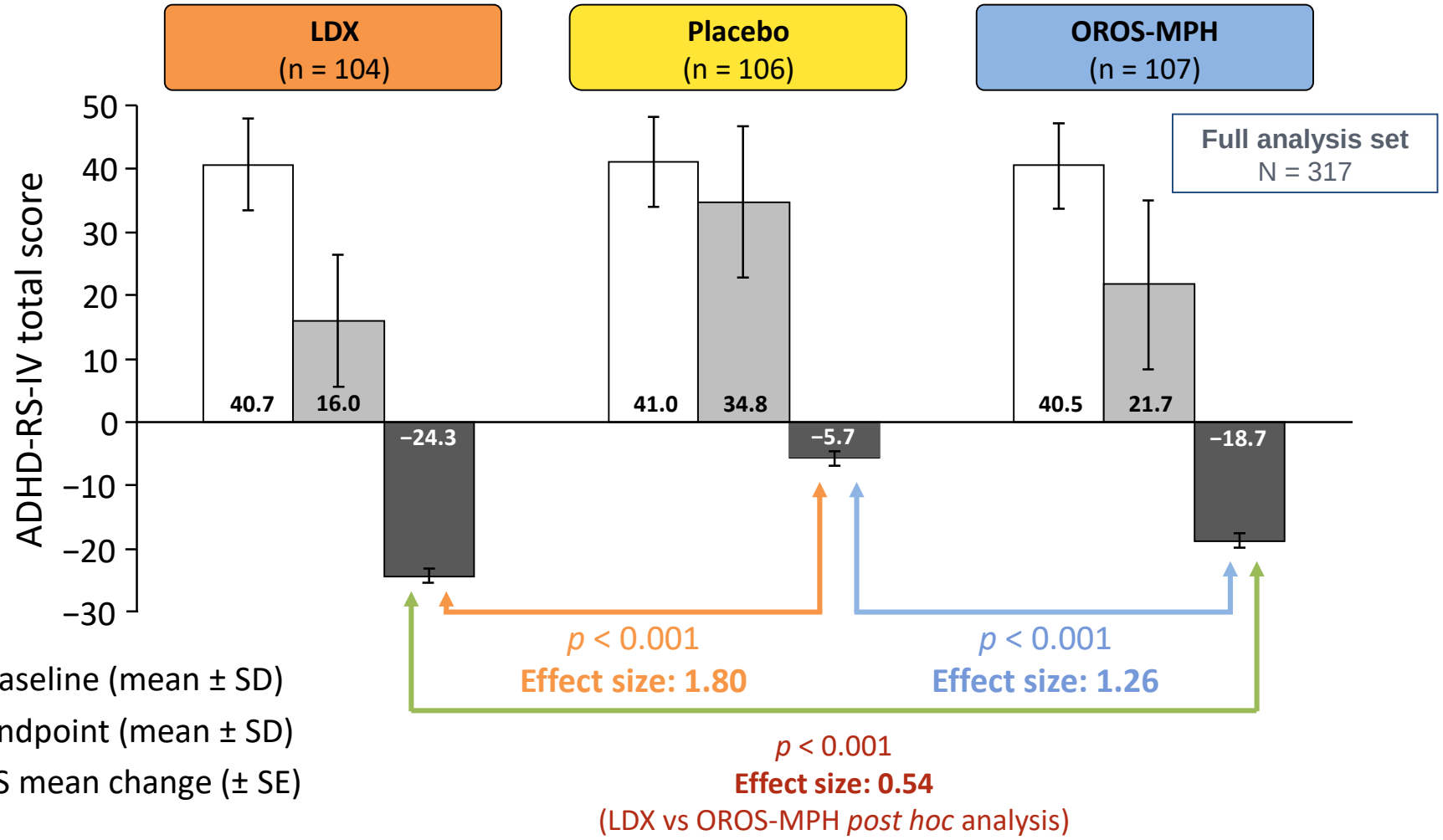
ATX, atomoxetine

European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/ hyperactivity disorder

European Neuropsychopharmacology (2013) 23, 1208-1218

David Coghill[a,*], Tobias Banaschewski[b], Michel Lecendreux[c], Cesar Soutullo[d], Mats Johnson[e], Alessandro Zuddas[f], Colleen Anderson[g], Richard Civil[g], Nicholas Higgins[g], Andrew Lyne[h], Liza Squires[g]

p-values and effect sizes from an ANCOVA: change in ADHD-RS-IV total score from baseline to endpoint



European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/ hyperactivity disorder

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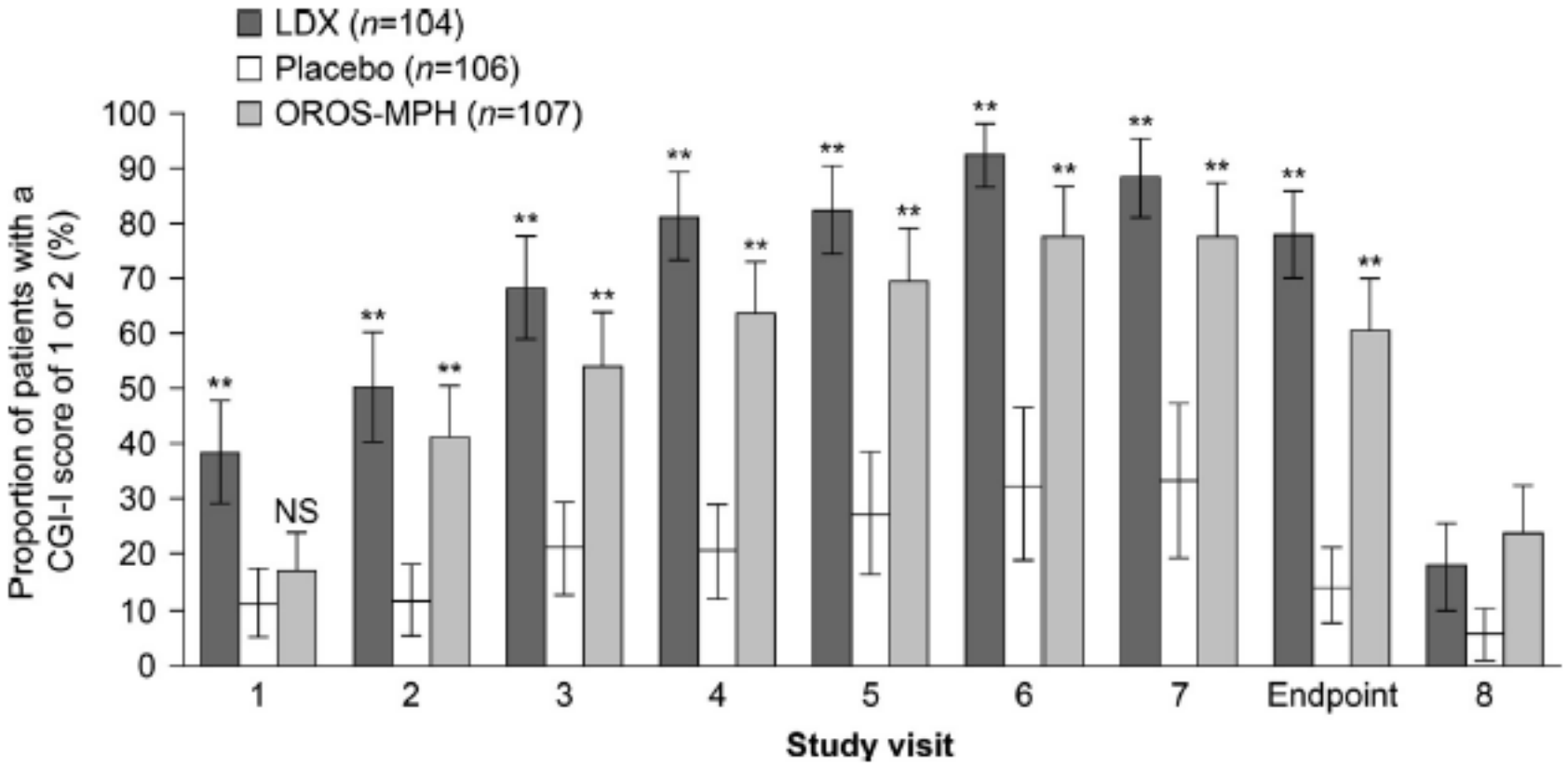
David Coghill[a,*], Tobias Banaschewski[b], Michel Lecendreux[c], Cesar Soutullo[d], Mats Johnson[e], Alessandro Zuddas[f], Colleen Anderson[g], Richard Civil[g], Nicholas Higgins[g], Andrew Lyne[h], Liza Squires[g]

Proportion (%) of CGI-I score of 1 or 2



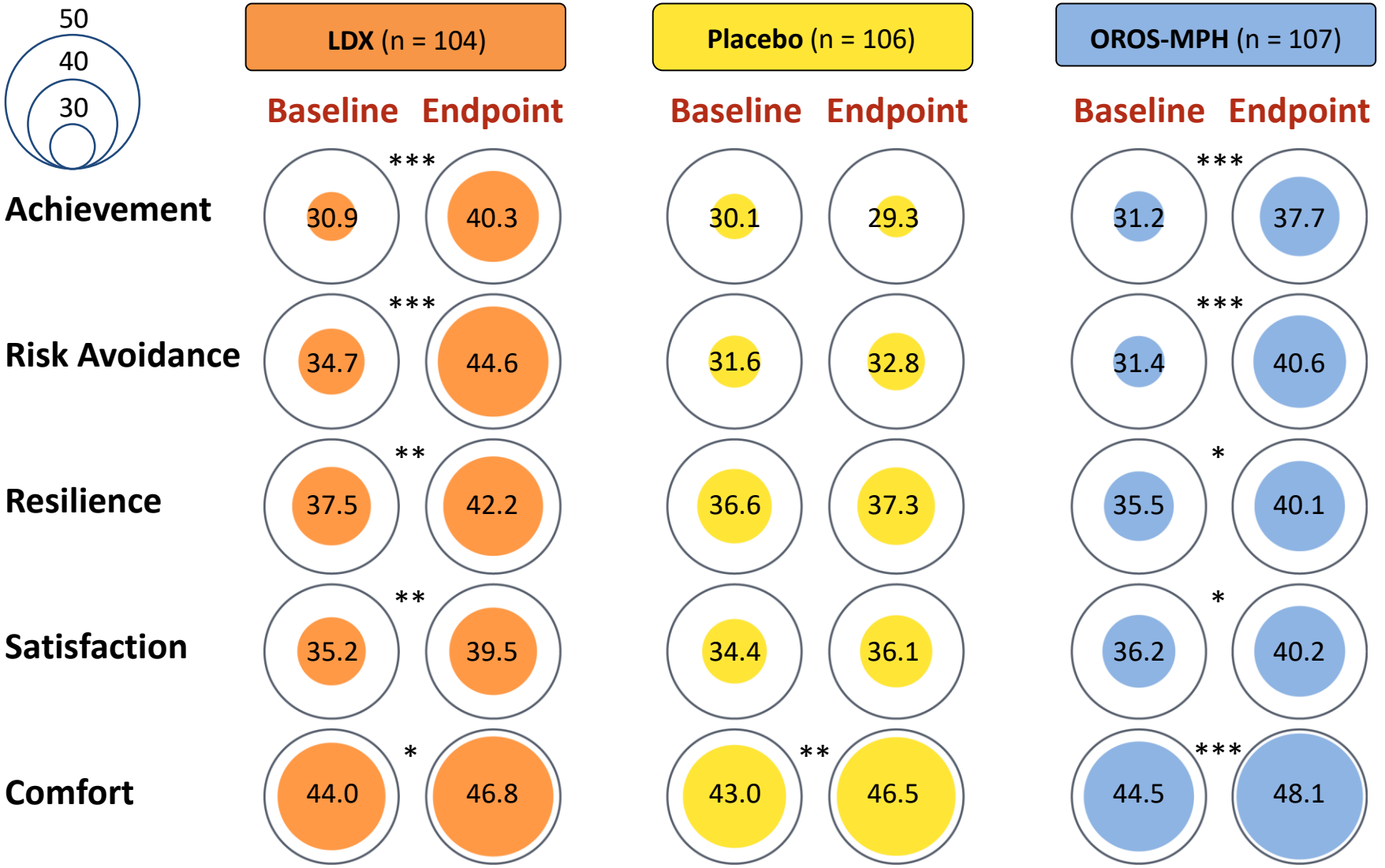
Health-Related Quality of Life and Functional Outcomes from a Randomized, Controlled Study of Lisdexamfetamine Dimesylate in Children and Adolescents with Attention Deficit Hyperactivity Disorder

Tobias Banaschewski · César Soutullo · Michel Lecendreux · Mats Johnson · Alessandro Zuddas · Paul Hodgkins · Ben Adeyi · Liza A. Squires · David Coghill

CNS Drugs (2013) 27:829–840

change from baseline to endpoint

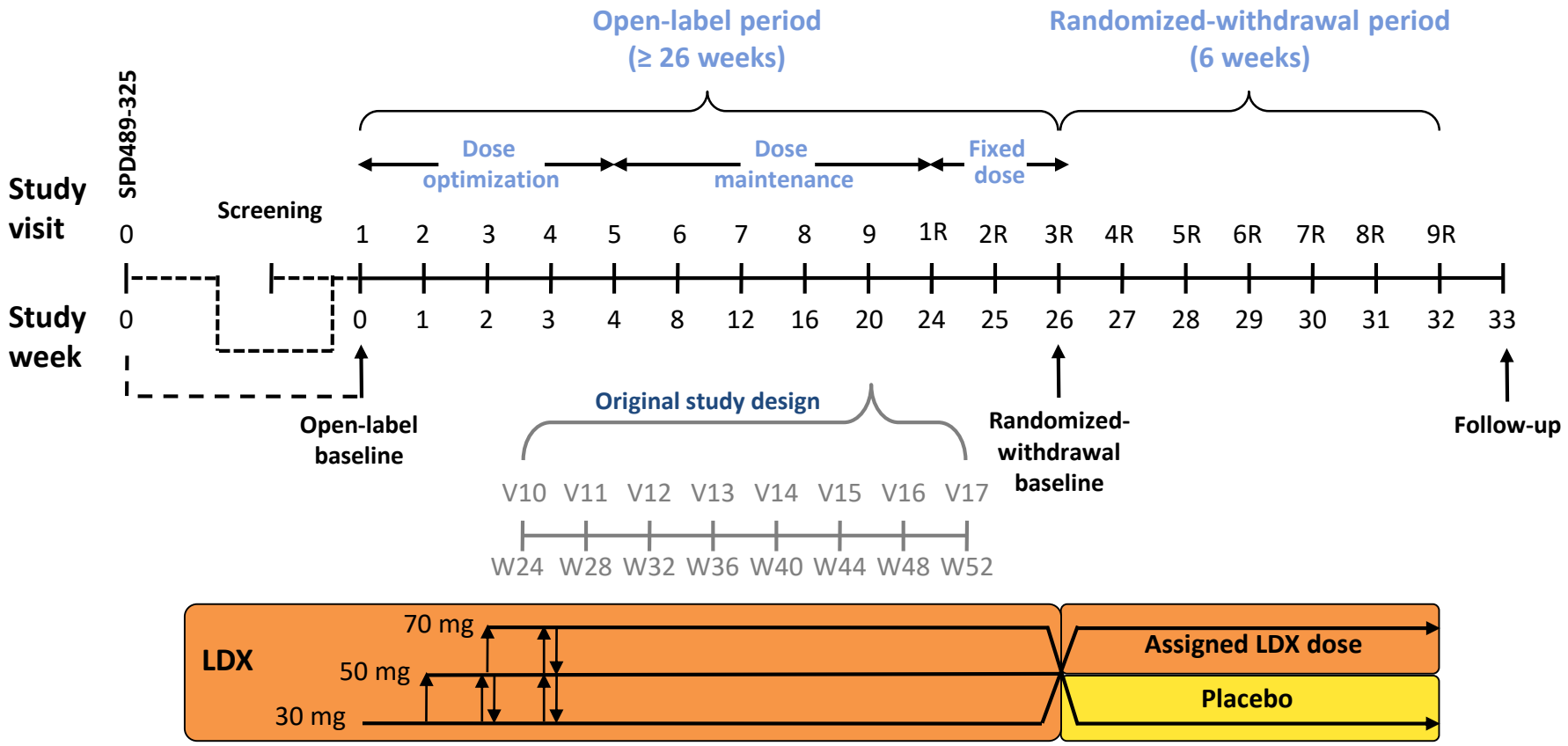
$^{***}p < 0.001$;
$^{**}p < 0.01$;
$^{*}p < 0.05$,



Maintenance of Efficacy of Lisdexamfetamine Dimesylate in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Randomized-Withdrawal Study Design

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 53 NUMBER 6 JUNE 2014

David R. Coghill, MD, FRCPsych, MBChB, Tobias Banaschewski, MD, Michel Lecendreux, MD, Mats Johnson, MD, Alessandro Zuddas, MD, Colleen S. Anderson, MEd, Richard Civil, MD, Matthew Dauphin, MS, Nicholas Higgins, BS, Andrew Lyne, MSc, CStat, Maria Gasior, MD, PhD, Liza A. Squires, MD



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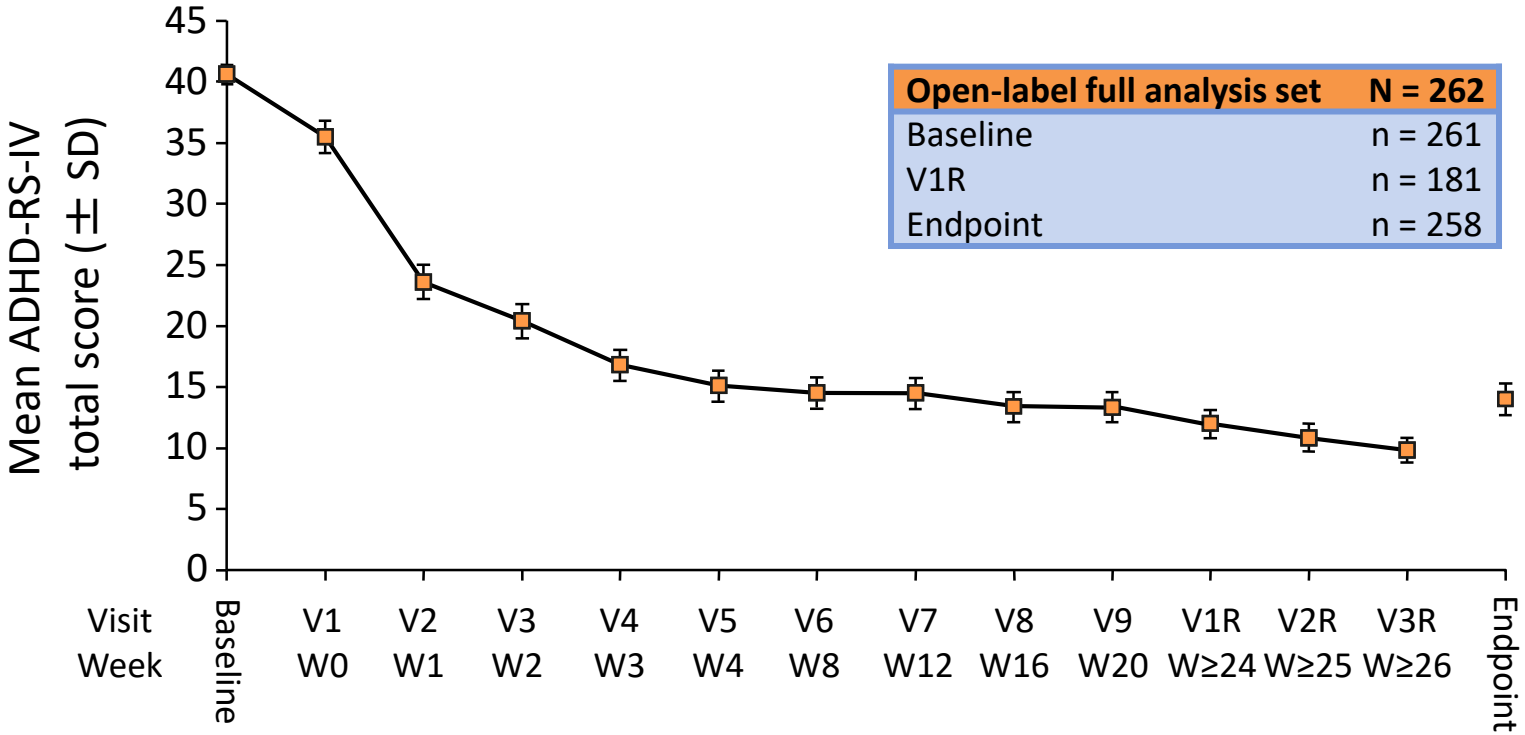
ADHD-RS-IV total score during the open-label period



Open-label full analysis set	N = 262
Baseline	n = 261
V1R	n = 181
Endpoint	n = 258

- At open-label endpoint,[a] the mean change (SD) from baseline in ADHD-RS-IV total score was –26.6 (11.4)

[a]Defined as the last valid assessment obtained while on investigational product, after visit 1 and up to and including visit 3R (or up to and including visit 17 for patients who continued past visit 9 but did not enter the fixed-dose period)

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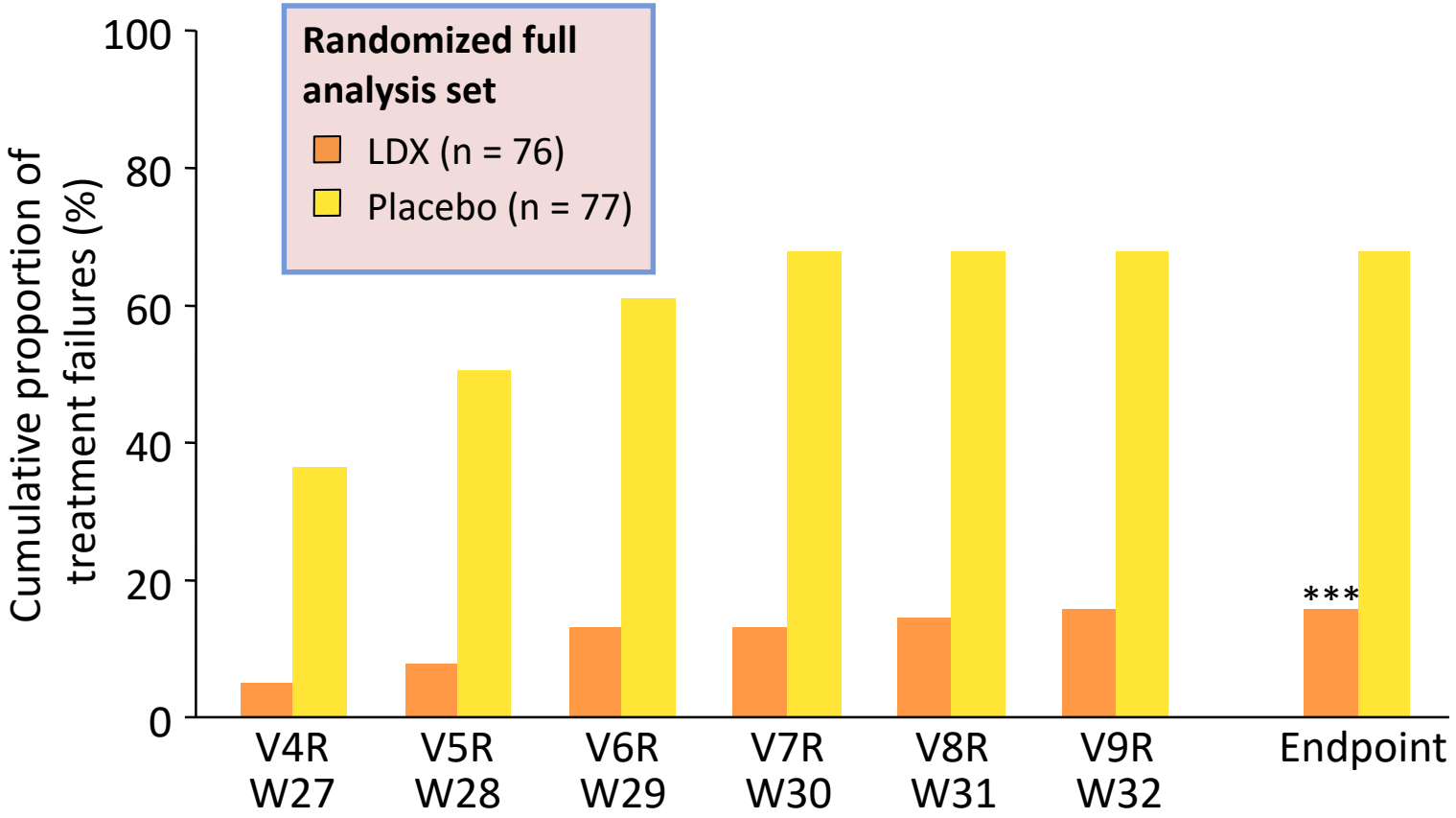


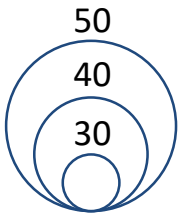
***$p < 0.001$ active drug versus placebo

≥ 50% increase in ADHD-RS-IV total score and a ≥ 2 point increase in Clinical Global Impressions-Severity rating relative to visit 3R. Endpoint was the last on-treatment, post-baseline visit of the randomized-withdrawal period (V4R–V9R) with a non-missing assessment

Health-Related Quality of Life and Functional Outcomes from a Randomized-Withdrawal Study of Long-Term Lisdexamfetamine Dimesylate Treatment in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Tobias Banaschewski · Mats Johnson · Michel Lecendreux · Alessandro Zuddas · Ben Adeyi · Paul Hodgkins · Liza A. Squires · David R. Coghill

CNS Drugs (2014) 28:1191–1203



Open label (≤ 26 weeks)

LDX (n = 262)

Randomized withdrawal (6 weeks)

LDX (n = 76)

Placebo (n = 77)

	Open label (≤ 26 weeks) LDX (n = 262)		Randomized withdrawal (6 weeks) LDX (n = 76)		Randomized withdrawal (6 weeks) Placebo (n = 77)	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Achievement	30.2	38.9	39.6	40.1	41.2	35.3
Risk Avoidance	32.3	44.1	45.8	47.5	46.8	41.3
Resilience	36.8	40.5	42.0	43.3	42.6	40.2
Satisfaction	35.5	40.3	41.9	44.9	43.3	39.3
Comfort	44.5	49.4	51.0	51.1	51.1	48.5

Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder

David R. Coghill[1,2,3] · Tobias Banaschewski[4] · César Soutullo[5] · Matthew G. Cottingham[6] · Alessandro Zuddas[7]

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-017-0986-y

Table 4 Summary of treatment effect sizes in children and adolescents

Study and instrument	Treatment	Effect sizes of active treatment versus placebo[a]						
Studies with HRQoL outcomes		*Symptoms*	*HRQoL*					
CHIP-CE:PRF[c] (parent-rated)		ADHD-RS-IV (or SNAP-IV ADHD)[g]	Achievement	Risk Avoidance	Resilience	Satisfaction	Comfort	
Banaschewski *et al.* 2013 [15]	LDX	1.80***	1.28***	1.08***	0.42**	0.37*	0.00[NS]	
	OROS-MPH	1.26***	0.91***	0.95***	0.40*	0.35*	0.18[NS]	
Banaschewski et al. 2014 [14]	*LDX continuation*	*1.49****	*0.70****	*0.83****	*0.28[NS]*	*0.64****	*0.35[NS]*	
Svanborg *et al.* 2009 [90, 91][b]	ATX	1.20***	0.53*	0.41*	0.03[NS]	–0.12[NS]	–0.17[NS]	
Dell'Agnello *et al.* 2009 [37][b,h]	ATX	0.73***	0.31[NS] across all domains; significant in Risk Avoidance* only					
Escobar *et al.* 2009 [42]	ATX	0.82*** [67]	0.29*	0.56***	0.11[NS]	0.03[NS]	0.16[NS]	
CHIP-CE:SRF/AE[c] (self-rated)		ADHD-RS-IV	Achievement	Risk Avoidance	Resilience	Satisfaction	Comfort	
Escobar *et al.* 2009 [42]	ATX	0.82*** [67]	0.09[NS]	0.39**	0.02[NS]	0.14[NS]	0.10[NS]	
CHQ-PF50[c,d] (parent-rated)		ADHD-RS-IV	Psychosocial summary score			Physical summary score		
Brown *et al.* 2006 [17]	ATX	0.62**	0.32[NS]			NR		
Michelson *et al.* 2001 [66][b]	ATX[e]	0.33 to 0.62*	0.47 to 0.87*			–0.12 to –0.29[NS]		
Michelson et al. 2004 [65][b]	*ATX continuation*	*0.43****	*0.29**			*NR*		
Newcorn *et al.* 2008 [68][b,f]	ATX	0.60**	0.37*			NR		
	OROS-MPH	0.80***	0.54*			NR		
JTJA (self-rated)		ADHD-RS-IV	Total score					
Svanborg *et al.* 2009 [90, 91][b]	ATX	1.20***	0.10[NS]					
KINDL-R (parent-rated)		SNAP-IV ADHD	Physical Well-Being [94]	Emotional Well-Being	Self-Esteem	Family	Friends	School	Total score
Wehmeier *et al.* 2011 [94]	ATX	0.72*** [38]	–0.39*	0.32*	0.60***	0.40*	0.39*	0.25[NS]	0.38*

Domande?

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