Nuevos tratamientos farmacológicos en el Trastorno del Espectro Autista

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Psiquiatria Infanto-Juvenil
15 Novembre, Lleida

Desarrollo de fármacos para el autismo:

Retos:

- Heterogeneidad

Oportunidades:

- Circuitos diana
- Dianas moleculares: Síndromes monogénicos

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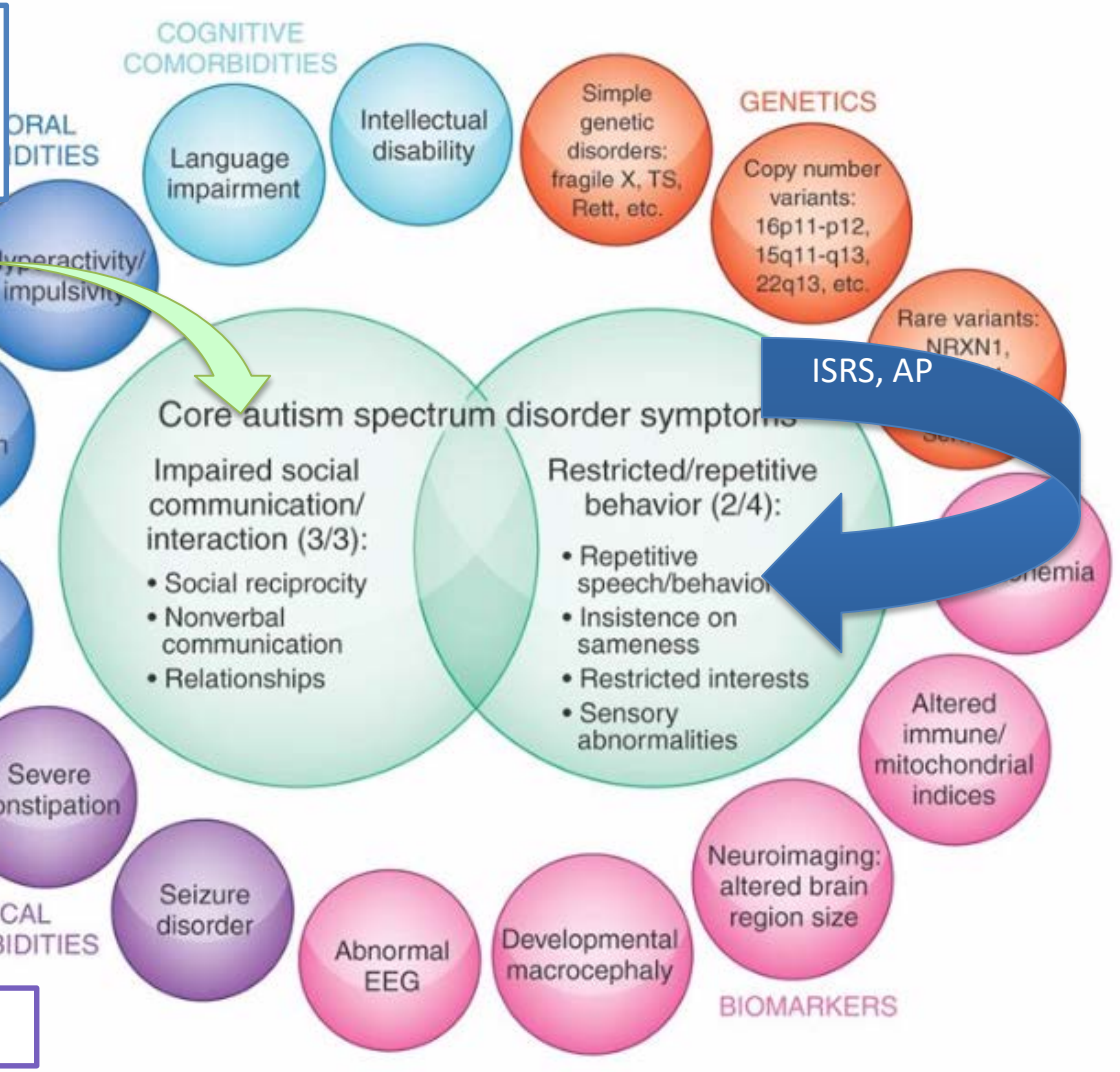
El reto de la heterogeneidad

Tratamientos TDAH
Antipsicóticos
ISRS

?



ISRS, AP

Anticonvulsivantes

Ameis et al, 2018

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2018: 1–22

DOI: 10.1111/acps.12918

ACTA PSYCHIATRICA SCANDINAVICA

Review

Systematic review and guide to management of core and psychiatric symptoms in youth with autism

Tratamientos TDAH
Antipsicóticos
ISRS

Clinical practice implications

- There is *emerging* evidence for positive effects of atypical antipsychotics, as a medication class, on stereotypic/repetitive behaviours in ASD based on studies evaluating this target

- Efficacy of short-term risperidone and aripiprazole for treatment of irritability in ASD is *established*. Due to risk of concerning side-effects, these medications should be used only in children with high irritability/aggression

Clinical practice implications

- Based on prior systematic reviews and recently published RCTs, there is now *emerging* evidence of positive treatment effects with methylphenidate, atomoxetine and guanfacine for targeting ADHD symptoms in ASD.

Clinicians should exercise caution when prescribing SSRIs, TCAs or other agents for the treatment of mood or anxiety symptoms as a target in individuals with ASD, using objective tools to screen for treatment targets and monitor benefits and side-effects as trials focused on treatment of this target in ASD are lacking.

Registro de EC con productos farmacológicos en autismo

NIH U.S. National Library of Medicine
ClinicalTrials.gov

59 EC en reclutamiento

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
2		Recruiting	Translating Neuroprediction Into Precision **Medicine** Via Brain Priming	• **Autism Spectrum Disorder**	• **Drug**: Oxytocin • Behavioral: Pivotal Response Treatment • **Drug**: Placebo	• Yale School of **Medicine** New Haven, Connecticut, United States
3		Recruiting	Impact of & ADHD	• **Autism Spectrum Disorde** • Attention Deficit Hyperactivi **Disorder**		r for Autism and Brain Development rth Carolina, United States
4		Recruiting	A Randor to Behavi	• **Autism Spectrum Disorde**		etts General Hospital ssachusetts, United States etts Institute of Technology Martinos Imaging Massachusetts, United States
5		Recruiting	A Pilot Tr **Autism S**	• **Autism Spectrum Disorder**	• **Drug**: IGF-1 • **Drug**: Placebo/saline	• Icahn School of **Medicine** at Mount Sinai New York, New York, United States
6		Recruiting	Trial of Pr **Disorder**	• **Autism Spectrum Disorder**	• **Drug**: Propranolol • **Drug**: Placebo • Device: Magnetic Resonance Imaging (MRI)	• Thompson Center for Autism & Neurodevelopmental Disorders Columbia, Missouri, United States
7		Recruiting	Improving **Disorder**	• **Autism Spectrum Disorder**	• **Drug**: Buspirone	• Massachusetts General Hospital Boston, Massachusetts, United States
8		Recruiting	Sulforaphane for the Treatment of Young Men With **Autism Spectrum Disorder**	• **Autism Spectrum Disorder** • **Autistic Disorder** • Neurodevelopmental **Disorder** • Childhood Developmental **Disorders**, Pervasive	• **Drug**: Sulforaphane • **Drug**: Placebo	• Carolina Institute for Developmental Disabilities, University of North Carolina School of **Medicine** Carrboro, North Carolina, United States
9		Recruiting	Combination Treatment for Augmenting Language in Children With ASD	• **Autism Spectrum Disorder**	• Behavioral: Behavioral Therapy • **Drug**: Aripiprazole • **Drug**: Placebo	• University of California Los Angeles, California, United States
10		Recruiting	The Efficacy of Robot-enhanced Therapy for Children With **Autism Spectrum Disorders**	• **Autistic Disorders Spectrum**	• Behavioral: (2) robot--enhanced intervention • Behavioral: (1) discrete trial training / cognitive-behavior therapy	• Babes-Bolyai University Psychological Clinic Cluj-Napoca, Romania

Showing: 1-10 of **59** studies 10 studies per page Paging: |< < > >|

Arbaclofen
Aripiprazol
Balovaptan
Bumetanida
Buspirona
Citalopram
Donezepilo
D-cicloserina

IGF-1
N-Acetilcisteína
Oxitocina
Riluzole……

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Circuitos diana

Oxitocina y Vasopresina

→ Conducta pro-social, ansiedad social, vínculo romántico y paternal, conducta agresiva

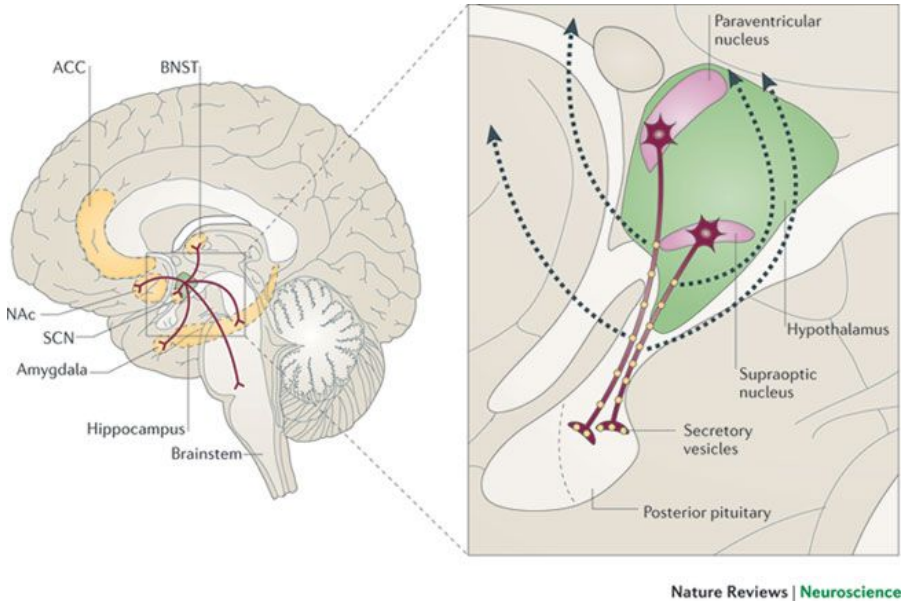
PNAS Proceedings of the National Academy of Sciences of the United States of America

Gordon et al, 2013

Oxytocin enhances brain function in children with autism

Ilanit Gordon[a,b,1], Brent C. Vander Wyk[a], Randi H. Bennett[a], Cara Cordeaux[a], Molly V. Lucas[a], Jeffrey A. Eilbott[a], Orna Zagoory-Sharon[c], James F. Leckman[d], Ruth Feldman[b,c,d], and Kevin A. Pelphrey[a]

[a]Center for Translational Developmental Neuroscience, Yale Child Study Center, Yale University, New Haven, CT 06520; [b]Department of Psychology, and [c]The Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan 52900, Israel; and [d]Yale Child Study Center, School of Medicine, Yale University, New Haven, CT 06520



Nature Reviews | Neuroscience

Oxitocina

TEA: sin diferencias

Vasopresina

TEA: 66% superior
Bosso et al (2007)

Balovaptan:

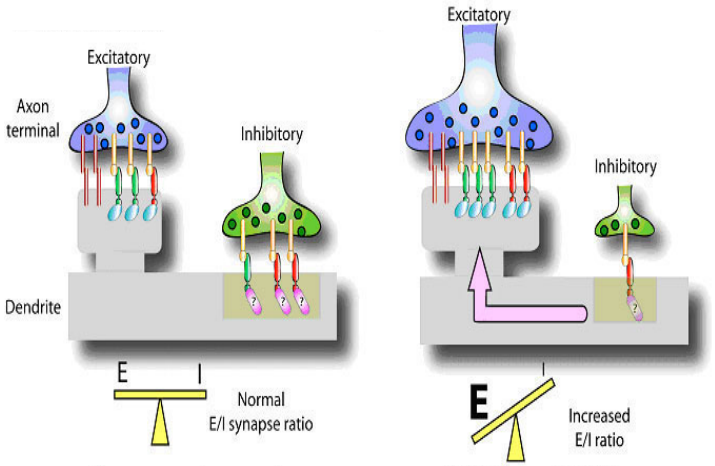
antagonista R de vasopresina

Roche

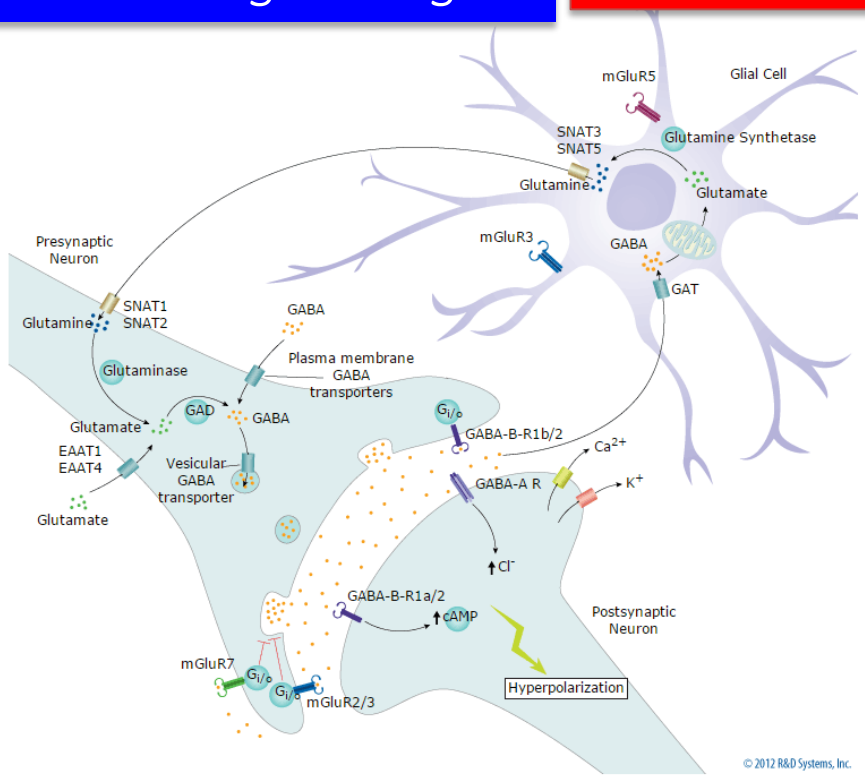
VANILLA Study, PhaseII
Bolognani et al, 2017

TEA, adultos n=224
12 semanas tto.
SRS-2 n.s.
VABS-II, soc com domain -> Dosis elevadas

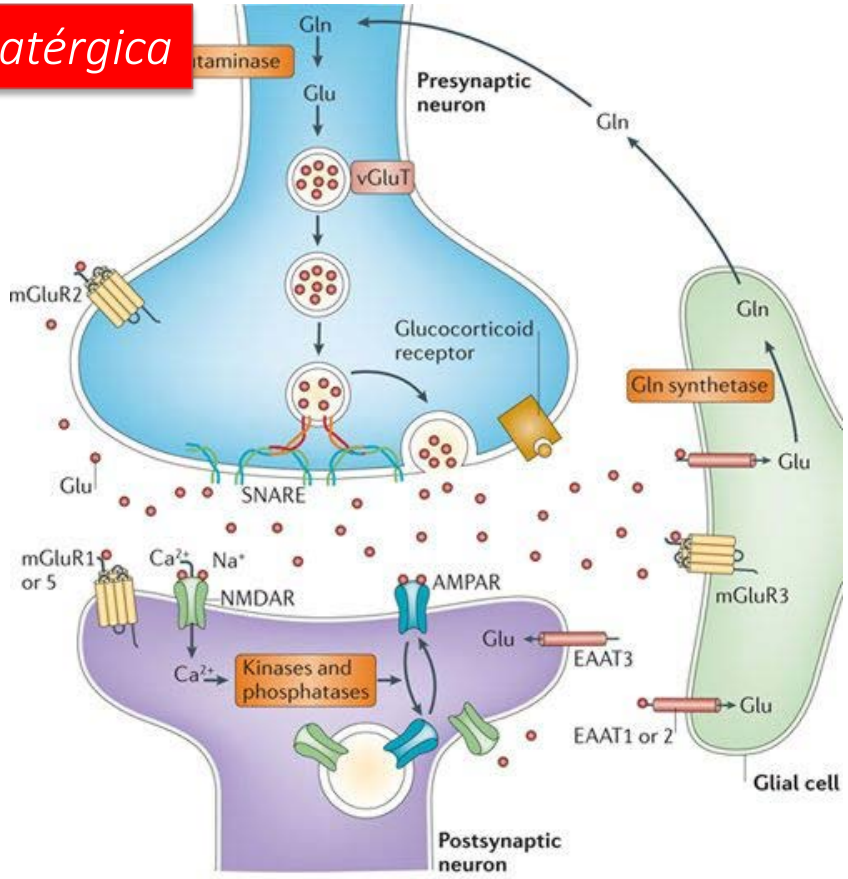
Circuitos diana



Inhibición: gabaérgica

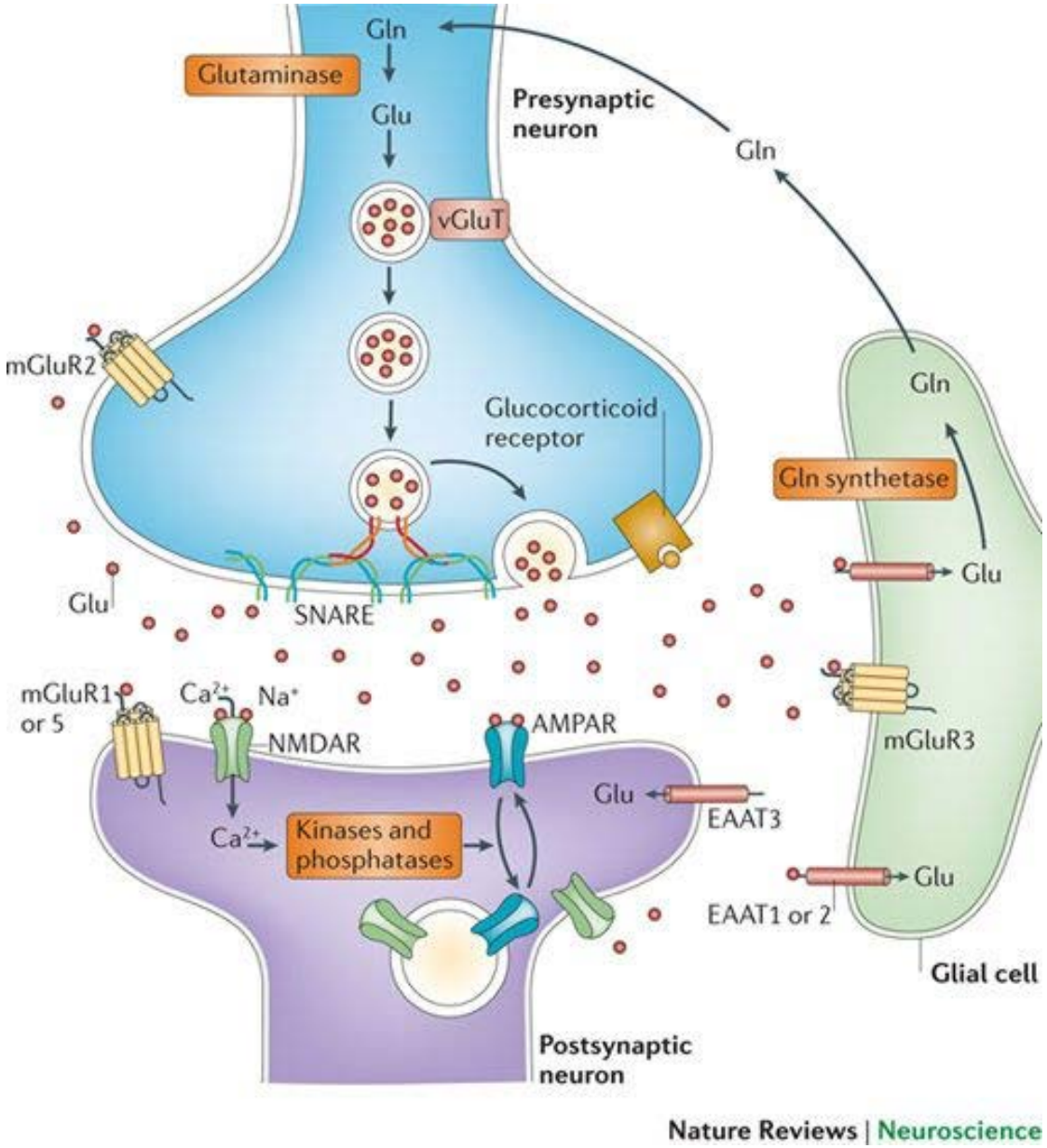


Excitación: glutamatérgica



Nature Reviews | Neuroscience

Excitación glutamatérgica → Comunicación entre neuronas, aprendizaje, memoria



Receptores Glutamato:

Ionotrópicos: "rápidos"
NMDA
AMPA
Kainate

Metabotrópicos:
Inician cascada (prot G)
mGluR1-8

mGluR1
mGluR5

Sd FrX

Circuitos diana

Gene	Protein	Loci	Protein Function
CDH8	Cadhedrin	16q21	Glycosylated transmembrane proteins that
CDH9	Cadhedrin	5p14.1	mediate cell–cell adhesion, neuronal migration,
CDH10	Cadhedrin	5p14.1	spine morphology, synapse formation, and
CDH13	Cadhedrin	16q23	synaptic remodeling
CNTNAP2	Contactin-associated protein-like 2 (CASPR2)	7q35-q36	Transmembrane scaffolding protein involved in the clustering of Kv1.1 at the nodes of Ranvier.
DLG4	PSD-95	17p13.1	Regulation of localization and trafficking of AMPA receptors
DYRK1A	Dual-specificity tyrosine phosphorylation-regulated kinase (DYRK)	21q22.13	DYRK1A-dependent phosphorylation of NR2A hinders the internalization of NR1/NR2A, causing an increase of surface NMDA receptor density
GAD1	GAD67	2q31.1	Catalyzes the conversion of glutamic acid to GABA
GRIN2A	NR2A of NMDAR	16p13.2	NR2A subunit of NMDA receptor
GRIN2B	NR2A of NMDAR	12p13.1	
NRXN1	Neurexin	2p16.3	Synaptic adhesion proteins that are located on the presynaptic membrane and bind to their postsynaptic counterpart, neuroligins.
NRXN2	Neurexin	11q13	
NRXN3	Neurexin	14q31	
NLGN1	Neuroligin	3q26	Synaptic adhesion proteins that are located on the postsynaptic membrane and bind to their presynaptic counterpart, neurexins.
NLGN3	Neuroligin	Xq13	
NLGN4	Neuroligin	Xp22.3	
PCDH9	Protocadhedrin	13q21.32	The largest subgroup of the cadherin superfamily (see above) of homophilic cell-adhesion proteins.
PCDH10	Protocadhedrin	4q28.3	
SLC25A12	AGC1	2q24-q33	Catalyze the exchange of aspartate for glutamate and a proton; involved in the malate/aspartate NADH shuttle; involved in the urea cycle.
SHANK3	Shank 3	22q13.3	Synaptic scaffolding proteins that bind neurexin-neuroligin and NMDAR complexes at the PSD of excitatory glutamatergic synapses
SHANK2	Shank 2	11q13.3-q13.4	
SHANK1	Shank 1	19q13.33	
SYNAPSIN 1	Synapsin 1	Xp11.23	Presynaptic phosphoproteins that account for 9% of the vesicle protein and can regulate neurotransmitter release and neurite outgrowth
SYNAPSIN 2	Synapsin 2	3p25.2	
SYNGAP1	SYNGAP1	6p21.32	Suppresses signaling pathways linked to NMDAR- mediated synaptic plasticity and AMPAR membrane insertion
TAOK2	TAOK2	16p11.2	A kinase involved in membrane blebbing and the MAPK14/ p38MAPK stress-activated MAPK cascade.

Genes de autismo (y proteínas) importantes para el funcionamiento de los receptores de glutamato asociados a TEA

Genes de autismo implicados en procesos sinápticos:
vía Akt-mTORC1
Phelan-McDermid (SHANK3)
Sd Rett y Sd Angelman

Fung and Hardan, 2015

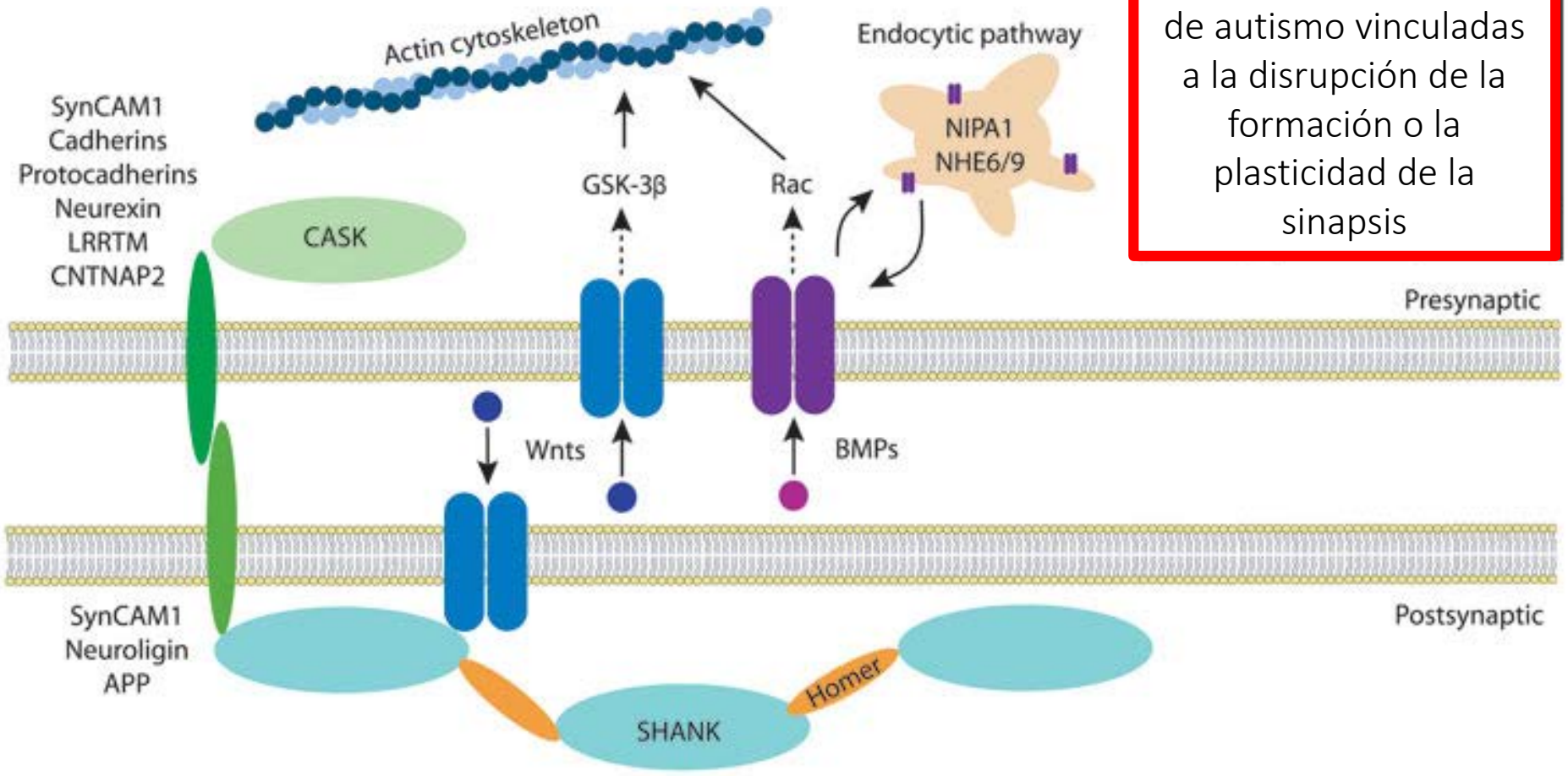
nature
International journal of science

Article | Published: 23 November 2011

Mutations causing syndromic autism define an axis of synaptic pathophysiology

Benjamin D. Auerbach, Emily K. Osterweil & Mark F. Bear

Múltiples mutaciones de autismo vinculadas a la disrupción de la formación o la plasticidad de la sinapsis



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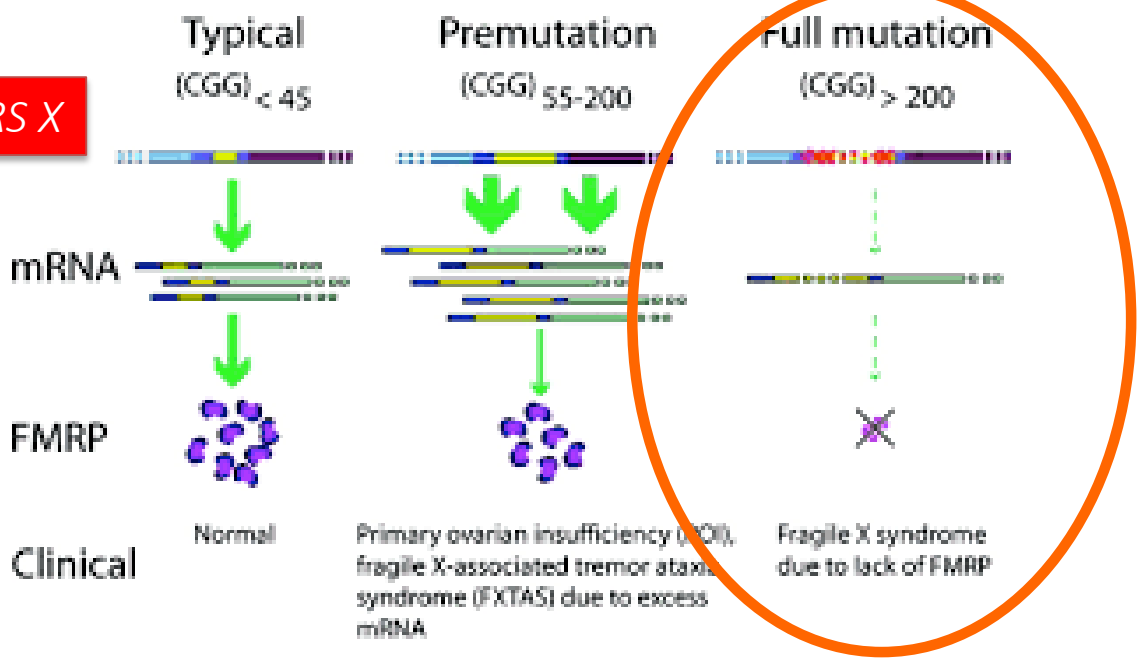
Dianas moleculares: síndromes monogénicos

CRS X



Sd Frágil X

20–50% ASD

Déficits FE
Procesamiento VE
Alteración CV

Ausencia FMRP

Modelo animal: knock-out FMR1

Alteraciones en la interacción social
Alteraciones en la comunicación (vocalizaciones ultrasónicas)
Conducta repetitiva y estereotipada (acicalamiento, excavar…)

Dianas moleculares: síndromes monogénicos

Modelo animal: knock-out FMR1

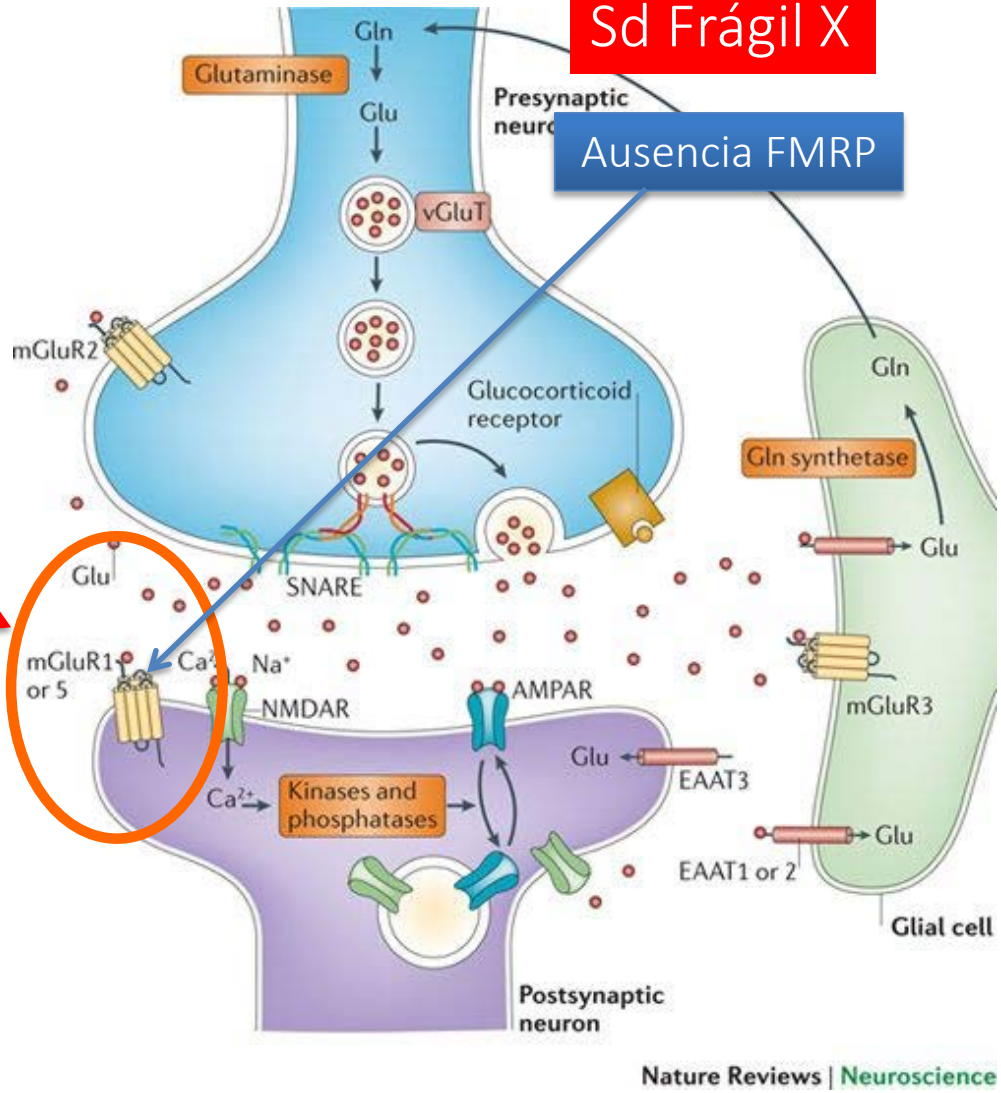
Antagonista mGluR:
AFQ056

3 semanas

Mejor interacción social: más olisqueo, más contactos
Disminución conducta repetitiva y estereotipada
Mejora aprendizaje

Sd Frágil X

Ausencia FMRP



Dianas moleculares: síndromes monogénicos

Antagonista mGluR5

NOVARTIS

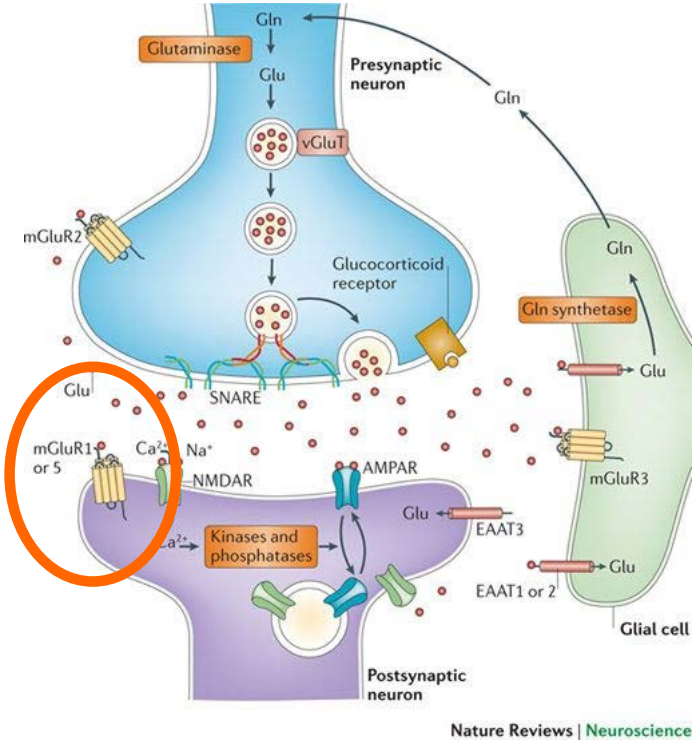
AFQ056

TEA (FrX), n=30
18-36 años
3 meses tto.
ABC-Irritability

Roche

RO4927523

TEA (FrX)
>14 años
5-13 años



- Outcome: Irritabilidad, en lugar de aprendizaje y comunicación
- Mayoría >13 años
- 3 meses es suficiente?

Biomarcadores
Objetivos conductuales específicos

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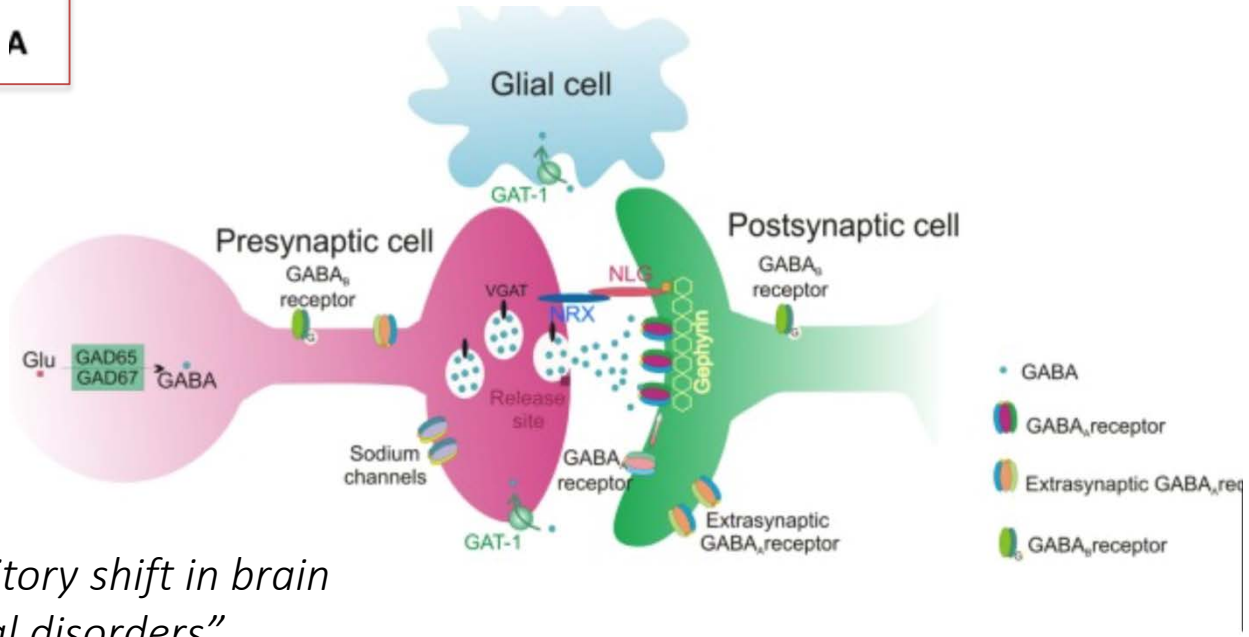
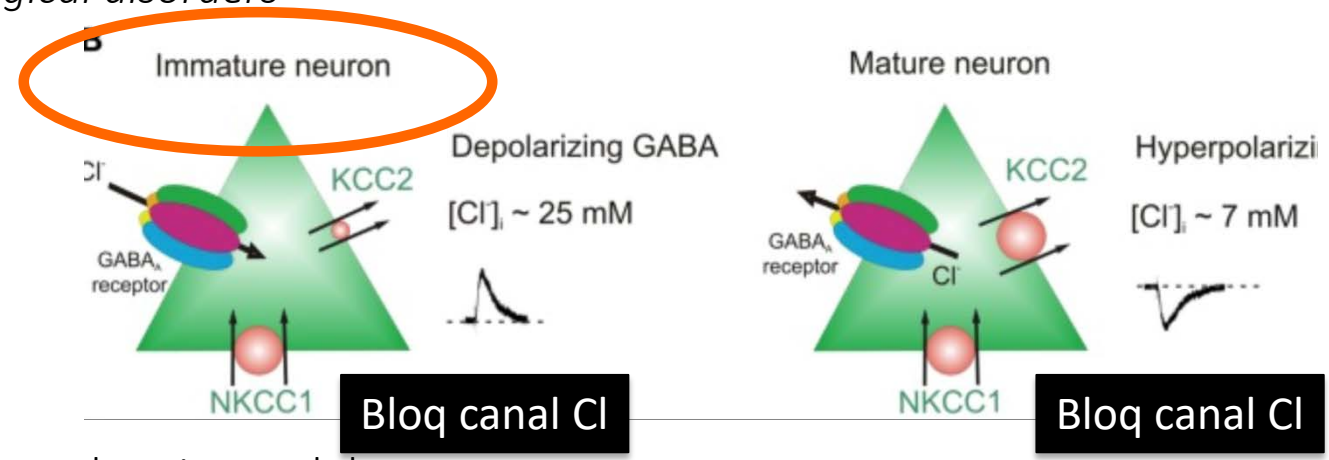
Circuitos diana

Inhibición gabaérgica



"The GABA excitatory/inhibitory shift in brain maturation and neurological disorders"



Exceso Cloro intracelular:
GABA→ excitación (salida Cl)
(Respuesta paradójica a GABAérgicos)

Menos Cl intracelular:
GABA abre canal Cl → Inhibición

Ben-Ari, Cherubini et al, 1989,2012

Bumetanida

Resultados previos

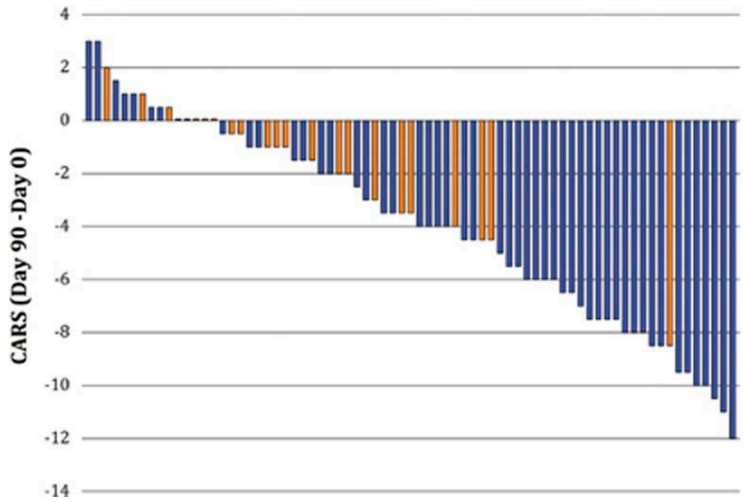
Lemonnier y Ben-Ari, 2010

88 niños y adolescentes

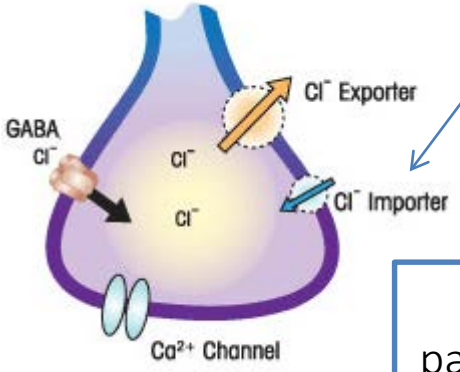
0,5 mg/12 hs

Mejoría en CARS2, SRS, CGI

Lemonnier E. et al. Transl. Psychiatry (2017)



Bumetanida:
Diurético, antiHTA



Bloqueo parcial canales Cl

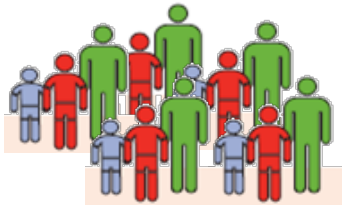
↓

Favorece despolarización

Bumetanida

Nuevo EC

370 niños y adolescentes con TEA
5-11
12-17
Gravedad:
SRS>66; CARS>34

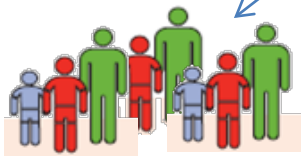


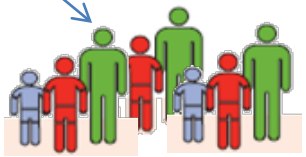
Europa

RANDOMIZACION

Placebo

Bumetanida





Bumetanida
6 meses

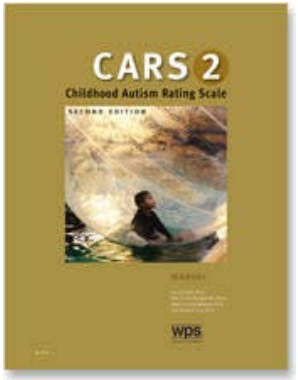
Bumetanida
6 meses

6 semanas FU

Hospital Universitari MútuaTerrassa

CLINIC BARCELONA Hospital Universitari

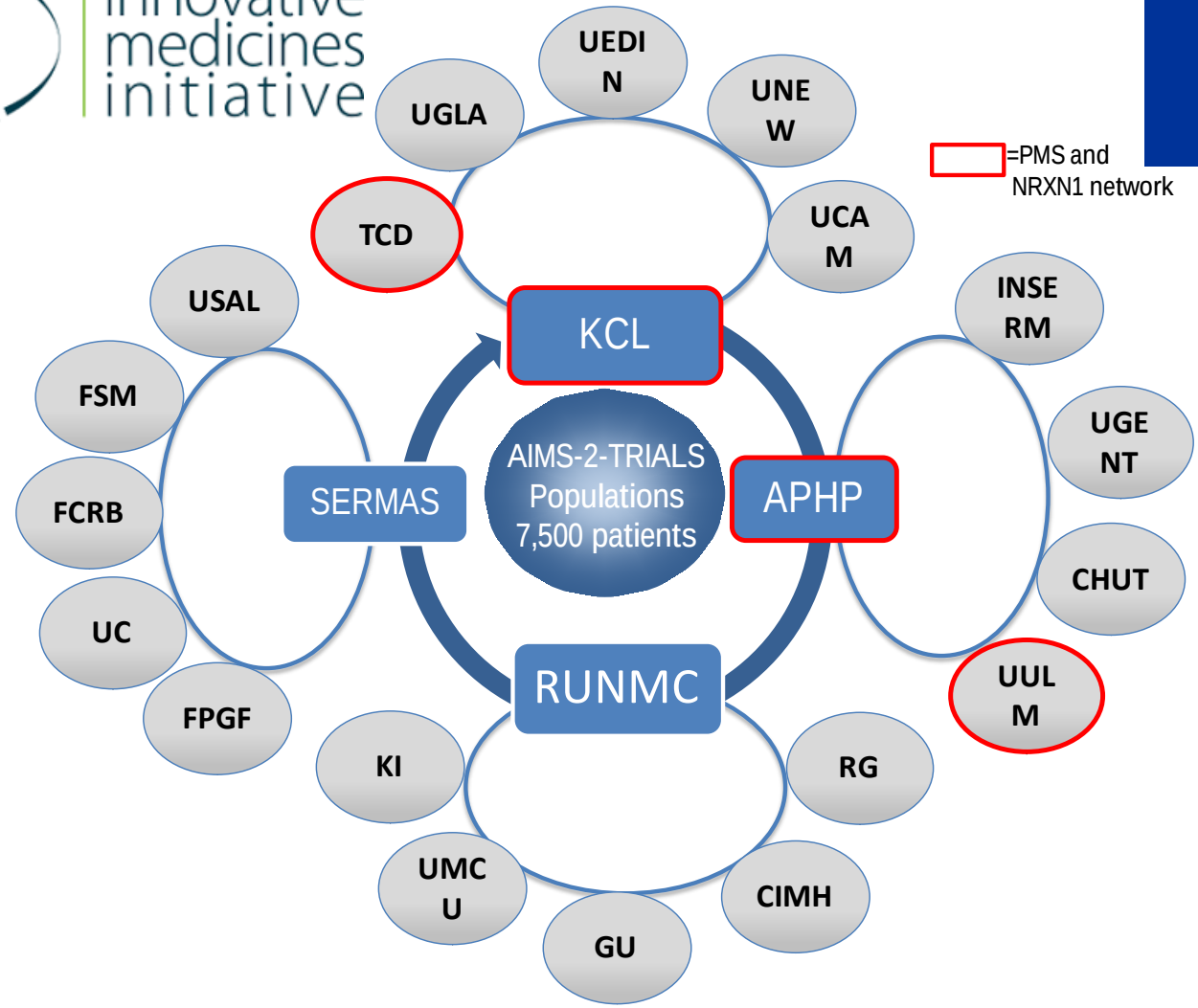
Childhood Autism Rating Scale 2



Limitaciones

- **Marcadores conductuales**

innovative medicines initiative

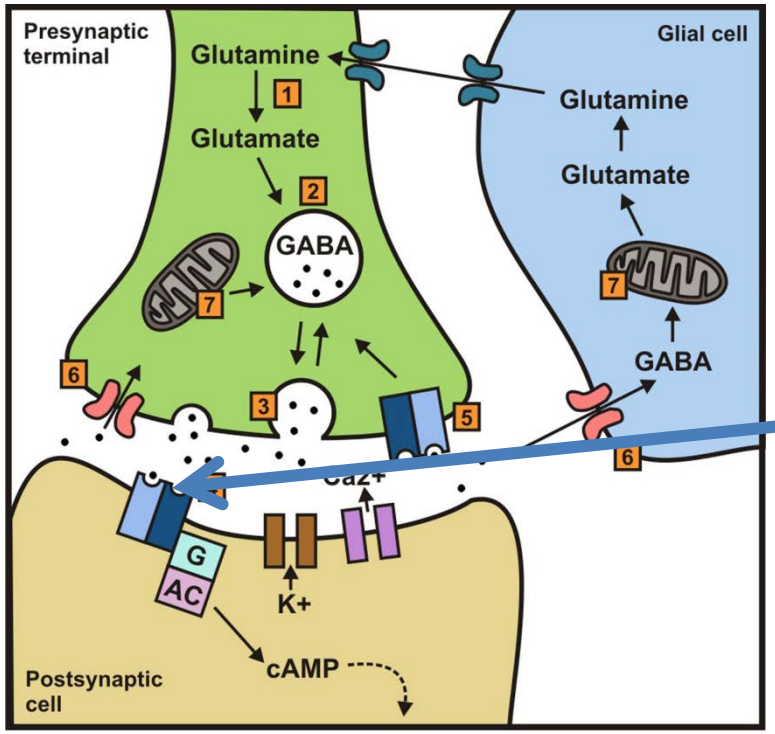


AIMS2TRIALS
Autism Research in Europe

AUTISTICA
With knowledge comes understanding

AIMS2TRIALS
Autism Research in Europe

Arbaclofen Trial for the treatment of social function in ASD



Arbaclofen

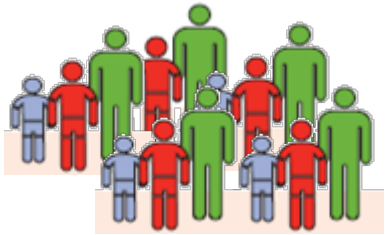
Agonista del R GABA-B

Aumenta Inhibición Gabaérgica

- Inhibición liberación pre-sináptica de Glu
- Modulación señal intracelular

Previous evidence

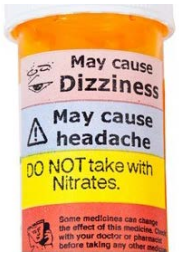
Seaside Therapeutics



150 individuals
Ages 5-21

- No sign diffs between Arbaclofen and placebo in ITT
- **BUT** younger and higher IQ individuals on Arbaclofen showed improvements on VABS Socialization

Veenstra-VanderWeele, et al., 2017

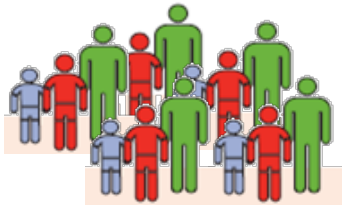


Event	Placebo, *n* (%) *N* = 74	Arbaclofen, *n* (%) *N* = 76
Any adverse event	58 (78.4%)	64 (84.2%)
Vomiting	7 (9.5%)	12 (15.8%)
Upper Resp infection	10 (13.5%)	10 (13.2%)
Affect lability[b]	1 (1.4%)	8 (10.5%)
Headache	4 (	
Irritability	8 (	
Somnolence[c]	1 (	
Insomnia	10 (	
Aggression	5 (	
Diarrhea	6 (	
Decreased appetite	2 (	
Hyperactivity	6 (	
Anxiety	5 (	
Sleep disorder	3 (	
Weight decreased	2 (	
Nasopharyngitis	5 (	
Cough	3 (4.1%)	4 (5.3%)
Nasal congestion	1 (1.4%)	4 (5.3%)
Pyrexia	6 (8.1%)	3 (3.9%)
Agitation	4 (5.4%)	2 (2.6%)
Rhinorrhea	6 (8.1%)	2 (2.6%)
Rash	5 (6.8%)	2 (2.6%)

Event	Placebo, *n* (%) *N* = 74	Arbaclofen, *n* (%) *N* = 76
Any adverse event	58 (78.4%)	64 (84.2%)
Vomiting	7 (9.5%)	12 (15.8%)
Upper Resp infection	10 (13.5%)	10 (13.2%)

Our current trial

130 volunteers with ASD
Ages 5-17
IQ > 75

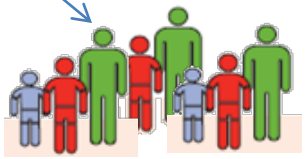


From UK, France and Spain
(+POND Network Canada)

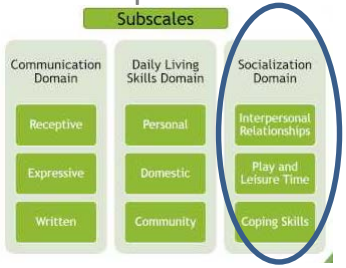
RANDOMIZATION

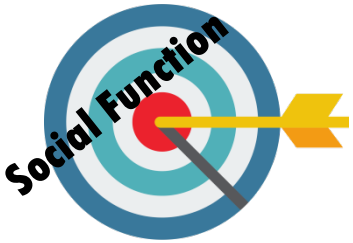
Placebo

Arbaclofen

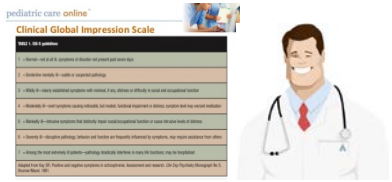


Vineland Adaptive Behavior Scales





Clinical Global Impression



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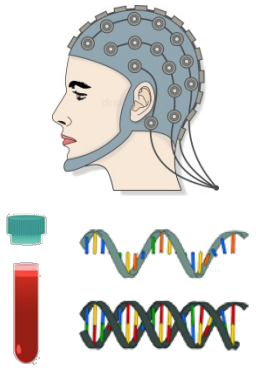
Stratification Biomarkers



CONCLUSIONES:

El reconocimiento de las vías implicadas en los síntomas nucleares del TEA contribuye al desarrollo de nuevos fármacos con dianas específicas

No toda la población con TEA presenta déficits en los sistemas glutamatérgico/gabaérgico o en eje HP

Importancia de identificar factores moleculares

El uso de medidas de resultado conductuales limita la valoración del efecto

Importancia de los biomarcadores

Niños con deficits moleculares y en los circuitos conocidos podrán beneficiarse de la mejora de neuroplasticidad con agentes específicos y tratamientos conductuales

IMPLICACIONES PARA EL FUTURO:

Los tratamientos farmacológicos específicos deben combinarse con intervenciones conductuales: si mejoran las conexiones sinápticas, deberían aumentarse y estimularse con las intervenciones educativas

Niños con dèficits moleculares/circuitos conocidos:
→agentes específicos para mejorar neuroplasticidad.
→intervenciones conductuales para adquirir habilidades

Individuos que ya han desarrollado síntomas:
→reversión de los síntomas con tratamiento farmacológico para dianas moleculares y de circuito e intervenciones conductuales

Importancia de inicio precoz de la intervención

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