XII Convegno Nazionale sulla Qualità della Vita per le disabilità

Il disturbo dello spettro dell'autismo: stato dell'arte

Milano, 12 Settembre 2017

Il trattamento farmacologico nell'autismo

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AO Brotzu

Financial Disclosure (2014-2017)

Research grants

- Shire
- Vifor
- Roche
- Lundbeck
- (Janssen)
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- AIFA-Farmacovigilanza (Italian Medication Regulatory Agency),
- Health Secretary Sardinia Region

Royalties

Giunti.OS, Oxford University Press

Speaker or advisory relationship with:

Angelini, Lilly, Otsuka, Shire, Takeda, Vifor.

Member of Data Safety Monitory Boards

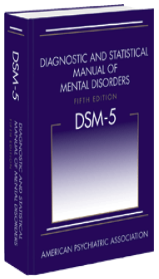
Otsuka, Lundbeck,

Università degli Studi di Cagliari

Il trattamento farmacologico nell'autismo

- L'autismo è un disturbo eterogeneo
- I farmaci sono frequentemente utilizzati: relativamente efficaci sui sintomi associati ma non sui sintoni *core*
- Autismo è il maggior *unmet need* in psicofarmacologia dello sviluppo
- Nuovi meccanismi, nuove metodologie

Autism Spectrum Disorder



Social Communicative Behaviors

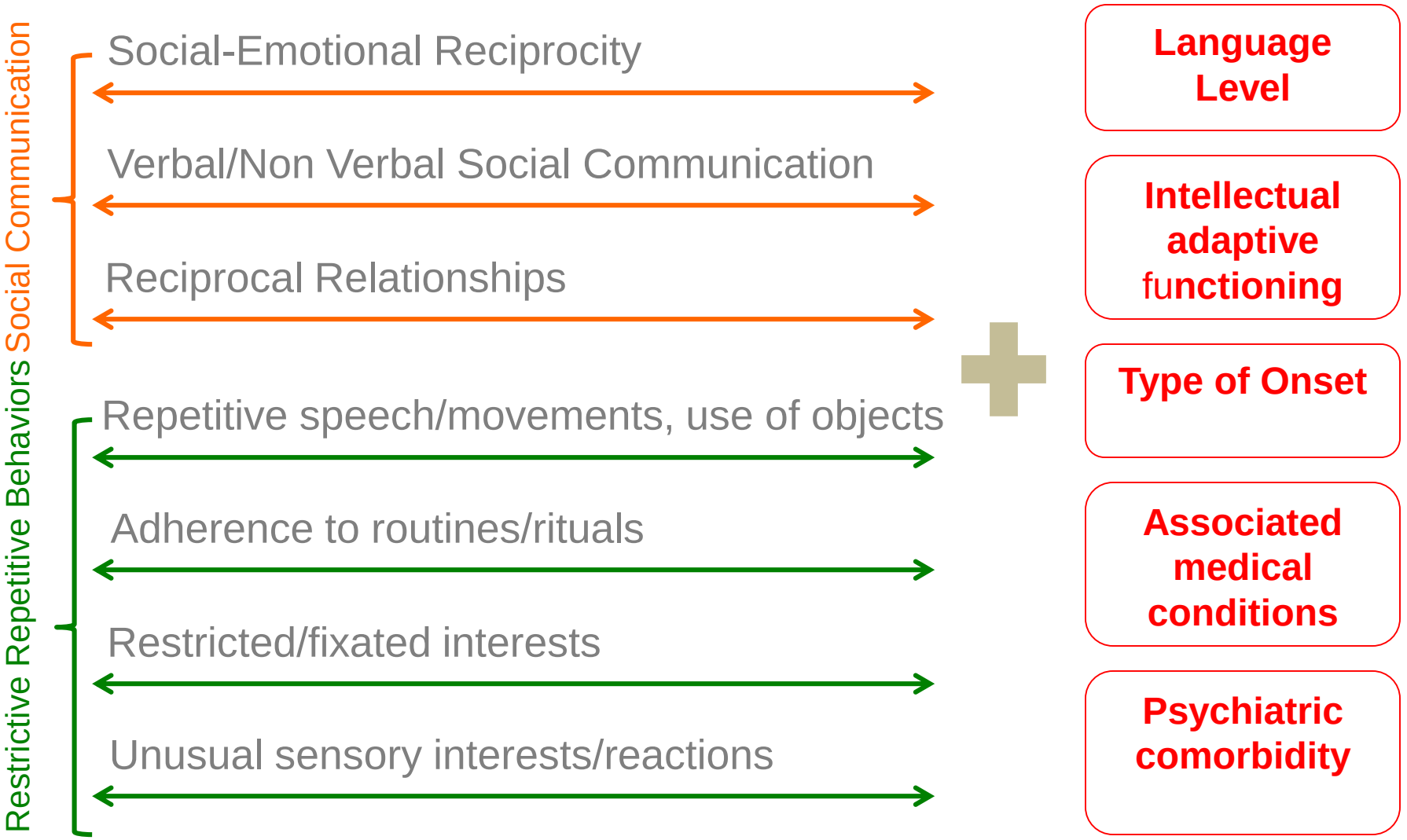
- Social-Emotional Reciprocity
- Verbal/Non Verbal Social Communication
- Reciprocal Relationships

Restrictive Repetitive Behaviors/Interests

- Repetitive speech/movements, use of objects
- Adherence to routines/rituals
- Restricted/fixated interests
- Unusual sensory interests/reactions

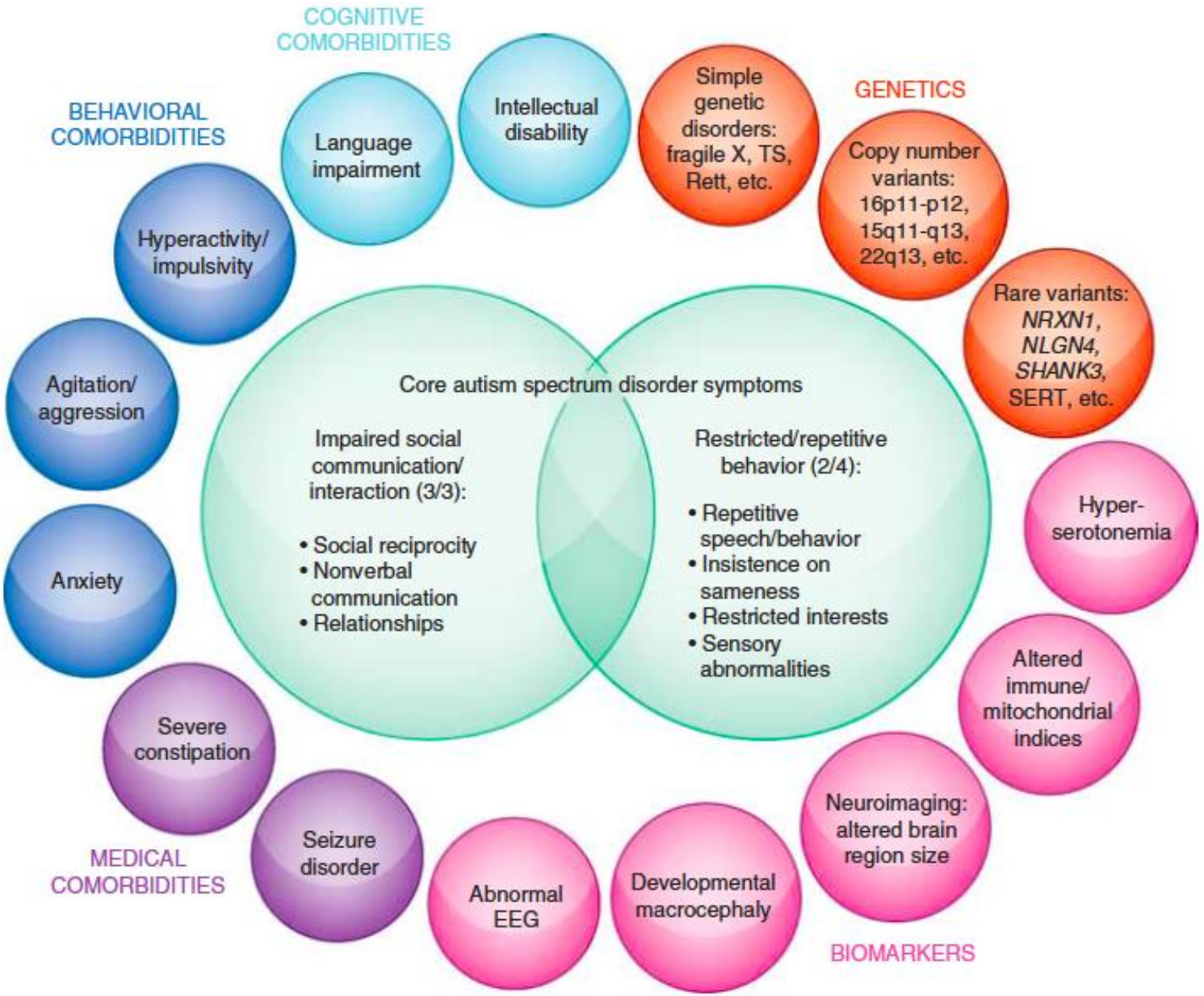
DSM 5; 2013

Highly Heterogeneous Presentation



DSM 5; 2013

Autism Spectrum Disorders



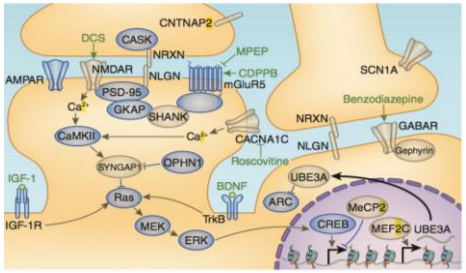
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

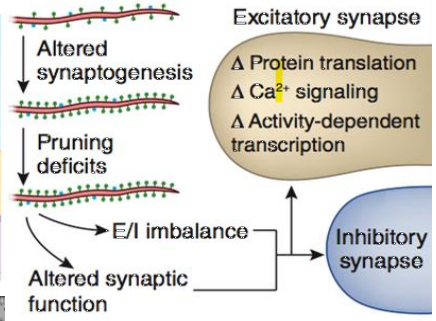
NUMBER OF CHILDREN IDENTIFIED WITH ASD

CDC 2016

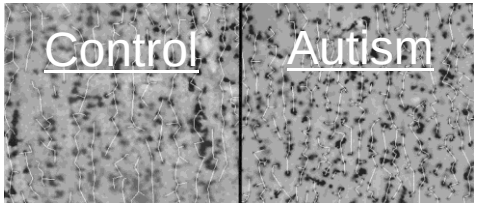
ASD: Dysconnection Syndrome

Microscopic



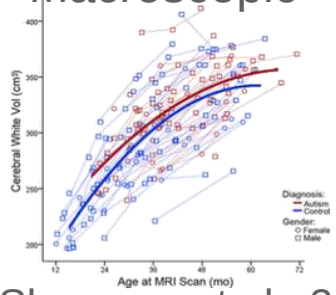


de la Torre-Ubieta, 2016

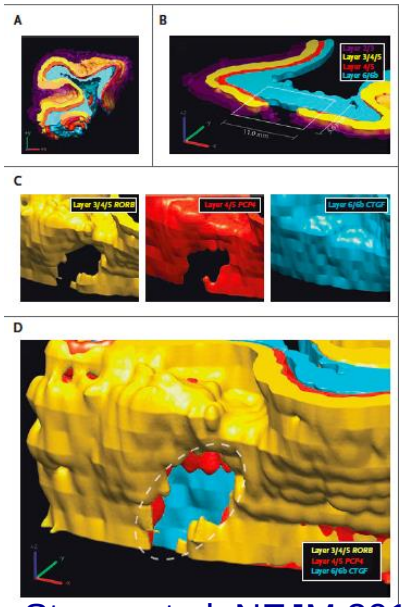


Casanova et al., 2002

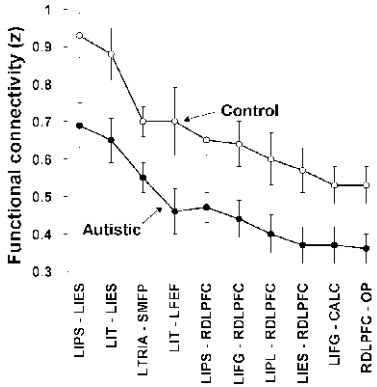
Macroscopic



Shumann et al., 2010



Stoner et al. NEJM 2014



Just et al., 2004

- **Genetics**

  Synaptic signaling genes

  (e.g., Shank family, CNTNAP2,…)

- **Anatomy** (postmortem)

  Minicolumns: more, smaller, dispersed

  Microdysplasias

Brain imaging

Awry white matter trajectories

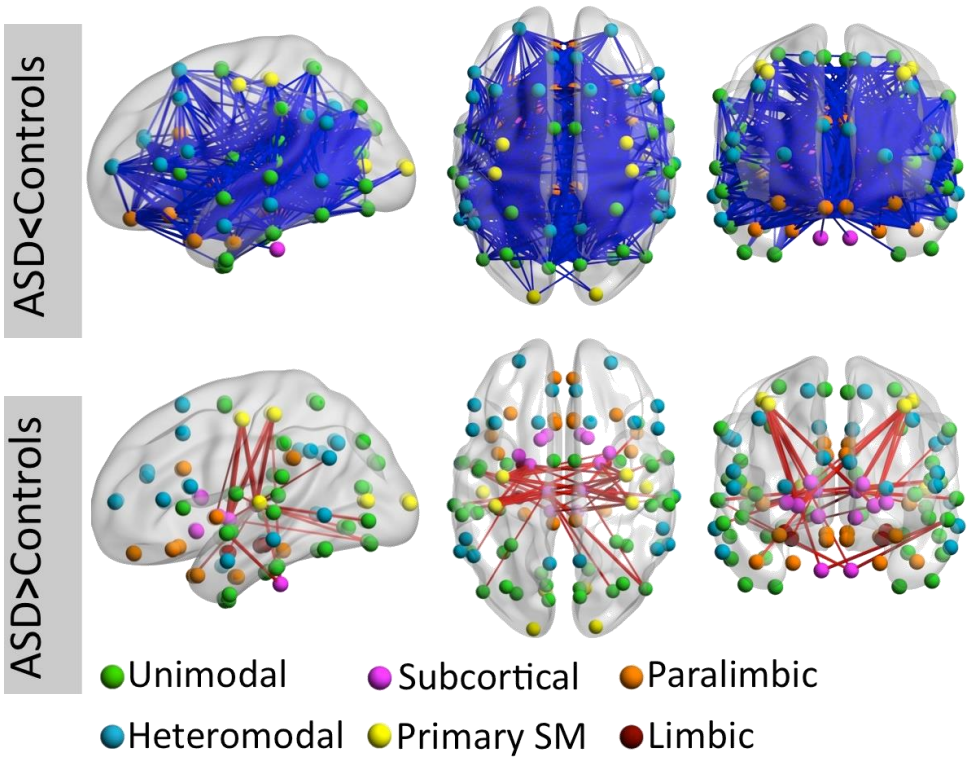
Decreased functional connectivity

Molecular Psychiatry (2013), 1–9

www.nature.com/mp

ORIGINAL ARTICLE

The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism



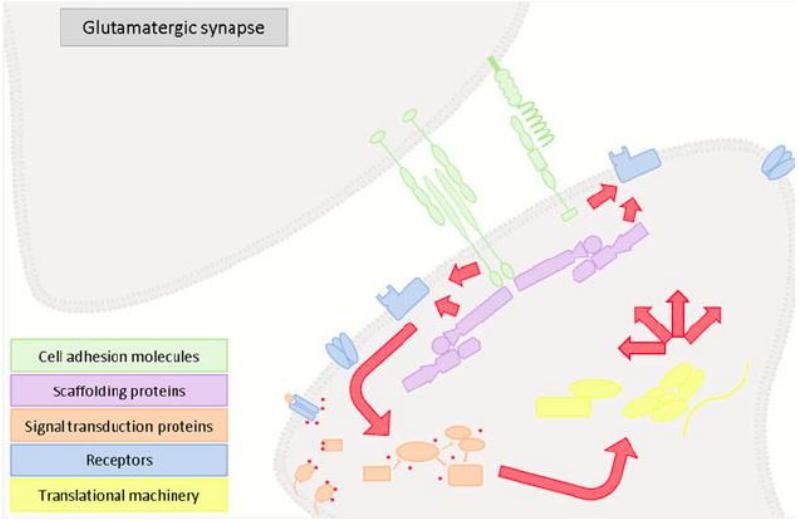
- Reconciling seemingly conflicting evidence of ASD Hypo- and Hyper- connectivity
- Both exist
- Vary with the functional territory involved

Total N=763 (ASD=360, Controls= 403); males only

Di Martino et al., 2014

Trans-membrane proteins/

- Cell adesion/ cell communication
- Neural migration
- Axon outgrowth & guidance
- Synaptogeesis
- Synaptic stability
- Dendritic aborization
- Spine dynamics



- *Neurorexins* *-NRXN1, NRXN3, NRXN4X*
  Contactin-Associted protein–like 2- (Cspr2)

- *Neuroligins*: Cadherin (CDH)
  Protocadherin (PCDH)
  Contactine (CNCTN)

Cyliation genes: AHI 1, DISC

Scaffolding proteins:

- SHANK 1, SHANK 2, SHANK 2
- SAP 97 (DLG1); PSD 95 (DLG4); SAPAP 2 (DLGAP 2)

Kleijer et al. *Neuropsychopharmacology* 2014

Intracellular trasmission

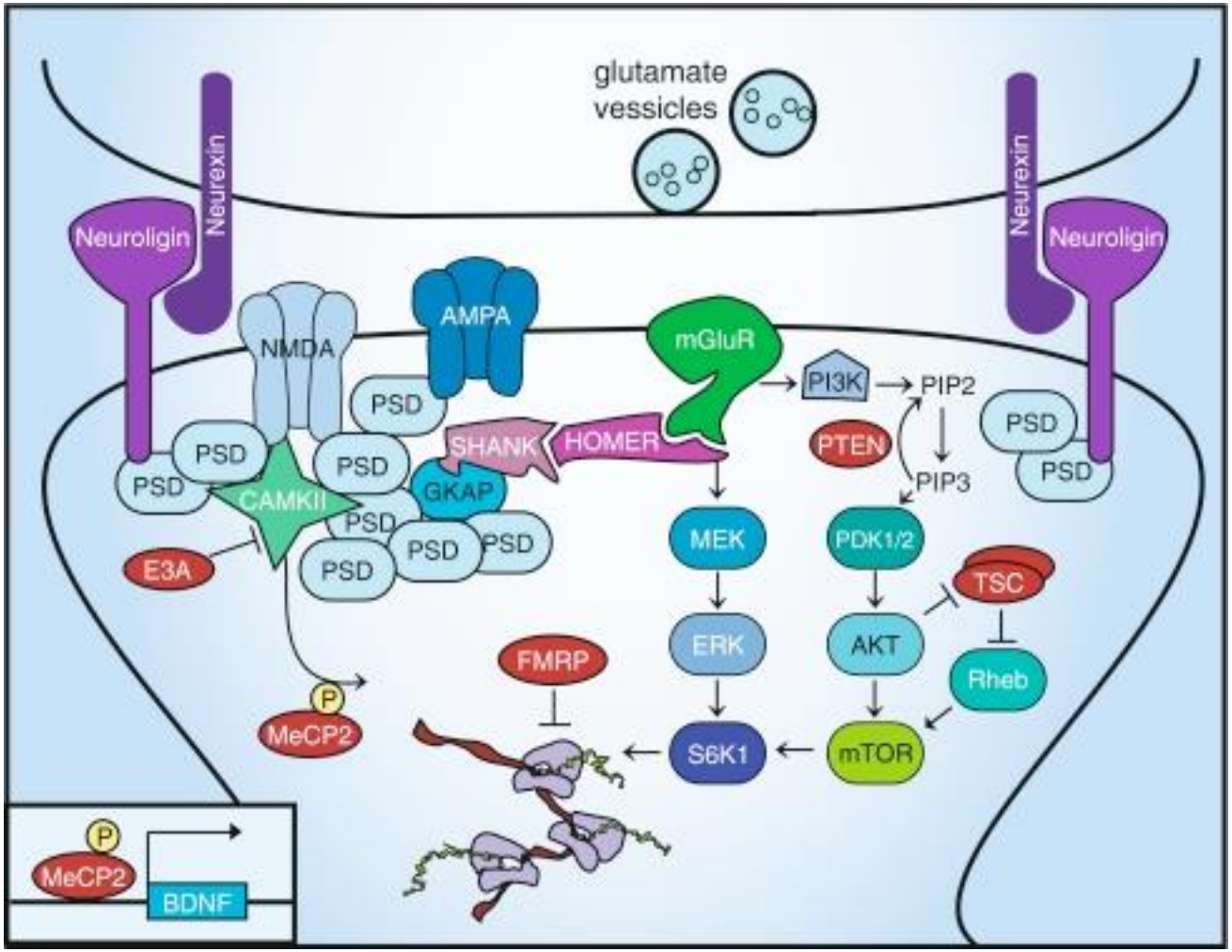
- PTEN (Phosfatase- TENSine homologus)
- TSC 1 , TSC 2
- FMR 1

Intracellular dinamics

- DISC

Gene expression, epigentic coding, gene transcription, RNA processing

- MECP 2 (methyl .CpG binding Protein)
- FMR 1 (FraX mental Retardation)


glutamate
vessicles
Neurexin
Neuroligin
Neurexin
Neuroligin
AMPA
NMDA
mGluR
PI3K
PIP2
PIP3
PTEN
PSD
SHANK
HOMER
GKAP
CAMKII
E3A
MEK
ERK
PDK1/2
AKT
TSC
Rheb
mTOR
S6K1
FMRP
P
MeCP2
P
MeCP2
BDNF

The Variation of Psychopharmacological Prescription Rates for People With Autism Spectrum Disorder (ASD) in 30 Countries

Angel Y.S. Wong, Yingfen Hsia, Esther W. Chan, Declan G.M. Murphy, Emily Simonoff, Jan K. Buitelaar, and Ian C.K. Wong

Autism Research 7: 543–554, 2014

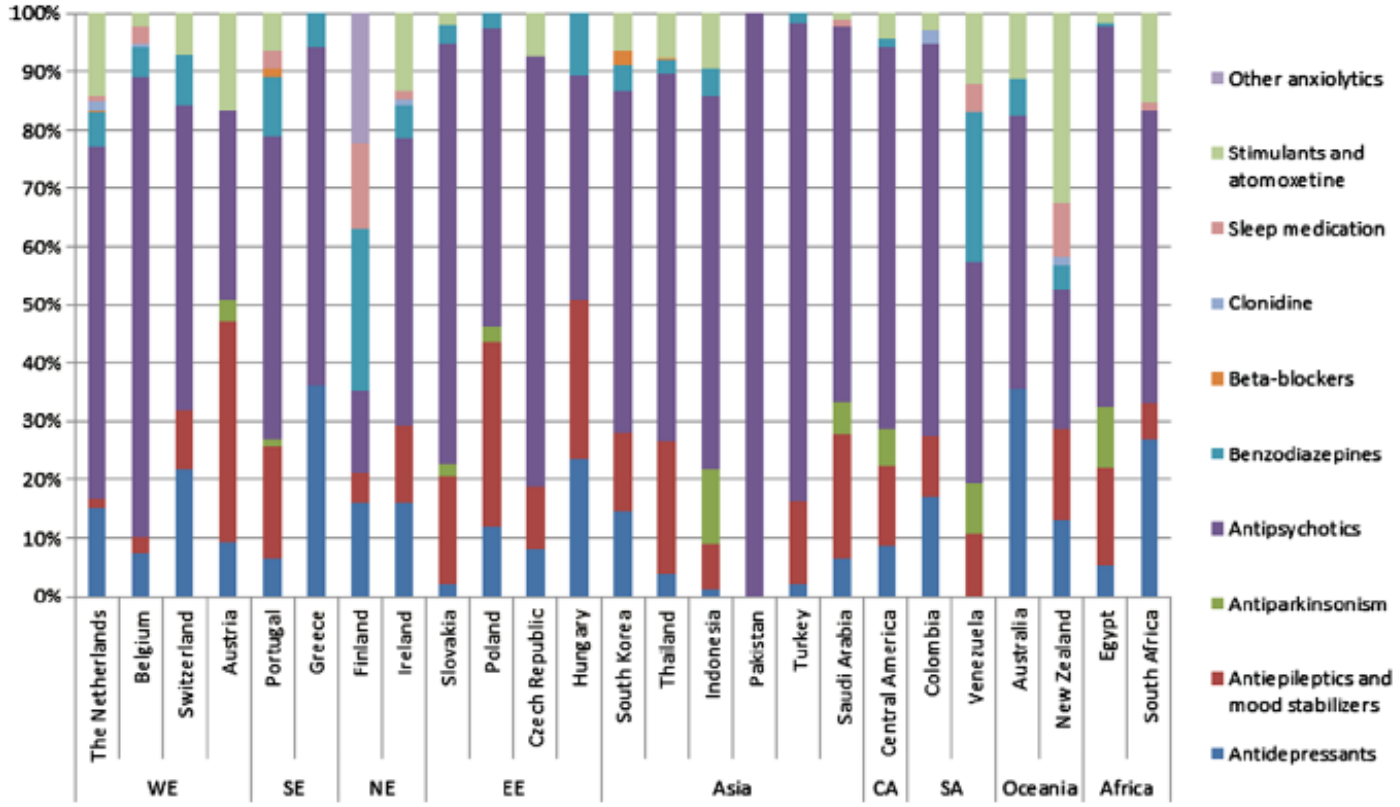


Figure 1. Percentage of different psychotropic drug classes for the treatment of autism spectrum disorder. WE, Western Europe; SE, Southern Europe; NE, Northern Europe; EE, Eastern Europe; CA, Central America; SA, South America.

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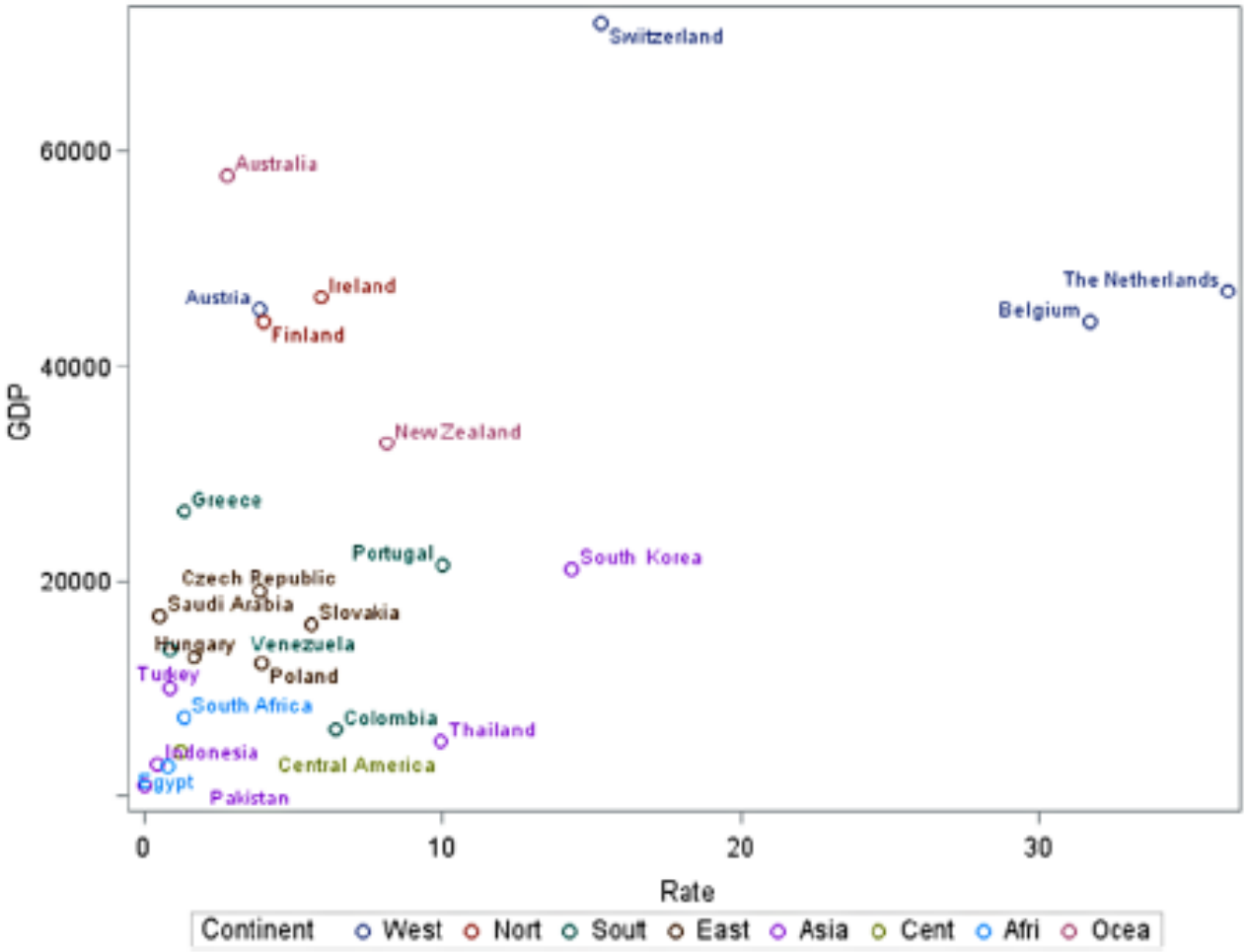

Acta Psychiatrica Scandinavica

Review

Use of psychotropic drugs in patients with autism spectrum disorders: a systematic review

Jobski et al 2016

Table 4. Prevalence of psychotropic drug use and commonly used drug classes*

	Number of studies	Number of patients	Median prevalence (%)	Minimum prevalence (%)	Maximum prevalence (%)
Psychotropic drugs	39	205 602	45.7	2.7	80
Studies predominantly including children†	18	86 595	41.9	2.7	80
Studies predominantly including adolescents‡	5	4413	42.5	30.5	45.7
Studies predominantly including adults§	4	1172	61.5	50.1	74.0
Other studies¶	12	113 422	51.5	12.8	66.3
Antipsychotic drugs	35	237 698	18.1	7.3	57.4
Studies predominantly including children†	15	120 478	16.6	8.4	57.4
Studies predominantly including adolescents‡	5	4413	16.8	12.2	18.1
Studies predominantly including adults§	6	1367	42.8	28.7	55.6
Other studies¶	9	111 440	27.5	7.3	41.0
Antidepressants	29	176 899	17.2	1.1	43
Studies predominantly including children†	13	60 393	12.2	6.2	32.1
Studies predominantly including adolescents‡	5	4413	21.7	6.1	23.8
Studies predominantly including adults§	3	778	35.7	25.6	43.0
Other studies¶	8	111 315	16.2	1.1	25.0
ADHD drugs/stimulants	32	187 703	16.6	6.2	52.4
Studies predominantly including children†	15	61 566	19.0	6.2	44.7
Studies predominantly including adolescents‡	5	4413	13.9	6.6	15.0
Studies predominantly including adults§	2	649	11.2	7.0	15.4
Other studies¶	10	121 075	20.5	6.4	52.4
Multiple psychotropic drugs	24	191 328	23.0	5.4	54.0
Studies predominantly including children†	10	75 975	21.5	9.0	34.6
Studies predominantly including adolescents‡	5	4413	21.6	8.5	25.5
Studies predominantly including adults§	4	1172	40.6	26.4	54.0
Other studies¶	5	109 768	11.1	5.4	28.3
	47	303 986			

J Autism Dev Disord (2017) 47:144–154
DOI 10.1007/s10803-016-2946-7

ORIGINAL PAPER

Psychotropic Medication Use among Insured Children with Autism Spectrum Disorder

Jeanne M. Madden[1,2] · Matthew D. Lakoma[2] · Frances L. Lynch[3] · Donna Rusinak[2,8] · Ashli A. Owen-Smith[4,5] · Karen J. Coleman[6] · Virginia P. Quinn[6] · Vincent M. Yau[7,9] · Yinge X. Qian[7] · Lisa A. Croen[7]

7901 ASD ; 79010 No-ASD
83% Male
23-17 y

Table 2 Prevalence psychotropic medication use and average months supplied by therapeutic class, for children with and without ASD in 2010

Therapeutic class	Percentage receiving any medication in class		Difference in likelihood of any use in year, ASD vs. no ASD		Average months supplied per user per year	
	Children with ASD (n = 7901)	Children with no ASD (n = 79,010)	Adjusted OR (95 % CI)	p value	Children with ASD and any use	Children with no ASD and any use
All psychiatric medications	48.47	7.7	11.44 (10.02,13.06)	<0.0001	18.3	9.3
All ADHD medications	30.24	5.13	8.44 (7.61, 9.37)	<0.0001	12.3	9.9
Stimulants	22.73	4.76	6.12 (5.51, 6.81)	<0.0001	11.5	9.4
Other ADHD[a]	12.35	0.84	17.53 (15.42,19.93)	<0.0001	9.0	7.1
Antipsychotics	20.50	0.64	40.50 (35.25,46.53)	<0.0001	10.5	7.2
2nd generation	20.30	0.60	42.58 (36.99,49.01)	<0.0001	10.4	7.4
1st generation	0.39	0.04	9.55 (5.85,15.60)	<0.0001	7.3	2.3
Antidepressants	17.83	1.42	13.65 (11.88,15.69)	<0.0001	9.5	6.7
All mood stabilizers	9.07	0.55	17.20 (14.77, 20.02)	<0.0001	11.7	9.3
Anticonvulsants	8.72	0.53	17.07 (14.67,19.88)	<0.0001	11.5	9.1
Lithium	0.58	0.03	19.80 (12.24,32.02)	<0.0001	9.5	10.4
Benzodiazepines	4.30	0.48	8.96 (7.68,10.46)	<0.0001	2.8	1.6
Anti-anxiety medications	3.00	1.16	2.62 (2.22, 3.10)	<0.0001	3.3	1.1
Hypnotics	0.20	0.02	(nonconvergent)	–	2.9	1.6

ASD cohort N = 7901; no-ASD cohort N = 79,010. Medication months supplied are added across all dispensings in class

[a]Other ADHD medications included alpha-2 adrenergic agonists and norepinephrine reuptake inhibitors (see online appendix). Logistic regression models controlled for SES (neighborhood education attainment and median household income quartile), age, sex, and health system site

J Autism Dev Disord (2017) 47:144–154
DOI 10.1007/s10803-016-2946-7

ORIGINAL PAPER

Psychotropic Medication Use among Insured Children with Autism Spectrum Disorder

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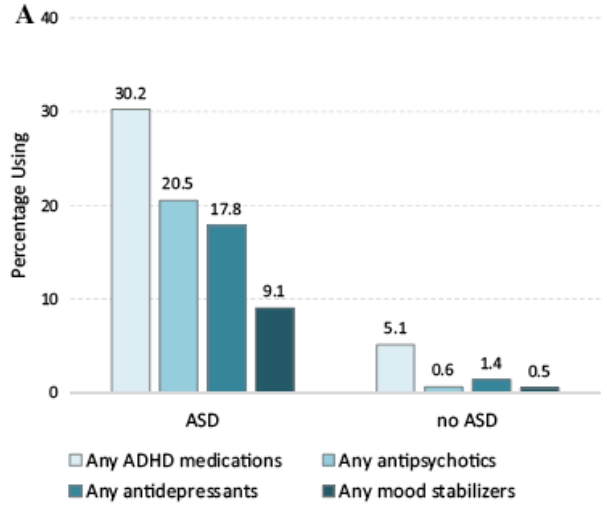
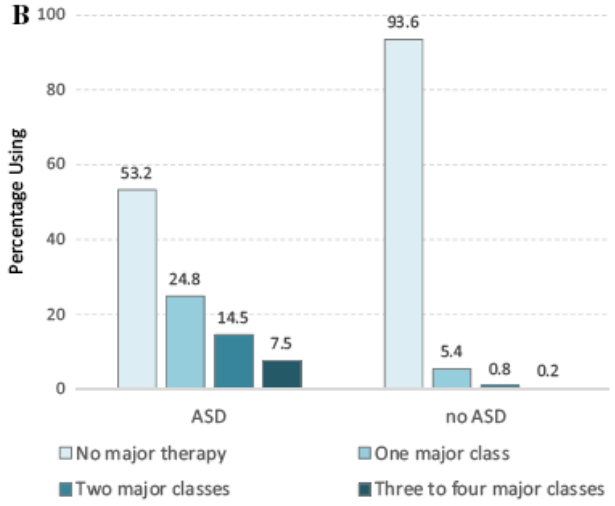
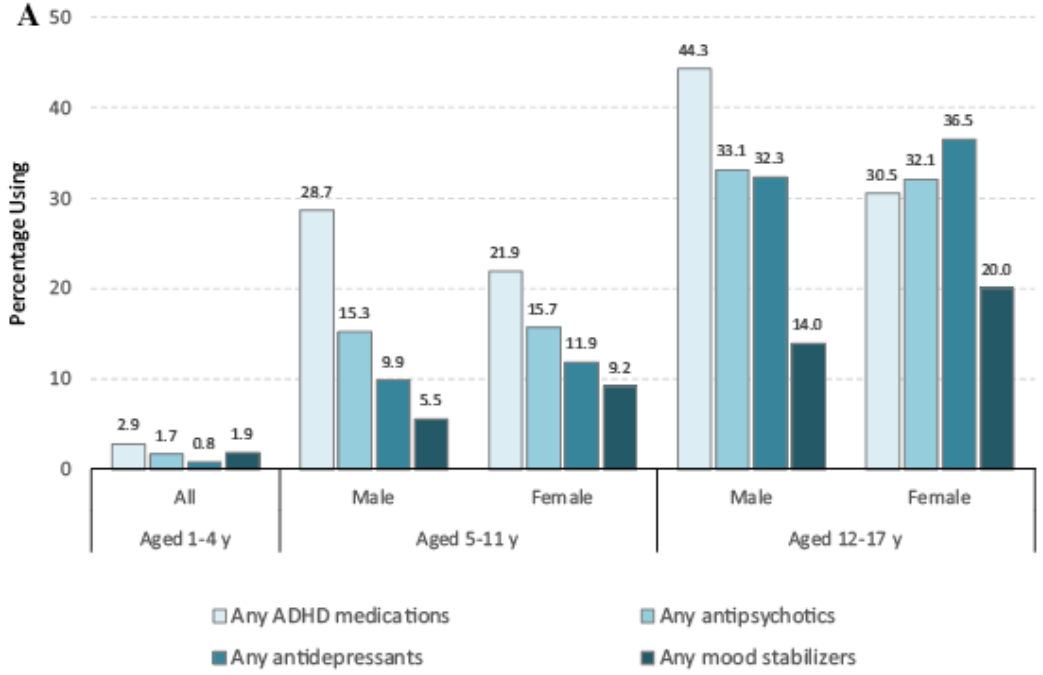


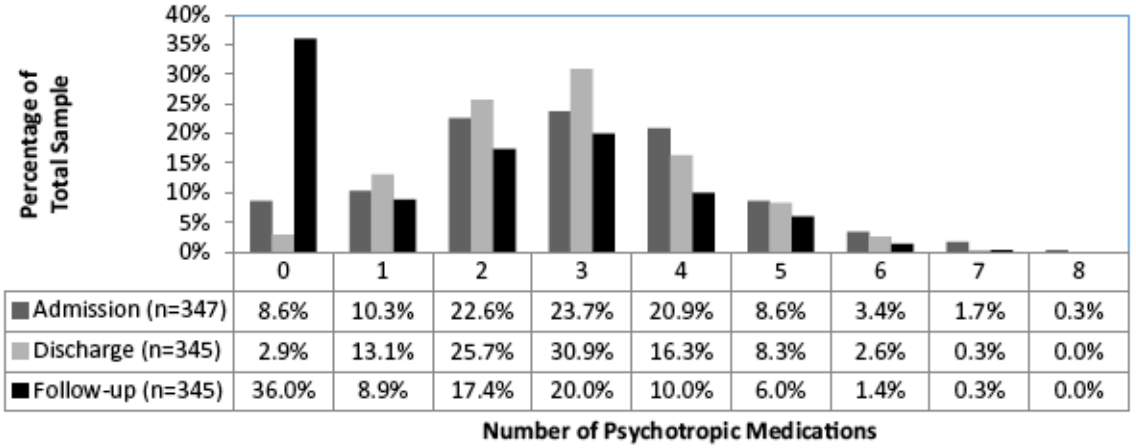




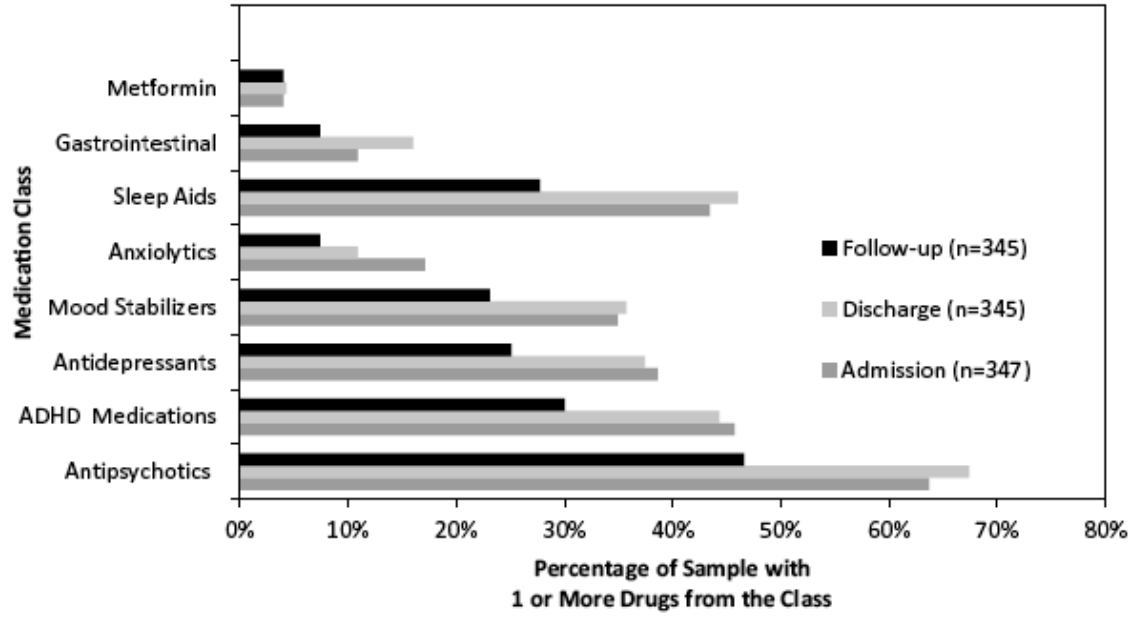
J Autism Dev Disord
DOI 10.1007/s10803-017-3153-x

Characterization of Medication Use in a Multicenter Sample of Pediatric Inpatients with Autism Spectrum Disorder

Logan K. Wink[1] · Ernest V. Pedapati[1] · Ryan Adams[2] · Craig A. Erickson[1] · Kahsi A. Pedersen[3] · Eric M. Morrow[4] · Desmond Kaplan[5] · Matthew Siegel[6] · for the Autism and Developmental Disorders Inpatient Research Collaborative (ADDIRC)



	0	1	2	3	4	5	6	7	8
Admission (n=347)	8.6%	10.3%	22.6%	23.7%	20.9%	8.6%	3.4%	1.7%	0.3%
Discharge (n=345)	2.9%	13.1%	25.7%	30.9%	16.3%	8.3%	2.6%	0.3%	0.0%
Follow-up (n=345)	36.0%	8.9%	17.4%	20.0%	10.0%	6.0%	1.4%	0.3%	0.0%



EMA-approved indications for antipsychotics in children and adolescents

Antipsychotic	Indication in psychosis	Other disorders	FDA
Chlorpromazine	Schizophrenia and other psychoses ≥ 1 year	Mania, agitation due to other causes, nausea-vomiting	Severe hyperactivity and behavioural disorders in children 1-12 years., tetanus, nausea-vomiting
Haloperidol	Schizophrenia and other psychoses > 2 years	Tourette, mania, other behavioural disorders (especially when associated wit hyperactivity and aggression).	Schizophrenia, conduct disorders , severe hyperactivity, Tourette in children older than 3 and adults
Clozapine	Schizophrenia ≥ 16 years	No	No
Aripiprazole	Schizophrenia ≥ 15 years Long-acting: adults	Mania up to 12 weeks ≥ 13 years	Schizophrenia ≥13, BD ≥ 10, irritability in ASD 6-17 years, Tourette 6-18 years
Paliperidone	Oral: schizophrenia ≥ 15 Long-acting: adults	No	Schizophrenia ≥12 Long-acting: adults
Risperidone	No (in some European countries schizophrenia ≥ 15 years) Long-acting: adults	Short-term treatment of aggressiveness in conduct disorder and intellectual disability 5-18 years	Schizophrenia ≥13, BD ≥10, irritability in ASD 5-17 years
Quetiapine	No	No	Schizophrenia ≥13, mania ≥10
Olanzapine	No	No	Schizophrenia and manic/mixed episodes ≥13. Second line because of side effects
Asenapine	No	No Mania in adults (studies underway for children 10-17 years)	No Schizophrenia and mania in adults
Amisulpride	Contraindicated in children. Could be used in some adolescents ≥ 15-18 years	No	No
Ziprasidone	No	Severe manic/mixed episodes ≥ 10 years	No

European Neuropsychopharmacology (2011) 21, 600–620

ELSEVIER

www.elsevier.com/locate/euroneuro

REVIEW

Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: A review of the randomized controlled studies

Alessandro Zuddas[a,*], Roberta Zanni[a], Tatiana Usala[a,b]

Misure di efficacia delle terapie

Effect Size

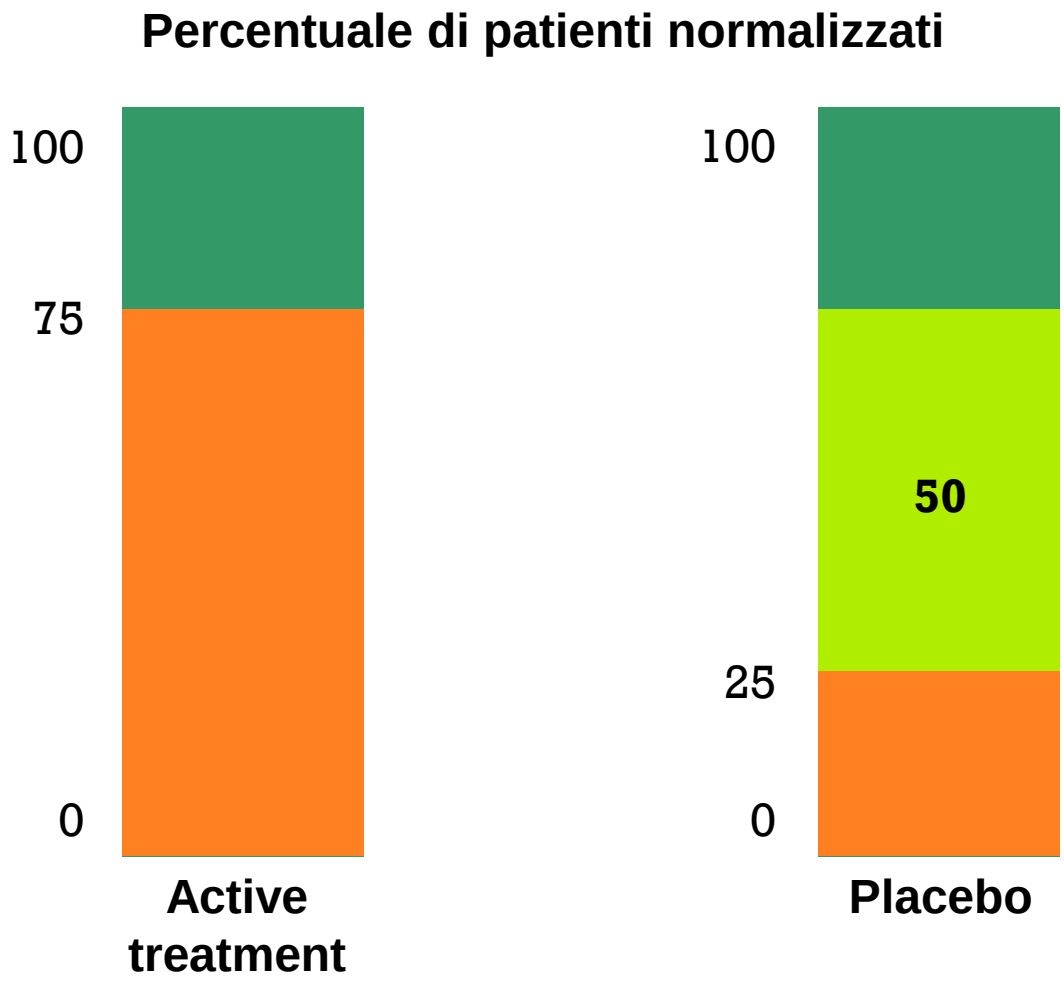
Differenza nei cambiamenti dal *baseline* tra due trattamenti (es. farmaco e placebo), diviso la media delle dev. standard (es. placebo e farmaco ad *end point)*.
L'*effect size* standardizza le unità di misura nei diversi studi.

	Basaline	EndPoint
Farmaco	38.5 ± 5.8	25.5 ± 4.2
Placebo	40.4 ± 6.1	32.7 ± 5.0

$$\mathbf{d} = \frac{(38.5-25.5) - (40.4-32.7)}{(4.2+5.0)/2} = \frac{13.0 - 7.7}{4{,}6} = \mathbf{ES\ 1.1}$$

Secondo la definizione di Cohen, ES > 0.2 è considerato basso, ES > di 0.5 è considerato medio; oltre 0.8 è considerato alto

Efficacia: Number Needed to Treat (NNT)



Numbers needed to treat = 100% / (% migliorato col farmaco – % i migliorato con Placebo)

Esempio:
Numbers Needed to Treat
= 100 / (75 – 25)
= 100 / 50
= 2

Maggiore la differenza, minore il numero

SGAs in Pervasive Developmental Disorders

ES: **0.6-1.3**
NNT: **1.3-5.5**

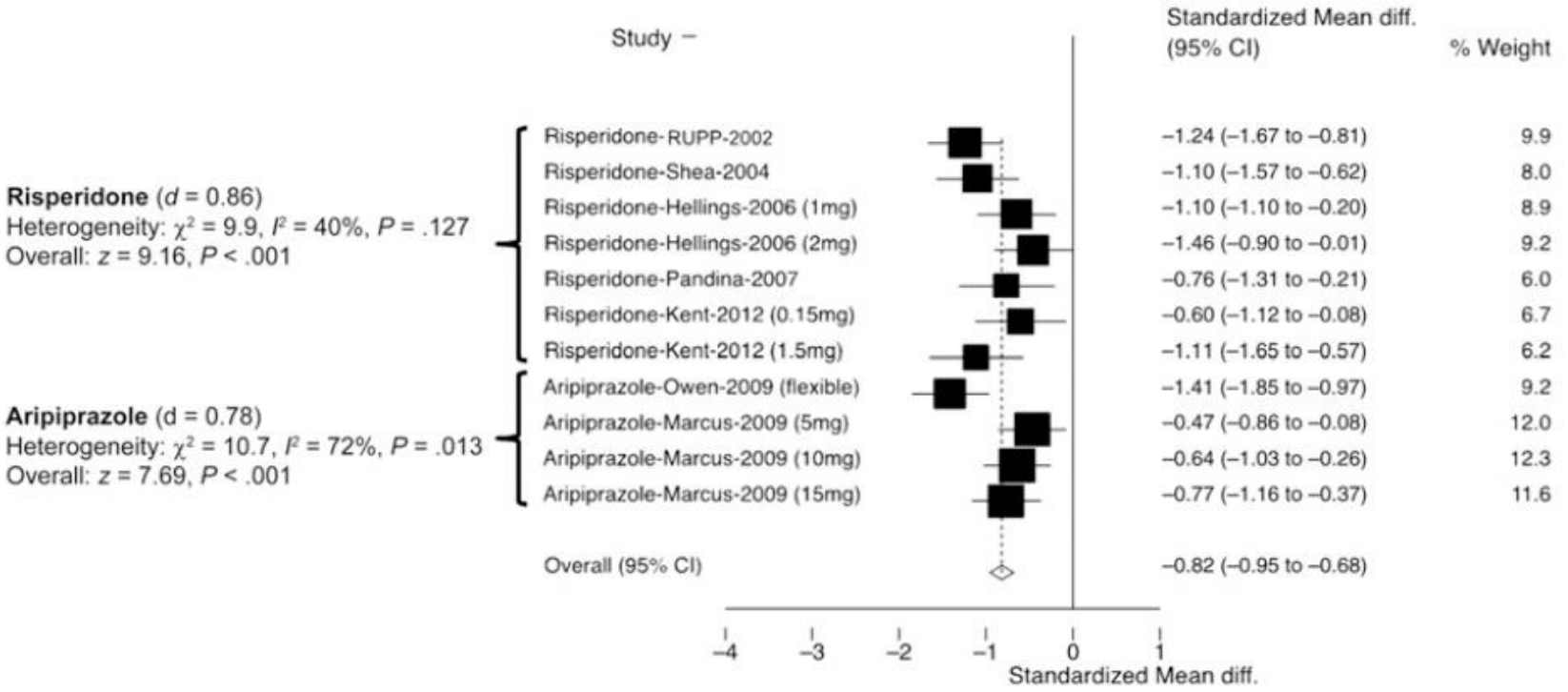
Study	n	Age & Gender	Daily dose	Duration	Main outcome measure	Comparison between groups	ES	NNT
McCracken *et al.* 2002	101	7-17 M=82	**Risperidone** 0.5-3.5 mg	8 weeks	ABC-I	p < 0.001	**1.2**	**1.5**
McDougle *et al.* 2005	63 (32 compl.)	7-17 M=49	0.5-3.5 mg	8 + 16 weeks	Relapse prevention (25% ABC-I worsening)	n/a	n/a	n/a
Shea *et al.* 2004	80 (77 compl.)	5-12 M=61	1.17	8 weeks	ABC-I	p < 0.001	**0.6**	**3**
Troost *et al.* 2005	36 (24 compl.)	5-17 M=22	0.5-3.5 mg	16 + 8 weeks	Relapse prevention (25% ABC-I worsening)	p = 0.049	n/a	n/a
Nagaraj *et al.* 2006	40 (39 compl.)	2-9 M=34	1 mg	6 months	CARS CGAS	p < 0.001 p = 0.035	n/a **1.06**	**1.6** **1.3**
Luby *et al.* 2006	24 (23 compl.)	2.5-6 M=17	0.5-1.5 mg	6 months	CARS	p < 0.05	**0.95**	**2.0**
Pandina *et al.* 2007	55 (49 compl.)	5-12 M=43	1.37 mg	8 weeks	ABC-I	p = 0.002	**0.7**	**2.7**
Miral *et al.* 2008	32 (30 compl.)	8-18 M=24	RIS 2.6 mg HAL 2.6 mg	12 weeks	ABC	p = 0.0063	**1.3**	n/a
Owen *et al.* 2009	98	6-17 M=86	**Aripiprazole** 5-15 mg	8 weeks	ABC-I	p < 0.001	**1.23**	**2.6**
Marcus *et al.* 2009	218 (178 compl.)	6-17 M=195	5 mg (A) 10 mg (B) 15 mg (C)	8 weeks	ABC-I	p = 0.032 p = 0.008 p = 0.001	**0.6** **0.7** **0.9**	**4.7** **6.9** **5.5**
Hollander *et al.* 2006	11 (8 comp.)	6-14 M=9	**Olanzapine** 7.5-12.5 mg	8 weeks	CGI-I	p = 0.006	**1,1**	**3.3**

RAAP = Rating of Aggression Against People and/or Property Scale;
ABC-I = Aberrant Behavior Checklist-Irritability;
NCBRF = Nisonger Child Behavior Rating Form;

Zuddas et al. *ENP 2011*

Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis

Lawrence K. Fung, MD, PhD,[a] Rajneesh Mahajan, MD,[b] Alixandra Nozzolillo, MS,[c] Pilar Bernal, MD,[d] Aaron Krasner, MD,[e] Booil Jo, PhD,[a] Daniel Coury, MD,[f] Agnes Whitaker, MD,[e] Jeremy Veenstra-Vanderweele, MD,[e] Antonio Y. Hardan, MD[a]



The New England Journal of Medicine

RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK*

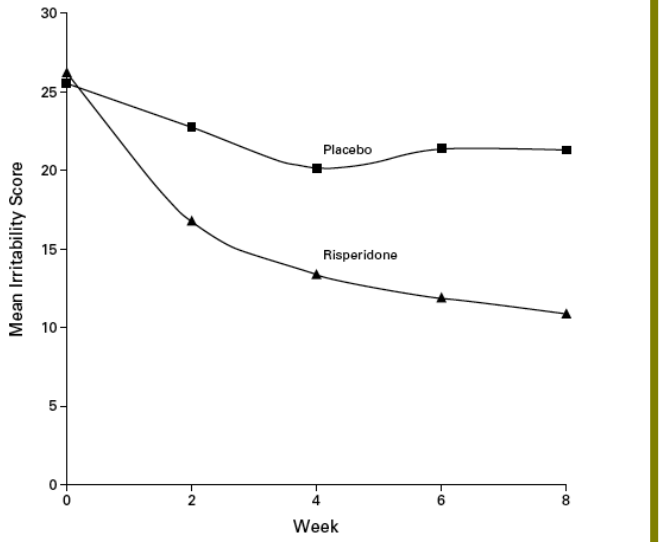
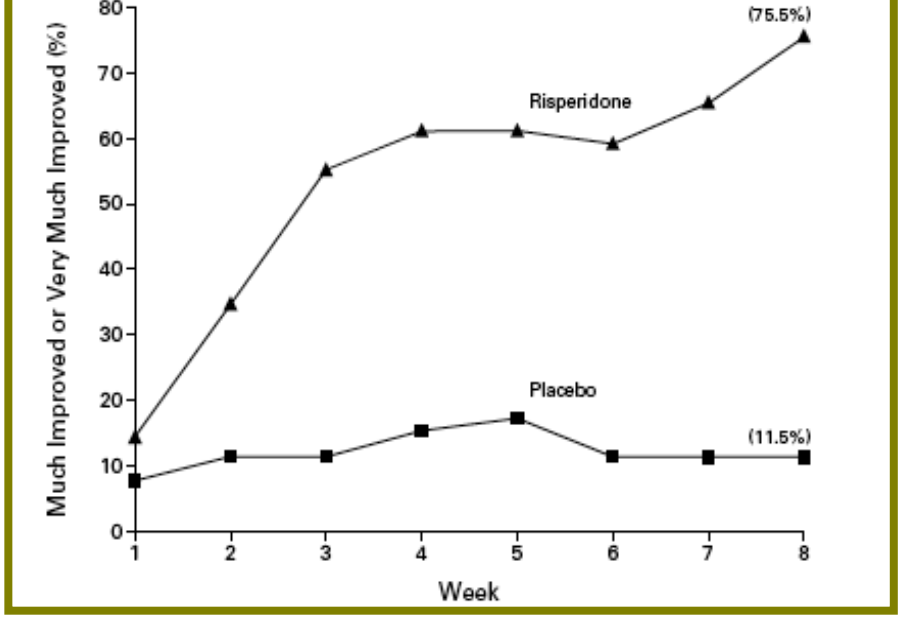


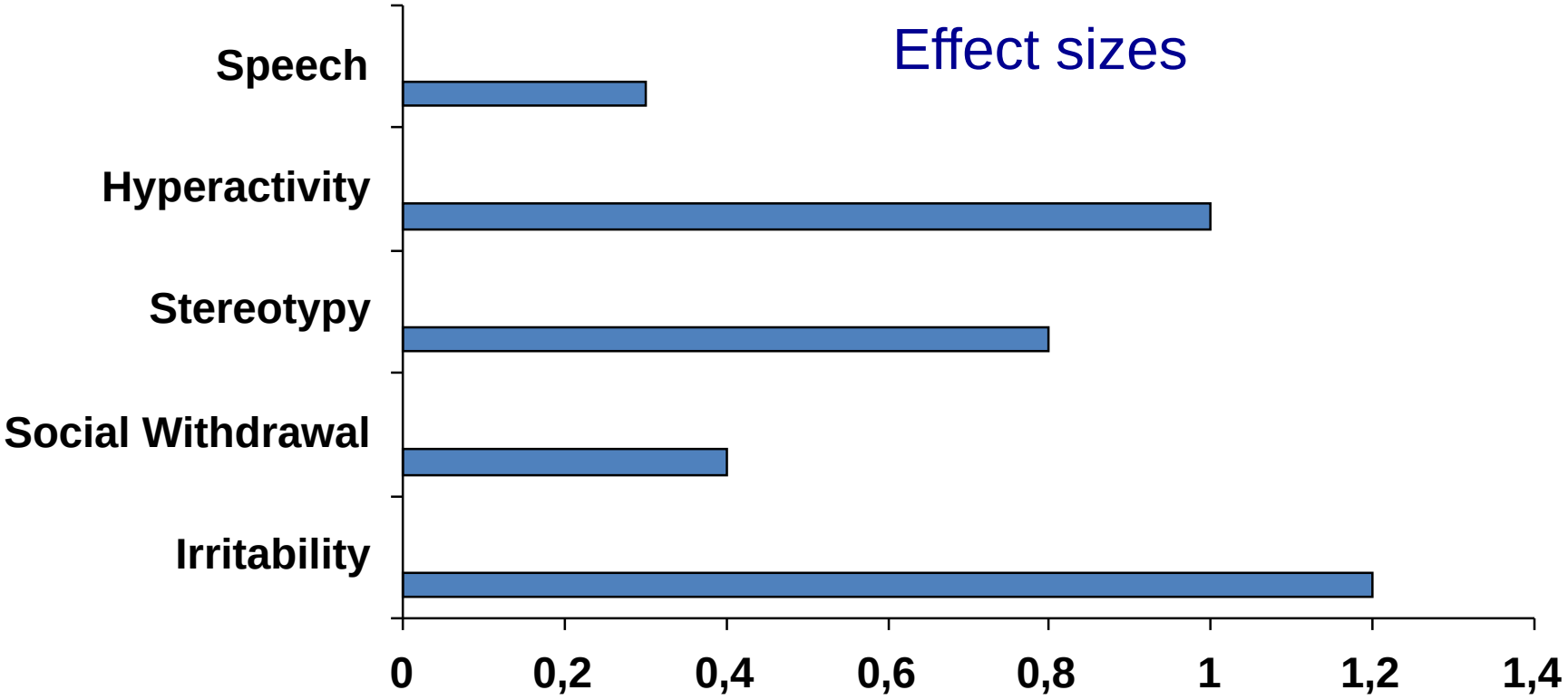
Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.



Effect size: 1.1

NNT: 1.6

Risperidone in children with autism and severe irritability



RUPP Autism Network, NEJM, 2002, 347-314-321

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 24, Number 9, 2014

Pp. 513–518
DOI: 10.1089/cap.2014.0055

Lack of Effect of Risperidone on Core Autistic Symptoms: Data from a Longitudinal Study

Natasha Marrus, MD, PhD,[1] Heather Underwood-Riordan, BA,[2] Fellana Randall, MA,[1] Yi Zhang, MS,[1] and John N. Constantino, MD[1]

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 25, Number x, 2015

Pp. 1–4
DOI: 10.1089/cap.2015.0123

Brief Report

Multiple Antipsychotic Medication Use in Autism Spectrum Disorder

Logan K. Wink, MD,[1] Ernest V. Pedapati, MD,[1] Paul S. Horn, PhD,[1] Christopher J. McDougle, MD,[2] and Craig A. Erickson, MD[1]

Risperidone for the core symptom of autism:

Results from the study of the Autism network
of the Research Unit on Pediatric Psychopharmacology AJP 2005

FIGURE 1. Scores for Compulsions on the Children's Yale-Brown Obsessive Compulsive Scale of Children and Adolescents in a Placebo-Controlled Risperidone Trial and Open-Label Continuation Study

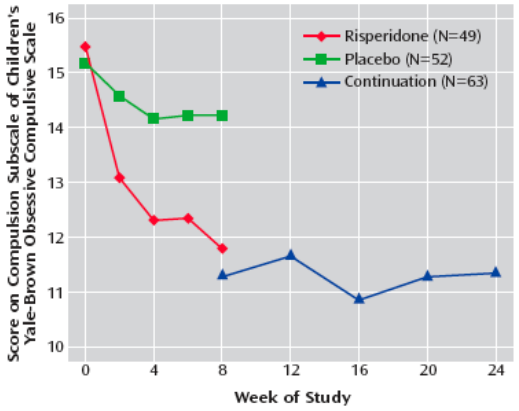


TABLE 1. Scores on the Ritvo-Freeman Real Life Rating Scale of Children and Adolescents With Autism in a Placebo-Controlled Risperidone Trial and Open-Label Continuation Study

Measure From Ritvo-Freeman Real Life Rating Scale	Score in Placebo-Controlled Trial (N=101)						Results of Placebo-Controlled Trial		
	Baseline		Week 4		Week 8		End-of-Study Effect Size (Cohen's d)	Interaction of Treatment With Time	
	Mean	SD	Mean	SD	Mean	SD		F (df=1, 87)	p
Subscale I: sensory motor behaviors							0.45	10.8	0.002
Risperidone	1.00	0.52	0.65	0.43	0.59	0.42			
Placebo	0.93	0.58	0.83	0.47	0.91	0.60			
Subscale II: social relationship to people							0.68	—	n.s.
Risperidone	0.60	0.43	0.20	0.43	0.15	0.42			
Placebo	0.72	0.43	0.47	0.51	0.46	0.52			
Subscale III: affectual reactions							1.10	15.4	<0.001
Risperidone	1.68	0.64	1.00	0.67	0.88	0.56			
Placebo	1.84	0.64	1.64	0.64	1.60	0.71			
Subscale IV: sensory responses							0.77	8.5	0.004
Risperidone	1.13	0.53	0.70	0.44	0.60	0.38			
Placebo	1.21	0.53	0.98	0.54	1.07	0.54			
Subscale V: language							0.81	—	n.s.
Risperidone	0.28	0.38	0.15	0.31	0.03	0.29			
Placebo	0.46	0.42	0.30	0.39	0.34	0.41			
Overall							1.08	15.3	<0.001
Risperidone	0.94	0.36	0.54	0.36	0.45	0.31			
Placebo	1.03	0.37	0.84	0.39	0.88	0.40			

Psychosis as a state of Aberrant Salience:

A framework linking biology, phenomenology and pharmacology in Schizophrenia

Kapur, AJP 2003

- Dopamine as the "*Wind of the Psychotic Fire*"
- Dopamine as a mediator of Motivational Salience
  - Bias in probabilistic reasoning
  - Tendency to jump to conclusion
  - Alteration in attributional style
  - "Theroy of mind", perceptual alteration, magical thinking

- Dampering of aberrant Salience by antipsychotics

  "the voice actually said those words, but it does not bother me anymore"

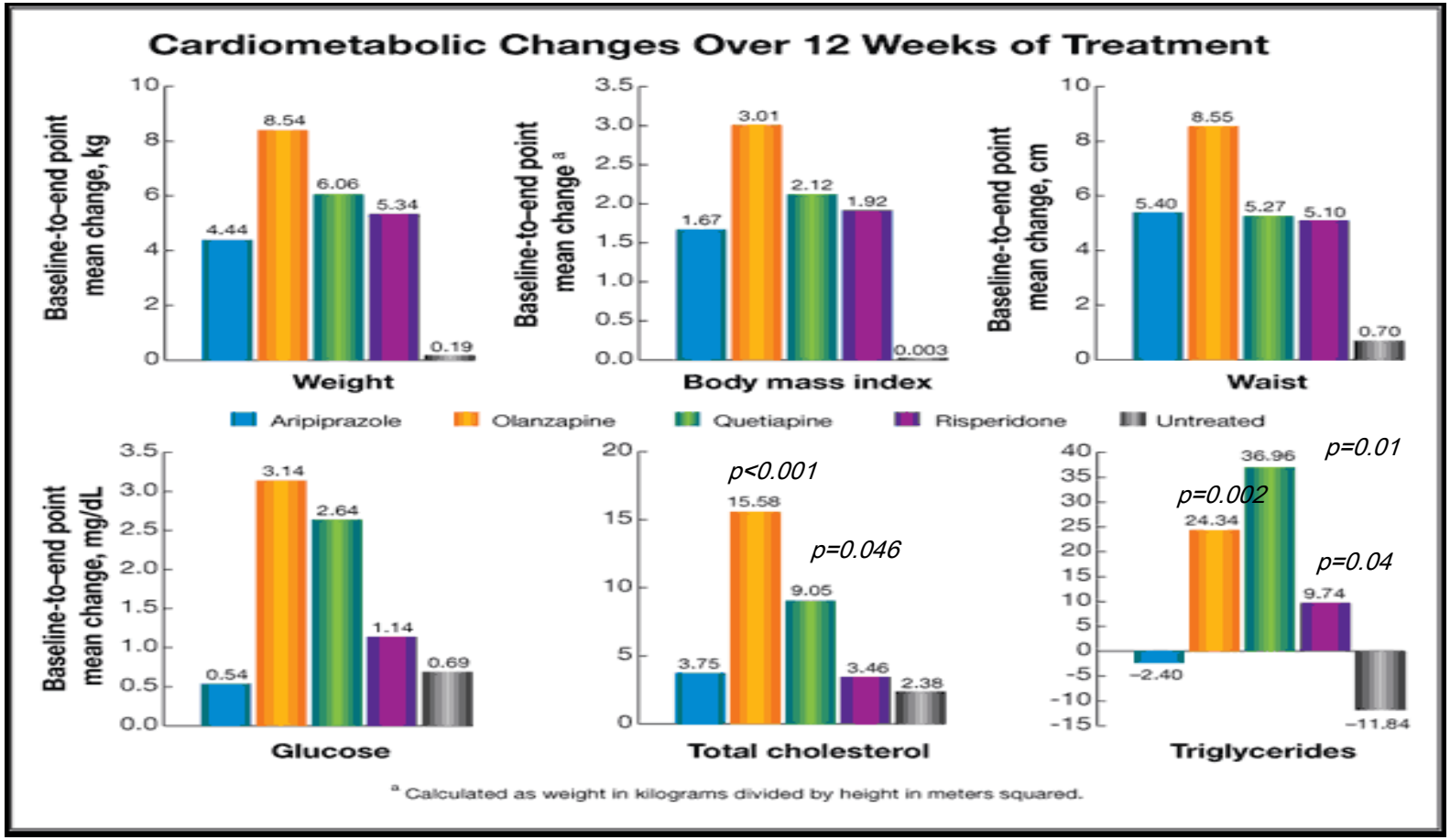
Risperidone in children with autism and severe irritability

	Risperidone	Placebo	
Increased appetite	24 (49 %)	12 (25 %)	*
Fatigue	29 (59 %)	14 (27 %)	*
Drowsiness	24 (49 %)	6 (12 %)	**
Drooling	13 (27 %)	3 (6 %)	*
Weight gain (kg)	2.7 ± 2.9	0.8 ± 2.2	**

RUPP Autism Network, NEJM, 2002, 347-314-321

Weight gain and metabolic changes in children and adolescents treated with antipsychotics

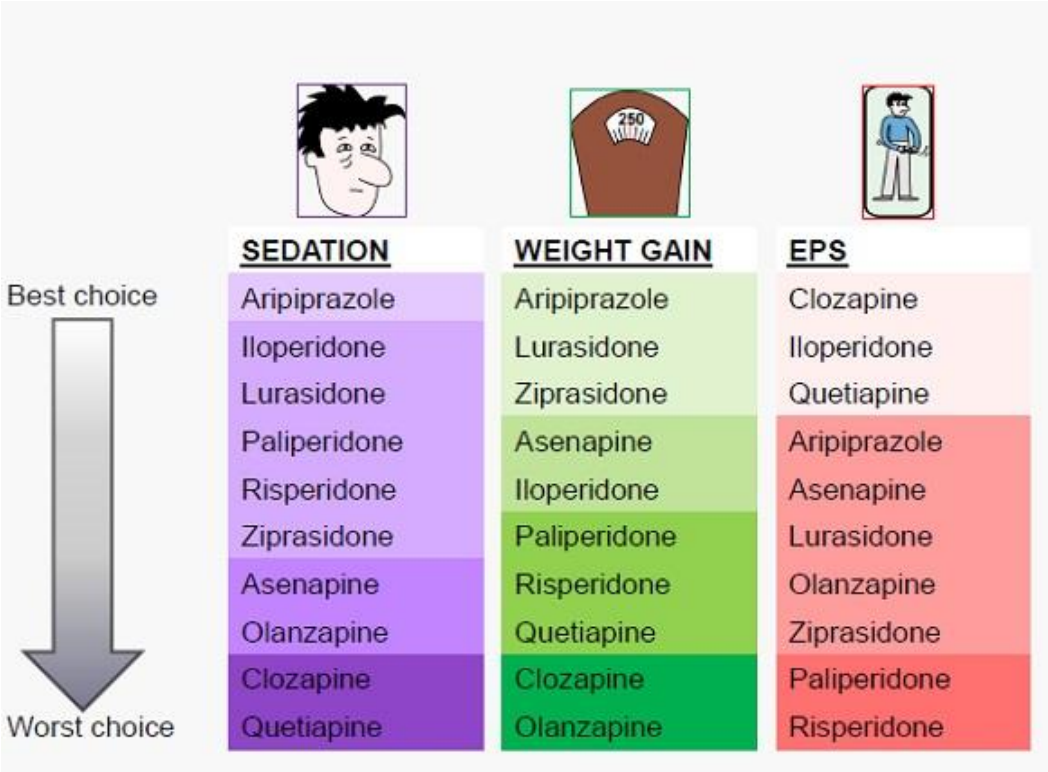
The SATIETY study



Correll et al. JAMA, 2009

Basic Algorithm For Selection of Antipsychotics

- Begin with antipsychotic that causes the less side effects or no side effects feared by the patients



Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity

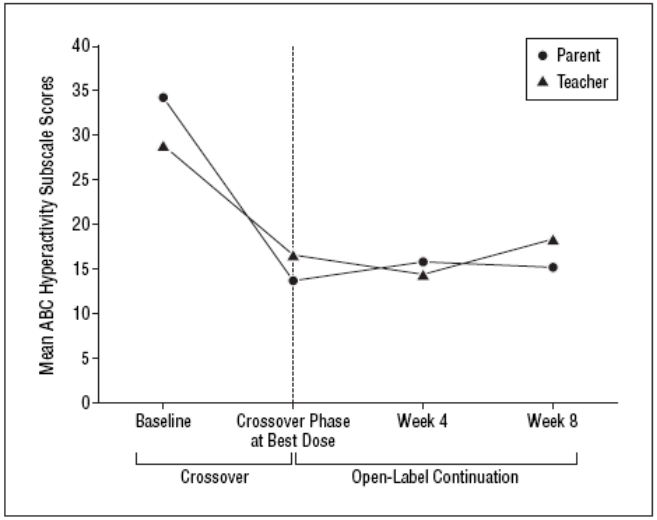


Table 3. Parent-Rated and Teacher-Rated Aberrant Behavior Checklist Hyperactivity Subscale Scores During Crossover Phase

	Sample Size*		Hyperactivity Subscale Score, Mean (SD)†		*P* Value‡		Effect Size§	
Dosage Level	Parent-Rated	Teacher-Rated	Parent-Rated	Teacher-Rated	Parent-Rated	Teacher-Rated	Parent-Rated	Teacher-Rated
Placebo	60	46	26.0 (9.90)	26.0 (11.66)				
Low Dose	62	45	23.0 (11.29)	22.9 (12.84)	.03	.03	0.29	0.25
Medium Dose	63	52	20.6 (10.27)	23.6 (12.53)	<.001	.008	0.54	0.20
High Dose	47	33	22.1 (9.67)	20.3 (11.94)	.003	.002	0.40	0.48
Optimal Dose‖	64	58	17.2 (9.87)	20.1 (12.40)	<.001	<.001	.89	.48

RUPP, Arch G.Psych. 2005

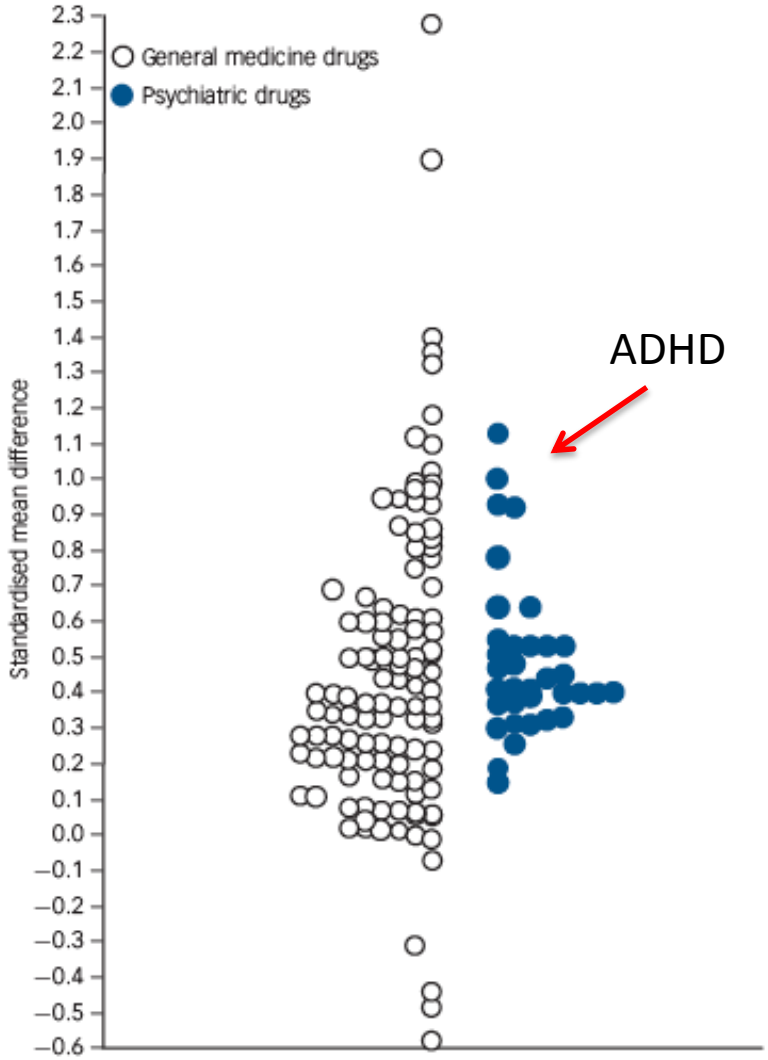


Fig. 1 Summary of effect sizes.

All effect sizes in online Tables DS3 and DS4 are presented except for duplicates (e.g. effect size on dichotomous response and continuous reduction of severity in schizophrenia). Online Fig. DS25 identifies which dot corresponds to which result, and Figs DS26–29 present the results of dichotomous outcomes as relative and absolute risk/responder differences. Data on older meta-analyses from Table DS1 are not included. Effect sizes of dichotomous outcomes were converted to standardised mean differences expressed as Hedges' g. Effect sizes of general medicine medication are presented on the left-hand side (median 0.37, mean 0.45, 95% CI 0.37–0.53) and psychiatric drugs on the right-hand side (median 0.41, mean 0.49, 95% CI 0.41–0.57).

ES in General Medicine

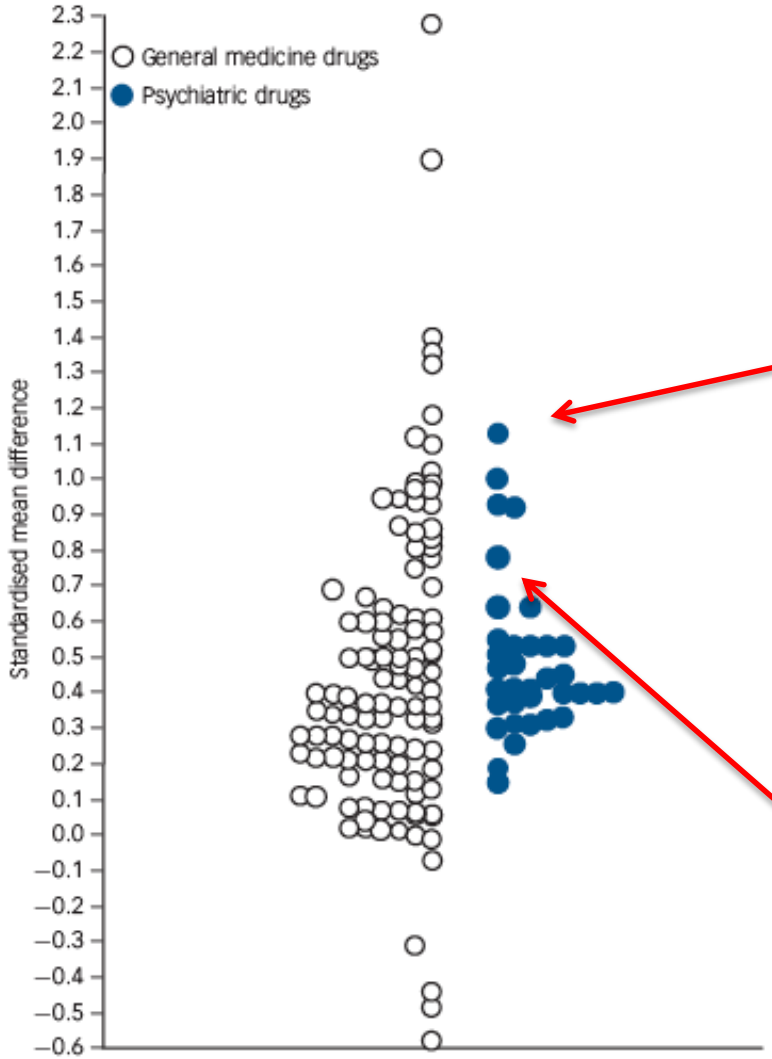
Aspirine for prevention cardiovascular disease	0.06
Antypertensive on long term mortality	0.11
Corticosteroids for asthma	0.54
Antypertensive for high blood pressure	0.55
Interferone for Chronic Hepatitis C	2.27

ES in General (Adult) Psychiatry

SGA for schizophrenia (PANS)	0.51
SSRI for depression (HAMD)	0.32
SSRI/ Bdz for Panic	0.41
SSRI for OCD	0.44

Leucht et al.2012

BJPsych The British Journal of Psychiatry (2012) 200, 97–106. doi: 10.1192/bjp.bp.111.096594



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European Neuropsychopharmacology (2013) 23, 1208–1218

ELSEVIER

www.elsevier.com/locate/euroneuro

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

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]

Relapse Prevention in Pediatric Patients With ADHD Treated With Atomoxetine: A Randomized, Double-Blind, Placebo-Controlled Study

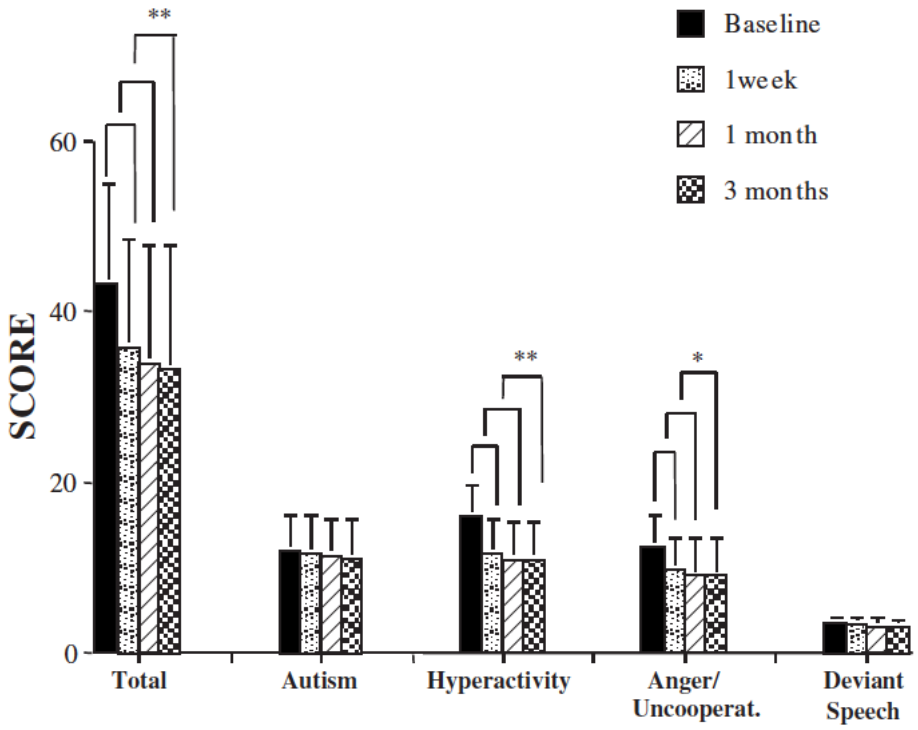
DAVID MICHELSON, M.D., JAN K. BUITELAAR, M.D., PH.D., MARINA DANCKAERTS, M.D., PH.D., CHRISTOPHER GILLBERG, M.D., PH.D., THOMAS J. SPENCER, M.D., ALESSANDRO ZUDDAS, M.D., DOUGLAS E. FARIES, PH.D., SHUYU ZHANG, M.S., AND JOSEPH BIEDERMAN, M.D.

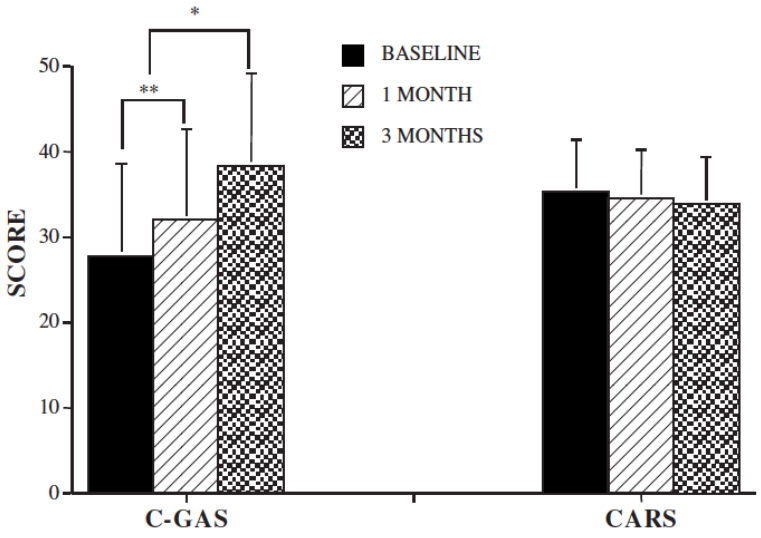
J. Am. Acad. Child Adolesc. Psychiatry, 2004;43(7):896–904.

Methylphenidate for Pervasive Developmental Disorders: Safety and Efficacy of Acute Single Dose Test and Ongoing Therapy: An Open-Pilot Study

Adriana Di Martino M.D.,* Gianluigi Melis, M.D.,
Carlo Cianchetti, M.D., and Alessandro Zuddas, M.D.

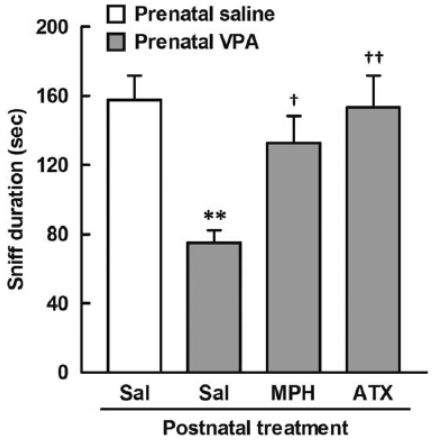
JCAP 2004

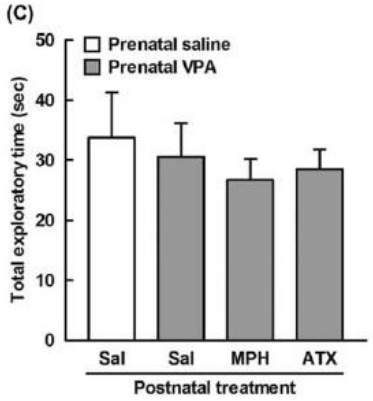


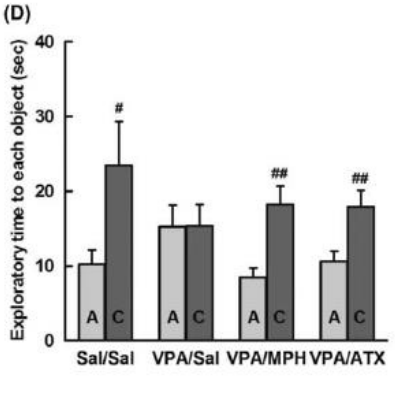


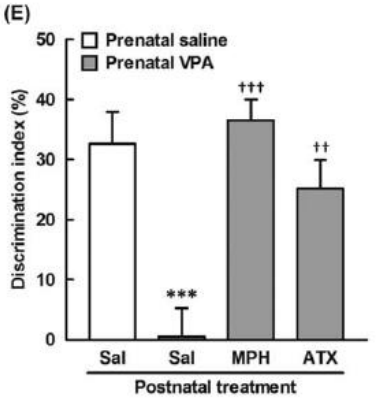
Improvement by Methylphenidate and Atomoxetine of Social Interaction Deficits and Recognition Memory Impairment in a Mouse Model of Valproic Acid-Induced Autism

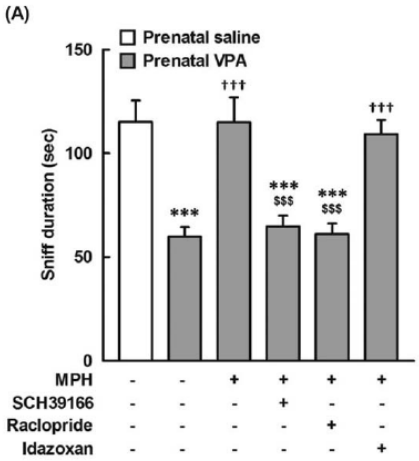
Yuta Hara,† Yukio Ago,† Atsuki Taruta, Keisuke Katashiba, Shigeru Hasebe, Erika Takano, Yusuke Onaka, Hitoshi Hashimoto, Toshio Matsuda, and Kazuhiro Takuma

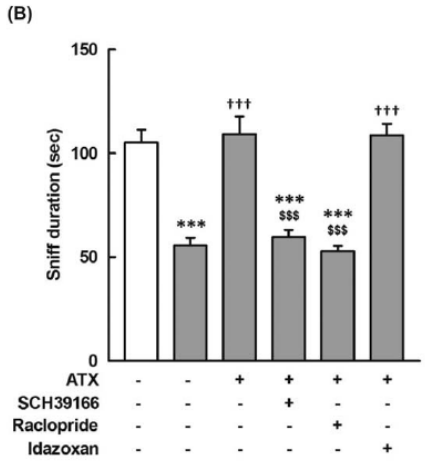












A Double-Blind Placebo-Controlled Trial of Fluoxetine for Repetitive Behaviors and Global Severity in Adult Autism Spectrum Disorders

Hollander et al. *AJP 2012*

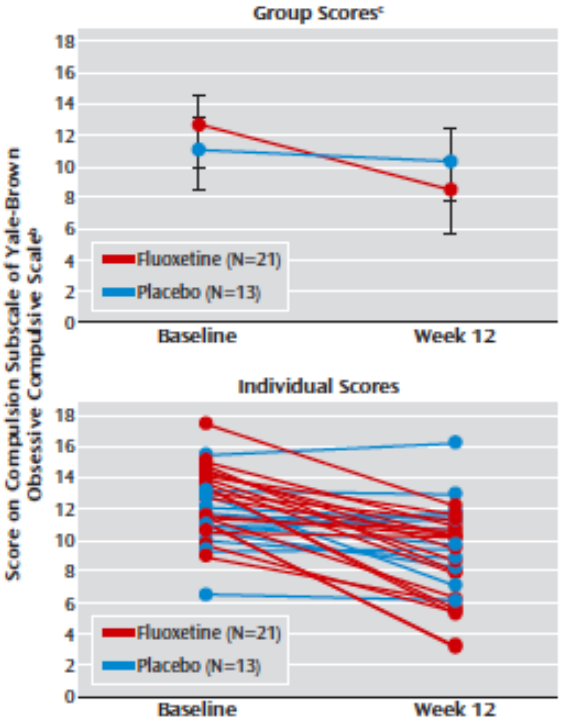
Objective: The effects of fluoxetine and placebo on repetitive behaviors and global severity were compared in adults with autism spectrum disorders (ASDs).

Method: Adults with ASDs were enrolled in a 12-week double-blind placebo-controlled fluoxetine trial. Thirty-seven were randomly assigned to fluoxetine (N=22) or placebo (N=15). Dosage followed a fixed schedule, starting at 10 mg/day and increasing as tolerated up to 80 mg/day. Repetitive behaviors were measured with the compulsion subscale of the Yale-Brown Obsessive Compulsive Scale; the Clinical Global Impression (CGI) improvement scale was used to rate improvement in obsessive-compulsive symptoms and overall severity.

Results: There was a significant treatment-by-time interaction indicating a significantly greater reduction in repetitive behaviors across time for fluoxetine than for placebo. With overall response defined as a CGI global improvement score of 2 or less, there were significantly more responders at week 12 in the fluoxetine group than in the placebo group. The risk ratio was 1.5 for CGI global improvement (responders: fluoxetine, 35%; placebo, 0%) and 1.8 for CGI-rated improvement in obsessive-compulsive symptoms (responders: fluoxetine, 50%; placebo, 8%). Only mild and moderate side effects were observed.

Conclusions: Fluoxetine treatment, compared to placebo, resulted in significantly greater improvement in repetitive behaviors, according to both the Yale-Brown compulsion subscale and CGI rating of obsessive-compulsive symptoms, as well as on the CGI overall improvement rating. Fluoxetine appeared to be well tolerated. These findings stand in contrast to findings in a trial of citalopram for childhood autism.

FIGURE 1. Change in Repetitive Behaviors for Adults With Autism Spectrum Disorders in a 12-Week Comparison of Fluoxetine and Placebo[a]



[a] Predicted linear change based on mixed-effects regression with random slopes and intercepts.
[b] Administered by evaluators independent of treatment.
[c] Mean values and standard deviations.

Preliminary Investigation of Lithium for Mood Disorder Symptoms in Children and Adolescents with Autism Spectrum Disorder

Matthew Siegel, MD,[1,2,3] Carol A. Beresford, MD,[4,5] Madisun Bunker, BS,[2] Mary Verdi, MA,[2]
Donna Vishnevetsky, MD,[4] Cassie Karlsson, MD,[4] Olivia Teer, BA,[2]
Amy Stedman,[2] and Kahsi A. Smith, PhD[3]

JCAP 2014

TABLE 2. CHI-SQUARE OR FISHER'S EXACT TESTS ANALYSIS COMPARING PROPORTION OF PATIENTS WHO "IMPROVED" AND "DID NOT IMPROVE" BY PRETREATMENT SYMPTOM

Pretreatment symptom	*Subjects* n *(%)*	*CGI 1 or 2 "Improved"*	*CGI≥3 "Not Improved"*	*Statistic*	p *value*
Aggression	21 (70%)	10	11	FET	1.000
Persistent irritability	14 (47%)	7	7	χ^2=0.000	1.000
Hyperactive-impulsive	14 (47%)	8	6	χ^2=0.343	0.558
Emotional dysregulation	24 (80%)	11	13	FET	0.596
Self-injurious behavior	12 (40%)	4	8	FET	0.252
Anxiety	17 (57%)	7	10	FET	0.440
Euphoria/elevated mood[a]	4 (13%)	4	0	FET	0.041*
Mania[a]	7 (23%)	6	1	FET	0.033*
Paranoia[a]	1 (3%)	0	1	FET	1.000
Hypersexuality[a]	8 (27%)	5	3	FET	0.420
Decreased need for sleep[a]	6 (20%)	3	3	FET	1.000

Chi-square with continuity correction and was calculated when cells were >5 for a 2×2 analysis.
[a]Mood disorder symptom.
*Significance at $p \leq 0.05$.
CGI, Clinical Global Impressions; FET, Fisher's Exact Test and was calculated when cells were ≤5.

Summary

Aggression, Irritability (self injurious behaviour)

Drug	Efficacy	Scientific evidence	Common side effects
antipsychotics			
Haloperidol	Proven effective	Improves aggressiveness, hyperactivity, social withdrawal, stereotipies; facilitates developing language skills.	Extrapiramidal side effects, tardive dyskinesia, metabolic syndrome
Risperidone	Proven effective	Improves aggressiveness and irritability	Weight gain, sedation, metabolic syndrome, hyperprolactinemia
Aripiprazole	Proven effective	Improves aggressiveness and irritability (6-17 y.o.)	Tension, weight gain, sedation, metabolic syndrome
Olanzapine	Suggestive evidence	Several open trials and case reports	Weight gain, sedation, metabolic syndrome

Summary

Aggression, Irritability (self injurious behaviour)

Drug	Efficacy	Scientific evidence	Common side effects
Mood stabilizers			
Sodium valproate, lamotrigine	Suggestive evidence	Several open trials and case reports	Aumento di peso, irritabilità
SSRIs			
Fluoxetine and others	No efficacy	Negative results	Headache, gastritis, diarrhoea, weight gain
Psychostimulants			
Metilfenidate	Proven effective	Useful aggressiveness is associated with hyperactivity and impulsivity	Irritability, insomnia, loss of appetite, paradoxical aggressiveness
a2-Agonists			
Clonidine	Suggestive evidence	Only one RCT published	Sedation and hypotension
Opioid antagonists			
Naltrexone	Suggestive evidence	II line treat emtn for self-injurious behaviors	Tension (usually minor and transient)

Summary

Hyperactivity, Impulsivity

Drug	Efficacy	Scientific evidence	Common side effects
Psychostimulants			
Metilfenidate	Proven efficacy	Hyperactivity and impulsivity improve to a greater extent than inattention	Irritability, insomnia, loss of appetite, paradoxical aggressiveness
Noradrenaline reuptake blockers			
Atomoxetine	Proven efficacy	Several open trials. Only one RCT	Sedation, irritability, constipation, nausea
a-Agonists			
Clonidine	Suggestive evidence	Two RCTs provide some evidence of improvement reported by parents	Sedation
Guanfacine	Suggestive evidence	Only open trials	Irritability and agitation

Summary

Repetitive Behaviours

Drug	Efficacy	Scientific evidence	Common side effects
SSRIs			
Fluoxetine	Proven efficacy	Effective at low doses on repetitive behaviors	Headache, gastritis, diarrhoea, weight gain
Citalopram	No efficacy	One multicentered 12-wk RCT sponsored by the NIH	Hyperexcitability, impulsivity, diarrhoea
Atypical antipsychotics			
Risperidone	Suggestive evidence	RUPP study: improvement in CY-BOCS scores	Weight gain, sedation, metabolic syndrome, hyperprolactinemia
Mood stabilizers			
Sodium valproate	Suggestive evidence	One RCT trial (8 wks)	Weight gain, irritability

REVIEW

Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives

Antonio M. Persico[a,b,*], Celso Arango[c], Jan K. Buitelaar[d], Christoph U. Correll[e], Jeffrey C. Glennon[d], Pieter J. Hoekstra[f], Carmen Moreno[c], Benedetto Vitiello[g], Jacob Vorstman[h], Alessandro Zuddas[i], the European Child and Adolescent Clinical Psychopharmacology Network[j]

European Neuropsychopharmacology 2015

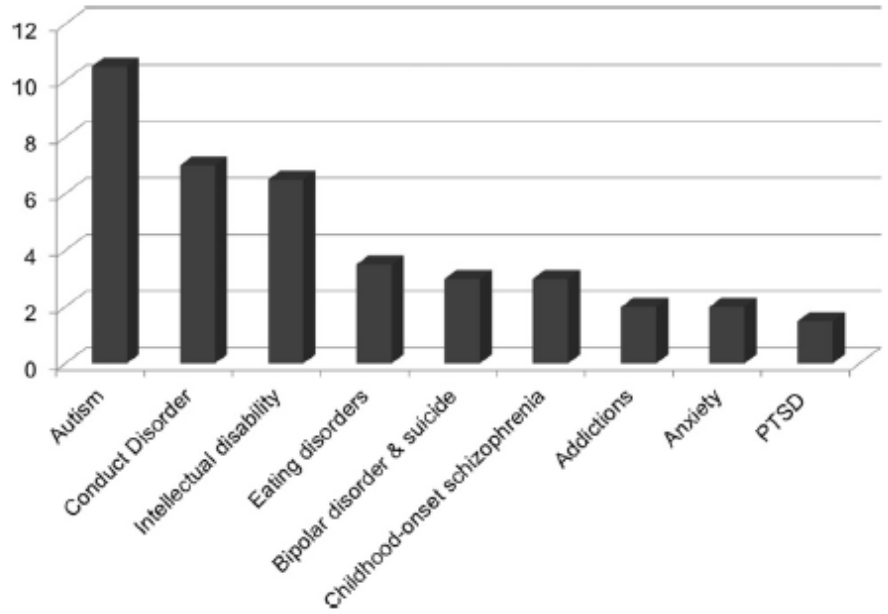


Fig. 1 Priority order for drug development in child and adolescent psychiatry by disorder or condition. Each expert attending the ECNP Targeted Network Meeting was awarded three priority options and ordinate values represent raw counts of disease priorities.

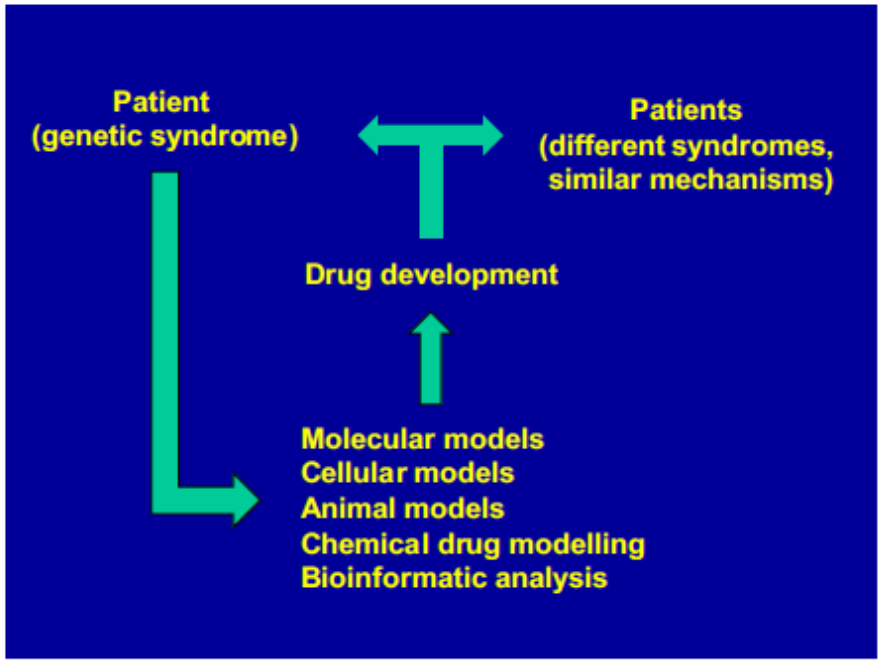
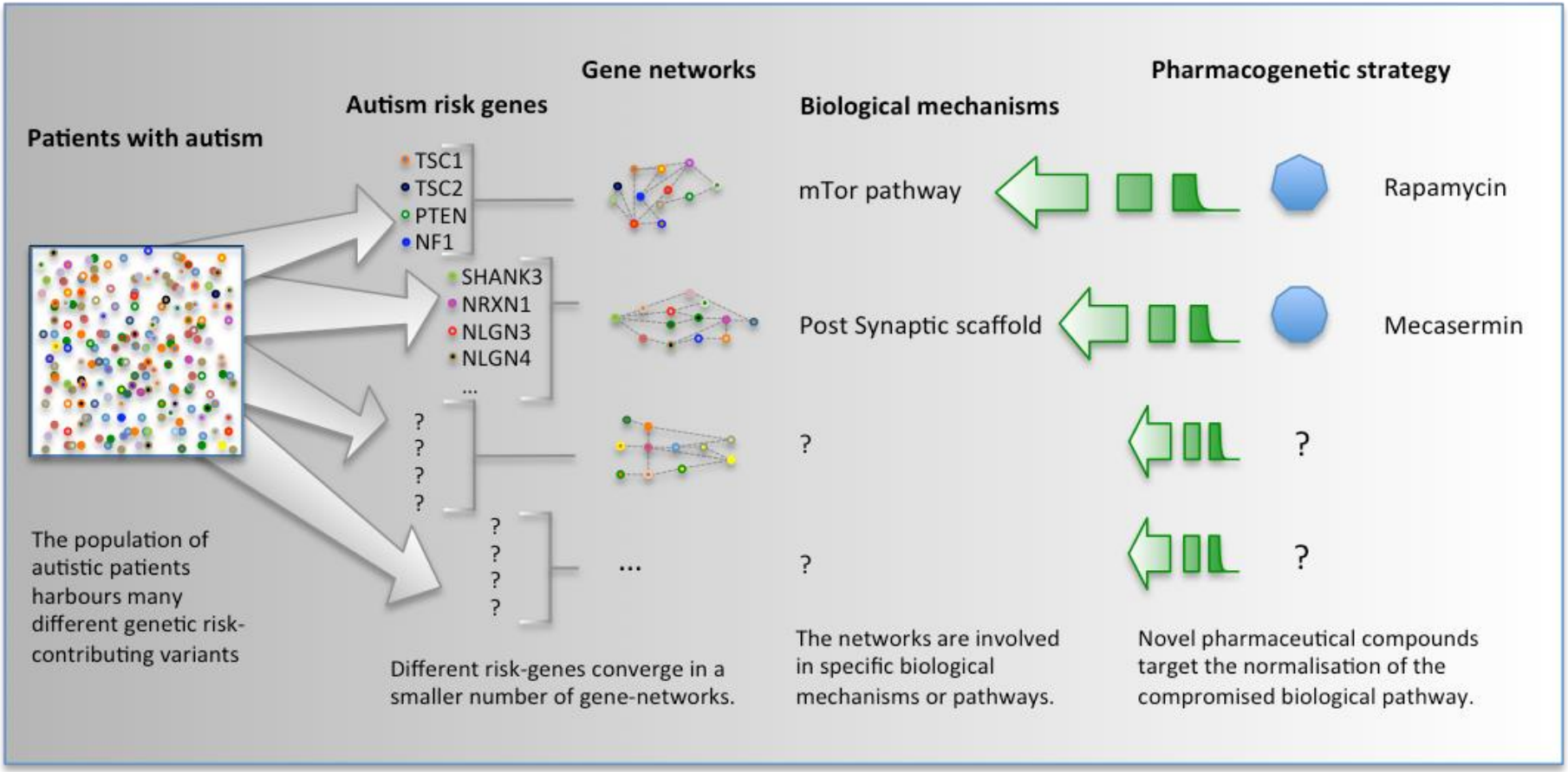


Fig. 2 Translational approach to paediatric psychopharmacology, starting from the characterization of rare genetic syndromes and applying discoveries to more common and often comorbid disorders (see text).

QUALE FARMACO
PER QUALE PAZIENTE?



Vorstman et al, Psychopharmacol 231: 1063, 2014

Ruggeri et al., Psychopharmacol 231: 1201, 2014

Remaining gap(s)

Need of sufficiently large samples to be able to

- Select discovery and replication samples
- Parse out ASD heterogeneity (stratified psychiatry)
  - Symptoms severity
  - Psychiatric comorbidity
  - Biological sex
    - Research on females remains a challenge

Patient heterogeneity and appropriate outcome measure

- Age and developmental stage
- Different stages of the disorder
- Heterogeneous neurobiology underpinning similar symptoms
- Relation among IQ, cognition, global functioning, symptoms
- Quality of life

Patient heterogeneity and appropriate outcome measure

Age and developmental stage (Therapeutic window)

- Thyroid hormone replacement effective only when started before 2 weeks form birth
- Oxytocine could be affective only when started in early infancy (autism, Prader-Willi S)
- When is appropriate to start medication for neurodevelopmental disorders?

Paediatric clinical trials:

methodological issues, problems and potential solutions

Incorporate Valid Biomarkers in the RCT

Stratification biomarkers:	patients that may benefit from a specific treatment
Mechanistic biomarkers:	difference in underlying psychopathology
Substituted endpoint:	predict later clinical responce

Biology: Genomics, epigenomics, trascriptomocs, metabolomic)

Complex level close to Brain function:

Electrophysiology, brain imaging, eye tracking, neuropsychological tests

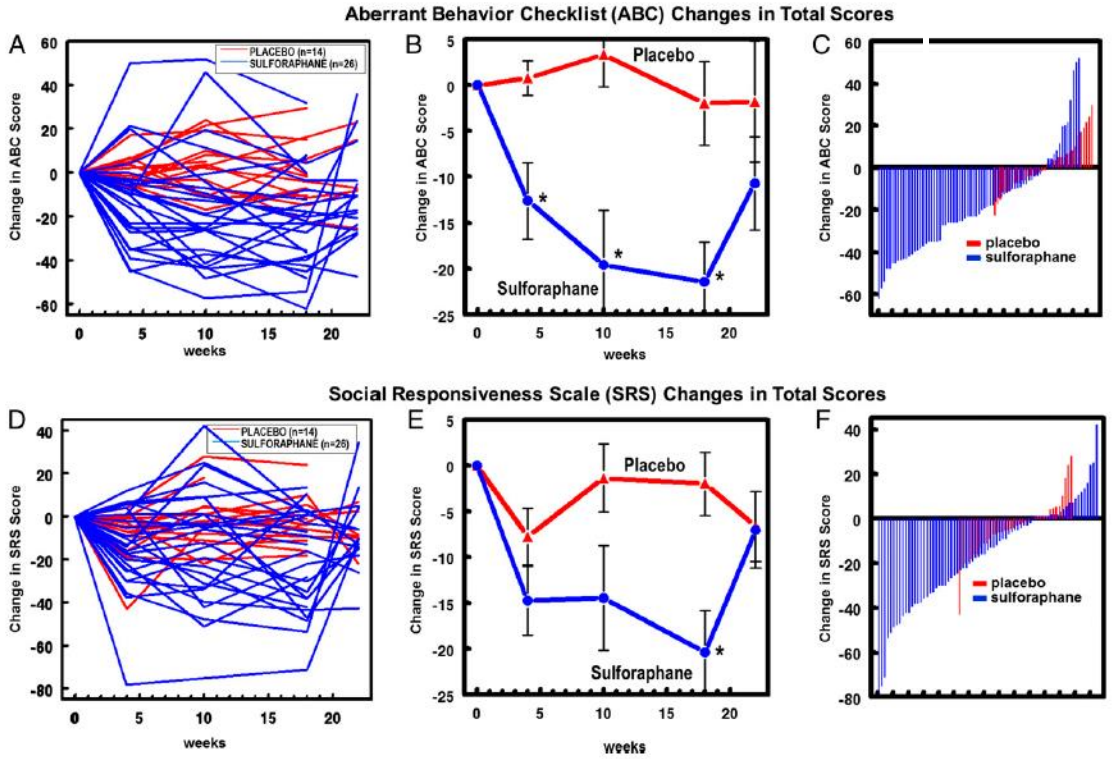
Sulforaphane treatment of autism spectrum disorder (ASD)

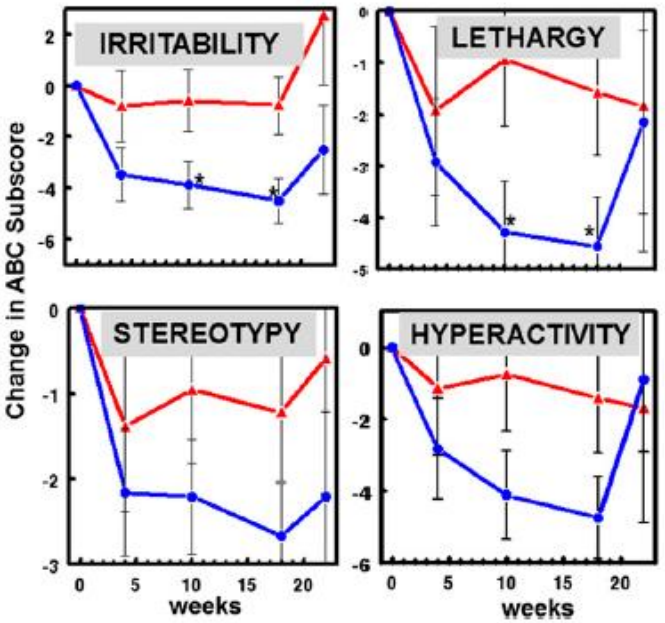
Kanwaljit Singh[a,b], Susan L. Connors[a], Eric A. Macklin[c], Kirby D. Smith[d], Jed W. Fahey[e], Paul Talalay[e,1], and Andrew W. Zimmerman[a,b,1]

PNAS | October 28, 2014 | vol. 111 | no. 43 | 15553

Sulforaphane:

- extracted from broccoli;
- up-regulate genes that protect from oxidative stress, inflammation, DNA .damaging electrophiles and radiation
- May protects ASD form oxidative stress, defects in glutatione synthesis, mitochondrial dysfunction, lipid peroxidation, and neur-oinflammation





Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome

Omar S. Khwaja[a,b,1], Eugenia Ho[a,c,1], Katherine V. Barnes[a], Heather M. O'Leary[a], Luis M. Pereira[d], Yaron Finkelstein[e,f], Charles A. Nelson III[g], Vanessa Vogel-Farley[g], Geneva DeGregorio[g], Ingrid A. Holm[h,i], Umakanth Khatwa[j], Kush Kapur[a,k], Mark E. Alexander[i,l], Deirdre M. Finnegan[a], Nicole G. Cantwell[a], Alexandra C. Walco[a], Leonard Rappaport[g], Matt Gregas[a,k], Raina N. Fichorova[m], Michael W. Shannon[f,i,2], Mriganka Sur[n], and Walter E. Kaufmann[a,3]

Table 2. Summary of breathing indices for all RTT subjects by time point (n = 9)

Breathing indices	Pre-MAD	Post-MAD	Pre-OLE	Post-OLE	Pre-MAD to Post-OLE
Apnea index (mean ± SE)	10.11 ± 19.34	5.11 ± 9.68	4.67 ± 6.81	3.00 ± 5.72	–7.12 ± 4.58
Student's t P	–	–	–	–	0.159
Wilcoxon signed rank P	–	–	–	–	0.094
RI model P	–	–	–	–	0.018
Hyperventilation index (mean ± SE)	3.55 ± 6.71	3.00 ± 6.59	6.44 ± 16.86	3.66 ± 8.97	0.12 ± 0.93
Student's t P	–	–	–	–	0.908
Wilcoxon signed rank P	–	–	–	–	0.875
RI model P	–	–	–	–	0.963

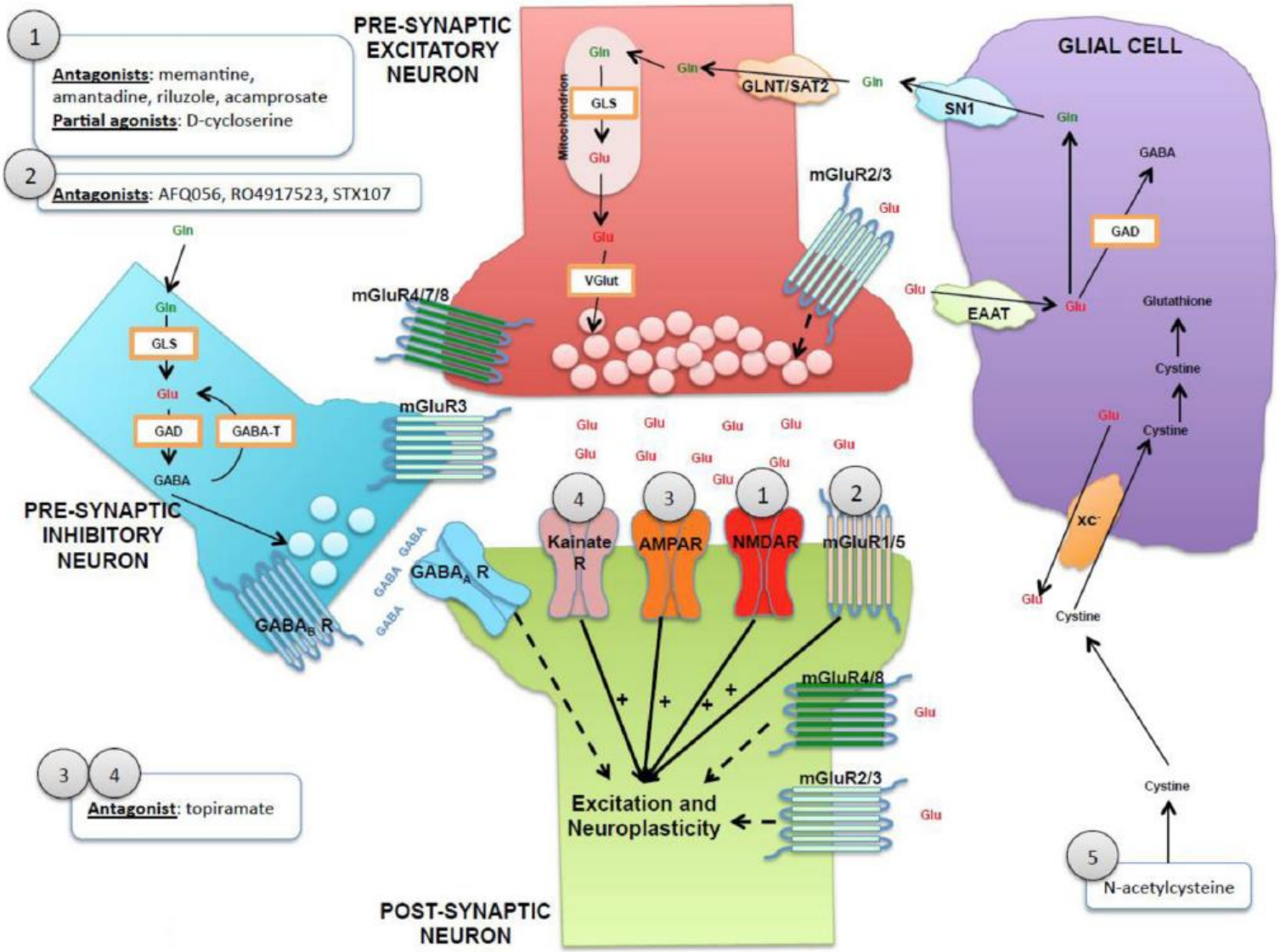
Table 3. Neurobehavioral measures between V1 and V5

Measure	V1 mean	V5 mean	Mean difference	Mean difference SE	Student's t P	Wilcoxon signed rank P
Behavioral subtotal (MBA)	24.00	19.88	–4.11	1.11	0.006	0.016
Passive/unengaged (CA)	0.33	0.00	–0.33	0.17	0.081	0.250
Intermittent laughter (CA)	0.33	0.00	–0.33	0.17	0.081	0.250
Fear/anxiety subtotal (RSBQ)	3.55	2.77	–0.79	0.66	0.274	0.281
Spells of laughter at night (RSBQ)	0.77	0.44	–0.33	0.17	0.081	0.250
Social avoidance subtotal (ADAMS)	4.55	3.11	–1.44	0.84	0.122	0.109

V1, visit 1 of OLE; V5, visit 5 of OLE.

Developing Medications Targeting Glutamatergic Dysfunction in Autism: Progress to Date

Lawrence K. Fung, M.D., Ph.D and **Antonio Y. Hardan, M.D**



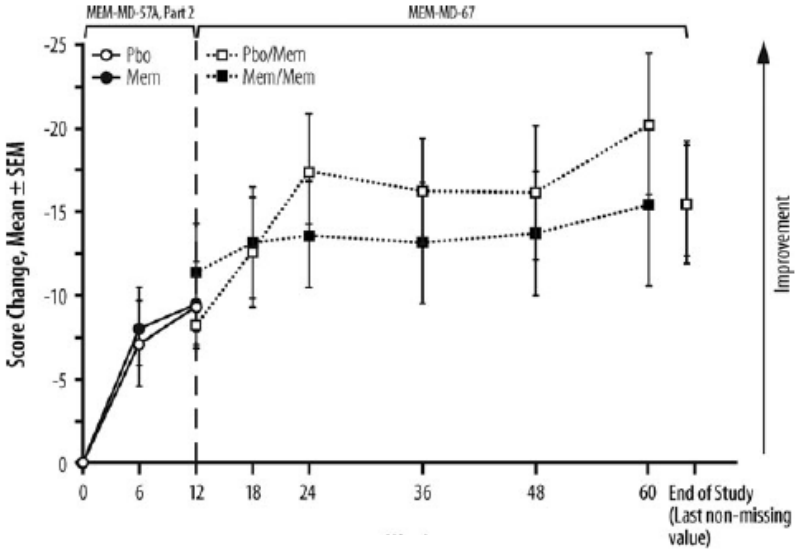
CNS Drugs 2015

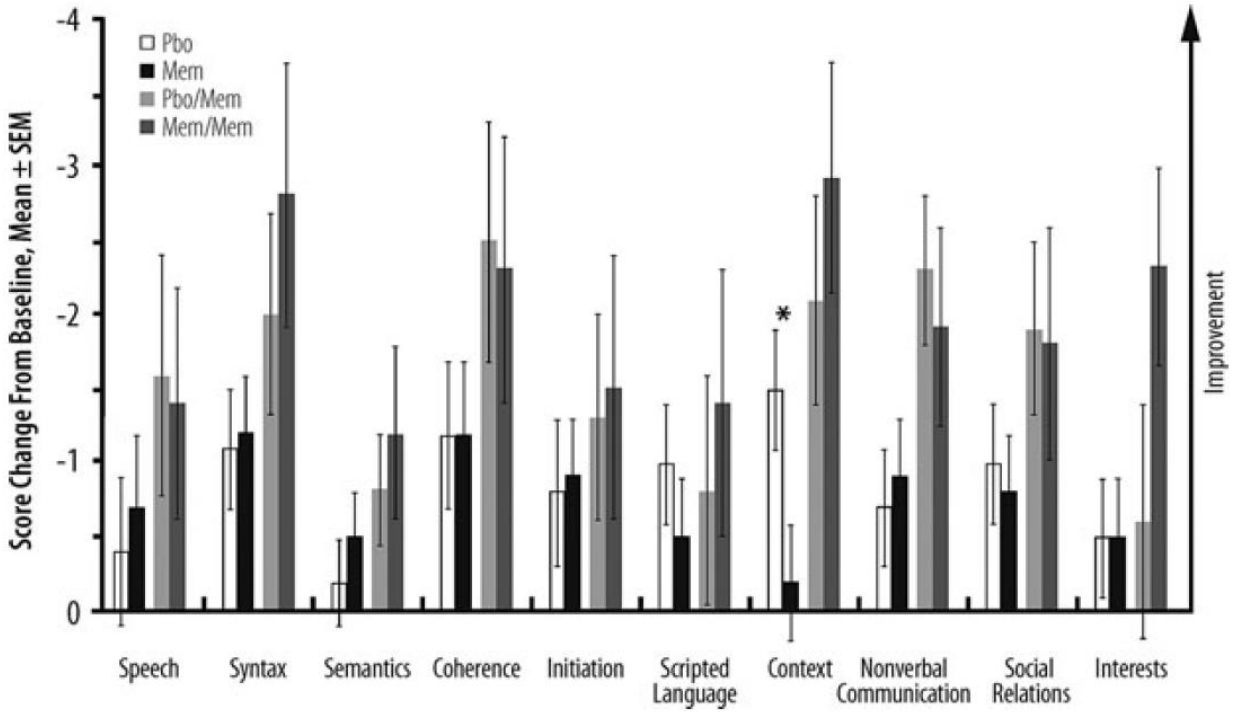
Safety and Efficacy of Memantine in Children with Autism: Randomized, Placebo-Controlled Study and Open-Label Extension

Michael G. Aman, PhD,[1] Robert L. Findling, MD, MBA,[2] Antonio Y. Hardan, MD,[3] Robert L. Hendren, DO,[4] Raun D. Melmed, MD,[5] Ola Kehinde-Nelson, BA,[6*] Hai-An Hsu, PhD,[6**] Joel M. Trugman, MD,[6] Robert H. Palmer, PhD,[6***] Stephen M. Graham, PhD,[6†] Allyson T. Gage, PhD,[6††] James L. Perhach, PhD, FCP,[6†††] Ephraim Katz, PhD[6‡]

121 Children 6-12 y

SRS – CCC-2





JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 27, Number 5, 2017

Wink et al. Molecular Autism (2017) 8:2
DOI 10.1186/s13229-017-0116-1

Molecular Autism

RESEARCH Open Access

D-Cycloserine enhances durability of social skills training in autism spectrum disorder

Logan K. Wink[1], Noha F. Minshawi[2], Rebecca C. Shaffer[1], Martin H. Plawecki[2], David J. Posey[3], Paul S. Horn[1], Ryan Adams[1], Ernest V. Pedapati[1], Tori L. Schaefer[1], Christopher J. McDougle[4], Naomi B. Swiezy[2] and Craig A. Erickson[1*]

Abstract

Background: D-Cycloserine (DCS) enhances extinction learning across species, but it has proven challenging to identify consistent benefit of DCS when added to therapeutic interventions. We conducted a placebo-controlled trial of DCS to potentiate social skills training in autism spectrum disorder (ASD) but found substantial improvement in both the DCS and placebo groups at the conclusion of active treatment. Here, we assess the impact of DCS 11 weeks following active treatment to evaluate the impact of DCS on treatment response durability.

Methods: Study participants included 60 outpatient youth with ASD, ages 5–11 years, all with IQ above 70, and significantly impaired social functioning who completed a 10-week active treatment phase during which they received weekly single doses of 50 mg of DCS or placebo administered 30 min prior to group social skills training. Following the 10-week active treatment phase, blinded follow-up assessments occurred at week 11 and week 22. The primary outcome measure for our durability of treatment evaluation was the parent-rated social responsiveness scale (SRS) total raw score at week 22.

Results: Analysis of the SRS total raw score demonstrated significant decrease for the DCS group compared to the placebo group ($p = 0.042$) indicating greater maintenance of treatment effect in the DCS group. DCS was well tolerated, with irritability being the most frequently reported adverse effect in both groups.

Conclusions: The findings of this study suggest that DCS may help youth with ASD to maintain skills gained during sort-term social skills training. Larger-scale studies with longer follow-up will be necessary to further understand the long-term impact of DCS paired with structured social skills training.

Trial registration: ClinicalTrials.gov, NCT01086475

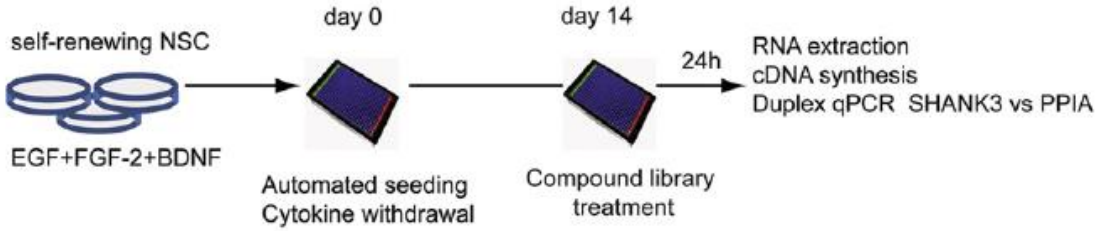
Keywords: Autism, Autism spectrum disorder, D-Cydoserine, Social skills training

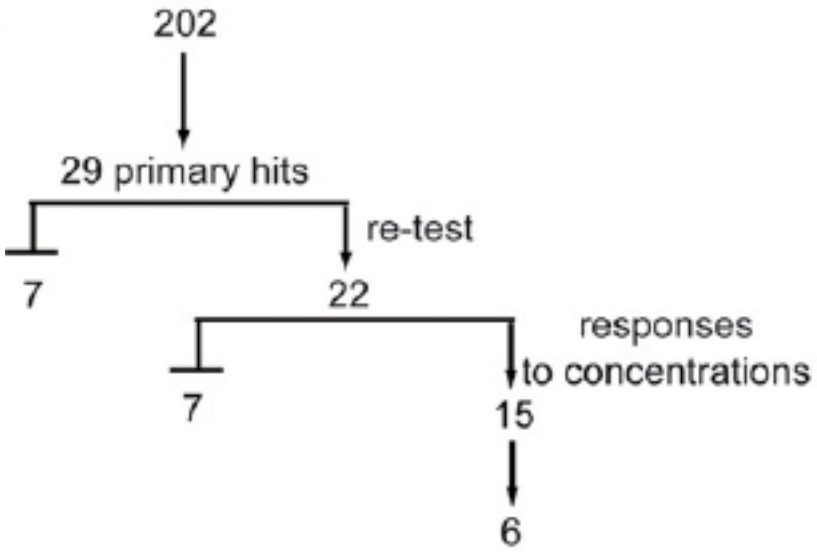
Research Paper

Human Pluripotent Stem Cell-derived Cortical Neurons for High Throughput Medication Screening in Autism: A Proof of Concept Study in SHANK3 Haploinsufficiency Syndrome

Darville et al. *BioMedicine* 2016

a





Compounds	Main Target	Mean	SD (n=4)
PD 166865	FGF receptor kinase activity inhibitor	1.37	0.28
Tyrphostin 46	EGF receptor kinase activity inhibitor	1.63	0.19
Dorsomorphin	BMP receptor inhibitor	1.48	0.37
Trichostatin A	HDAC inhibitors	1.55	0.21
Fluoro-SAHA		1.43	0.50
Oxamflatin		1.37	0.14
Vorinostat (SAHA)		1.77	1.00
Valproic acid		1.34	0.06
BWB 70C	5-lipooxygenase inhibitor	1.37	0.19
BML-259	Cyclin-dependant Kinases inhibitors	1.44	0.35
Roscovitine		1.50	0.11
Fendiline HCl	Ca2+ channel inhibitor	1.80	0.75
Lithium	GSK-3 inhibitor	1.38	0.19
Aripiprazole	Serotonin and Dopamine receptors	1.36	0.47
Fluoxetine	Serotonin reuptake inhibitor	1.34	0.28

Research Paper

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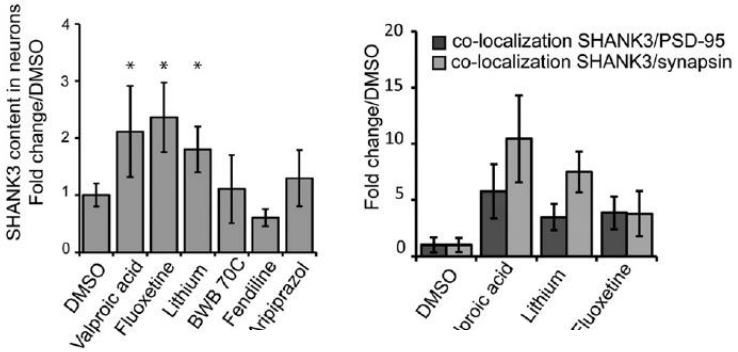

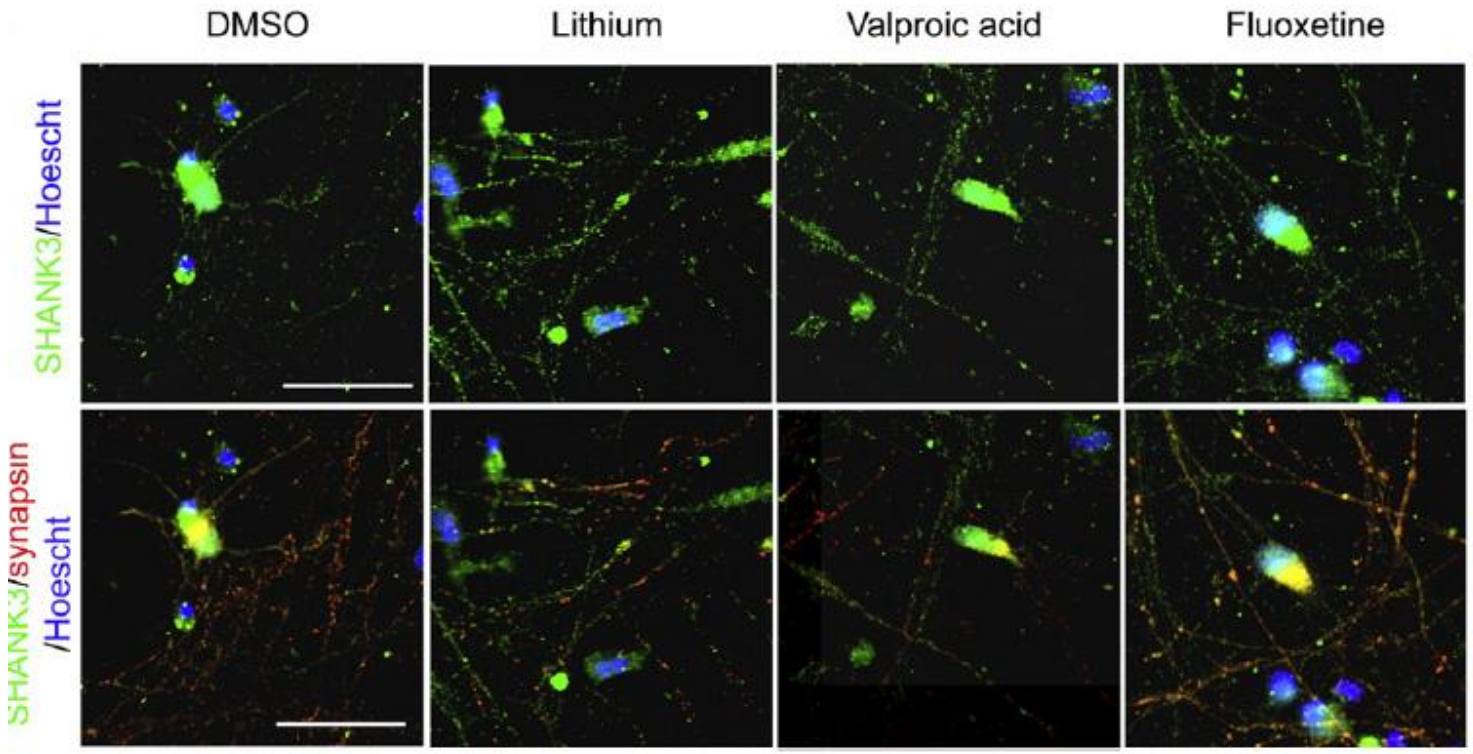

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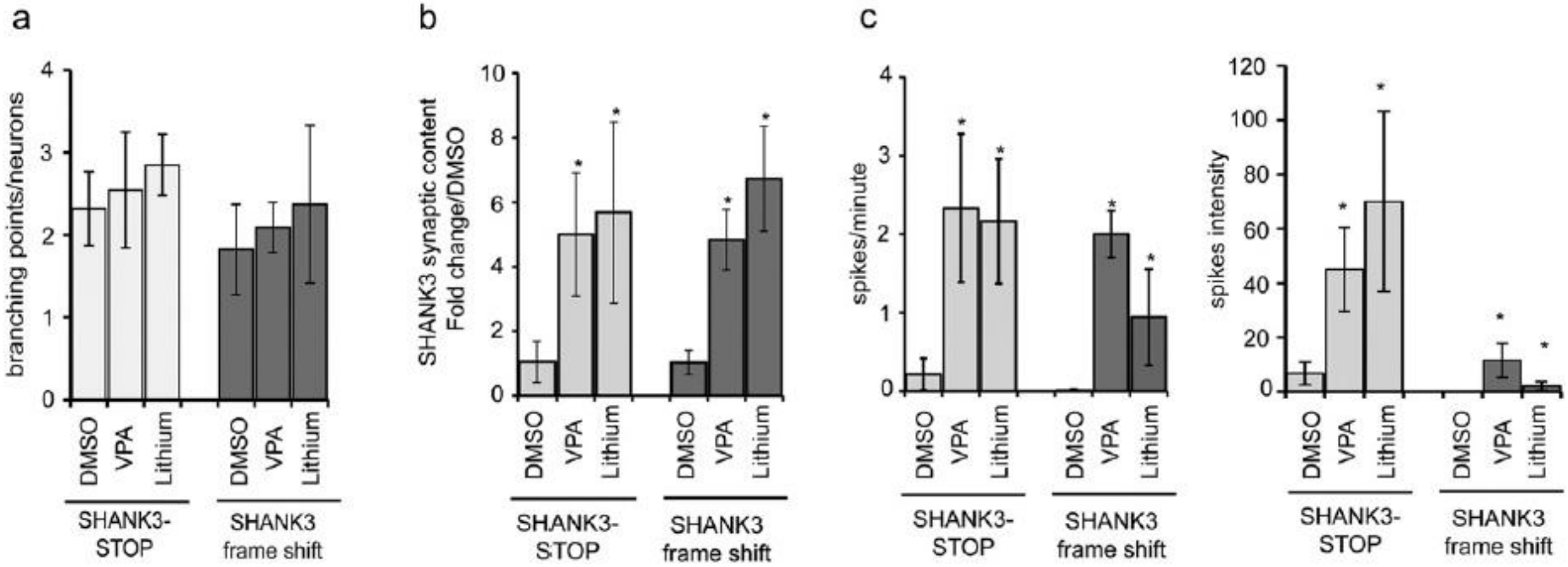

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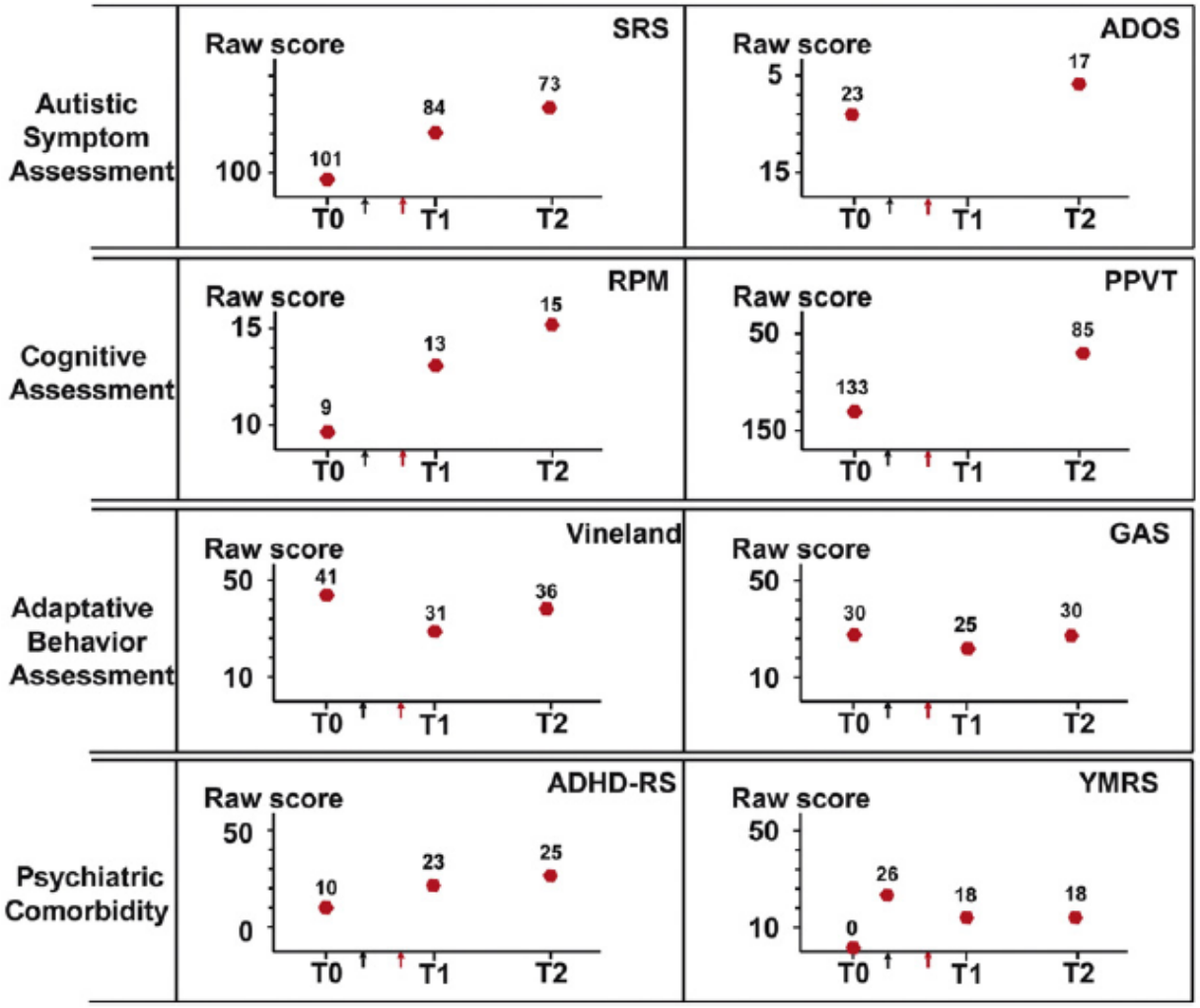


T1: 8 month FU

T2: 1 year FU

Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: case reports

Sylvie Serret*, Susanne Thümmler, Emmanuelle Dor, Stephanie Vesperini, Andreia Santos and Florence Askenazy

BMC Psychiatry (2015) 15:107

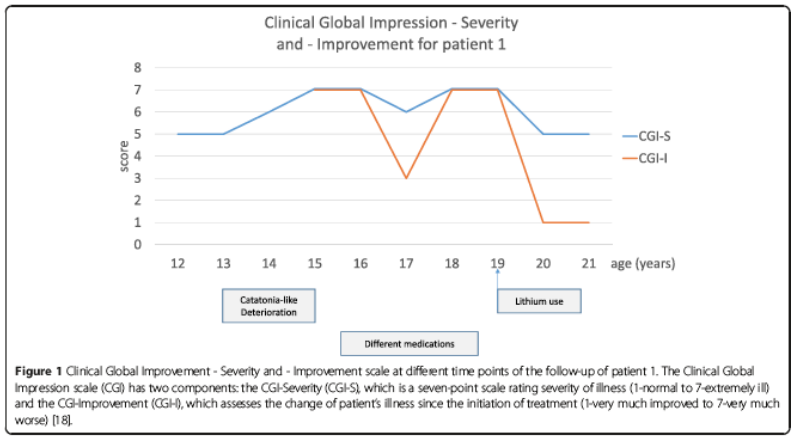


Figure 1 Clinical Global Improvement - Severity and - Improvement scale at different time points of the follow-up of patient 1. The Clinical Global Impression scale (CGI) has two components: the CGI-Severity (CGI-S), which is a seven-point scale rating severity of illness (1-normal to 7-extremely ill) and the CGI-Improvement (CGI-I), which assesses the change of patient's illness since the initiation of treatment (1-very much improved to 7-very much worse) [18].

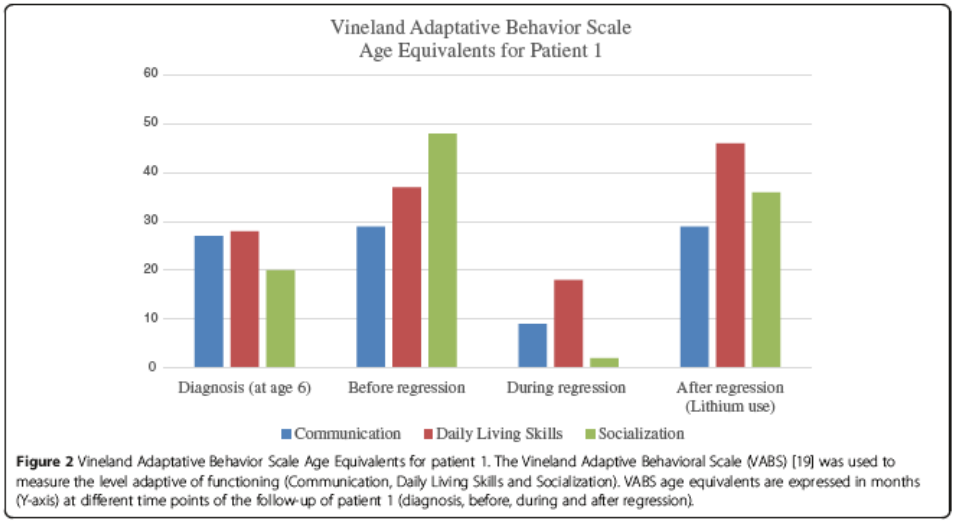


Figure 2 Vineland Adaptative Behavior Scale Age Equivalents for patient 1. The Vineland Adaptive Behavioral Scale (VABS) [19] was used to measure the level adaptive of functioning (Communication, Daily Living Skills and Socialization). VABS age equivalents are expressed in months (Y-axis) at different time points of the follow-up of patient 1 (diagnosis, before, during and after regression).

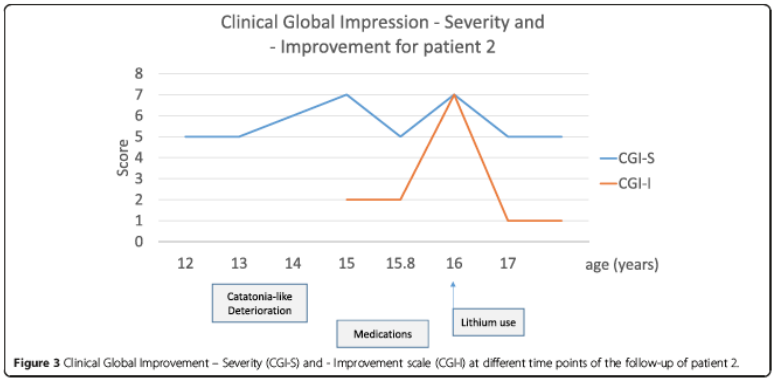


Figure 3 Clinical Global Improvement – Severity (CGI-S) and - Improvement scale (CGI-I) at different time points of the follow-up of patient 2.

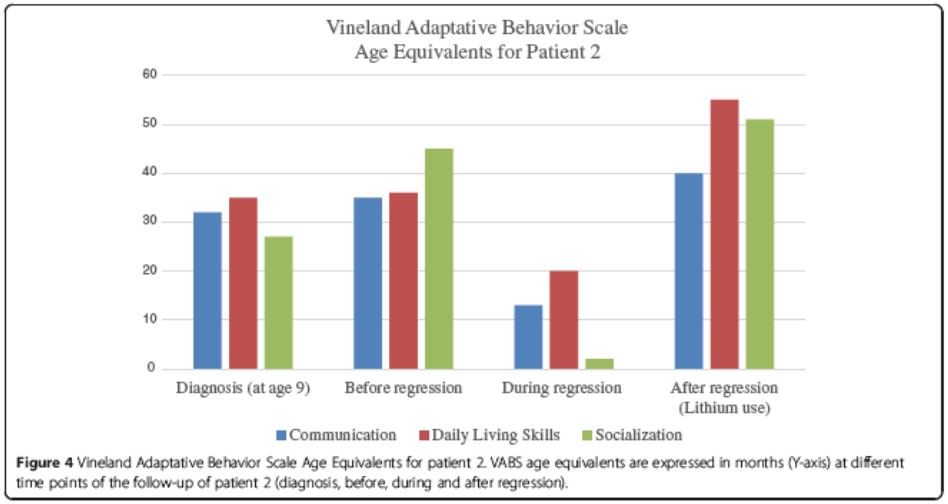
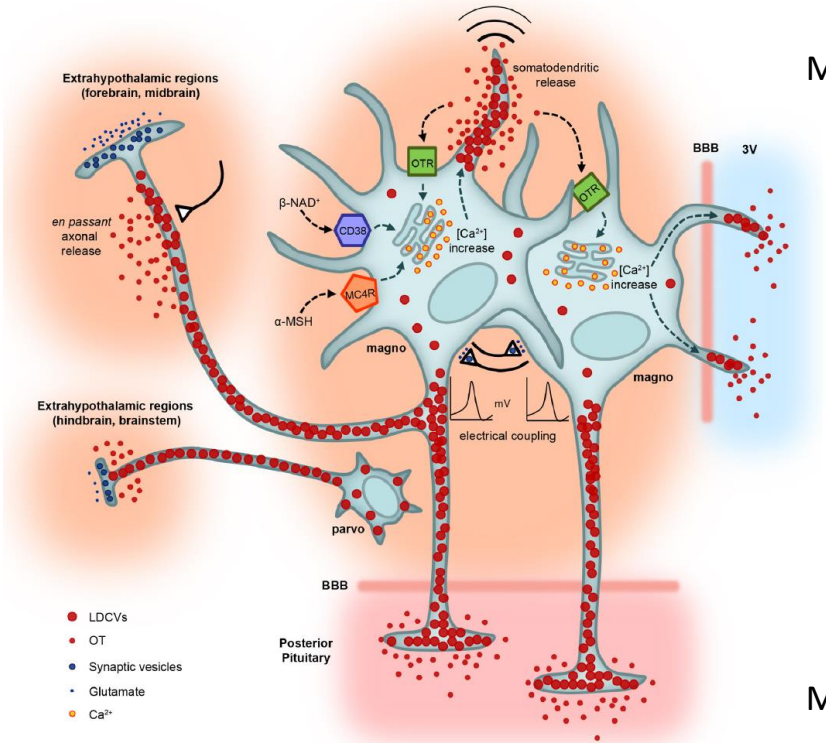


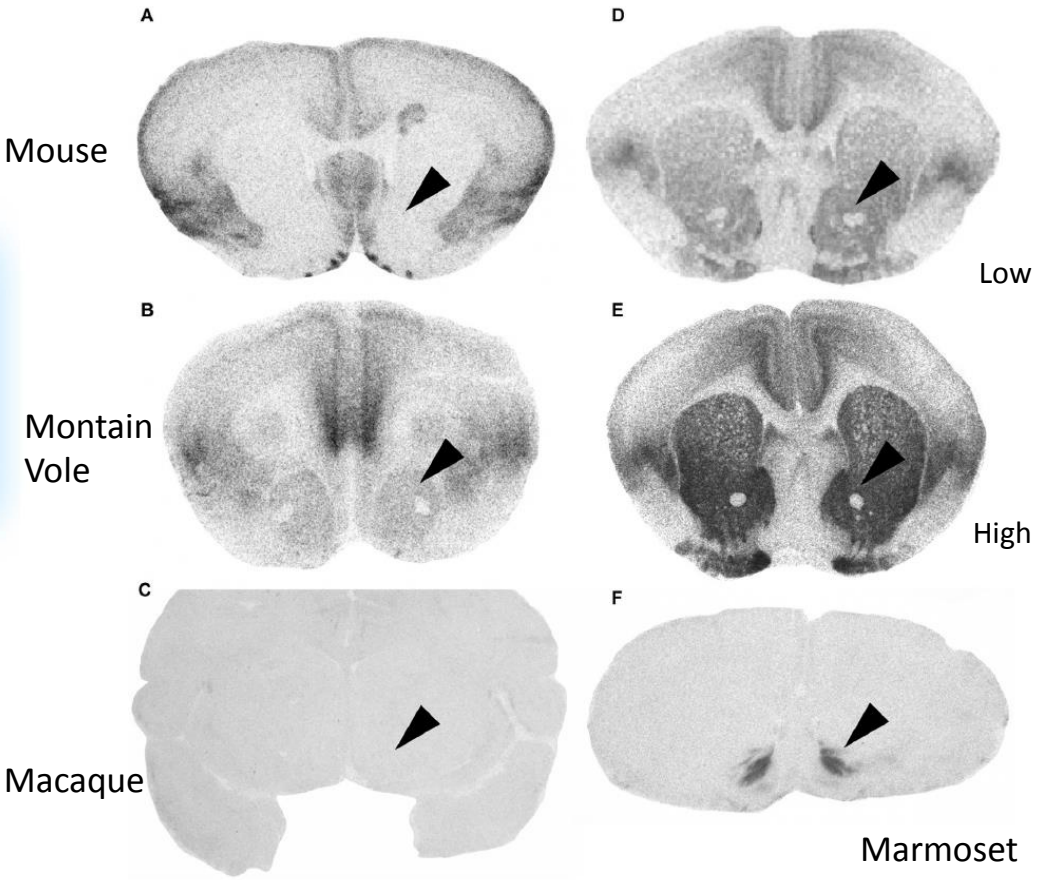
Figure 4 Vineland Adaptative Behavior Scale Age Equivalents for patient 2. VABS age equivalents are expressed in months (Y-axis) at different time points of the follow-up of patient 2 (diagnosis, before, during and after regression).

Oxytocin and vasopressin neural networks: Implications for social behavioral diversity and translational neuroscience

Zachary V. Johnson [a,b,*], Larry J. Young [a]

Neuroscience and Biobehavioral Reviews 76 (2017) 87–98





Oxytocin and vasopressin neural networks: Implications for social behavioral diversity and translational neuroscience

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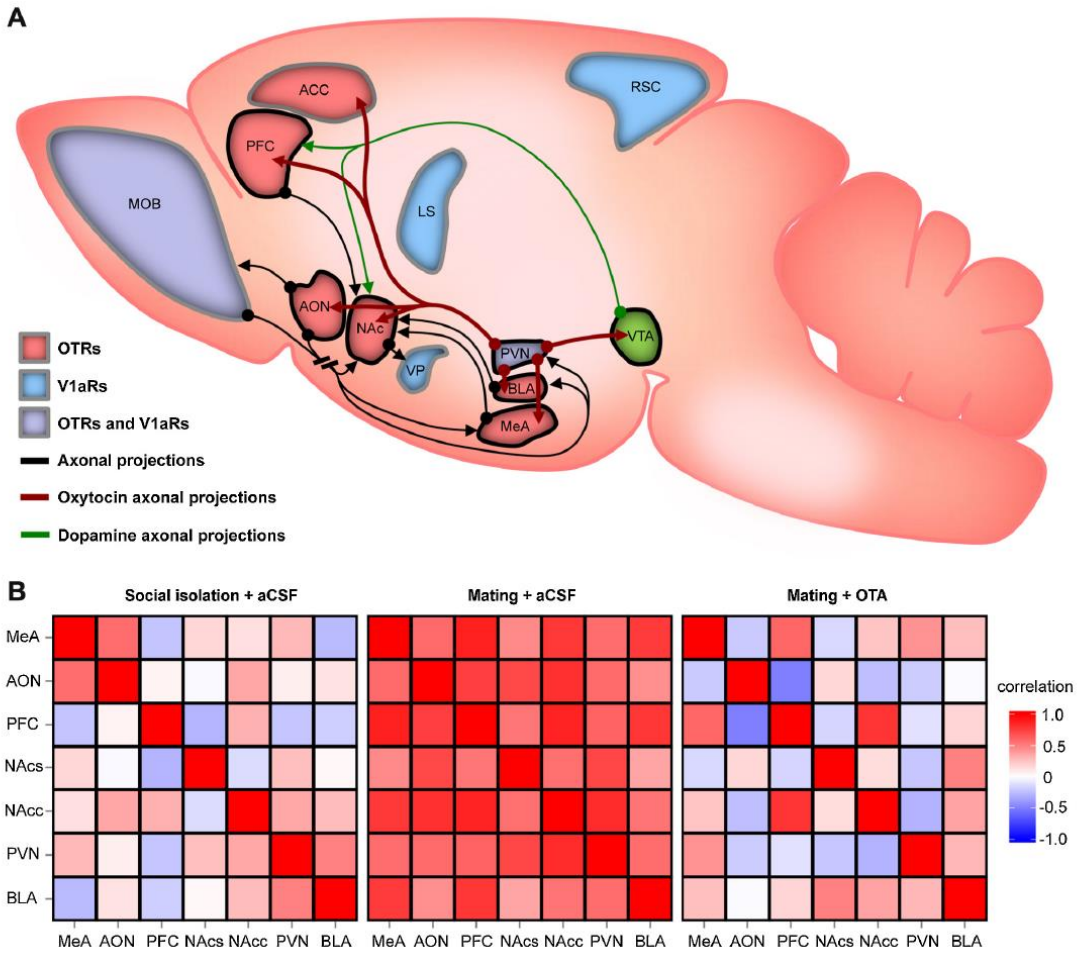


Genes Related to Oxytocin and Arginine-Vasopressin Pathways: Associations with Autism Spectrum Disorders

Rong Zhang[1,2,3] · Hong-Feng Zhang[4] · Ji-Sheng Han[1,2,3] · Song-Ping Han[1,2,3]

Table 1 Polymorphisms of genes encoding elements of the OXT and AVP pathways that are associated with ASD and autistic symptoms.

Genes	Year	Design	Sample size	Ethnicity	Significant polymorphism	Refs.
OXT	2009	Family	149 families	Israeli	rs6133010	[22]
	2014		1771 children	Swedish	rs2770378	[23]
	2016	Family	156 families	Not specified	rs6084258, rs6133010 and rs2740204	[25]
OXTR	2005	Family	195 families	Han Chinese	rs2254298, rs53576	[35]
	2007	Family	57 families	Caucasian	rs2254298	[37]
	2008	Family	133 families	Israeli	rs2268494, rs1042778	[38]
	2010	Family	215 families	Japanese	No	[39]
	2010	Case-control	280 cases, 440 controls	Japanese	rs237887, rs2264891, rs2254298, rs2268495	[39]
	2010	Family	199 families	Caucasian	No	[44]
	2010	Family	100 families	Caucasian	rs2270465	[45]
	2011	Family	1238 families	Caucasian	rs2268493, rs1042778, rs7632287	[43]
	2013	Case-control	132 cases, 248 controls	Japanese	rs35062132-G	[42]
	2014	Case-control	76 cases, 99 controls	Swiss	rs2254298, rs53576	[36]
	2014	Case-control	118 cases, 412 controls	Caucasian	rs2268493	[41]
	2015		105 cases	Japanese	28 variants	[46]
	2015 (a meta-analysis)	Family and case-control	2525 families, 454 cases, 595 control	Han Chinese, Israeli, Caucasian, Japanese	rs7632287, rs237887, rs2268491, and rs2254298	[11]
	2016	Family	175 families	German	rs237889-A	[40]
AVPR1a	2002	Family	115 families	Caucasian, African- and Asian-American	RS3	[72]
	2004	Family	65 families	Not specified	RS1 and RS3	[12]
	2006	Family	116 families	Not specified	Haplotype RS1-RS3-AVR	[73]
	2010	Family	148 families	Korean	RS1 and RS3	[74]
	2011	Family	177 families	Irish	RS1 (short alleles), rs11174815	[75]
	2015	Family	205 families	Finnish	RS1 (short alleles), Haplotype rs7307997-rs1042615, and RS3-rs1042615	[76]
AVPR1b	2016	Family	207 families	Caucasian, African- and Asian-American	rs35369693 and rs28632197	[78]
CD38	2010	Family	104 families	Caucasian	rs6449197, rs3796863	[66]
	2010	Family	170 families	Israeli	rs3796863, rs3796878, rs3796867, rs4516711, rs10805347, rs1803404, rs1130169	[15]
	2010	Family	188 families	Japanese	–	[66]
	2014		1771 children	Swedish	rs6449182	[23]

OXT, oxytocin; *OXTR*, oxytocin receptor; *AVPR1a*, AVP receptor 1a; *AVPR1b*, AVP receptor 1b; *CD38*, cyclic ADP ribose hydrolase; RS1 and RS3, promoter microsatellites of *AVPR1a*.

RESEARCH ARTICLE

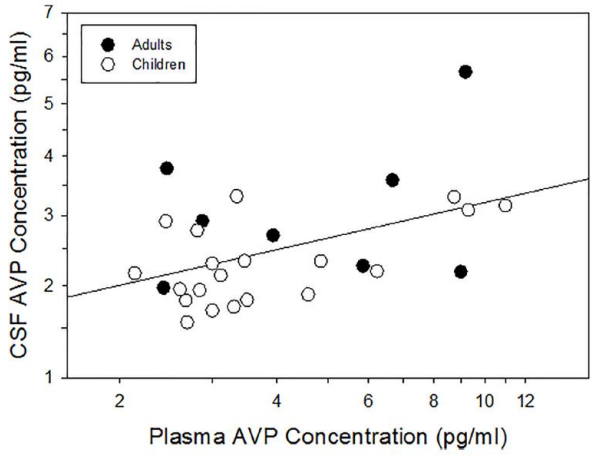
Arginine Vasopressin Is a Blood-Based Biomarker of Social Functioning in Children with Autism

Dean S. Carson[1], Joseph P. Garner[1,2], Shellie A. Hyde[1], Robin A. Libove[1], Sean W. Berquist[1], Kirsten B. Hornbeak[1], Lisa P. Jackson[1], Raena D. Sumiyoshi[1], Christopher L. Howerton[2], Sadie L. Hannah[3], Sonia Partap[4], Jennifer M. Phillips[1], Antonio Y. Hardan[1], Karen J. Parker[1]*

PLOS ONE | DOI:10.1371/journal.pone.0132224 July 22, 2015

Table 2. Participant characteristics.

Participants		Sex*		Ethnicity*					
	N	Female	Male	Caucasian	Asian	Other	Age*	Full-scale IQ*	Blood collection time, min[ns]
ASD									
Autistic	29	3	26	15	7	7	7.92 ± 0.45[ab]	83.55 ± 3.53[a]	12:25 PM ± 15.98
PDD-NOS	28	6	22	22	2	4	9.25 ± 0.44[a]	99.79 ± 4.00[b]	12:18 PM ± 14.14
Sibling	47	20	27	24	15	8	7.89 ± 0.43[ab]	109.18 ± 1.84[c]	12:38 PM ± 9.42
Control	55	19	36	41	3	11	7.31 ± 0.41[b]	115.60 ± 1.30[c]	12:33 PM ± 7.38



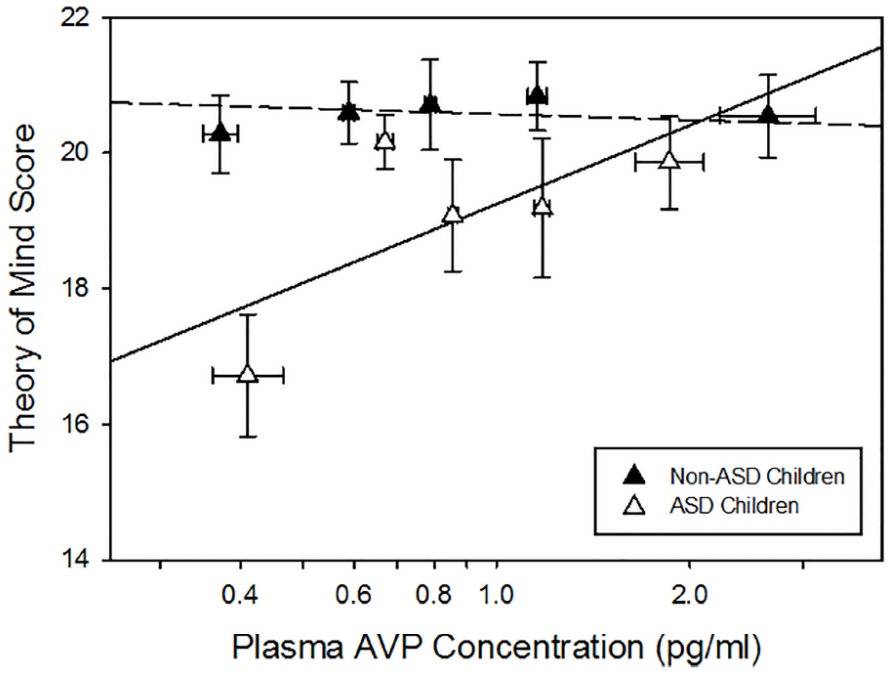
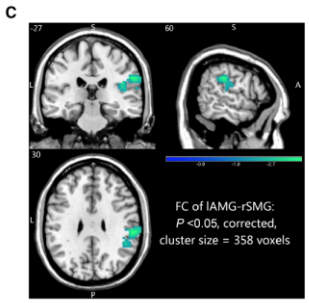


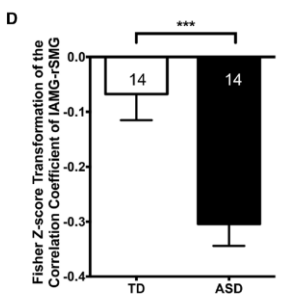
Fig 2. Blood AVP concentration predicts NEPSY Theory of Mind score in ASD children (autistic and PDD-NOS) but not in non-ASD children (sibling and neurotypical control). Data have been corrected for the following blocking factors: age, sex, ethnicity, blood sample collection time, and full scale IQ. Data are plotted as a mean and standard error for each AVP quintile within the ASD and non-ASD groups. The means shown are of the log transformed plasma AVP values used in the analysis itself. ASD Quintile (Q) Q1 $n = 11$, Q2 $n = 12$, Q3 $n = 11$, Q4 $n = 11$, Q5 $n = 12$; Non-ASD Q1 $n = 20$, Q2 $n = 21$, Q3 $n = 21$, Q4 $n = 19$, Q5 $n = 21$.

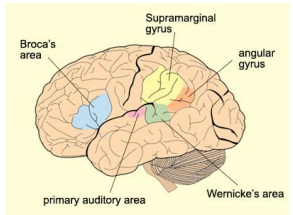
A Volumetric and Functional Connectivity MRI Study of Brain Arginine-Vasopressin Pathways in Autistic Children

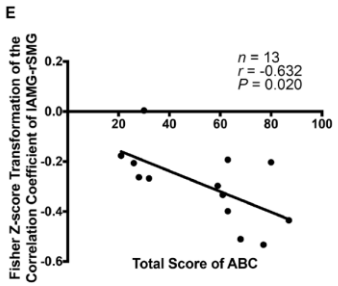
Xiao-Jing Shou[1,2,3] · Xin-Jie Xu[1,2,3] · Xiang-Zhu Zeng[4] · Ying Liu[4] · Hui-Shu Yuan[4] · Yan Xing[5] · Mei-Xiang Jia[6,7] · Qing-Yun Wei[8] · Song-Ping Han[1] · Rong Zhang[1,2,3] · Ji-Sheng Han[1,2,3]

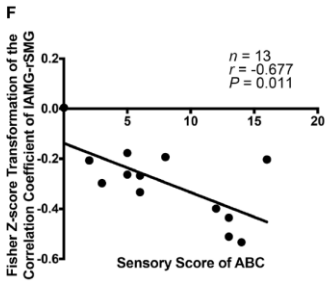
Neurosci. Bull. April, 2017, 33(2):130–142

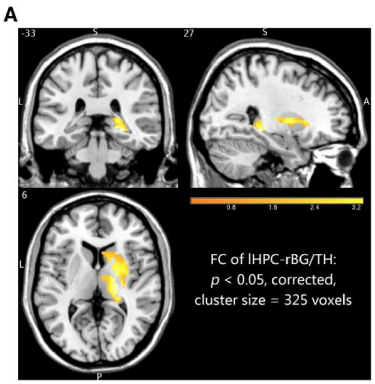


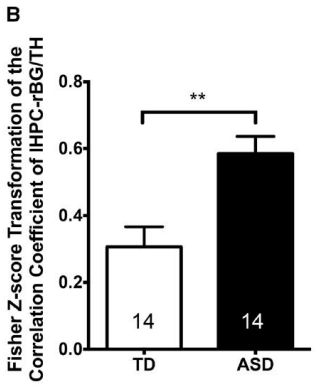


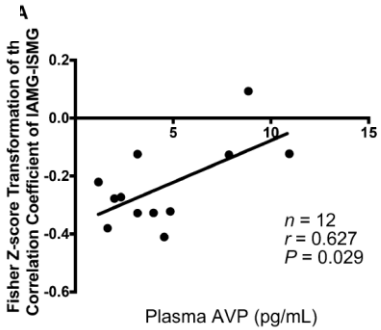


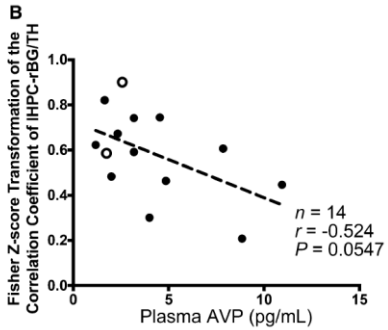


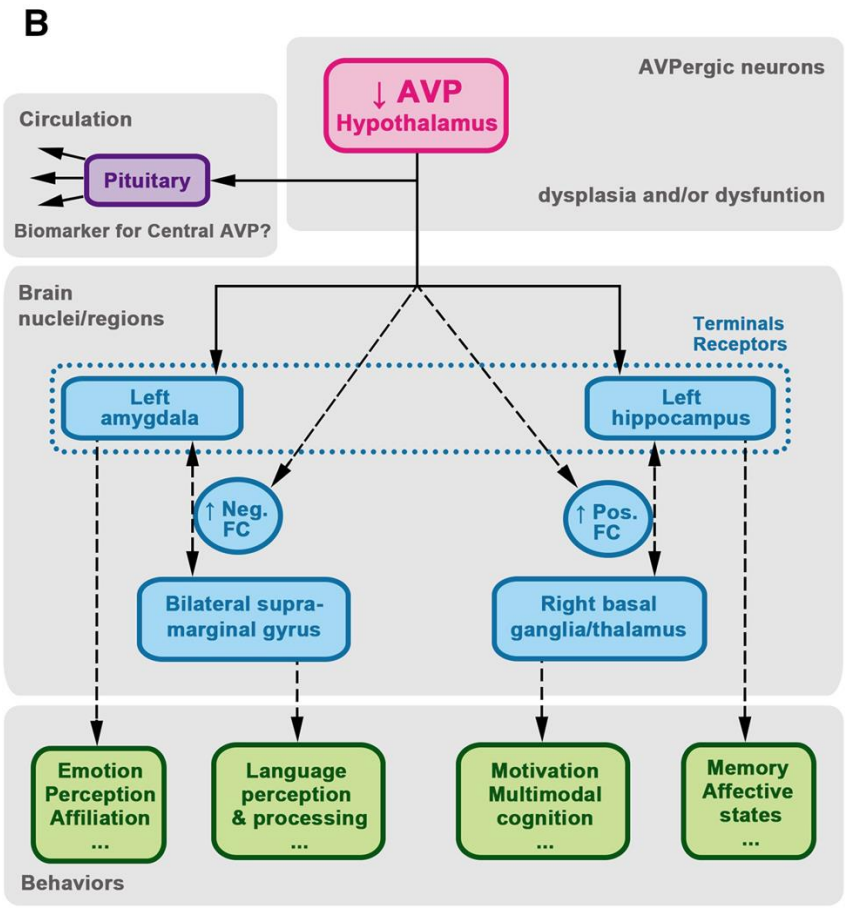








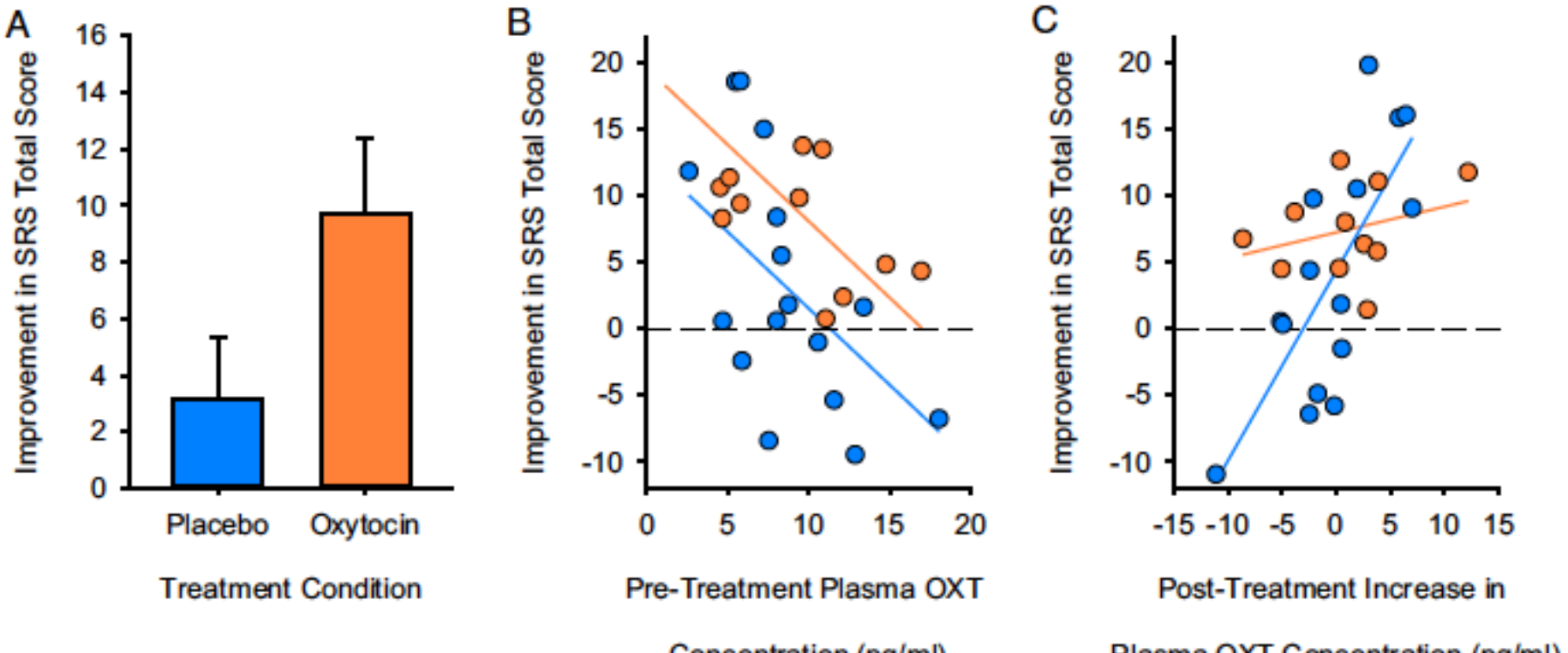




Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism

Karen J. Parker[a,1], Ozge Oztan[a], Robin A. Libove[a], Raena D. Sumiyoshi[a], Lisa P. Jackson[a], Debra S. Karhson[a], Jacqueline E. Summers[a], Kyle E. Hinman[a], Kara S. Motonaga[b], Jennifer M. Phillips[a], Dean S. Carson[a], Joseph P. Garner[a,c], and Antonio Y. Hardan[a]

		Sex		Ethnicity					
Treatment	*N*	Female	Male	Caucasian	Asian	Other	Age, y	Full-scale IQ	Pretreatment SRS Total Raw Score
Oxytocin	14	1	13	6	4	4	9.35 ± 2.34	65.21 ± 28.91	106.61 ± 30.65
Placebo	18	4	14	8	5	5	8.13 ± 1.87	67.39 ± 26.43	106.33 ± 25.00



Future research trends

Innovative Medicine Initiative

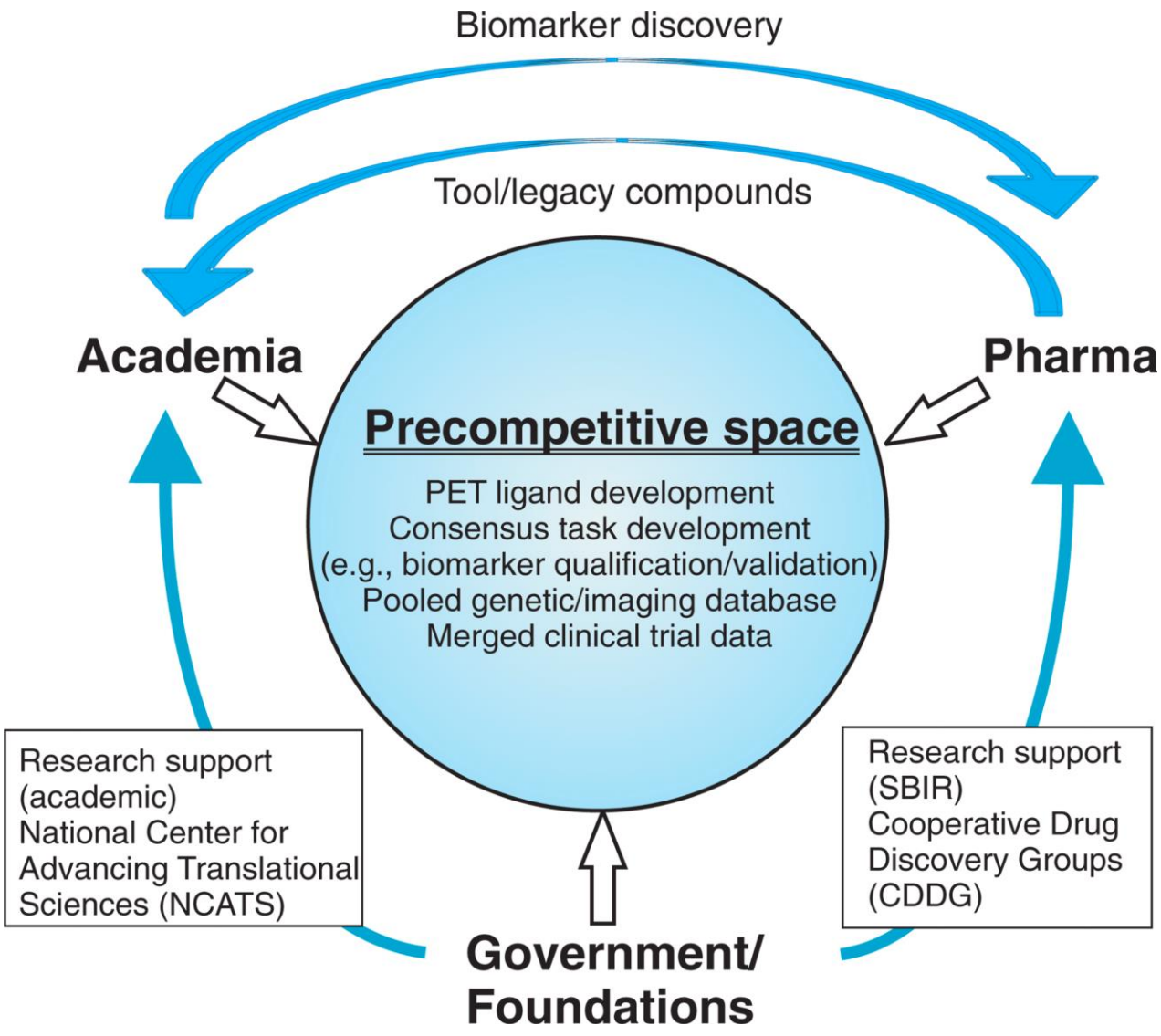
Translational Endpoints in Autism:

Development and validation of translational approaches for the advancement of novel therapies to treat ASD

Setting of new standards in research and clinical development to aid the drug discovery process

Identification and development of expert clinical sites across Europe to run clinical studies and trials and so create an interactive platform for ASD professionals and patients

New research prospective for the use of medications



IMI2

10th Call for proposals

Innovative Medicine Initiative

Topic 8: **Personalised medicine approaches in autism spectrum disorders**

Topic identifier: IMI2-2016-10-08

Topic 4: **Creation of a pan European peadiatric clinical Trial network**

Topic identifier: : IMI2-2016-10-04

conect 4children
COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS 4 CHILDREN

European clinical network: autism spectrum disorder assessments and patient characterisation

Karen L. Ashwood · Jan Buitelaar · Declan Murphy · Will Spooren · Tony Charman

EU-AIMS
Autism Research in Europe

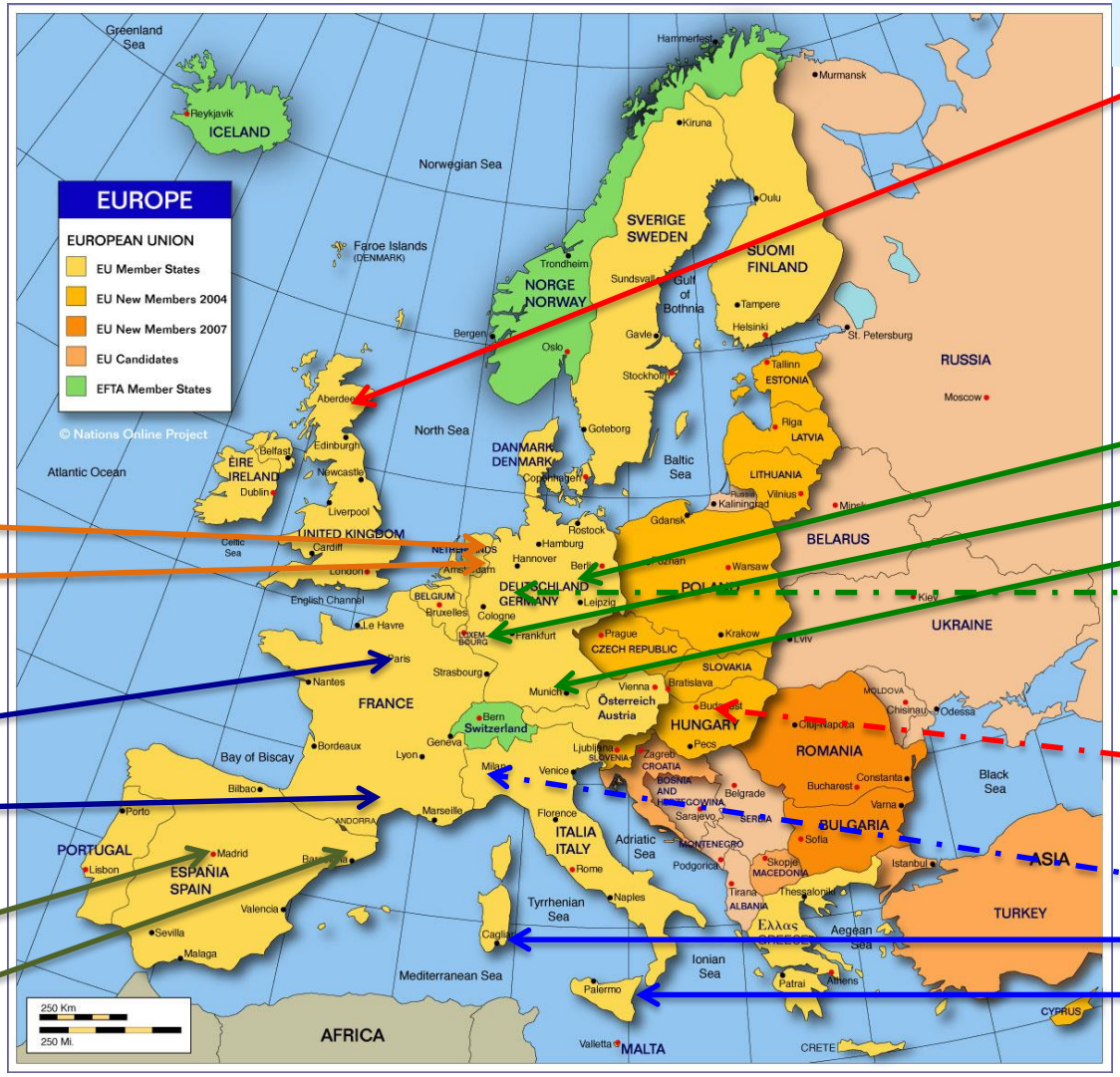
May indicate multiple sites in the same city/area

ECAP 2014

EnprEMA
European network of paediatric research at the European Medicines Agency

Child & Adolescent Psychopharmacology Network-ECAPN

Melbourne



Groningen
Nijmegen

Paris
Montpellier

Madrid
Barcelona

Dresden
Mannheim
Ulm
Wurzburg

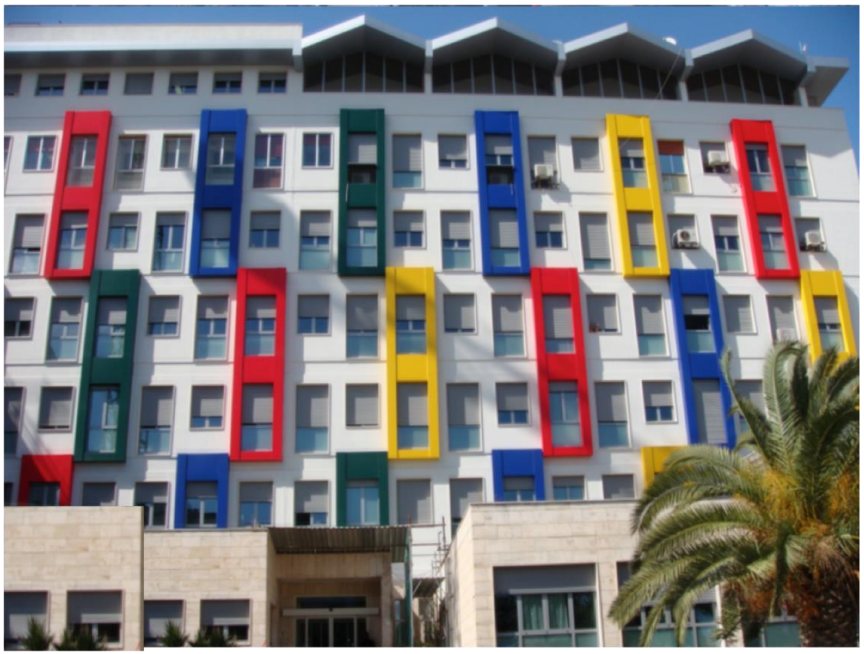
Budapest

Torino
Cagliari
Messina

Linee guida per l'uso dei farmaci negli ASD

- Identificare specifici ***sintomi target*** della terapia farmacologica
- Iniziare alle ***minime dosi*** possibili
- Incrementi posologici a dosaggi minimi per volta
- Incrementi posologici dopo un periodo di *tempo sufficiente* per valutare i massimi effetti della dose in corso
- ***Monitorare*** gli effetti su specifici sintomi target
- ***Monitorare routinariamente*** gli effetti collaterali
- Evitare di usare *politerapie* quando è possibile
- Cambiare farmaco solo dopo un periodo sufficiente per valutare effetti della dose massima (salvo gravi effetti coll.)
- La combinazione con altri farmaci dovrebbe avvenire introducendo ***un farmaco per volta*** in un intervallo di tempo sufficientemente lungo da permettere una valutazione adeguata degli effetti di questo (ameno che un ritardo non determini seri rischi)

Domande ?



azuddas@unica.it

Cost per Genome