Opportunità e limiti della psicofarmacologia nell'età evolutiva

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Sommario

- Uso esteso di farmaci *off-label* (sintomi associati)
- Tentativi di sviluppo di nuovi target su modelli fisiopatologici (sintomi *core*)
- Risultati non incoraggianti degli studi controllati (FraX, mTOR)
- Prospettive future: network collaborativi (fondi pubblico-privati)

What parents value most as outcome

- Happiness
- Anxiety
- Hypersensitivity
- Sleep problem
- Distress
- Relation with siblings
- Parent stress

Interventi Terapeutici

	Target group	Evidence for effectiveness*	Intervention framework and goals
Targeted behavioural intervention for anxiety and aggression			
Cognitive behavioural therapy; ABA	Children, adolescents, and adults	Not established	Cognitive behavioural therapy to reduce anxiety: modifies dysfunctional thoughts; compared with ordinary cognitive behavioural therapy, therapy modified for autism relies less on introspection and more on teaching of practical adaptive skills with concrete instructions; often combined with social skill training; systematic desensitisation is useful particularly for individuals with intellectual disability ABA to reduce aggression: applies functional behaviour assessment and teaches alternative behaviours; skills include antecedent manipulations, changes in instructional context, reinforcement-based strategies, and behaviour reduction strategies
Parent-mediated early intervention			
Training for joint attention, parent–child interaction, and communication; or models like pivotal response training, parent delivery of the ESDM, and More Than Words	Young children	Insufficient or low	Teaches parent or caregiver intervention strategies that can be applied in home and community settings, potentially increasing parental efficacy and enabling child's generalisation of skills to real-life settings
Drugs			
Antipsychotic drugs			
Risperidone; aripiprazole	Children, adolescents, and adults	Children: moderate (risperidone) or high (aripiprazole) for effect, and high for adverse effect; adolescents and adults: insufficient, but might have effects as in children	To reduce challenging behaviours and repetitive behaviours; potential adverse effects include weight gain, sedation, extrapyramidal symptoms, and hyperprolactinaemia (risperidone)
Selective serotonin reuptake inhibitors			
Citalopram; escitalopram; fluoxetine; and others	Children, adolescents, and adults	Insufficient for effect and adverse effect	To reduce repetitive behaviours; potential adverse effects include activation symptoms (agitation) and gastrointestinal discomfort
Stimulant			
Methylphenidate	Children, adolescents, and adults	Insufficient for effect and adverse effect; might be helpful; clinical guideline established	To reduce attention-deficit hyperactivity disorder symptoms; potential adverse effects include insomnia, decreased appetite, weight loss, headache, and irritability

Baron-Cohen , *Lancet* 2013

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

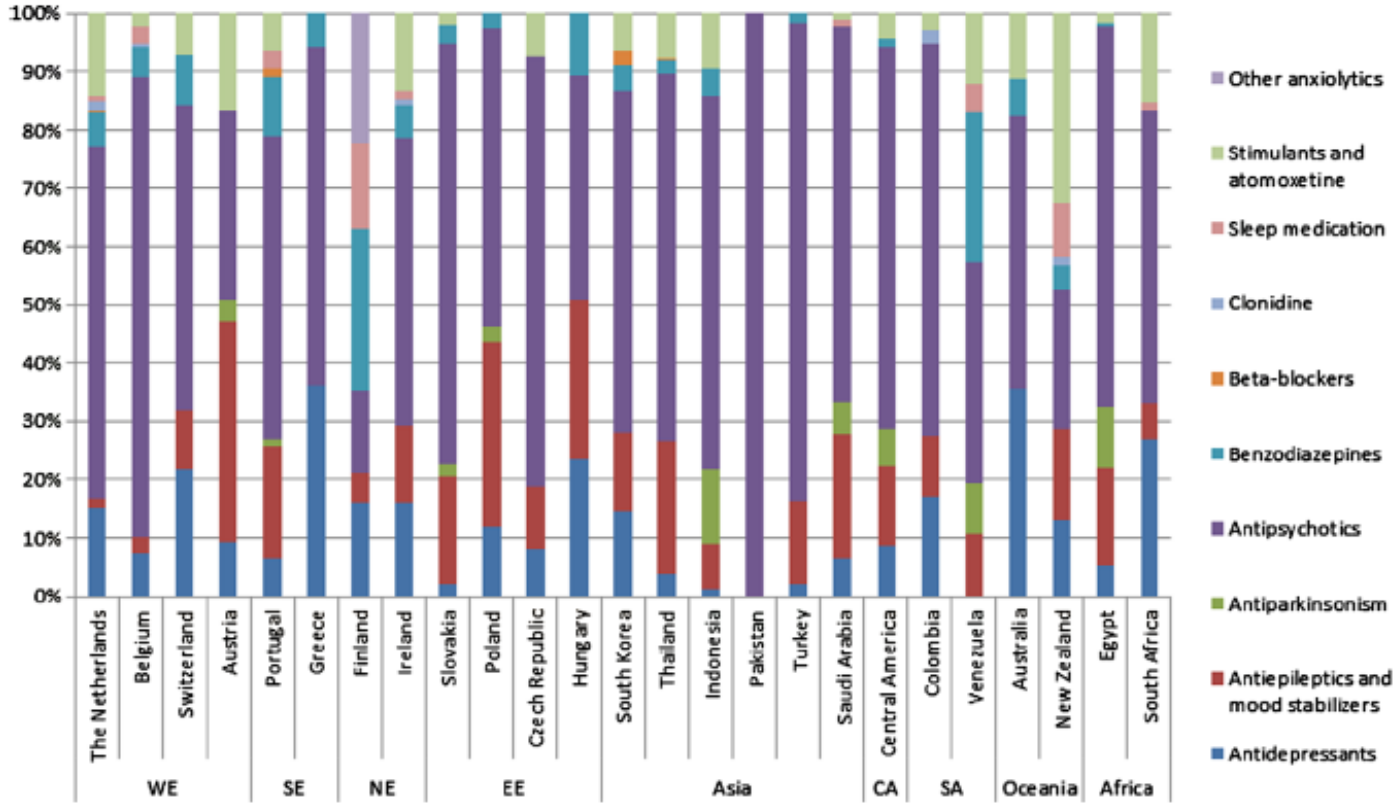


Figure 1. Percentage of different psychotropic drug classes for the treatment of autism spectrum disorder. WE, Western Europe; SE, Southern Europe; NE, Northern Europe; EE, Eastern Europe; CA, Central America; SA, South America.

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 behavioural problems in **autism** 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

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			

The New England Journal of Medicine

RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK*

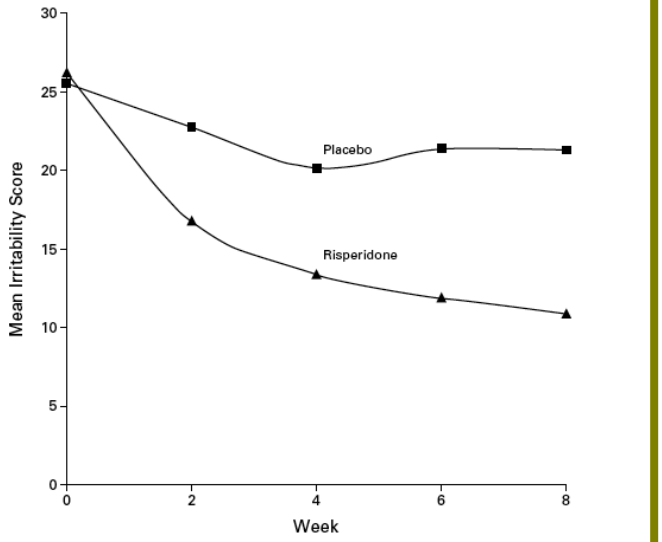
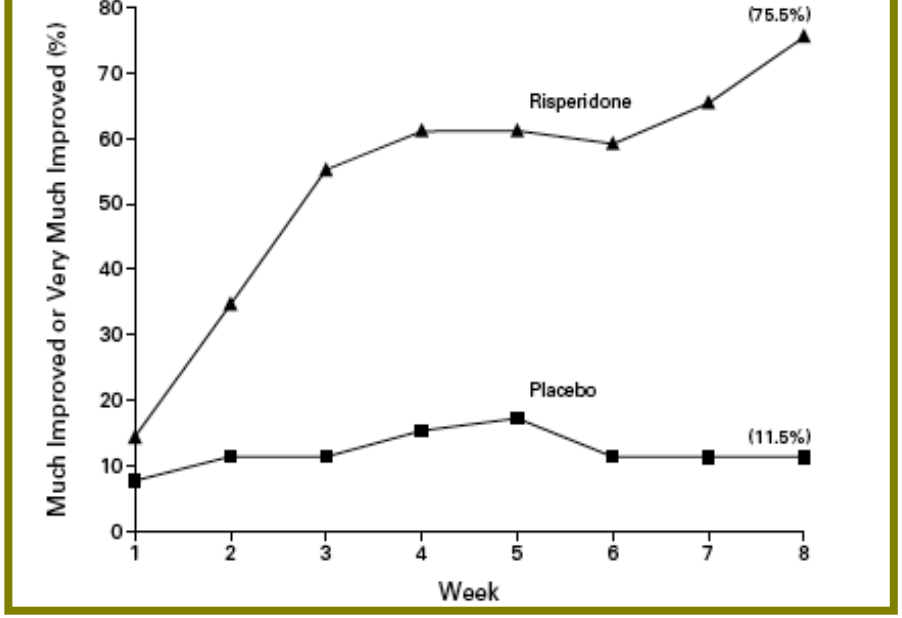


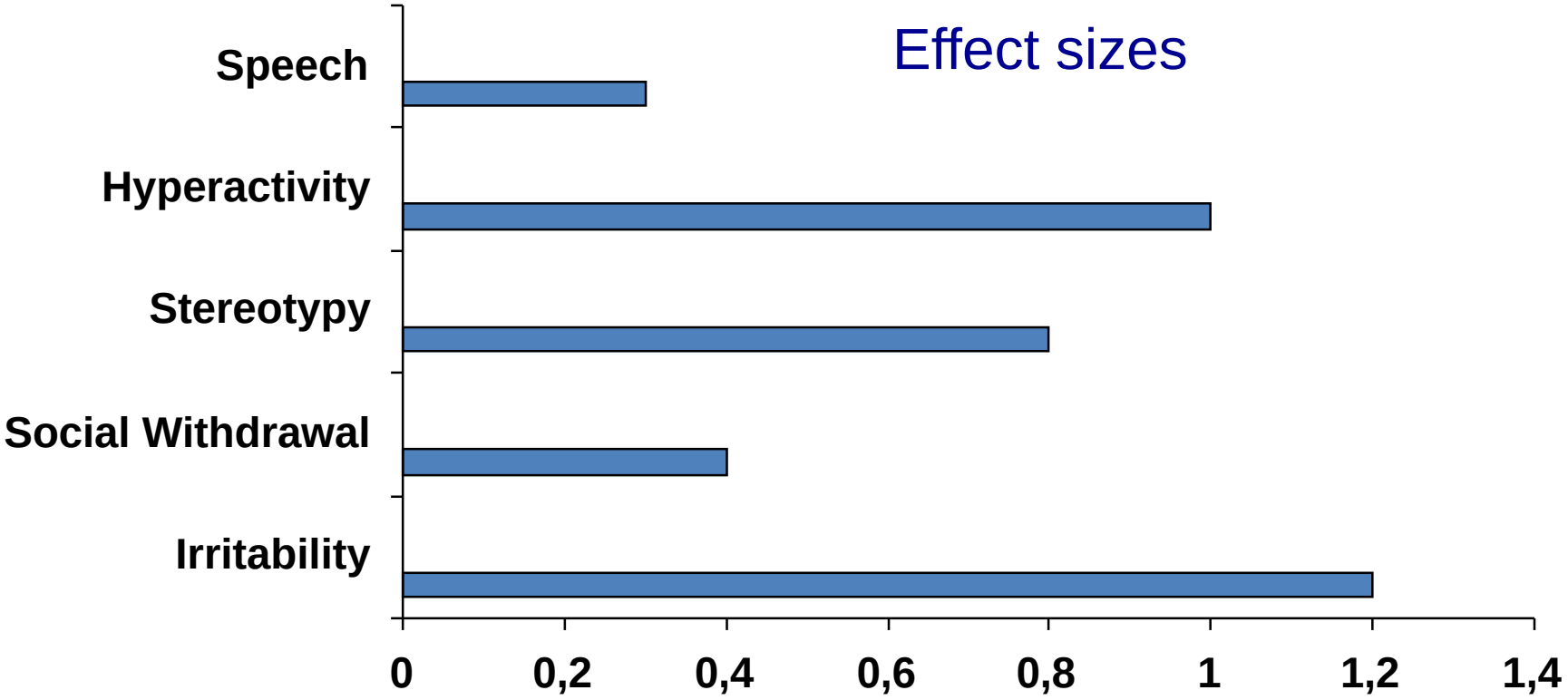
Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.



Effect size: 1.1

NNT: 1.6

Risperidone in children with autism and severe irritability



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

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

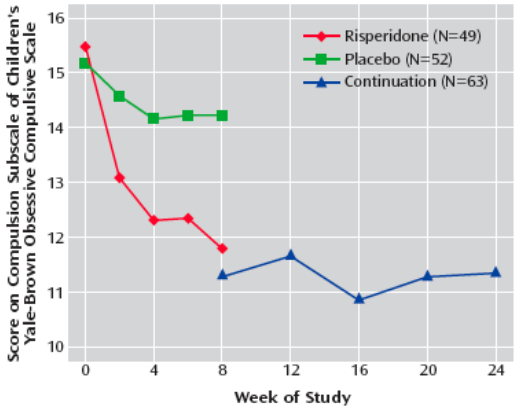


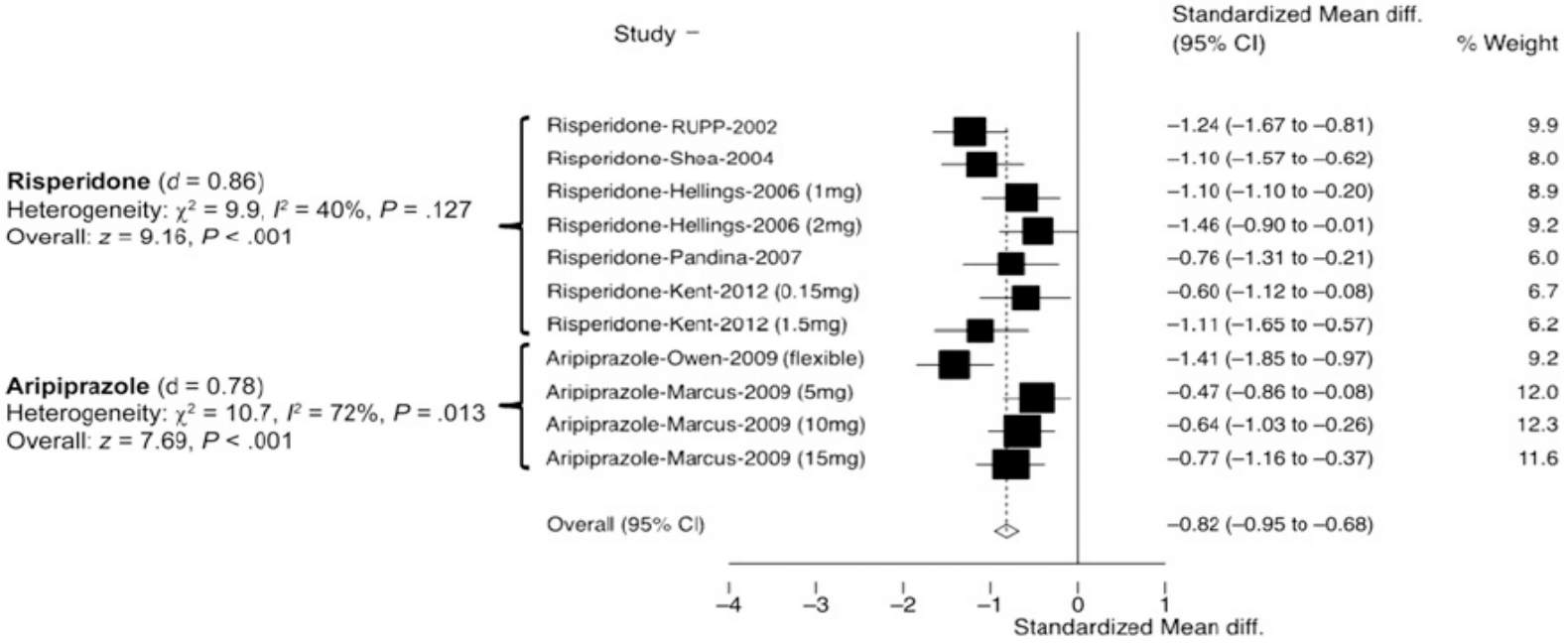
TABLE 1. Scores on the Ritvo-Freeman Real Life Rating Scale of Children and Adolescents With Autism in a Placebo-Controlled Risperidone Trial and Open-Label Continuation Study

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			

Un secondo studio del RUPP Network ha mostrato che il Risperidone non migliora la compromissione nell'area della comunicazione e le competenze sociali, ma può migliorare significativamente interessi e comportamenti ripetitivi *(McDougle et al. 2005*).

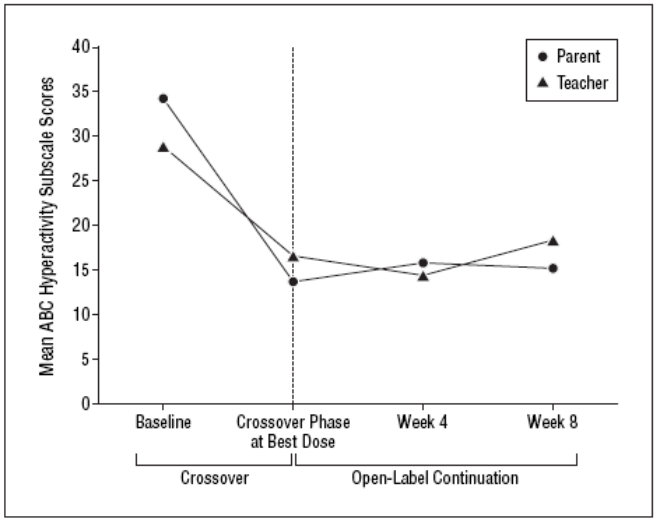
Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis

PEDIATRICS Volume 137, number S2, February 2016



Due RCT (*Marcus et al, 2009; Owen et al, 2009*) di 8 settimane hanno esaminato l'efficacia dell' Aripiprazolo nel trattamento dell'irritabilità in bambini e adolescenti (dai 6 ai 17 anni) con diagnosi di disturbo autistico e sintomi quali rabbia, aggressività e autolesionismo. Nello studio di Owen 98 pazienti hanno concluso le valutazioni previste, mentre in quello di Marcus 178 pazienti.

In entrambi gli studi l'aripiprazolo è risultato significativamente più efficace del placebo nel trattamento dell'irritabilità, dell'iperattività e delle stereotipie motorie (misurate con le sottoscale corrispondenti dell'ABC, *Aberrant Behavior Checklist*). Lo studio di Owens ha inoltre evidenziato miglioramento nella sottoscala sul linguaggio inappropriato e lo studio di Marcus ha evidenziato miglioramento dei sintomi ossessivo-compulsivi (valutati alla scala CY-BOCS- *Children Yale-Brown Obsessive-Compulsive Scale*).



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

-Responder: 'much' or 'very much improved' ed almeno 25% di riduzione ai punteggi di iperattività
-35/72 soggetti (49%) hanno risposto al MPH
13/72 (18%) dei soggetti esposti a MPH hanno sospeso per eventi avversi
• L'irritabilità (n = 6) è la causa più frequente di interruzione
• Riduzione di appetito, ritardato addormentamento ed instabilità affettiva sono stati più frequenti con MPH che con placebo

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

– test-dose per 7 giorni
– Doppio cieco per 4 settimane a 3 livelli di dosaggio (0.125, 0.25, 0.50 mg/kg/dose) di MPH o placebo in ordine casuale dato 3 volte al giorno
– Disegno "within subject" (crossover study: ogni bambino riceveva le tre dosi ed il placebo)

RUPP, Arch G.Psych. 2005

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

Hollander et al. *AJP 2012*

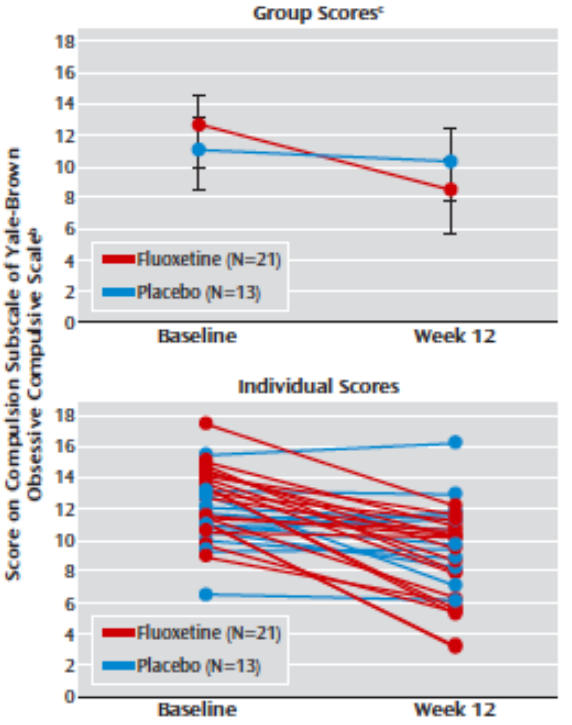
Objective: The effects of fluoxetine and placebo on repetitive behaviors and global severity were compared in adults with autism spectrum disorders (ASDs).

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]



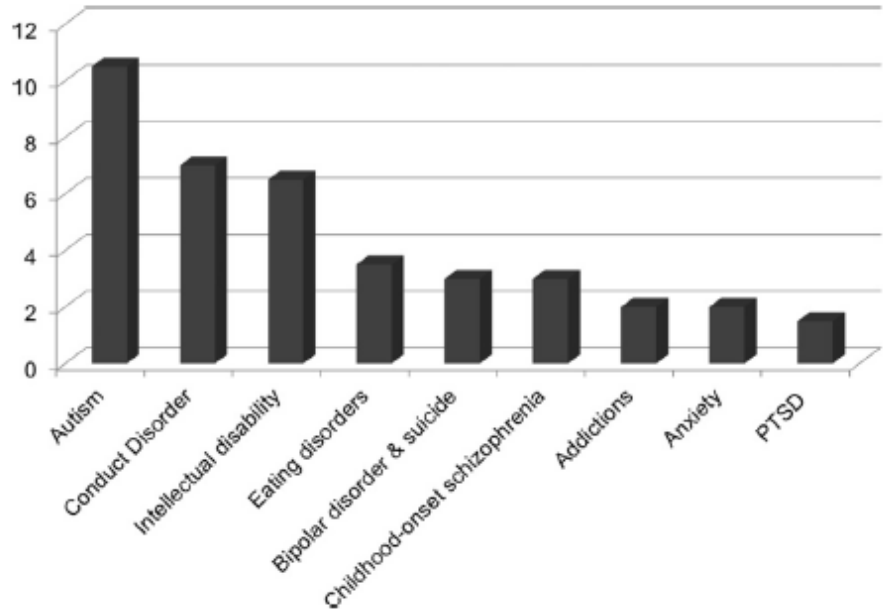
[a] Predicted linear change based on mixed-effects regression with random slopes and intercepts.
[b] Administered by evaluators independent of treatment.
[c] Mean values and standard deviations.

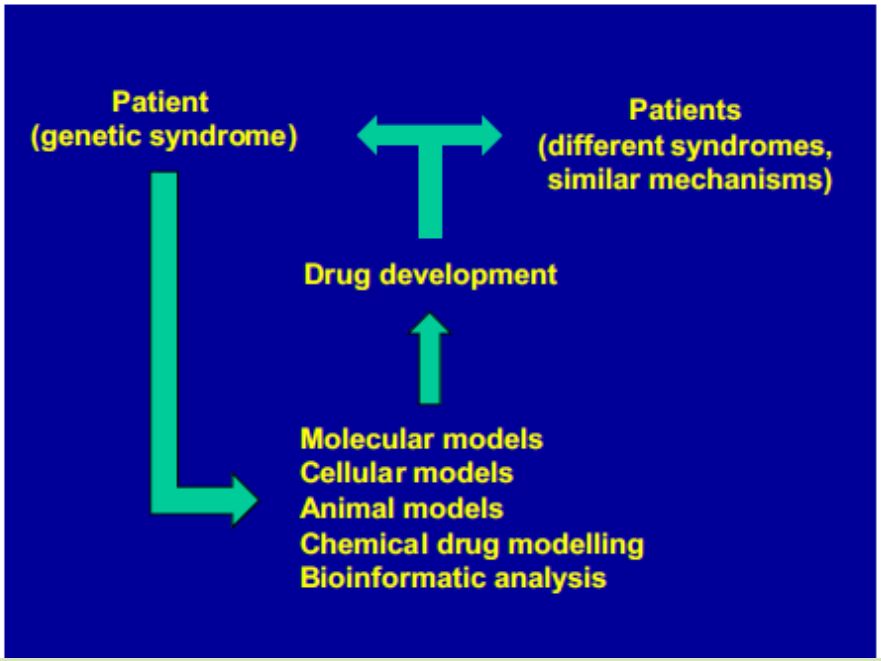
REVIEW

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

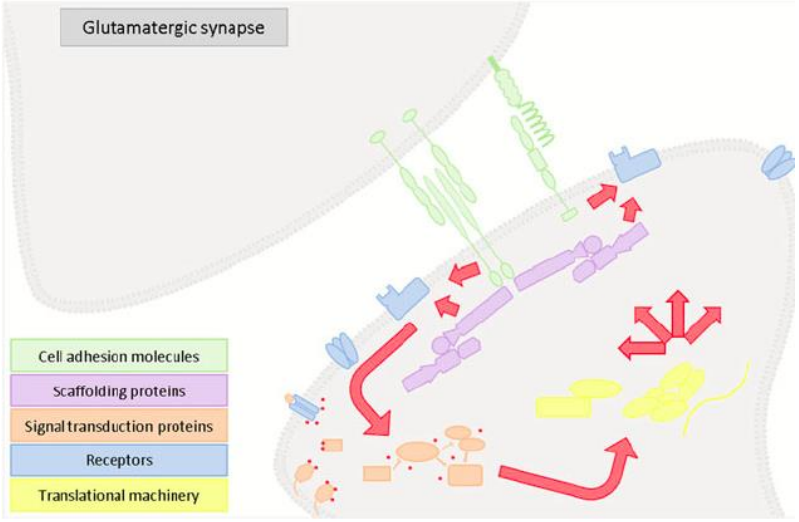




Le recenti ricerche si stanno rivolgendo verso i fattori eziologici nel campo della genetica, epigenetica, fattori ormonali, immunologici, prenatali e ambientali che contribuiscono allo sviluppo dei Disturbi dello Spettro Autistico.
La comprensione dell'eziologia del Disturbo da un punto di vista biologico consentirà una definizione più accurata e da un punto di vista clinico, permetterà lo sviluppo di farmaci mirati verso le basi biologiche dell'ASD e quindi essendo maggiormente specifici, potranno migliorare i sintomi nucleari che caratterizzano il Disturbo *(Posey DJ, 2008).*

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* *(maturazione e stabilizzazione sinaptica):*
- Cadherin (CDH)
- Protocadherin (PCDH)
- Contactine (CNCTN)

Cyliation genes: AHI 1, DISC

Scaffolding proteins:

- SHANK 1, SHANK 2, SHANK 2 (sintesi di proteine sinaptiche
- 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 transcript)ion, RNA processing

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

Genes & Syndromic autism (20%)

- Fragile X	FMR1
- Rett Syndrom	MECP2
- Tubererous Sclerosis	TSC 1 / TSC 2
- Angelman Syndrome	UBE3A
- Neurofibromatosis 1	NF1
- Hamartoma Tumor Syndrome	PTEN

Mutazioni a carico di geni che regolano la sintesi di proteine sinaptiche (FMR1, TSC1/2, EIF4E, PTEN), aumentati livelli di plasticità correlati all'aumentata disponibilità di proteine nello spazio sinaptico può interferire con la connettività sinaptica compromettendo le performance e determinando una compromissione cognitiva (*Kelleher, 2008).*

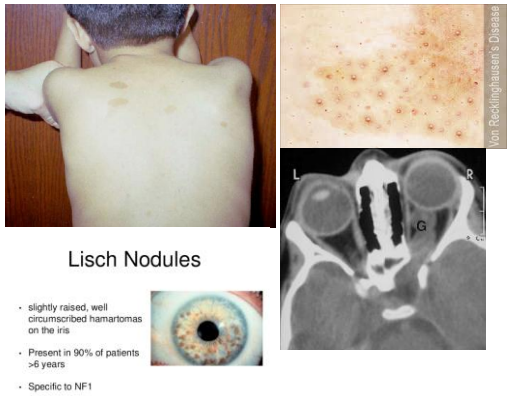
- *Joubert Syndrome*	Abelson's Helper Interation (AHI 1)
- *Phelan-Mc Dermitt*	SHANCK 3
- *3 p deletion*	cell adesion molecules (CNTN4, CHL1, CNTN6)
- *Timoty Syndrome*	L-type Ca++ channel (CACNA1Ctype)

Kleijer et al. *Neuropsychopharmacology* 2014

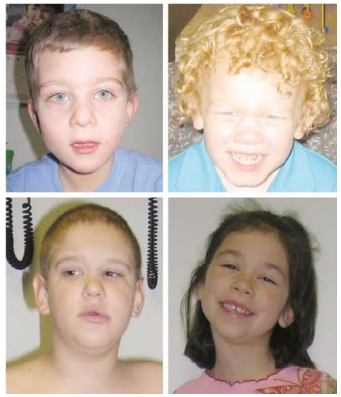
Genes & Syndromic autism (20%)

S. Phelan-Mc Dermitt 22q13 Deletion

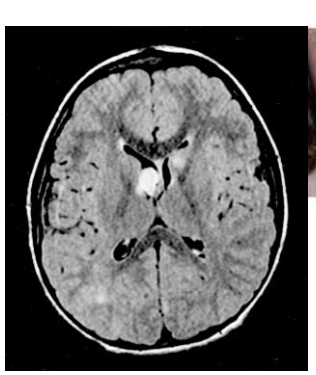
SHANCK 3



Neurofibromatosis 1 NF1



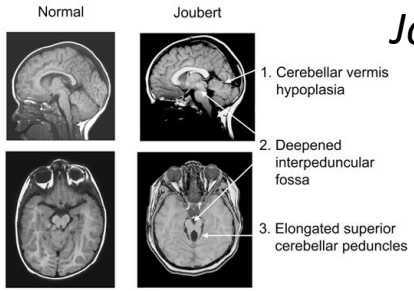
Fragile X FMR1



Tubererous Sclerosis TSC 1 / TSC 2

- Hand and foot syndactyly: 100%
- Facial dysmorphysms: 89%, including low set ears, flat nasal bridge, thin upper lip
- Neuropsychiatric involvement: 82%, including autism, autism spectrum disorder, social development delay, mental retardation, seizures, language delay, motor delay

Timoty Syndrome CACNA1C-type



Joubert Syndrome AHI 1

PTEN inactivation yields tumors, overgrowth, and autism or intellectual disability

Ref.	Mut. carriers	De novo mutations	Clinical phenotype
Butler et al., 2005	**3/18 (13m, 5f) with macrocephaly** ***16,6%***	**H93R (exon 4)** **D252G (exon 7)** **F241S (exon 7)**	**Extreme macrocephaly and macrosomy**

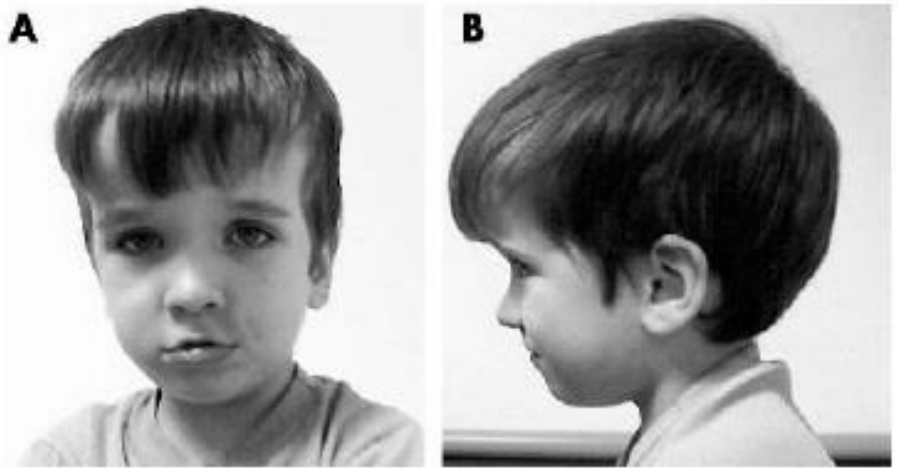


Figure 1 Frontal and profile views of subject two with a *PTEN* mutation (D252G) at 3.5 years of age showing macrocephaly. (Photograph reproduced with permission.)

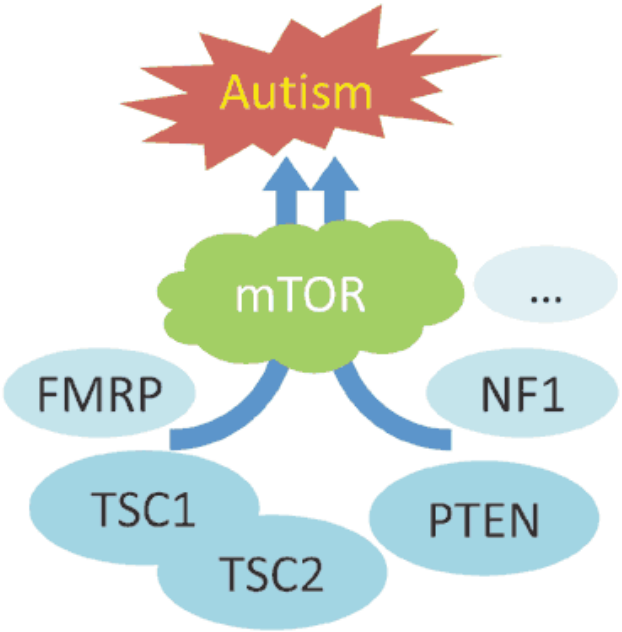
Il gene PTEN (*phosphatase and tensin homolog gene*, cromosoma 10q23) si tratta di un tumor suppressor gene favorisce l'arresto del ciclo cellulare in G1 e l'apoptosi. Pazienti ASD con mutazioni a carico del gene PTEN si caratterizzano per la presenza di macrocefalia, l'incidenza in pazienti con ASD di mutazioni PTEN de novo è del 4,7%, questi pazienti mostrano un rischio aumentato di sviluppare tumori PTEN-correlati in età adulta *(Lintas C., 2009).*

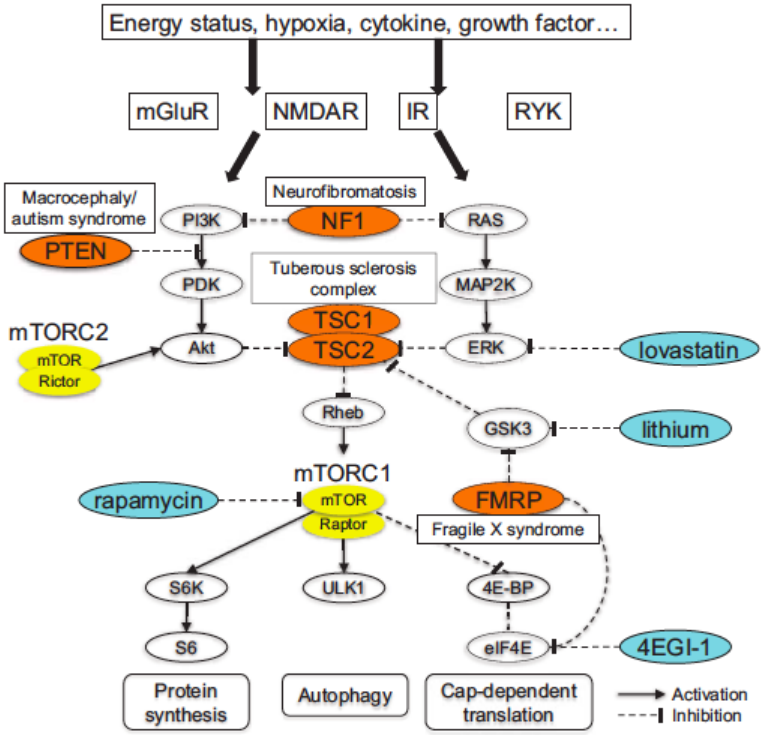
Butler et al, *J Med Genet*, 2005

CNS & Neurological Disorders - Drug Targets, 2016, *15*, 533-543

BENTHAM SCIENCE

mTOR, a Potential Target to Treat Autism Spectrum Disorder

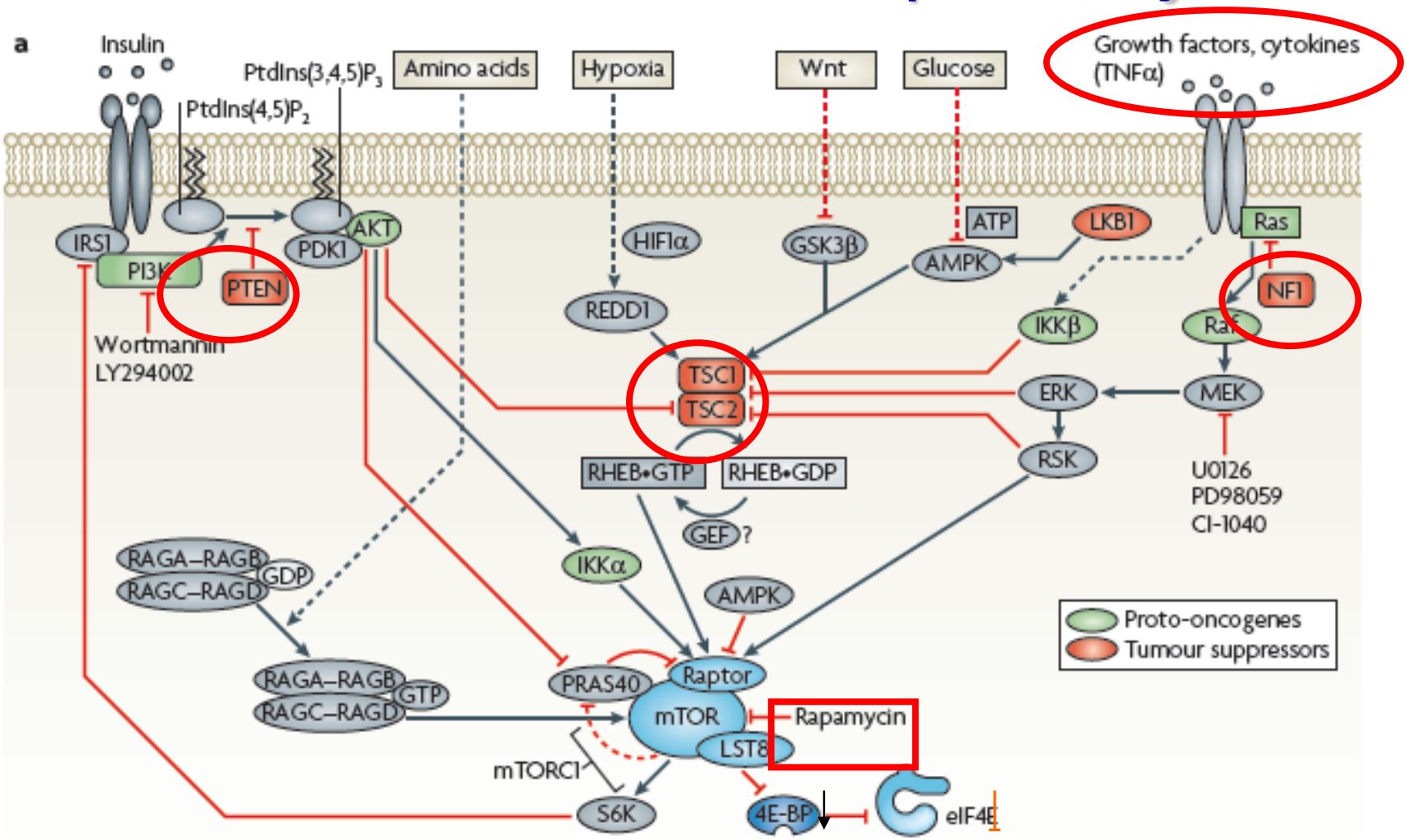




Mutazioni nei geni coinvolti nella via mediata dal sistema mTOR *(Mammalian target of rapamycin)* che portano ad un'iperattivazione del sistema, sono stati identificati in molti casi di ASD sindromici *(Sato A., 2016).*

Per tali motivi utilizzare dei farmaci inibitori del sistema mTOR potrebbe rappresentare una potenziale farmacoterapia per i Disturbi dello Spettro Autistico.

PTEN and the mTOR pathway

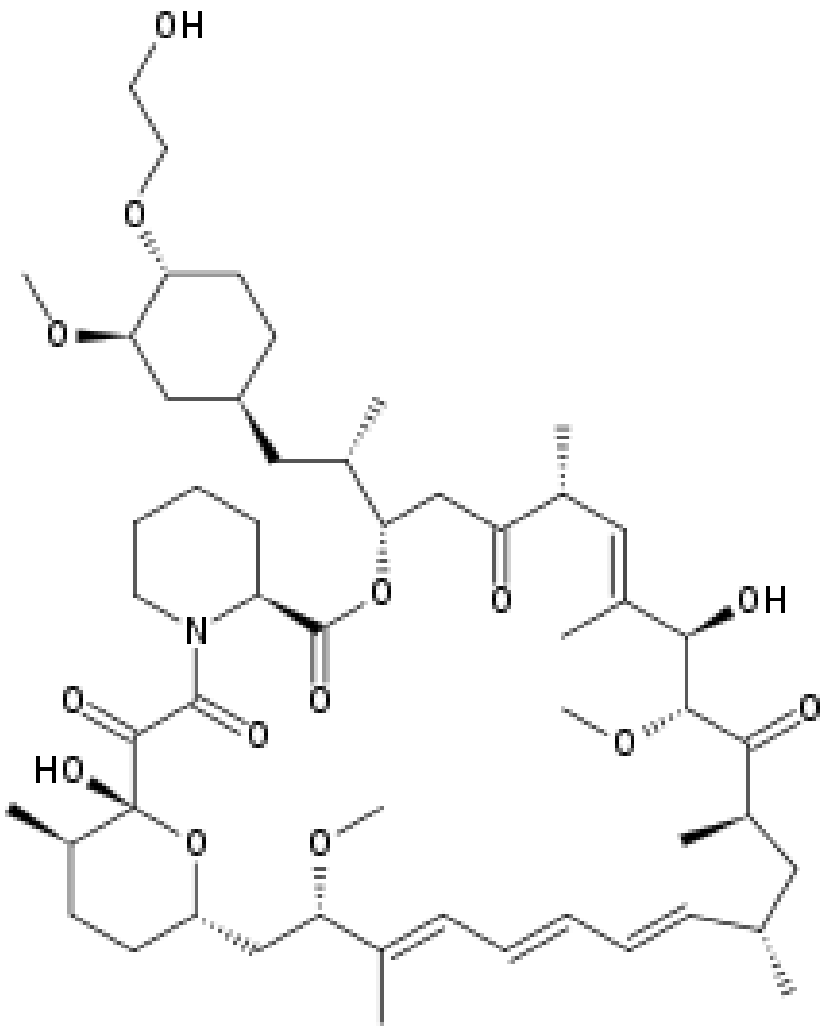


mRNA translation

Cell proliferation

I Disturbi dello Spettro Autistico sono spesso accompagnati da disordini monogenici come Sclerosi Tuberosa, Neurofibromatosi di tipo 1, sindrome dell'x-fragile caratterizzati da un'iperattivazione del sistema mTOR *(Mammalian target of rapamycin)*: si tratta di una proteina regolatrice di vari processi cellulari, quali crescita cellulare, espressione genica, funzioni sinaptiche.

Ma & Blenis, Mol Cell Biol 10:307, 2009

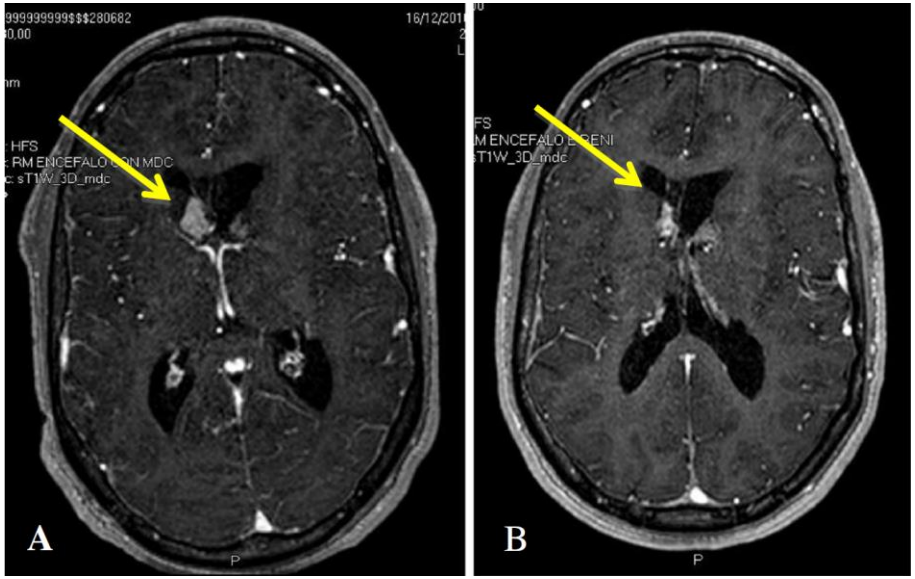


RAPAMYCIN (Sirolimus)
A macrolide compound obtained from Streptomyces hygroscopicus that acts by selectively blocking the transcriptional activation of cytokines thereby inhibiting cytokine production.

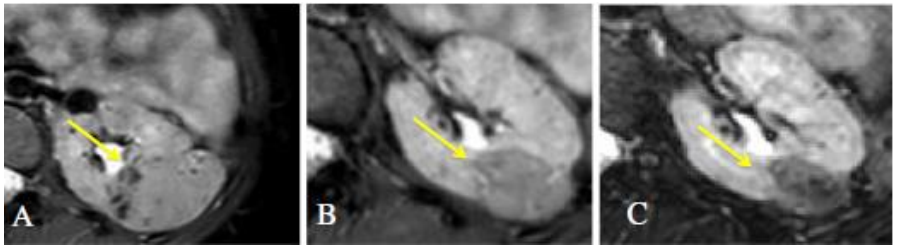
It is bioactive only when bound to IMMUNOPHILINS. Sirolimus is a potent immunosuppressant and possesses both antifungal and antineoplastic properties.

Everolimus (**RAD-001**)
is the 40-O-(2-hydroxyethyl) derivative of sirolimus and works similarly to sirolimus as an mTOR inhibitor.
It is currently used as an immunosuppressant to prevent rejection of organ transplant and the treatment of renal cell cancer. Much research has also been conducted on everolimus and other mTOR inhibitors for use in a number of cancers..

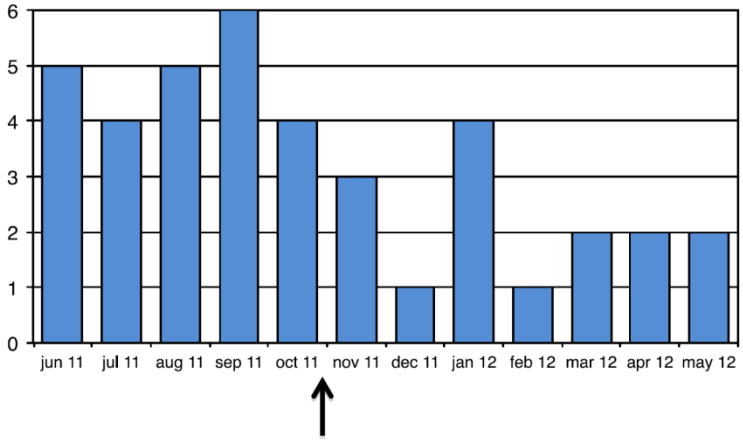
Everolimus has been approved for TS



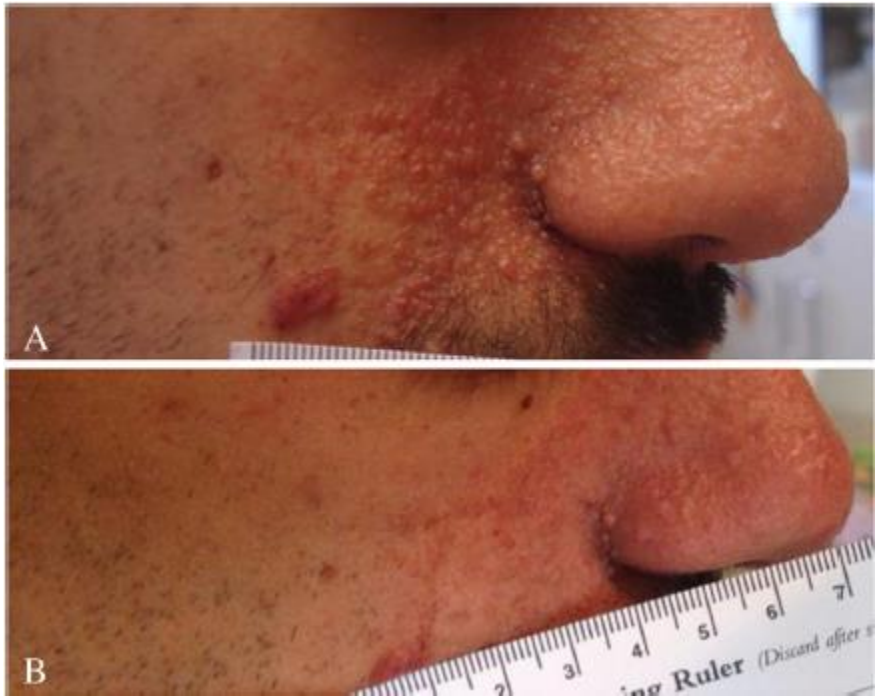
Subependymal giant-cell astrocytomas



Renal angiomyolipomas



Treatment-refractory seizures



Facial angiofibromas

Efficacy of RAD001/Everolimus in Autism and NeuroPsychological Deficits in Children With Tuberous Sclerosis Complex (RAPIT)

This study is currently recruiting participants. (see Contacts and Locations)

Verified May 2015 by Erasmus Medical Center

Sponsor:
Erasmus Medical Center

Collaborator:
Utrecht University

Information provided by (Responsible Party):
M.C.Y. de Wit, MD PhD, Erasmus Medical Center

ClinicalTrials.gov Identifier:
NCT01730209

First received: October 26, 2012
Last updated: May 4, 2015
Last verified: May 2015
History of Changes

Purpose

Tuberous sclerosis complex (TSC) is a genetic disease that leads to mental retardation in over 50% of patients, and to learning problems, behavioral problems, autism and epilepsy in up to 90% of patients. The underlying deficit of TSC, loss of inhibition of the mammalian target of rapamycin (mTOR) protein due to dysfunction of the tuberin/hamartin protein complex, can be rescued by everolimus. Everolimus has been registered as treatment for renal cell carcinoma and giant cell astrocytoma (SEGA). Evidence in human and animal studies suggests that mTOR inhibitors improve learning and development in patients with TSC.

Trial of RAD001 and Neurocognition in Tuberous Sclerosis Complex (TSC)

ClinicalTrials.gov

RCT vs Placebo Age 6 – 21. IQ>60, Stable anti-epileptic drugs, Adequate renal function
Study currently recruiting (Children's Hospital Boston, Feb 2012)
Tuberous Sclerosis Alliance, Autism Speaks, Novartis Pharmaceuticals, Seizure Tracker LLC

Primary Outcome Measures:
To evaluate **the safety** of RAD001 compared with placebo in patients with TSC focusing on NCI CTCAE Grade 3 and 4 **adverse events, serious adverse events**, and Grade 3 and 4 **laboratory toxicities**.

To evaluate **the efficacy** of RAD001 on **neurocognition** in patients with TSC compared to placebo **as measured by well-validated, standardized, direct and indirect neurocognitive tools.**

Secondary outcome

- frequency of epileptiform events
- sleep disturbances
- autism spectrum disorders features (ADOS & SRS)
- academic skills (WRAT4)
- behavioural problems (RIEF, BASC, SDQ, CHQ and SRS)

Everolimus for treatment of tuberous sclerosis complex-associated neuropsychiatric disorders

Darcy A. Krueger[1], Anjali Sadhwani[2], Anna W. Byars[1], Petrus J. de Vries[3], David N. Franz[1], Vicky H. Whittemore[4], Rajna Filip-Dhima[5], Donna Murray[5,7], Kush Kapur[6] & Mustafa Sahin[6]

OBIETTIVO: valutare l'efficacia a breve termine di Everolimus su parametri neurocognitivi e comportamentali.

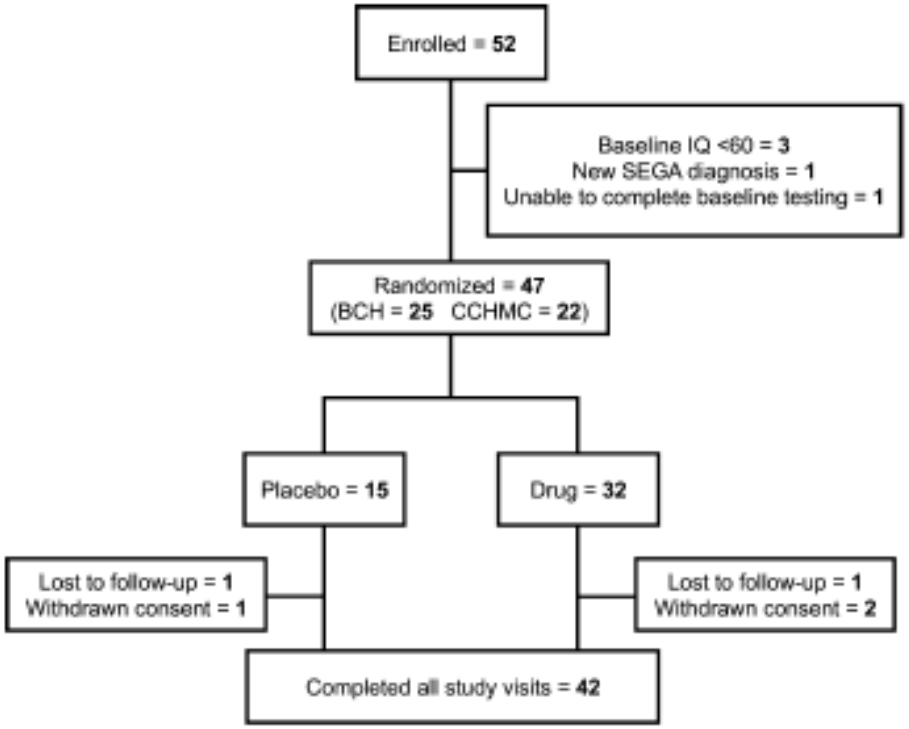
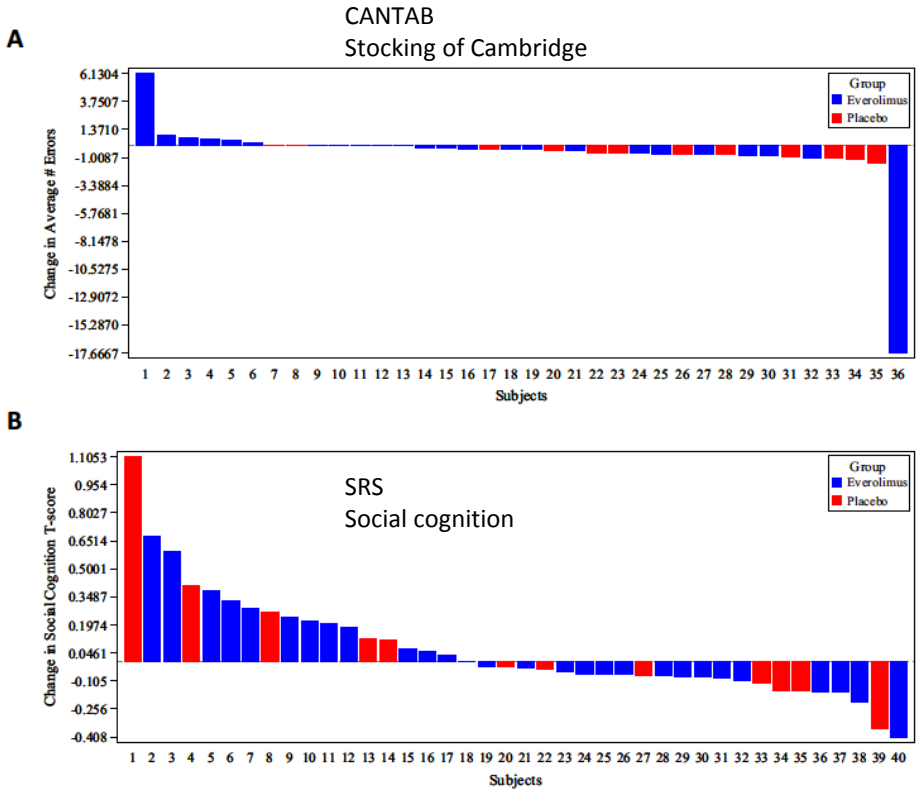
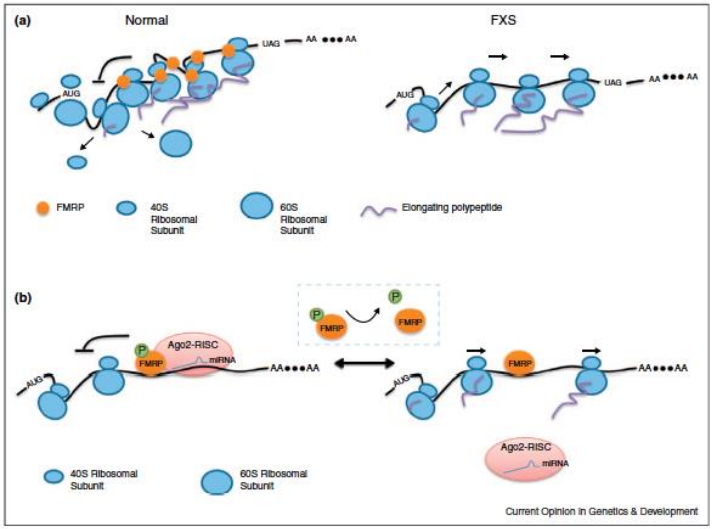


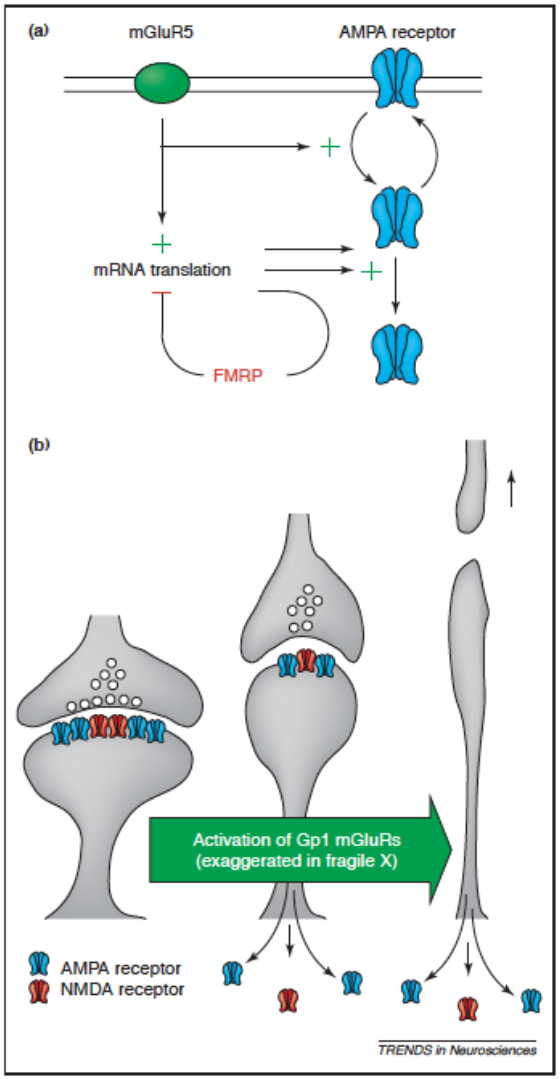
Figure 1. Patient flow diagram.

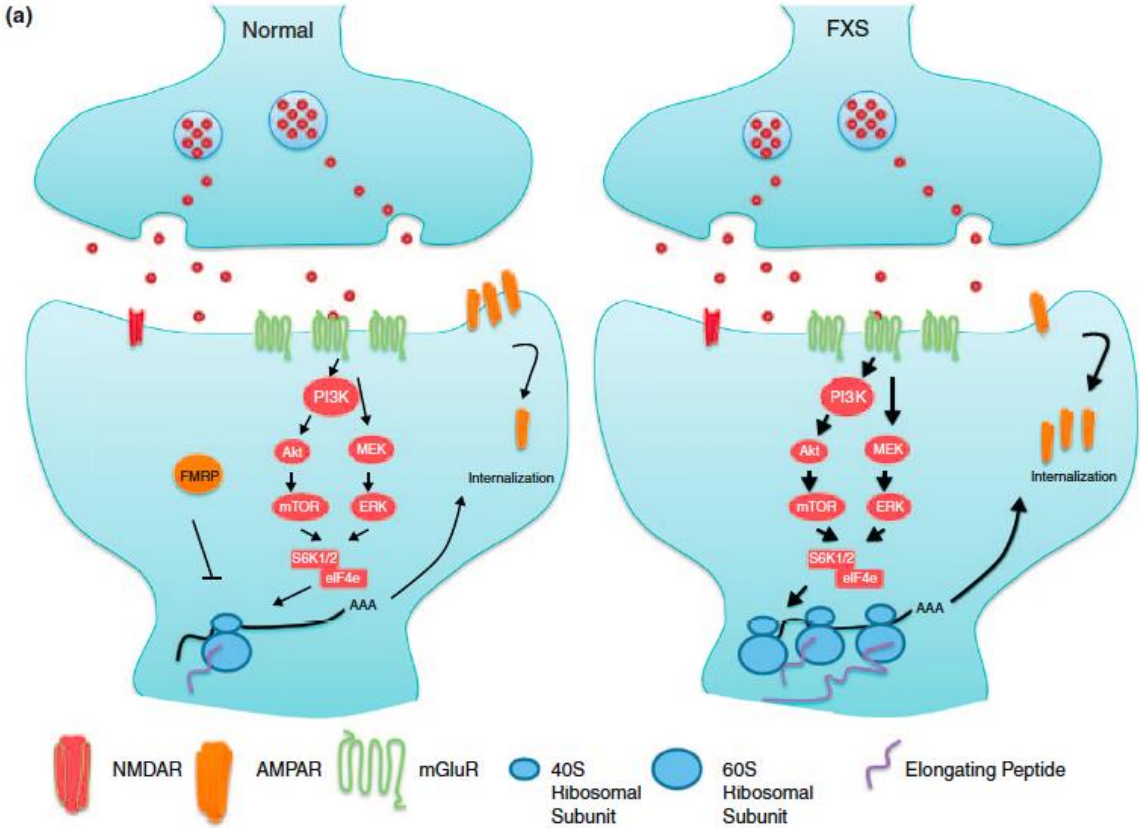


Studio randomizzato in doppio cieco del 2017, con pazienti di età compresa fra 6 e 21 anni con diagnosi TSC trattati con everolimus o placebo per 6 mesi. Nel gruppo trattato con placebo si osserva un miglioramento maggiore sulle fuzioni esecutive, nel gruppo trattato con everolimus nella sottoscale social cognition del questionario SRS. Effetti indesiderati invariati nei due gruppi.

mGLU 5 & Fragile x





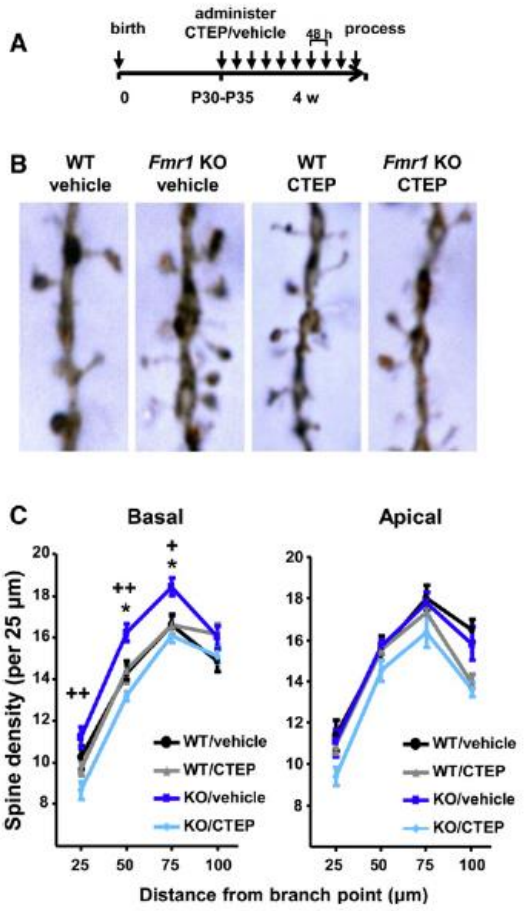


Chronic Pharmacological mGlu5 Inhibition Corrects Fragile X in Adult Mice

Aubin Michalon,[1,4] Michael Sidorov,[3,4] Theresa M. Ballard,[1] Laurence Ozmen,[1] Will Spooren,[1] Joseph G. Wettstein,[1] Georg Jaeschke,[2] Mark F. Bear,[3,*] and Lothar Lindemann[1,*]

Neuron 2012

Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. Previous studies have implicated mGlu5 in the pathogenesis of the disease, but a crucial unanswered question is whether pharmacological mGlu5 inhibition is able to reverse an already established FXS phenotype in mammals. Here we have used the novel, potent, and selective mGlu5 inhibitor CTEP to address this issue in the *Fmr1* knockout mouse. Acute CTEP treatment corrects elevated hippocampal long-term depression, protein synthesis, and audiogenic seizures. Chronic treatment that inhibits mGlu5 within a receptor occupancy range of 81% ± 4% rescues cognitive deficits, auditory hypersensitivity, aberrant dendritic spine density, overactive ERK and mTOR signaling, and partially corrects macro-orchidism. This study shows that a comprehensive phenotype correction in FXS is possible with pharmacological intervention starting in young adulthood, after development of the phenotype. It is of great interest how these findings may translate into ongoing clinical research testing mGlu5 inhibitors in FXS patients.



Glutamate Neurotransmission (1)

- ✓ **Memantine**, an *N*-methyl-d-aspartate receptor antagonist, has been investigated for its ability to improve social function in both open-label and controlled studies.

- ✓ Two small (*n* = 30; *n* = 18 open-label studies) reported improvements in **eye contact** and **social withdrawal** in children with ASD. *(Erickson CA et al. A retrospective study of memantine in chil- dren and adolescents with pervasive developmental disorders. Psychopharmacology (Berl). 2007)*

- ✓ A large (*n* = 151) open-label study reported improved **social behavior** in children and young adults with ASD. Memantine significantly improved SRS scores in a small (*n* = 18) 12-week open-label trial of adults with HFASD *(Joshi G et al. A prospective open-label trial of memantine hydrochlo- ride for the treatment of social deficits in intellectually capable adults with autism spectrum disorder. J Clin Psychopharmacol. 2016).*

Glutamate Neurotransmission (2)

- ✓ Two DBPC studies have examined the effect of memantine on social function. A medium-sized (*n*= 40) DBPC add on to risperidone study of children with ASD reported improvements in ABC **Irritability, Stereotypy, and Hyperactivity**, **but not Social Withdrawal** subscales *(Ghaleiha A et al. Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. Int J Neuropsychophar- macol. 2013).*

- ✓ In a large (*n* = 121) DBPC 12-week study, once-daily extended-release memantine did not significantly affect the SRS owing to a large improvement in the placebo group. Thus, DBPC studies **do not show improvement in social symptoms** with memantine, although they do suggest an excellent safety profile. *(Aman MG et al. Safety and efficacy of memantine in children with autism: randomized, placebo-controlled study and open-label extension. J Child Adolesc Psychopharmacol. 2017).*

Neuron

Hoffman 2016

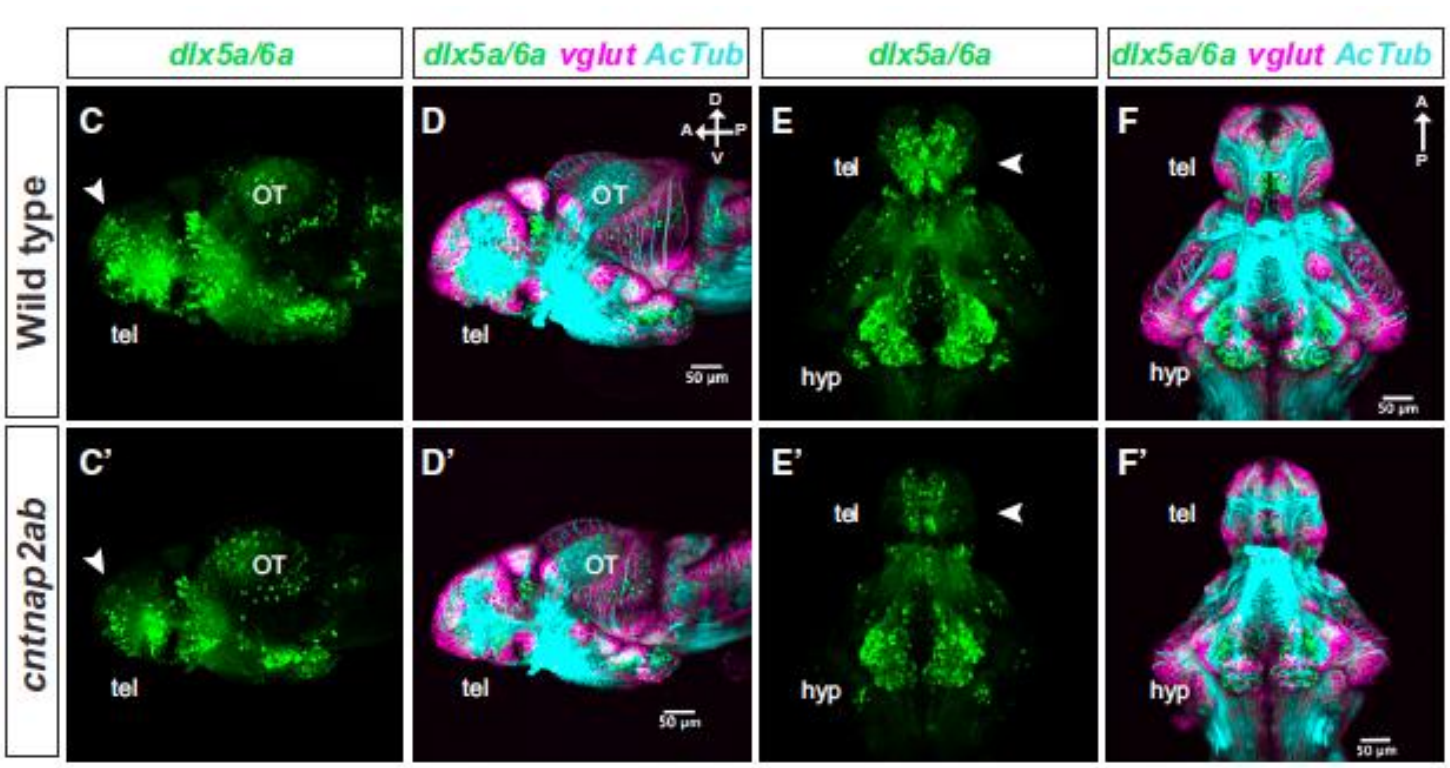
Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the Autism Risk Gene, *CNTNAP2*

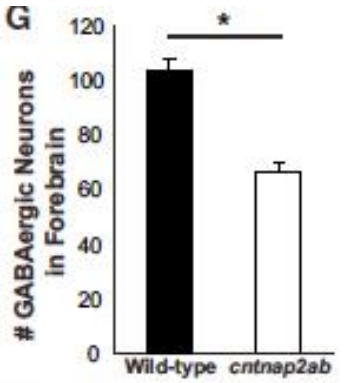
CNTNAP2 *Contactine Associted Protein-like 2*

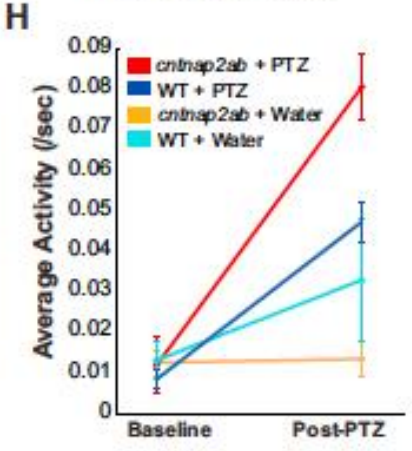
- Adesion molecule (neurexin family)
- Localize voltage-gate K Channel/node of mielinated axons

Loss of CNTNAP2 (mice):

- Abnormal neuronal migration
- Reduced GABA neurons
- Seizure
- Hyperactivity
- Social deficit
- Increased repetitive behaviour





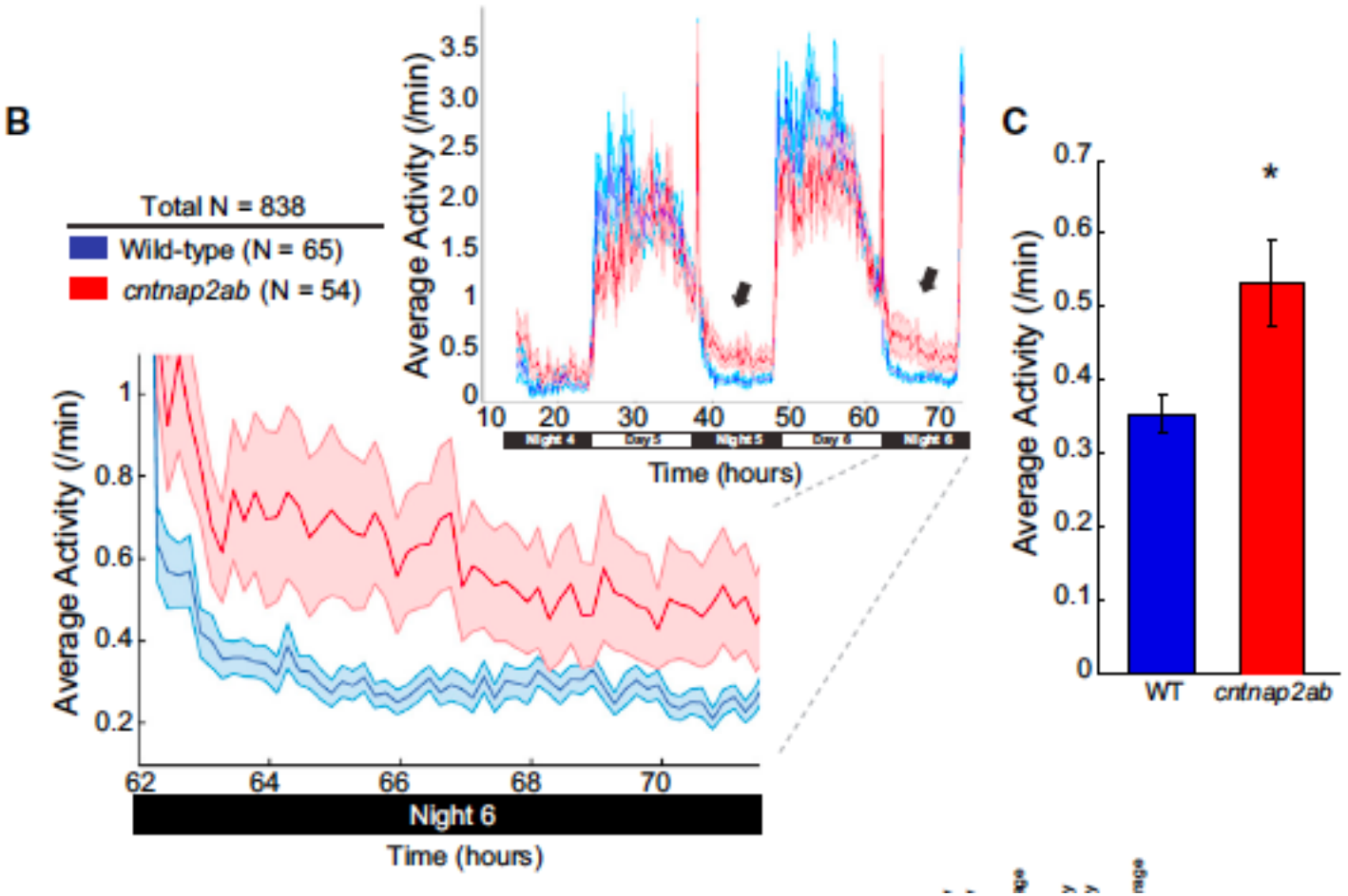


Neuron

Hoffman 2016

Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the Autism Risk Gene, *CNTNAP2*

Night activity



Neuron

Hoffman 2016

Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the Autism Risk Gene, *CNTNAP2*

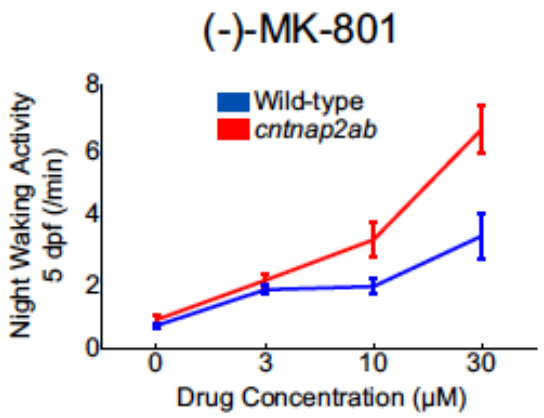
Night activity

A

Psychoactive Drugs Tested

Compound Name	Biological Target(s)	Rationale for Selection
L-701,324	NMDA glycine site antagonist	Correlating
(-)-MK-801	Non-competitive NMDA receptor antagonist	Correlating
Amantadine	Dopaminergic; increases dopamine synthesis/release, inhibits reuptake	Anti-Correlating
(+)-Baclofen	GABA-B receptor agonist	Anti-Correlating
β-Estradiol	Estrogen receptor-β agonist	Anti-Correlating
β-Estradiol 17-cypionate	Estrogen receptor-β agonist	Anti-Correlating
Biochanin A	Estrogen receptor-β agonist	Anti-Correlating
CGS-12066	5HT1B serotonin receptor agonist	Anti-Correlating
Chlorzoxazone	Centrally acting muscle relaxant	Anti-Correlating
Clonidine	α2-adrenergic receptor agonist	Anti-Correlating
Ticlopidine	Platelet aggregation inhibitor	Anti-Correlating
Risperidone	Dopamine (D2) and serotonin (5-HT2A) receptor antagonist	FDA-approved for irritability in ASD
Zolpidem	Nonbenzodiazepine GABA-A receptor agonist	GABAergic deficit
Diazepam	Benzodiazepine; positive allosteric GABA-A receptor modulator	GABAergic deficit

B



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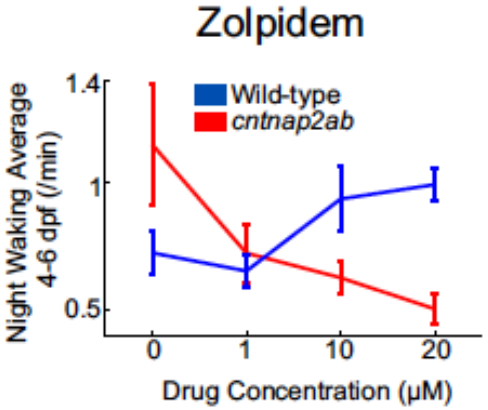
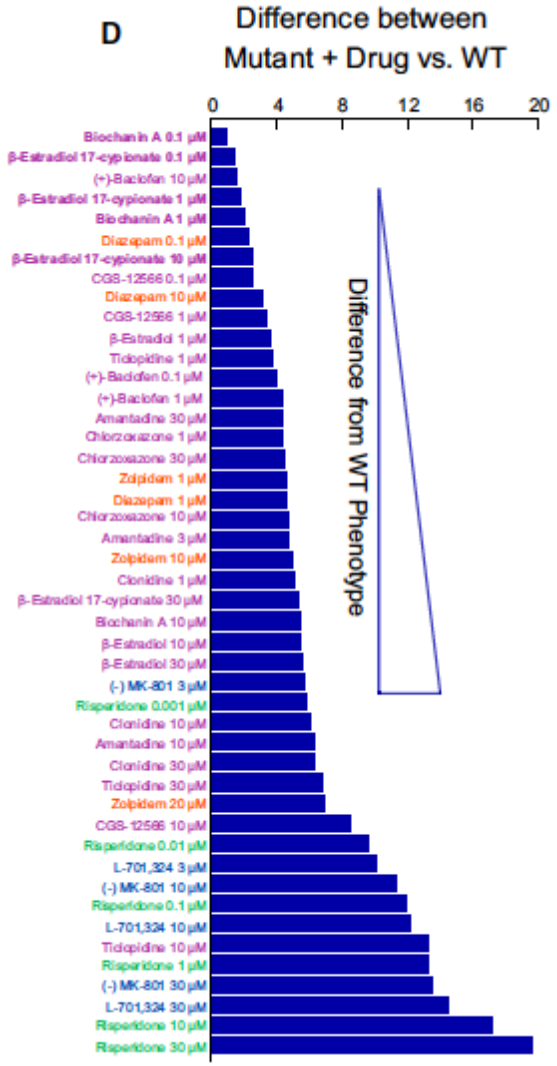
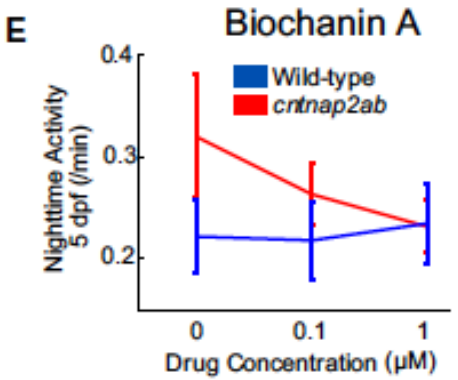


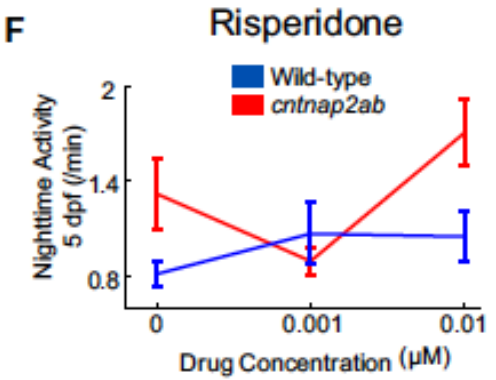
Neuron

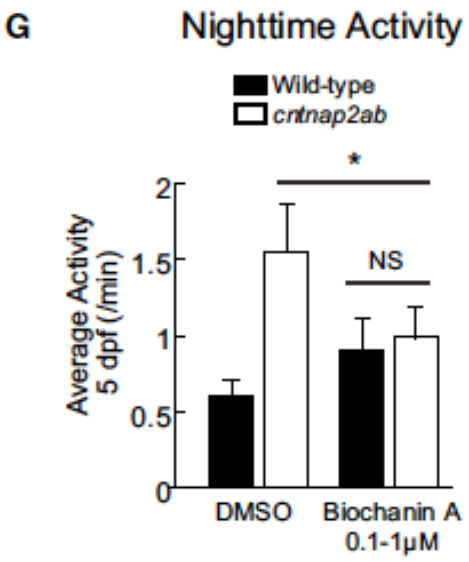
Hoffman 2016

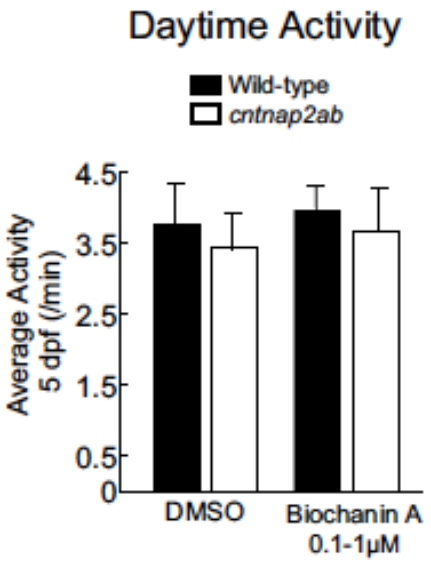
Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the Autism Risk Gene, *CNTNAP2*







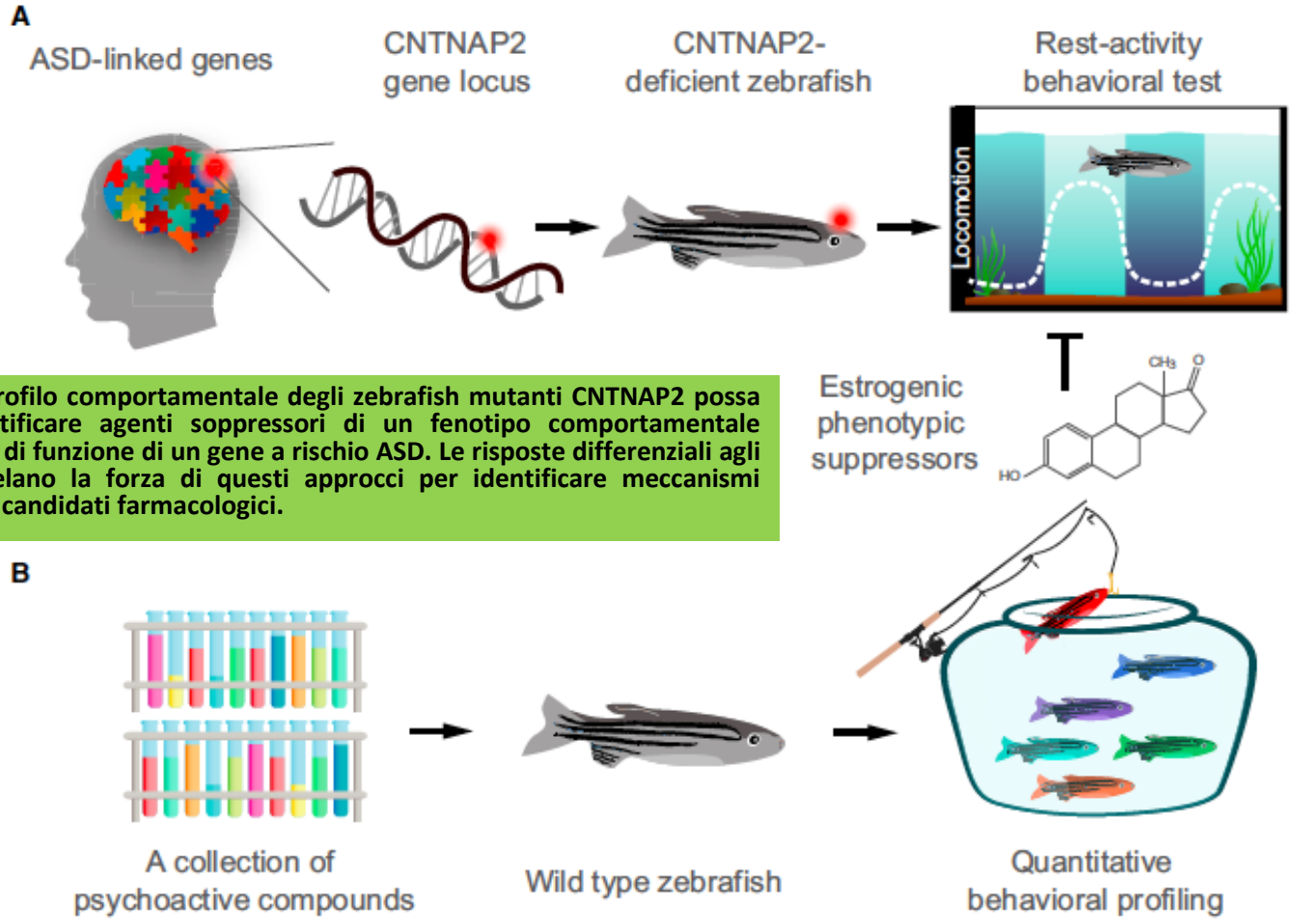




Neuron

Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the Autism Risk Gene, *CNTNAP2*

Hoffman 2016



Interessante come il profilo comportamentale degli zebrafish mutanti CNTNAP2 possa essere utile per identificare agenti soppressori di un fenotipo comportamentale derivante dalla perdita di funzione di un gene a rischio ASD. Le risposte differenziali agli agenti psicoattivi, rivelano la forza di questi approcci per identificare meccanismi molecolari e potenziali candidati farmacologici.

Figure 1. Behavioral Drug-Effect Profiling Reveals Phenotypic Suppressors of *cntnap2* Mutant

(A) The *CNTNAP2* gene is linked to ASD in human. Zebrafish *cntnap2* mutants display heightened nighttime activity (Hoffman et al., 2016).

(B) Quantitative behavioral profiling of wild-type zebrafish larvae treated with a collection of psychoactive compounds identifies small molecules that phenocopy the *cntnap2* mutant phenotype (correlating) as well as compounds eliciting a behavioral signature opposite to that of mutant larvae (anti-correlating). This screen showed that molecules with estrogen-like activity suppress the *cntnap2* mutant phenotype.

Sindrome	Fisiopatologia	Farmaco	Meccanismo terapeutico	Studio clinico (n. NCT)
Sindrome di Rett [MeCP2]	Anomala regolazione dell'espressione genica, che interferisce con la crescita neuritica e la sinaptogenesi	(1-3) IGF1 [Mecasermin, Increlex]	Promuove la crescita neuritica e la sinaptogenesi	01253317, 01777542
Delezione 22q13/Sindrome di Phelan-McDermid [SHANK3]	Alterata impalcatura dell'elemento post-sinaptico, che cause una diminuzione delle spine dendritiche e della sinaptogenesi			01525901
Sindrome dell'X fragile [FMR1]	Eccessiva traduzione di alcuni mRNA nelle spine dendritiche	MPEP	Antagonisti del recettore mGLUR5	Nessuno
		Fenobam		01806415
		STX107		01325740, 00965432
		AFQ056 [Mavoglurant]		01357239, 01253629, 01482143, 01348087, 01433354, 00718341
		RO4917523		01750957, 01015430, 01517698
		STX209 [Arbaclofen]	Agonista del recettore GABA-B	00788073, 01282268, 01555333 (interrotto), 01325220
		CX516 [Ampalex]	Modulazione allosterica positiva dei recettori AMPA	00054730
Sindrome dell'X fragile ed autismo idiopatico [neuroinfiammazione]	Attivazione microgliale	Minociclina	Inibizione della microglia	00409747
	Aumentata espressione ed attività della MMP9		Inibizione della MMP9	01053156, 0858689
Sclerosi tuberosa [TSC1/TSC2]	Disinibizione della via biochimica di mTOR	Rapamicina [Sirolimus]	Inibizione di mTOR	00457808
		Everolimus [RAD001, Afinitor]		01289912, 01070316, 01730209, 01713946
Autismo con macrocefalia (PTEN)				Nessuno
Neurofibromatosi (NF1)	Disinibizione dell'attività di RAS & della via biochimica di mTOR	Lovastatina	Inibizione dell'attività di RAS	00352599
Varianti geniche nel gene OXTR, che codifica il recettore per l'ossitocina	Ridotta attività dell'ossitocina	Ossitocina	Aumentata attività dell'ossitocina	01337687, 01788072, 01624194, 01308749, 01183221, 1256060
CNV localizzati nella regione 15q11-13, che coinvolgono i geni GABRB3, GABRA5 e GABRG3 (autismo ed epilessia)	Effetto eccitatorio del GABA dovuto ad un elevato livello di cloro intracellulare nei neuroni	Bumetanide	Potenziamento dell'inibizione GABAergica mediante riduzione dei livelli intracellulari di cloro	01078714

Vorstman et al, Psychopharmacol 2014

Oxytocin and Autism Spectrum Disorders.

Yamasue H[1], Domes G[2].

Author information

Abstract

Autism spectrum **disorder** (ASD) is a neurodevelopmental **disorder** whose core symptoms include deficits in social interaction and communication besides restricted and repetitive behaviors. Although ASD is highly prevalent, affecting 1/100 in the general population, no medication for the core symptoms has been established. Therefore, the **disorder** is considered a huge unmet medical need and a heavy burden on individuals with ASD, their families, and entire society. **Oxytocin** is expected to be a potential therapeutic resource for the social core symptoms of ASD, since this neuropeptide can modulate human social behavior and cognition. This review article provides an overview of both experimental and clinical studies on effects of **oxytocin** administration on behavior, neural underpinnings, and symptomatology of ASD. Although the number of studies is increasing, several issues remain for further development of clinical application of the neuropeptide. The issues include optimization of administration route, doses, treatment duration, interval of administrations, and timing of starting treatment. Additional issues involve investigating neurobiological mechanisms of treatment and developing a reliable tool to accurately and objectively assess longitudinal changes in the core symptoms of ASD. Some of these issues are discussed in this review.

Neuropeptide che ha un ruolo importante nei comportamenti affiliativi e sessuali, nella risposta allo stress, memoria sociale e nel riconoscimento, nella regolazione dei comportamenti alimentari.

Ricerche recenti hanno dimostrato come l'ossitocina possa avere un ruolo nell'eziologia dell'ASD *(Green JJ, 2010).*
Varianti geniche nel gene OXTR, che codifica il recettore per l'ossitocina con conseguente ridotta attività.

In particolare l'infusione di ossitocina ha determinato riduzione dei comportamenti ripetitivi e miglioramento delle capacità sociali in 13 pazienti ASD 117, in un altro studio è stato dimostrato che dopo l'infusione dell'ossitocina la fMRI mostrava una maggiore attività dell'amigdala destro nei test di riconoscimento facciale, negli ASD rispetto ai controlli. *(Domes G., 2013).*

Bumetanide

CNV localizzati nella regione 15q11-13, che coinvolgono i geni GABRB3, GABRA5 e GABRG3 (autismo ed epilessia)

- ✓ Effetto eccitatorio del GABA dovuto ad un elevato livello di cloro intracellulare nei neuroni.

- ✓ Il bumetanide determina un potenziamento dell'inibizione GABAergica mediante riduzione dei livelli intracellulari di cloro.

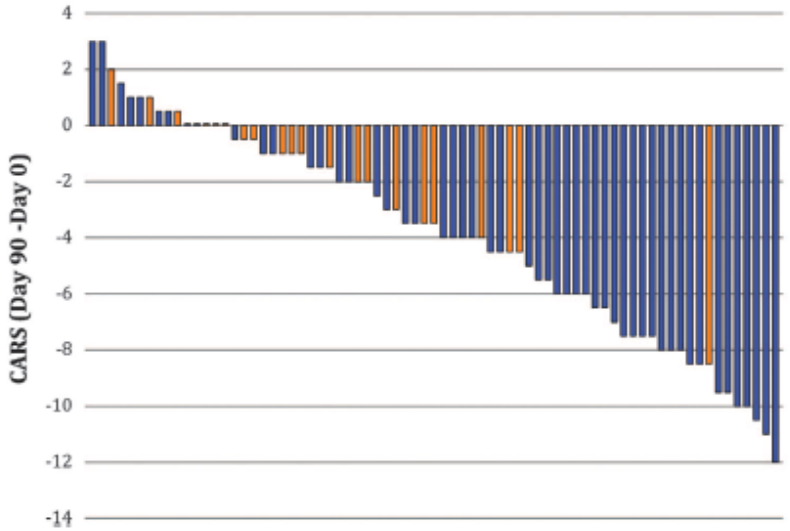
- ✓In the first single-center trial, 60 children with ASD received 1 mg of bumetanide daily for 3 months. Bumetanide improved scores on the CARS but the ADOS Reciprocity subscale did not improve *(Lemonnier E, et al. A randomised controlled trial of bumetanide in the treatment of autism in children Transl Psychiatry. 2012).*

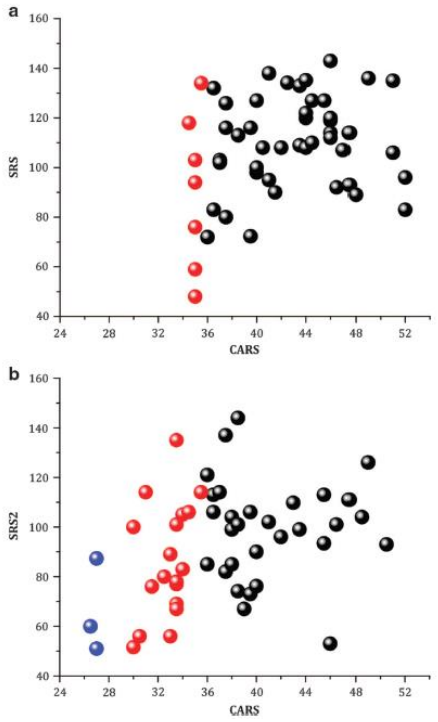
ORIGINAL ARTICLE

Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders

E Lemonnier[1], N Villeneuve[2], S Sonie[3], S Serret[4], A Rosier[5], M Roue[6], P Brosset[1], M Viellard[2], D Bernoux[3], S Rondeau[5], S Thummler[4], D Ravel[7] and Y Ben-Ari[7,8]

Transl Psychiatry (2017) **7**, e1056;





- ✓ In a large (n = 80), six-center 3-month DBPC with three doses (0.5 mg, 1.0 mg, or 2.0 mg twice daily), bumetanide improved scores on the CARS and SRS *(Lemonnier E et al. Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders. Transl Psychiatry. 2017).*

- ✓ The treatment was well tolerated in these trials with some patients showing mild hypokalemia requiring potassium supplementation.

Arbaclofen in Children and Adolescents with Autism Spectrum Disorder: A Randomized, Controlled, Phase 2 Trial

150 participants, aged 5–21 years, with ASD across 24 centers in the United States

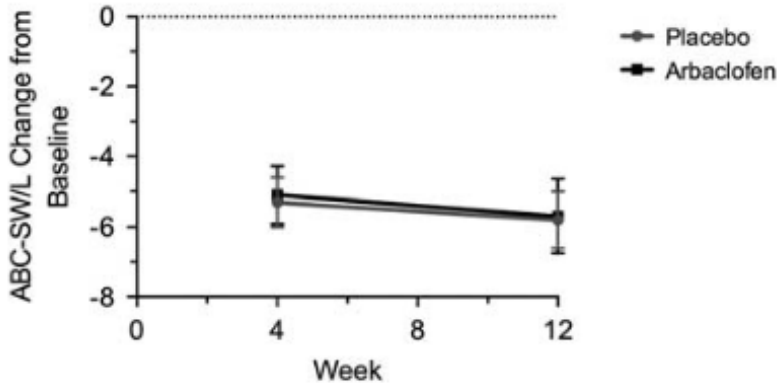


Figure 2 Change in outcome measures over time. The change (mean and SEM) in parent ratings on the Aberrant Behavior Checklist–Community Version (ABC) Social Withdrawal/Lethargy score is shown over the course of the study. The primary outcome measure was assessed at baseline, week 4, and week 12. Uncorrected $p = 0.477$.

-No difference from placebo was detected on the primary outcome measure, the parent-rated Aberrant Behavior Checklist Social Withdrawal/Lethargy subscale.

-Improvement on the clinician-rated Clinical Global Impression of Severity.

-Improvement on the Vineland Adaptive Behavior Scales II socialization domain in participants receiving arbaclofen

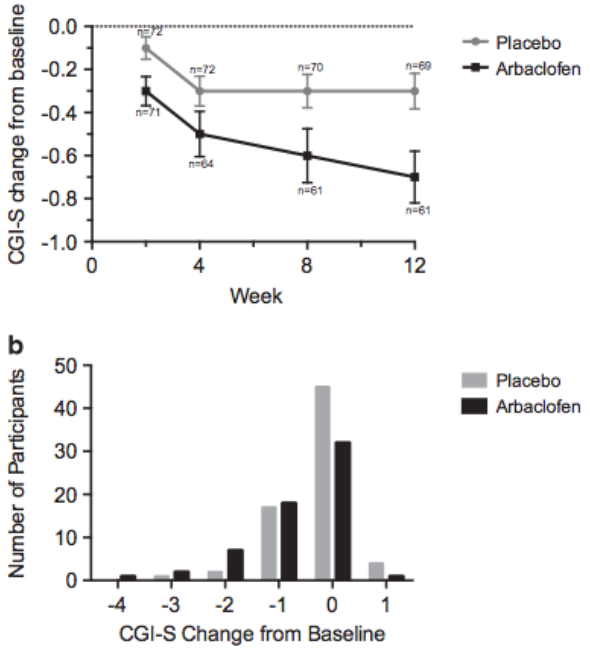
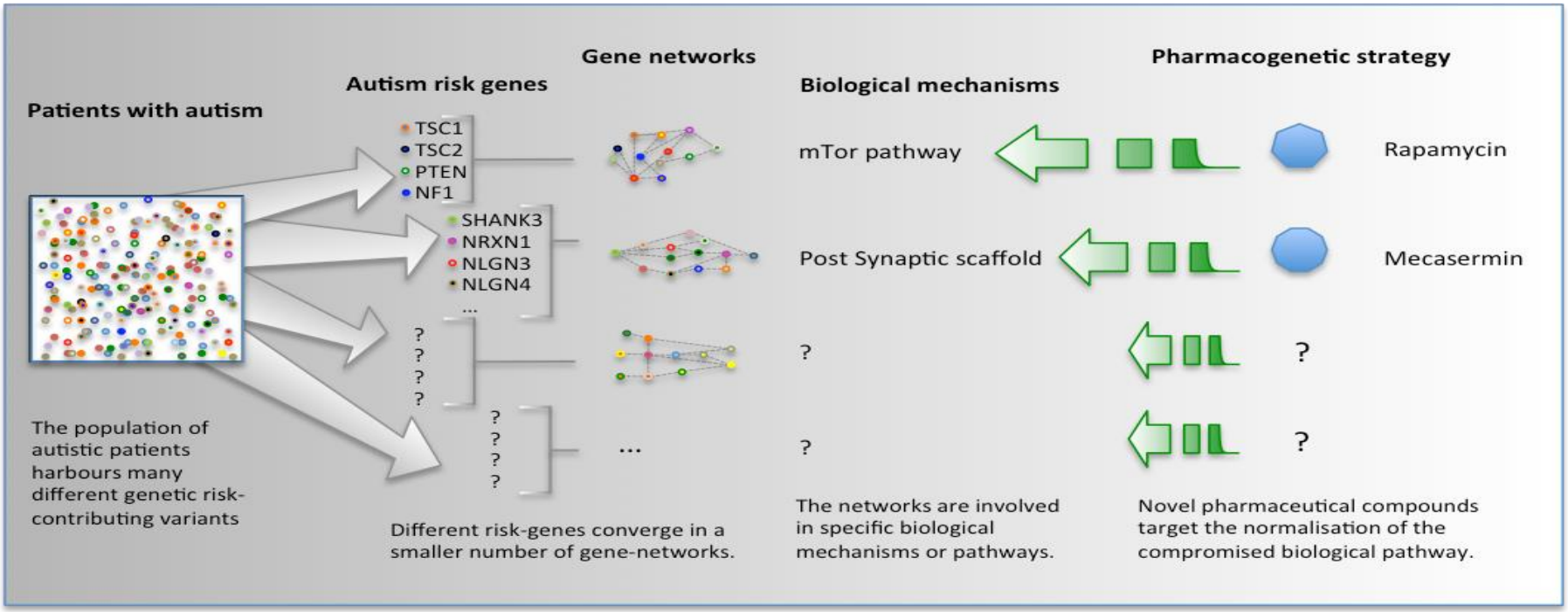


Figure 3 Change in the Clinical Global Impression of severity. (a) The change (mean and SEM) in clinician ratings on the Clinical Global Impression of Severity (CGI-S), one of six secondary outcome measures, is shown over the course of the study. The CGI-S was assessed at baseline, week 2, week 4, week 8, and week 12. Uncorrected $p = 0.009$. (b) The number of participants is shown for each degree of change on the CGI-S from baseline to week 12.

Affect lability (11%) and sedation (9%) were the most common adverse events

QUALE FARMACO
PER QUALE PAZIENTE?

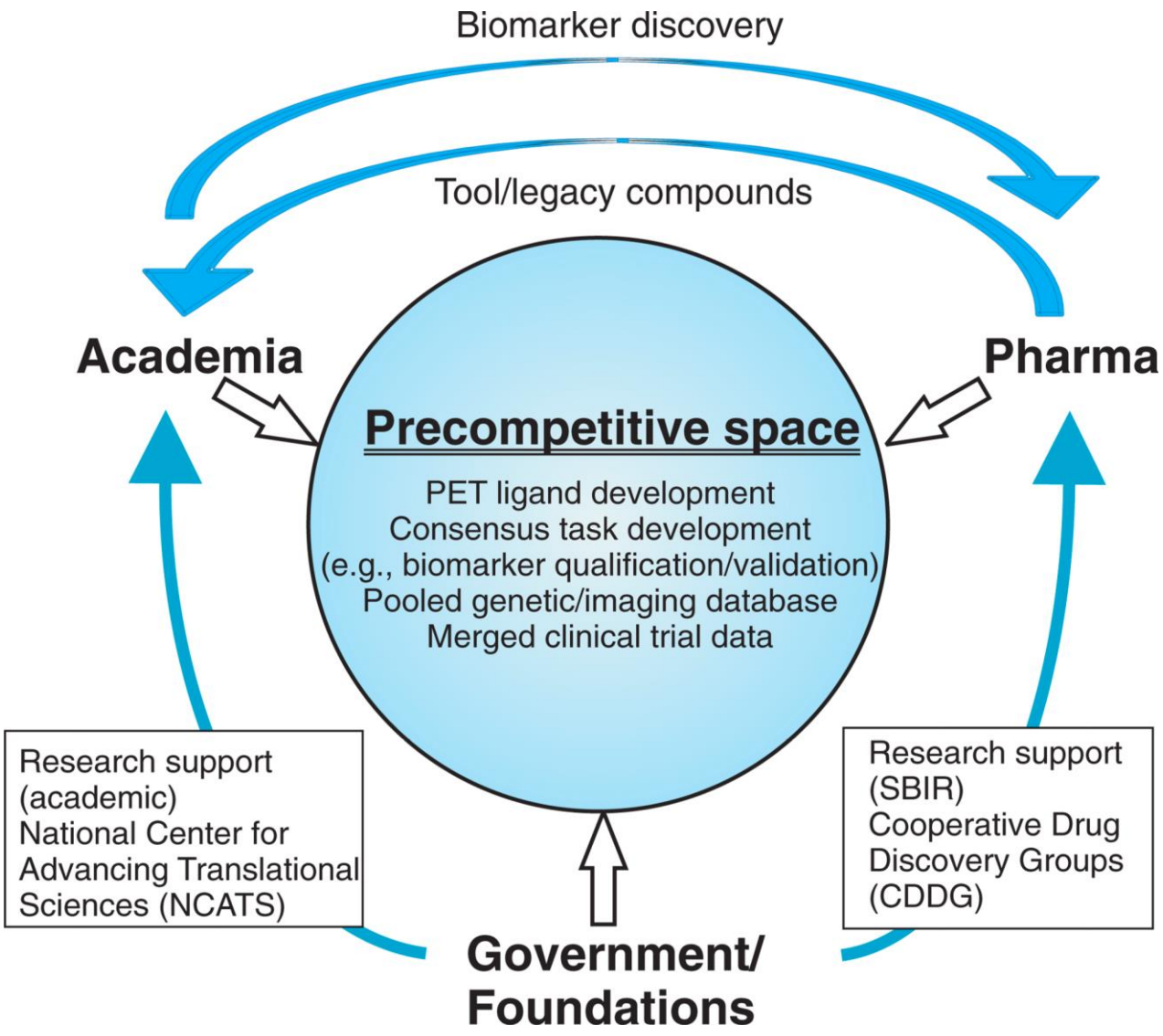


Negli ultimi anni sono state sviluppate strategie mirate a correggere farmacologicamente anomalie fisiopatologiche correlate a mutazioni di singoli geni la cui manifestazioni includono frequentemente sintomi autistici. Sebbene i risultati di tali studi siano ancora da considerarsi molto preliminari, sono in corso di definizione strategie di ricerca innovative (definizione accurata di specifiche sottopopolazioni di soggetti, messa a punto di strumenti valutazione più adeguati, combinazione di interventi farmacologici e psico-educativi, migliore definizione dei periodi in cui la maggiore plasticità neuronale può permettere risultati terapeutici più significativi, etc) che indicano la possibilità di definire e validare potenziali strategie terapeutiche innovative nei prossimi anni.

Vorstman et al, Psychopharmacol 231: 1063, 2014

Ruggeri et al., Psychopharmacol 231: 1201, 2014

New research prospective for the use of medications



Lo studio e l'utilizzo di strategie innovative deve rispettare gli stringenti criteri di efficacia e tollerabilità definiti dalle autorità regolatorie nazionali ed internazionali per i farmaci utilizzabili in età evolutiva.

Future research trends

Innovative Medicine Initiative

Translational Endpoints in Autism:

-Sviluppo e validazione di approcci traslazionali per lo sviluppo di nuove terapie per il trattamento dell'Autismo.

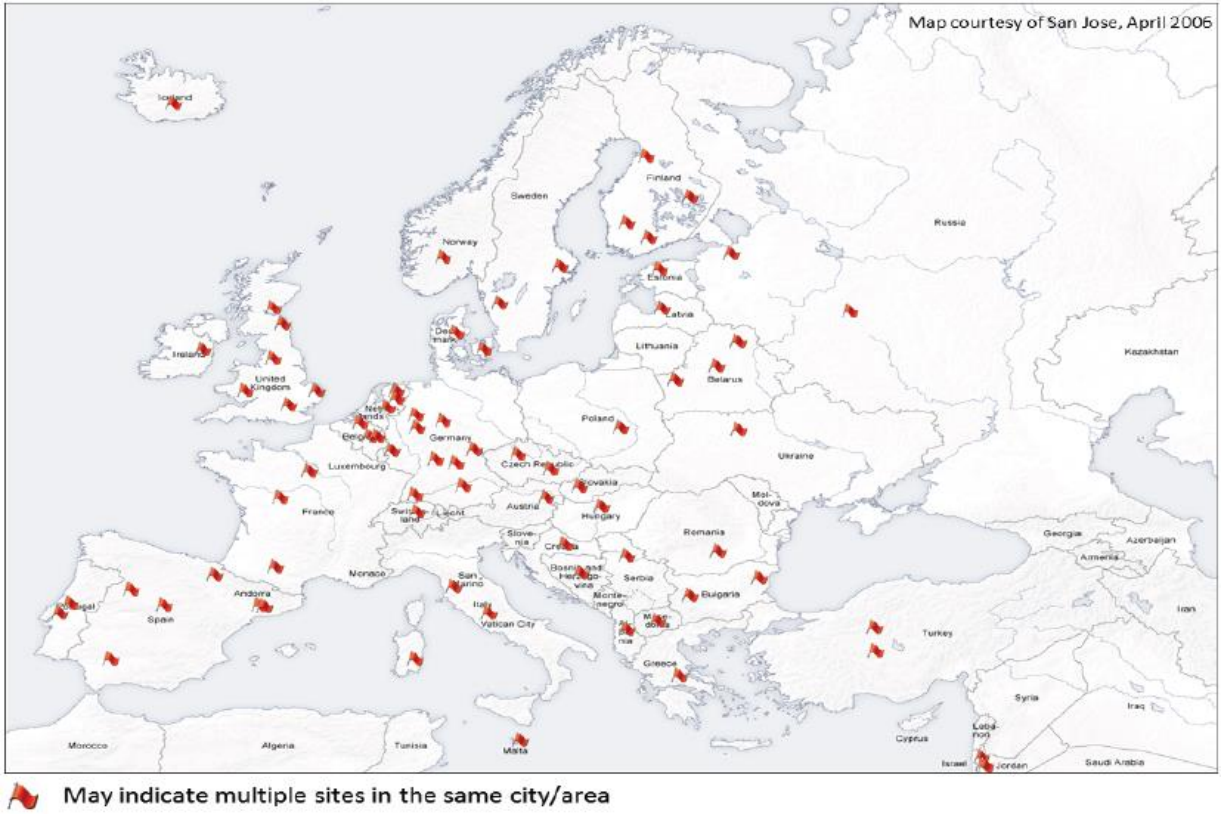
-Stabilire nuovi standards di ricerca e di sviluppo clinico per contribuire al processo di identificazione di nuovi target farmacologici.

-Identificazione e sviluppo di siti clinici esperti in Europa per condurre studi clinici e creare una piattaforma interattiva tra professionisti e pazienti/famiglie.

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



-Indagine sulle misure utilizzate per la caratterizzazione dei pazienti nei maggiori centri clinici e di ricerca ASD in tutta Europa raccolti tra giugno 2013 e gennaio 2014.

-L'obiettivo era quello di mappare l'uso di diversi strumenti usati per caratterizzare l'ASD, la comorbilità psicopatologica e cognitiva e capacità di adattamento per scopi diagnostici e di caratterizzazione dei pazienti in tutta Europa.

-Sessantasei siti di ricerca clinica che diagnosticano 14.844 pazienti all'anno hanno fornito dati. La maggior parte dei siti utilizza gli ormai consolidati Autism Diagnostic Observation Schedule (ADOS) e gli Autism Diagnostic Interview (ADI), con delle differenze tra Europa Occidentale e Orientale

-Circa la metà dei siti utilizzava anche il Social Communication Questionnaire (SCQ) e la Social Responsiveness Scale (SRS),

Vi sono benefici clinici e scientifici nell'incoraggiare l'ulteriore convergenza delle misure di caratterizzazione clinica tra la ricerca ASD ei centri clinici in Europa per facilitare la condivisione e la collaborazione di dati su larga scala, compresi studi clinici su nuovi farmaci e interventi psicologici.

ECAP 2014

INCiPiT Italian Network for Paediatric Clinical Trials

WHO WE ARE

INCiPiT is a no profit Consortium composed by the main italian children's hospitals, the largest departments of paediatrics as well as national and international paediatric therapeutic networks coordinated by italian institutions.

THE MISSION

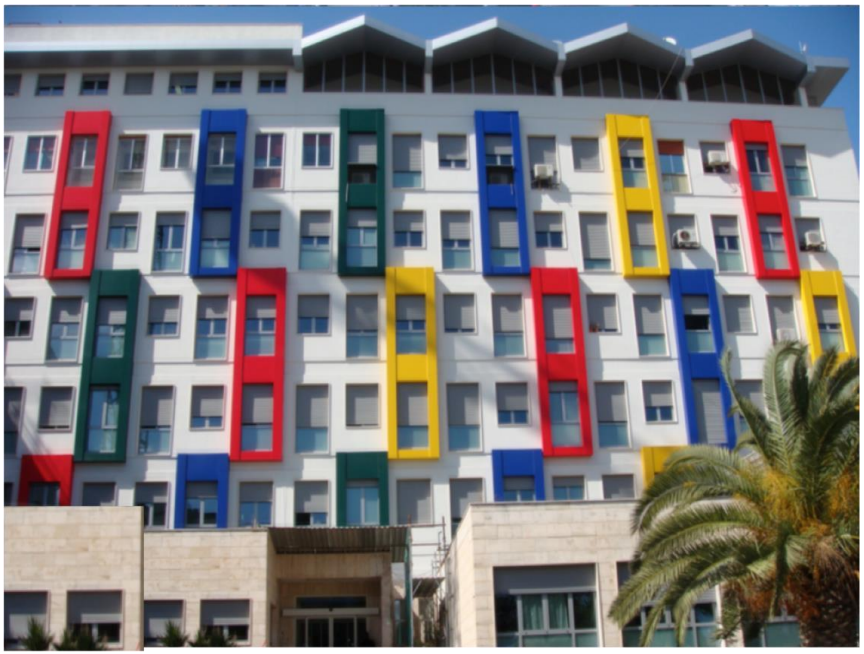
The mission of INCiPiT is to foster and support the planning, conduct and completion of all types of clinical studies conducted in Italy in the paediatric population by all kinds of sponsor (not for profit and for profit).

INCiPiT Italian Network for Paediatric Clinical Trials

The partners

www.incipit-ped.net

Grazie per l'attenzione!



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