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Update on clinical trials in ASD

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Current approaches

Medications to target symptom domains based on phenotypic overlap of such domains with other disorders, i.e.

- *SSRI for repetitive behaviors (from OCD)*
- *Atypical antipsychotics for maladaptive behaviors (irritability and aggression across several other disorders)*
- *Stimulants, non-stimulants for inattention (overlap with ADHD)*

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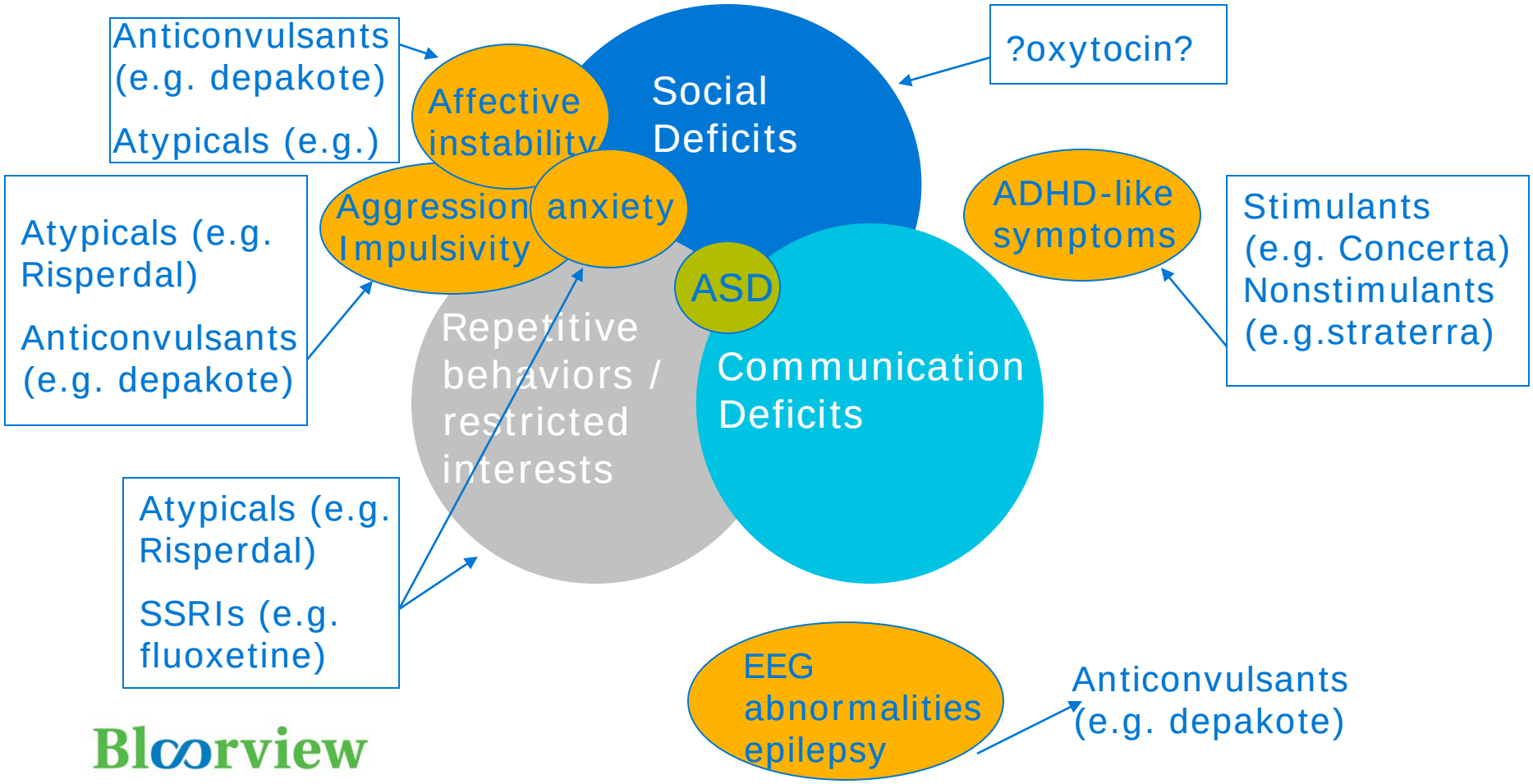

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Irritability / Impulsive aggression

- Atypical neuroleptics
  - FDA indication for:
    - *Risperidone*
    - *Aripiprazole*

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Atypical Antipsychotics

Drug	Starting Dose	Effective Dose	Dosing Frequency	Side-effect Consideration	Monitoring Considerations
Risperidone	0.25-0.5	0.5-6	QDAY-TID	Weight gain, EPS/TD Hyperprolactinemia Sedation	Weight, BMI, Fasting glucose and lipid profile AIMS, Prolactin
Olanzapine	2.5-5	5-40	QDAY-TID	Weight gain, EPS/TD Hyperprolactinemia[1] Sedation	Weight, BMI, Fasting glucose and lipid profile, AIMS
Quetiapine	25-50	75-800	QDAY-TID	Weight gain, EPS/TD Hyperprolactinemia[1] Sedation	Weight, BMI, Fasting glucose & lipid profile, AIMS
Ziprasidone	20-40	20-160	QDAY-TID	Weight neutral, EPS, QT prolongation Hyperprolactinemia	Weight, BMI, Fasting glucose and lipid profile AIMS, ECG
Aripiprazole	2.5-5	5-30	QDAY-BID	Weight neutral EPS/TD	Weight, BMI, Fasting glucose & lipids, AIMS

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Modified from Posey et al 2007

RUPP risperidone study

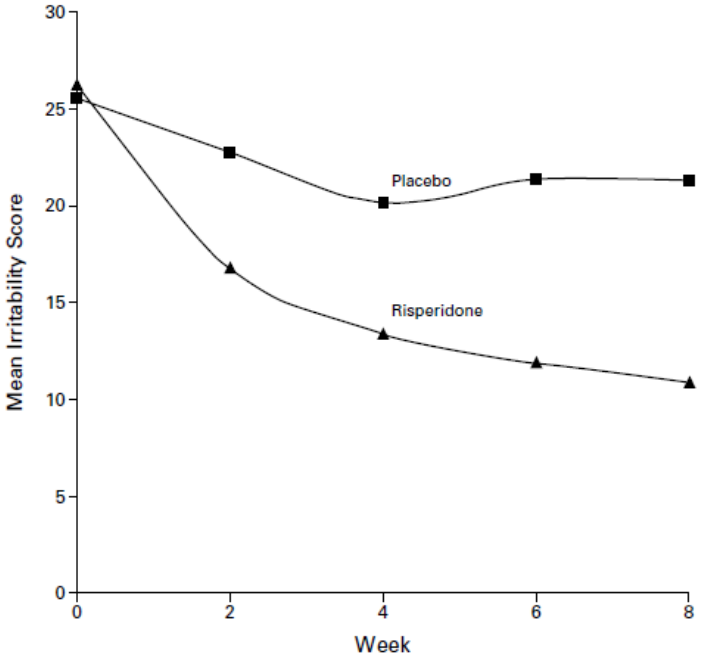

Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.

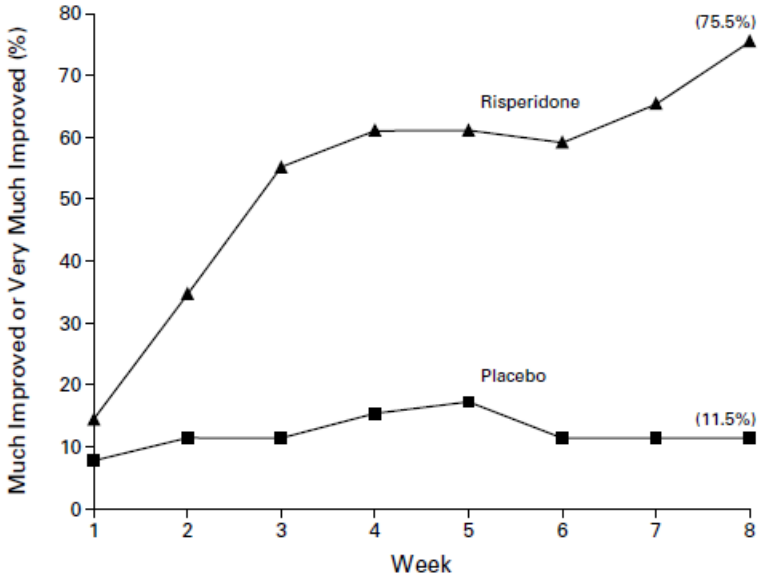

Figure 2. Percentage of Children with a Rating of Much Improved or Very Much Improved on the Clinical Global Impressions — Improvement Scale during the Eight-Week Trial. Data are for all 49 children assigned to the risperidone group and for all 52 assigned to the placebo group.

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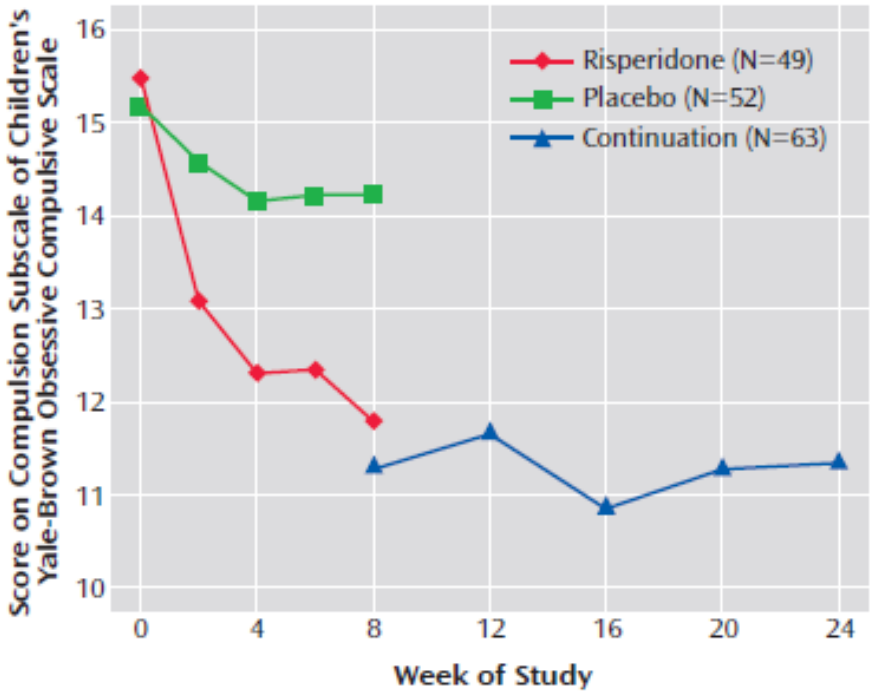
RUPP risperidone study

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



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RUPP risperidone study

Event	(N=49)	(N=51)†	Value‡
Increased appetite — no. (%)			
Mild	24 (49)	13 (25)	0.03
Moderate	12 (24)	2 (4)	0.01
Nasal congestion — no. (%)	25 (51)	20 (39)	0.32
Fatigue — no. (%)	29 (59)	14 (27)	0.003
Enuresis — no. (%)	15 (31)	15 (29)	0.93
Drowsiness — no. (%)	24 (49)	6 (12)	<0.001
Vomiting — no. (%)	16 (33)	12 (24)	0.43
Insomnia — no. (%)	7 (14)	15 (29)	0.11
Anxiety — no. (%)	12 (24)	10 (20)	0.73
Diarrhea — no. (%)	9 (18)	11 (22)	0.88
Constipation — no. (%)	14 (29)	6 (12)	0.06
Sleep problems — no. (%)	11 (22)	9 (18)	0.73
Skin irritation — no. (%)	11 (22)	7 (14)	0.38
Drooling — no. (%)	13 (27)	3 (6)	0.02
Headache — no. (%)	9 (18)	6 (12)§	0.52
Stomachache — no. (%)	5 (10)	9 (18)	0.43
Dry mouth — no. (%)	9 (18)	5 (10)	0.34
Increased thirst — no. (%)	6 (12)	5 (10)	0.94
Dizziness — no. (%)	8 (16)	2 (4)	0.05
Dyskinesia — no. (%)	6 (12)	3 (6)	0.45
Nausea — no. (%)	4 (8)	5 (10)	0.95
Decreased appetite — no. (%)	3 (6)	5 (10)	0.76
Tremor — no. (%)	7 (14)	1 (2)	0.06
Tachycardia — no. (%)	6 (12)	1 (2)	0.06
Upper respiratory tract infection — no. (%)	5 (10)	2 (4)	0.40
Earache — no. (%)	2 (4)	4 (8)	0.71
Muscle rigidity — no. (%)	5 (10)	1 (2)	0.11
Sore throat — no. (%)	5 (10)	1 (2)	0.11
Restlessness — no. (%)	3 (6)	3 (6)	0.71
Weight gain — kg	2.7±2.9	0.8±2.2	<0.001

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Aripiprazole randomized controlled trial in ASD

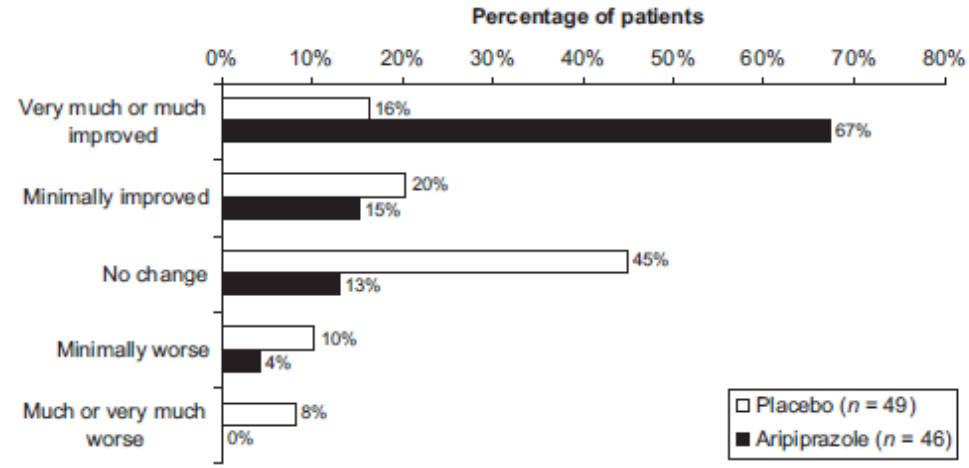

FIGURE 3
Distribution of CGI-I score at week 8 (LOCF; efficacy sample).

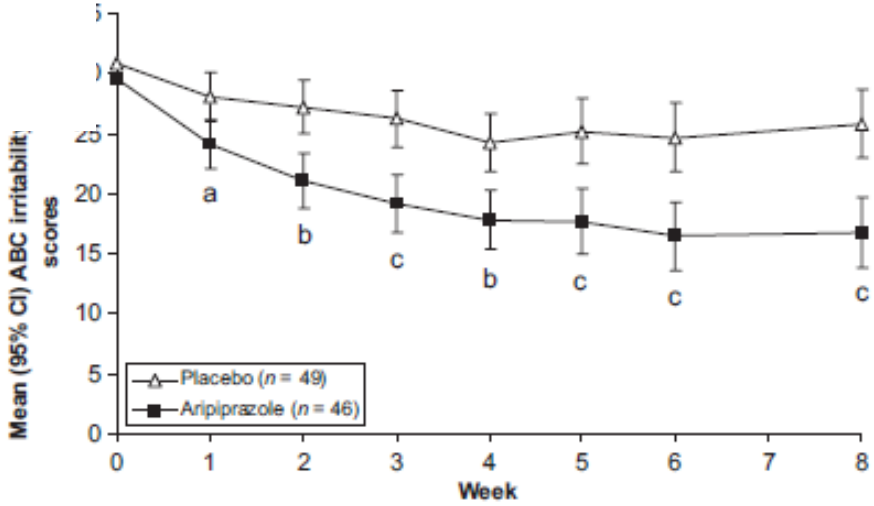

FIGURE 2
Mean ABC irritability subscale score according to week (LOCF; efficacy sample). [a] $P < .05$ [b] $P < .005$, and [c] $P < .001$ versus placebo.

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Aripiprazole randomized controlled trial in ASD

TABLE 3 Treatment-Emergent AEs

AE	Placebo ($N = 50$), n (%)	Aripiprazole ($N = 47$), n (%)
Occurring in ≥5% of any group		
Any AE	36 (72.0)	43 (91.5)
Headache	8 (16.0)	3 (6.4)
Somnolence	2 (4.0)	8 (17.0)
Sedation	1 (2.0)	5 (10.6)
Drooling	0 (0.0)	4 (8.5)
Tremor	0 (0.0)	4 (8.5)
Diarrhea	5 (10.0)	4 (8.5)
Vomiting	2 (4.0)	7 (14.9)
Insomnia	4 (8.0)	3 (6.4)
Aggression	4 (8.0)	1 (2.1)
Fatigue	2 (4.0)	10 (21.3)
Pyrexia	1 (2.0)	4 (8.5)
Upper respiratory tract infection	5 (10.0)	1 (2.1)
Nasopharyngitis	3 (6.0)	2 (4.3)
Nasal congestion	1 (2.0)	3 (6.4)
Increased appetite	5 (10.0)	7 (14.9)
Enuresis	4 (8.0)	3 (6.4)
EPSs		
Any EPS event[a]	4 (8.0)	7 (14.9)
Tremor	0 (0.0)	4 (8.5)
Extrapyramidal disorder	0 (0.0)	1 (2.1)
Muscle rigidity	0 (0.0)	1 (1.2)
Muscle spasms	1 (2.0)	0 (0.0)
Akathisia	1 (2.0)	0 (0.0)
Psychomotor hyperactivity	2 (4.0)	1 (2.1)
Hypokinesia	0 (0.0)	1 (2.1)
Hyperkinesia	1 (2.0)	0 (0.0)

[a] Patients with multiple EPS events were counted only once toward the total.

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SRIs in Autism

- Clomipramine (Anafranil)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox, Faverin)
- Sertraline (Zoloft)
- Paroxetine (Paxil, Seroxat)
- Citalopram (Celexa, Cipramil, Actavis)
- Venlafaxine (Effexor)
- Escitalopram (Lexapro, Cipralex)

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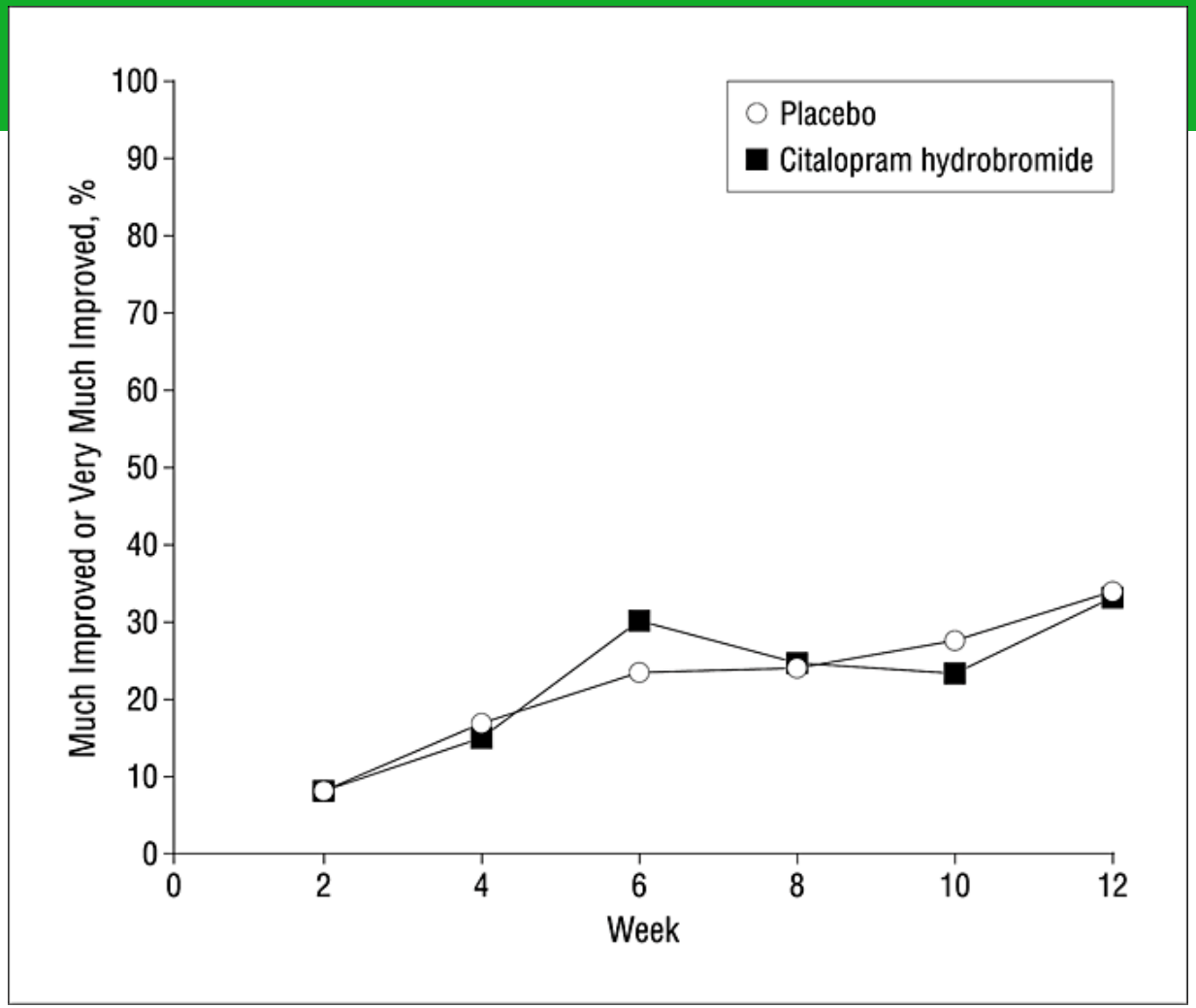
Percentage of children with a rating of much improved or very much improved on the Clinical Global Impressions, Improvement subscale during the 12-week trial



King, B. H. et al. Arch Gen Psychiatry 2009;66:583-590.

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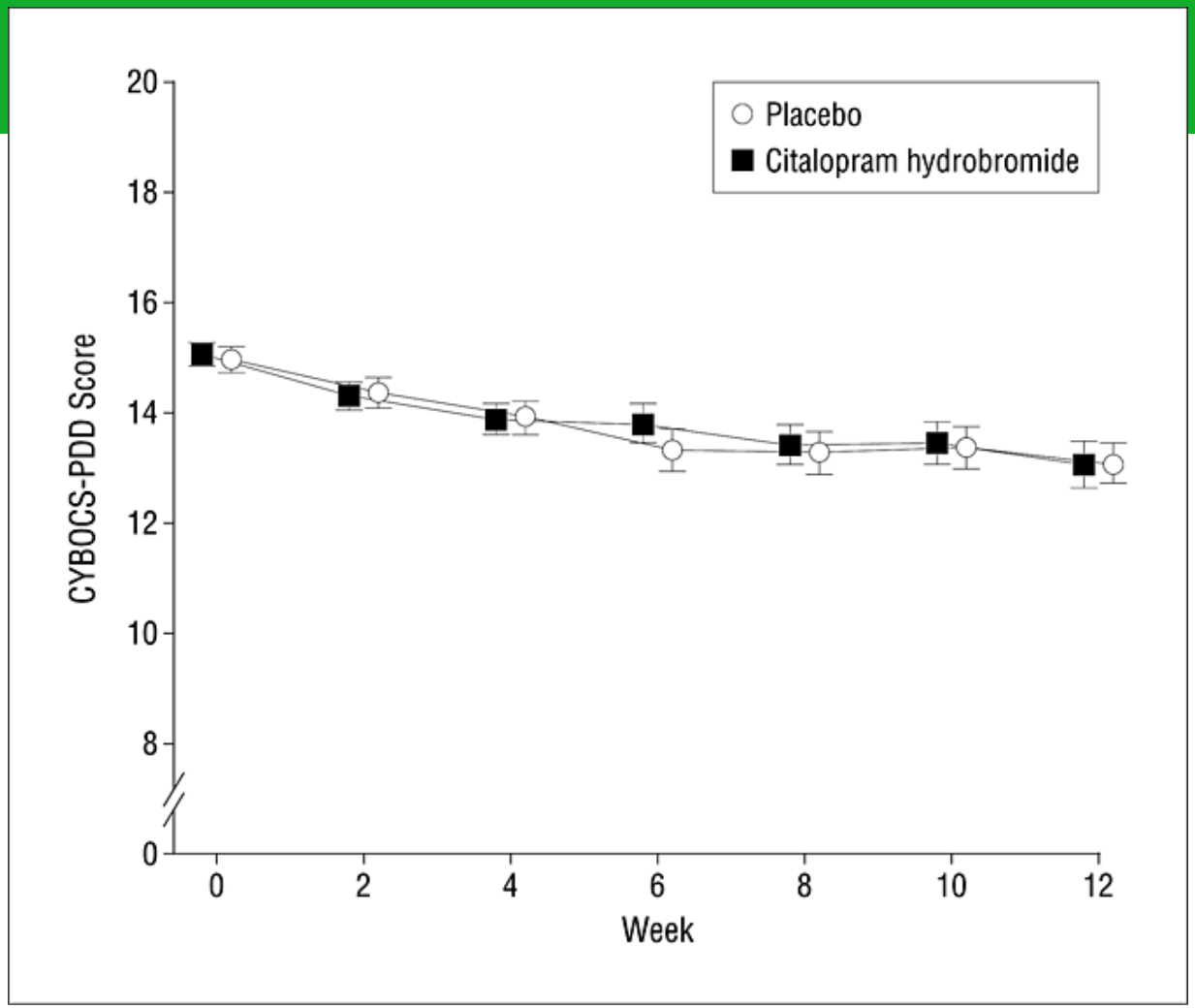
The mean scores on the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders (CYBOCS-PDD) over time



King, B. H. et al. Arch Gen Psychiatry 2009;66:583-590.

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Table 3. Adverse Events Elicited During the Trial by Treatment Group

Adverse Event[a]	No. (%) Citalopram Hydrobromide–Treated Group (n=73)	No. (%) Placebo Group (n=76)	*P* Value[b]
Any adverse event	71 (97.3)	66 (86.8)	*.03*
Neuropsychiatric Disorders			
Energy level increased	28 (38.4)	15 (19.7)	*.02*
Anger or irritability	18 (24.7)	13 (17.1)	.31
Aggression or hostility	17 (23.3)	13 (17.1)	.42
Headache or migraine	15 (20.5)	10 (13.2)	.28
Restlessness or difficulty settling down	13 (17.8)	7 (9.2)	.15
Disinhibited, impulsive, or intrusive behavior	14 (19.2)	5 (6.6)	*.03*
Silliness	9 (12.3)	10 (13.2)	>.99
Anxiety	8 (11.0)	9 (11.8)	>.99
Mood lability	7 (9.6)	9 (11.8)	.79
Increased speech	8 (11.0)	4 (5.3)	.24
Attention and concentration decreased	9 (12.3)	2 (2.6)	*.03*
Hyperactivity	9 (12.3)	2 (2.6)	*.03*
Stereotypy	8 (11.0)	1 (1.3)	*.02*
Gastrointestinal Disorders			
Diarrhea or loose stools	19 (26.0)	9 (11.8)	*.04*
Abdominal discomfort	13 (17.8)	9 (11.8)	.36
Vomiting or nausea	14 (19.2)	6 (7.9)	.06
Sleep Disturbance			
Any insomnia	28 (38.4)	17 (22.4)	*.05*
Insomnia, initial or difficulty falling asleep	17 (23.3)	7 (9.2)	*.03*
Insomnia, midcycle or other	13 (17.8)	9 (11.8)	.36
Infections and Infestations			
Cold, flu, or other systemic infection	31 (42.5)	26 (34.2)	.32

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ADHD like symptoms and autism

- STIMULANTS
- Dextro-amphetamine (Dexedrin), Methylphenidate (Ritalin, Concerta), amphetamine (Adderral)
  - Multiple double-blind placebo-controlled trials of Methylphenidate
    - *Increased sensitivity to SE*
    - *Improvements in hyperactivity and irritability*
      - *RUPP, Quintana et al. 1995, Handen et al. 2000*
- Atomoxetine
  - One randomized trial, effect sizes similar to Ritalin

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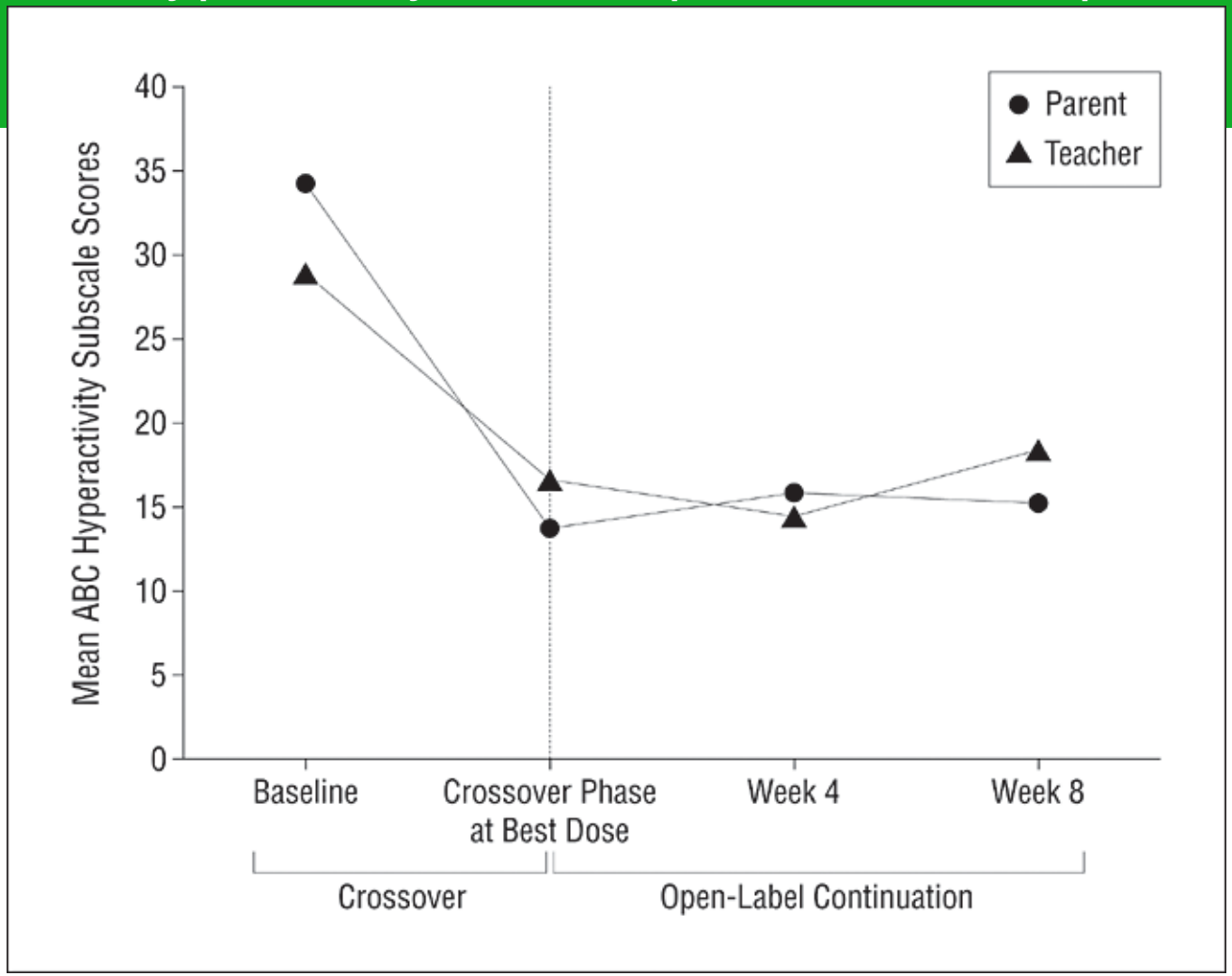
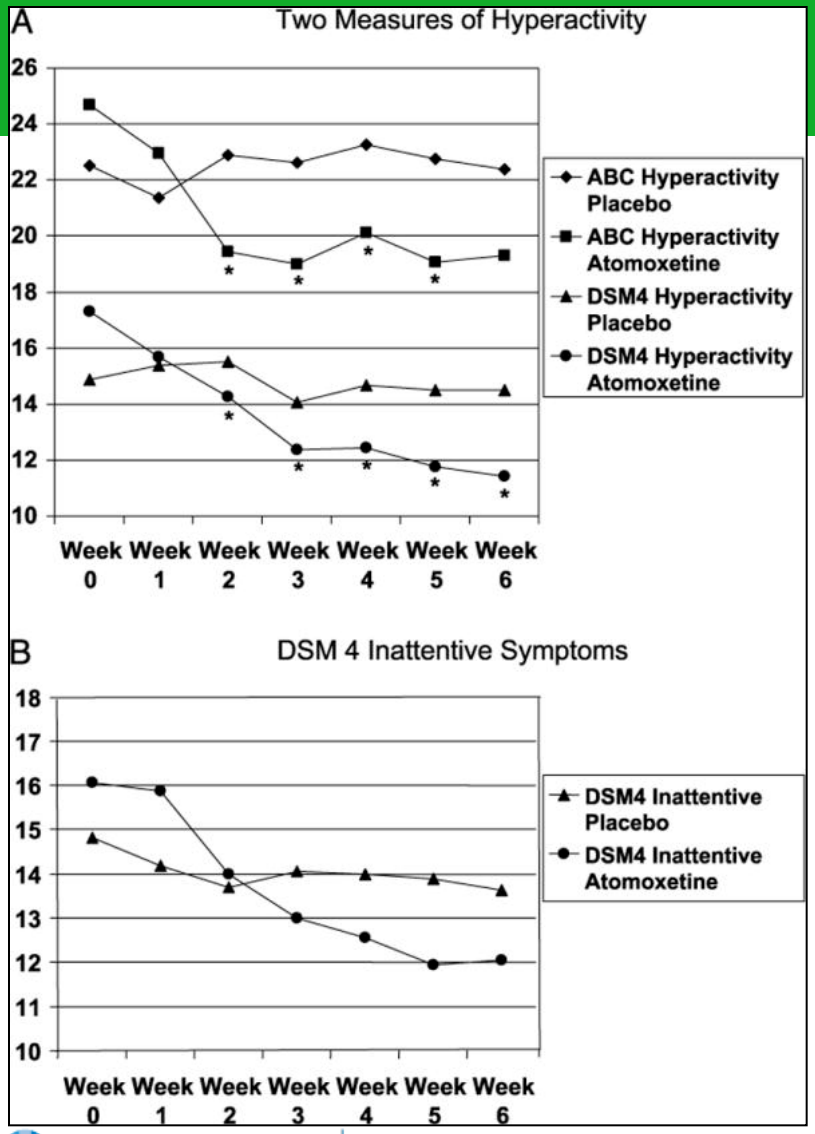
Mean Aberrant Behavior Checklist (ABC) hyperactivity subscale scores as rated by teachers and parents at baseline, at the best dose of methylphenidate during the crossover phase, and during the methylphenidate hydrochloride open-label continuation phase



Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, Arch Gen Psychiatry 2005;62:1266-1274.

Atomoxetine cross over study



Atomoxetine for Hyperactivity in Autism Spectrum Disorders: Placebo-Controlled Crossover Pilot Trial.
ARNOLD, L; AMAN, MICHAEL; COOK, AMELIA; WITWER, ANDREA; HALL, KRISTY; THOMPSON, SUSAN; RAMADAN, YASER

Journal of the American Academy of Child & Adolescent Psychiatry. 45(10):1196-1205, October 2006.
DOI: 10.1097/01.chi.0000231976.28719.2a

Evidence for medications targeting hyperactivity

ABC hyperactivity subscale

	N	% change from baseline	Evidence
Ritalin	66	34%	+++
Guanfacine	25	25%	+
Risperdal	180	46-55%	+++
Haldol	36	27 %	+++
Clomiparmine	36	11 %	+++
Amantadine	30	22 %	+++
Atomoxetine	16	30 %	+++

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Scahill et al 2007

- What we have not done

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Future approaches

Based on new info on neurobiology of disorder

- *Developmental studies*
- *Immunomodulation*
  - *Steroids, IV IG, poor NNT for SE profile*
  - *Other immunomodulators*
- *Glutamate/GABA modulation*
  - ***Memantine**, Valproate, metabotropic glutamate receptor modulation*
- *epilepsy*
- *Neuropeptide modulation*
  - *?**oxytocin***
- *Target executive function abnormalities*
  - *NE modulation vs. cognitive remediation programs*
- *Studies targeting specific mutations: ?design issues, RCTs? etc*

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Future approaches

- COMPLEMENTARY AND ALTERNATIVE TREATMENTS
  - Of interest: **Omega 3 fatty acids**, methylation/demethylation agents, GABA enhancing compounds

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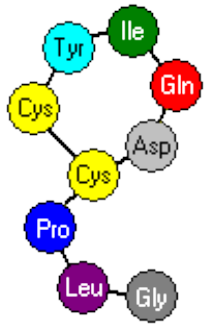
Oxytocin

- 9 aminoacid neuropeptide
- Synthesized in PVN and SON (for systemic release)
  - Separate neuronal groups synthesize OT for central release, PVN, amygdala , BnST (Vries & Buijs, 1983)
- Peripheral release is important for delivery, and lactation
- Central release important for social cognition (recognition and memory), bonding, trust



Oxytocin

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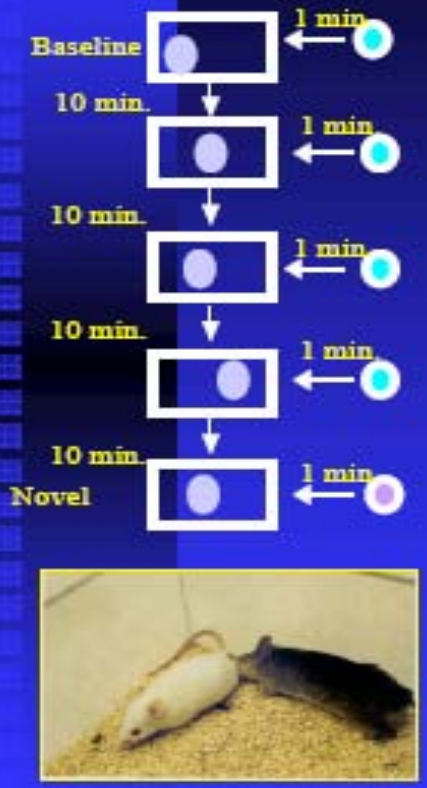
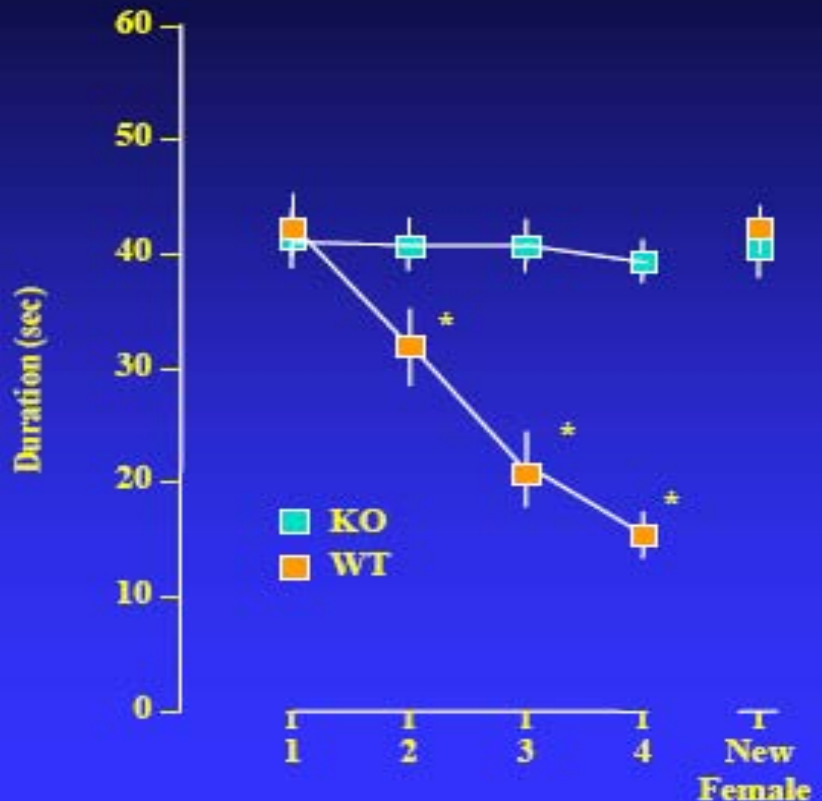
Oxytocin and social deficits

- Animal Studies
  - Social recognition and processing
    - *Central administration of oxytocin facilitates social memory (Popik et al 1992, Benelli et al 1995) in small doses*
    - *OTR antagonists cause social recognition deficits in female rats (Benelli et al 1995, Engelmann et al 1998)*
    - *Transgenic male mice that lack Oxytocin gene are unable to recognize familial conspecific (Ferguson et al 2000), not due to olfaction, learning and memory deficits*
    - *In the oxytocin knockout, ICV oxytocin prior to exposure to conspecific rescues social recognition (Ferguson 2001)*
    - *Effects seen in males and females (Choleris et al 2003)*
    - *Oxytocin KO mouse, after 90 sec of social encounter, absent Fos induction in medial amygdala, BdST and medial preoptic area but not in the olfactory bulb vs.. wild type (Ferguson et al, 2001)*
    - *Social recognition in oxytocin knock out also rescued by bilateral microinjections of oxytocin into medial amygdala prior to exposure to conspecific (Ferguson et al 2001)*
    - *Oxytocin important in social memory (Crawley, 2007)*

OT-KO Mice: Deficit In Social Recognition



Test mouse
Stimulus mouse
Stimulus #2



Fergusen et al. *Nature Genetics* 2000

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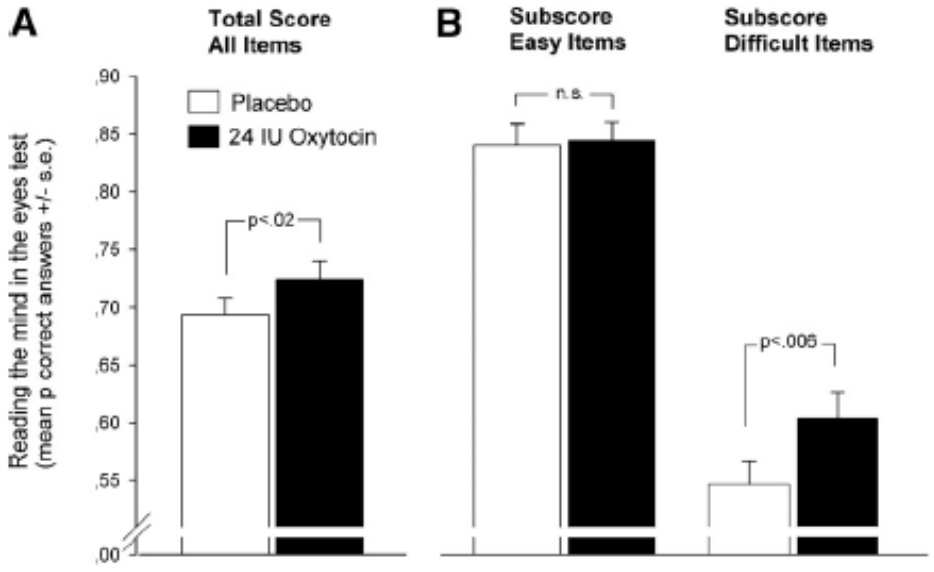
Oxytocin Improves “Mind-Reading” in Humans , Domes et al 2007



30 healthy controls, 21-30 yoa

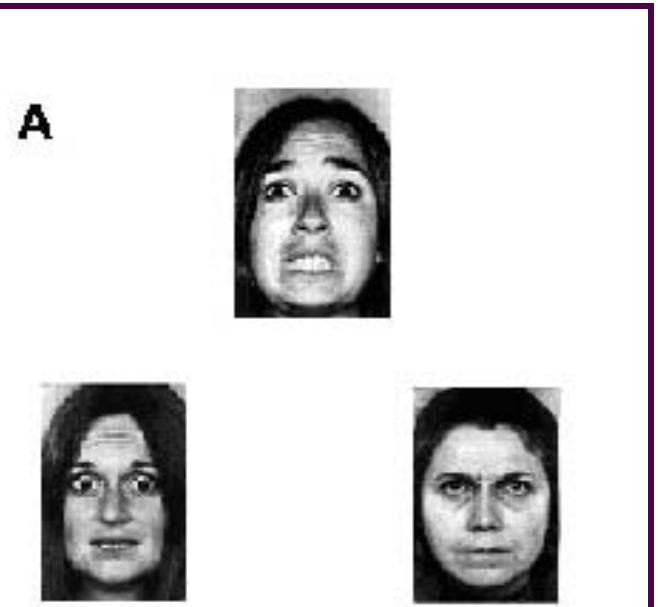
24 IU of oxytocin vs. placebo 1 week apart

No Axis I disorders

No meds or substance abuse

Testing started 45 min after administration

Emotion matching task illustrates fMRI activation of the amygdala, Kirsh et al 2005



13 participants, ages 18-40

No axis I

No meds, or substance abuse

27 IU of oxytocin vs. placebo 1 week apart

Administration of OT was 30 min before the start of the fMRI scan.

Participants were asked to select, from the two faces on the bottom, the one that expressed the same emotion as the face on the top.

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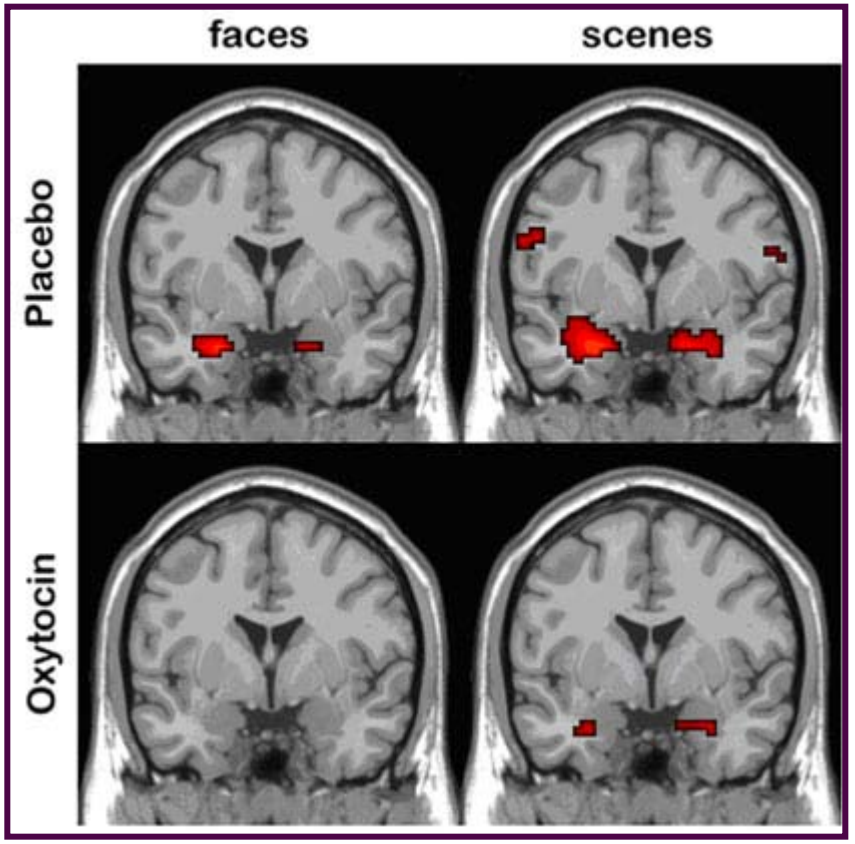
Dramatic reduction in amygdala activity when shown frightful faces after administration of nasal oxytocin

Suggests that oxytocin mediates social fear and trust via the amygdala and related circuitry.



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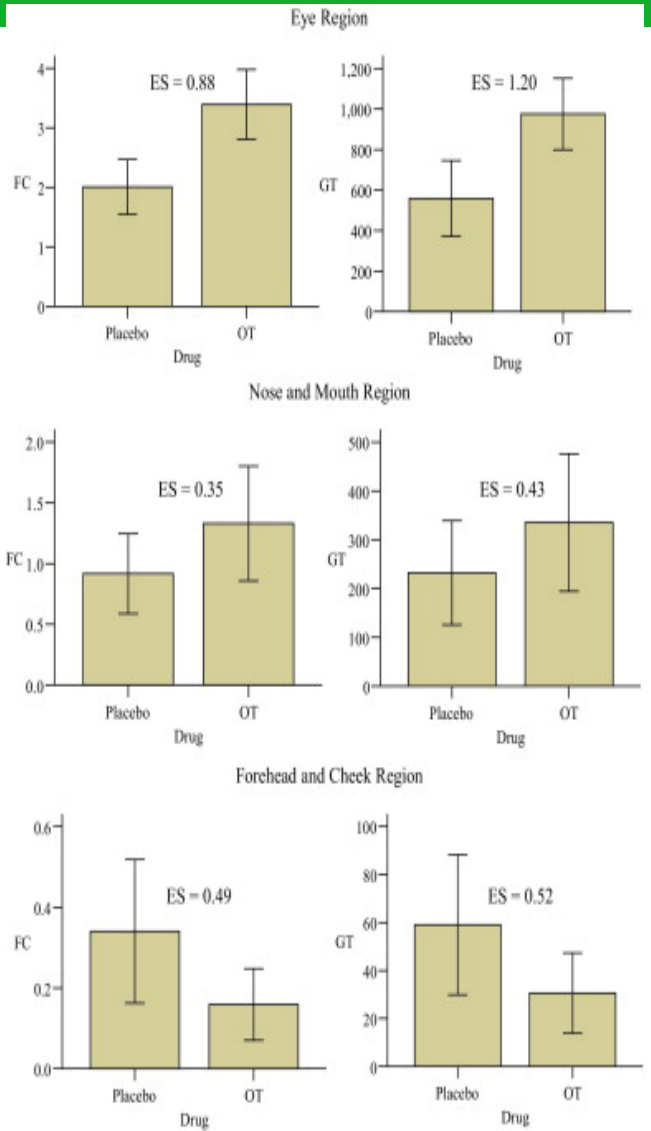
Source: NIMH Genes, Cognition and Psychosis Program

Oxytocin increases Gaze to the Eye region (Guastella et al 2008)

- 52 healthy controls, 18-28 years
- Placebo controlled challenge, dose: 24 IU
- Measure:
  - 24 human female and male faces
  - eyetracker



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Oxytocin improves face identity memory (Savaskan et al 2008)

- Single blind, single dose, IN oxytocin challenge
- 36 volunteers, ages 18-44

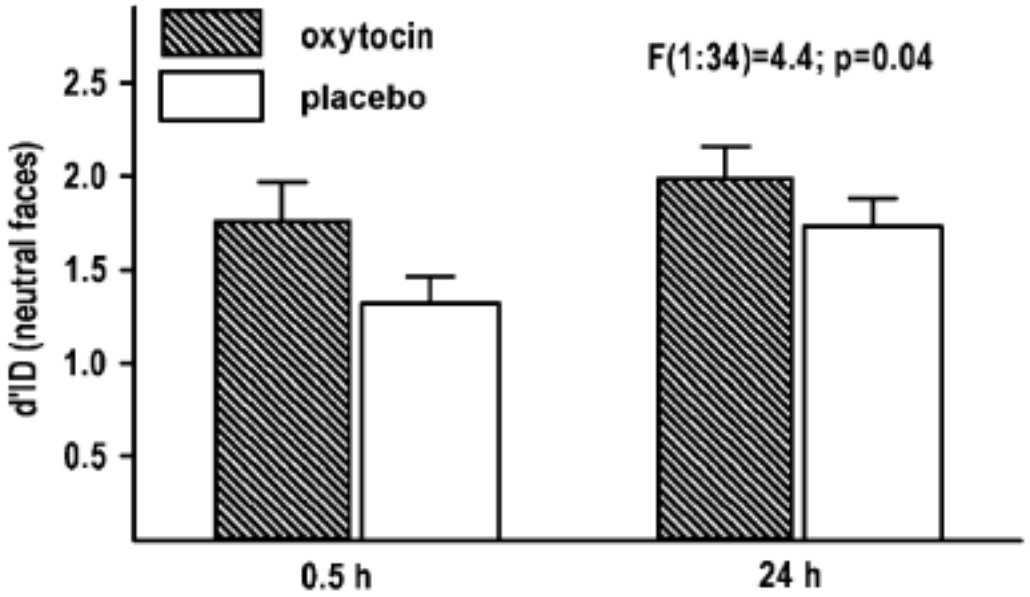

Figure 1 Oxytocin vs. placebo effects on identity memory for neutral faces (error bars are standard error).

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Oxytocin and autism

- Decrease blood levels oxytocin in autism

and

- Absence of normal developmental increase in oxytocin blood levels with age in autism
  - *Altemus et al 1994, Modahl et al 1998, Green et al 2001, Kosfeld et al, 2005, Kirsch et al, 2005*
- Genetic associations
  - Wu et al (2005), 195 Chinese Han family trios: Transmissive disequilibrium for two nucleotide polymorphisms in OTR gene.
  - Jacob et al (2007), + association of OXTR and autism in a Caucasian sample
  - Ylisaukko-oja et al (2006), AGRE + Finish cohort
  - Kim et al (2002), disequilibrium between 1 SNP in AVPR1a and autism
  - Other AVPR1a + findings: Wassink et al, 2004, Yirmiya et al, 2006 (social skills)
  - Allelic associations between PRL, PRLP and OXTR and affiliative behaviors: Yrigollen et al, 2008
  - Liu et al 2010, Japanese trios
  - Wermter AK , 2010, Caucasian

- Gene expression studies:
  - Increased methylation of CpG island know to regulate OXTR expression in peripheral blood and temporal cortex. (Gregory et al BMC medicine 2009)

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Oxytocin vs. Placebo Infusions in Autism

- Repetitive behaviors
- Social cognition

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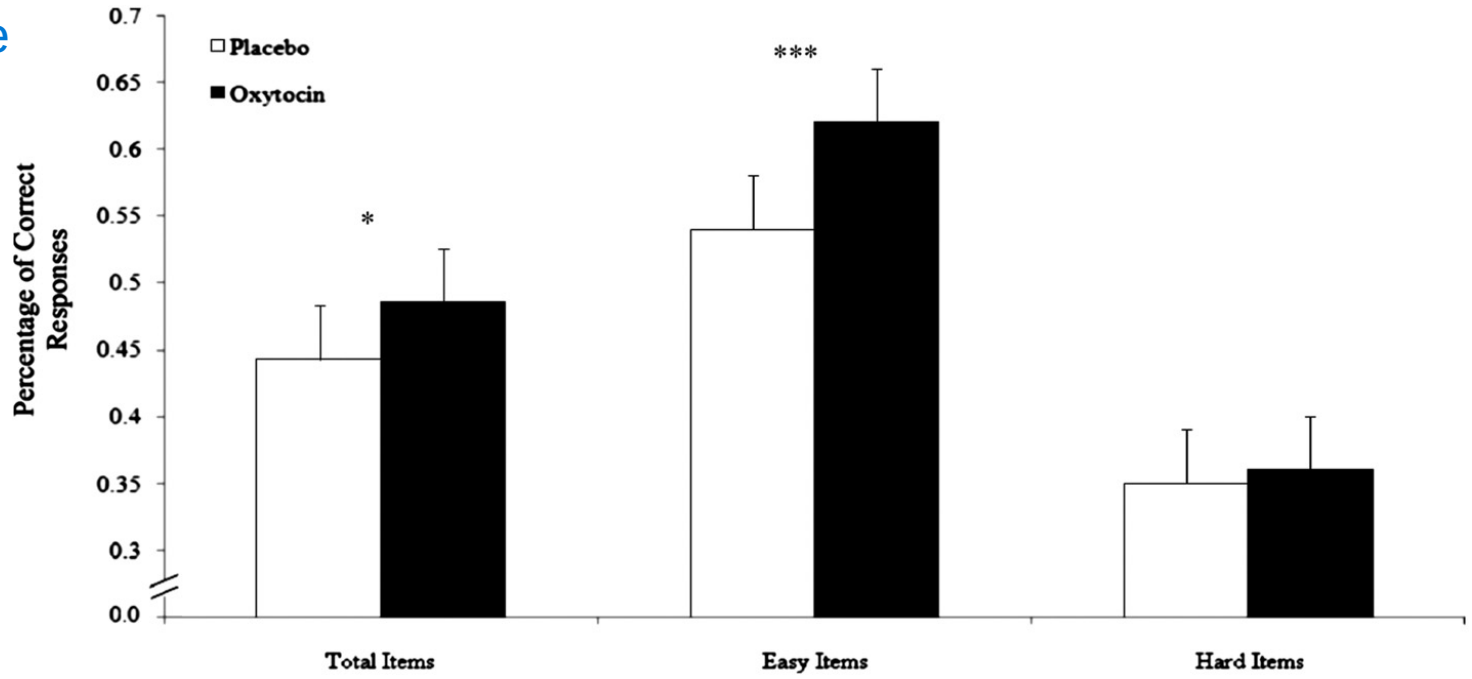
Intranasal Oxytocin Improves Emotion Recognition for Youth with Autism Spectrum Disorders

Adam J. Guastella, Stewart L. Einfeld, Kylie M. Gray, Nicole J. Rinehart, Bruce J. Tonge,Timothy J. Lambert, and Ian B. Hickie

16 adolescents with ASD

Crossover single dose study

RMES



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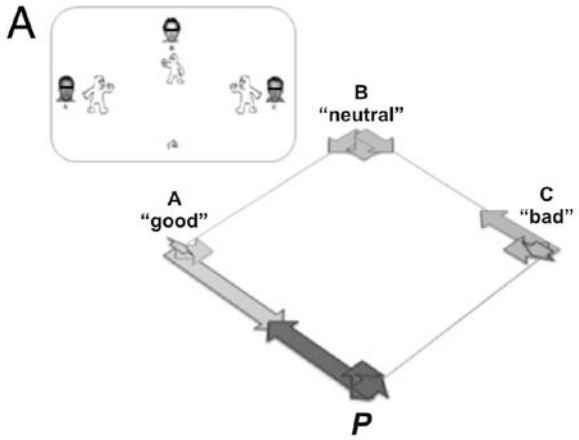
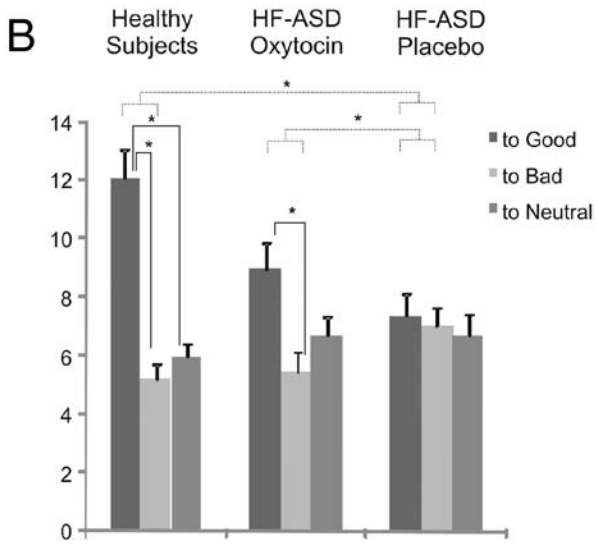
Promoting social behavior with oxytocin in high-functioning autism spectrum disorders

Andaria E, Duhamela JR, Zallab T, Herbrechtb E, Leboyerb M, Sirigua, A

- 13 adults with ASD
- Cross over single dose study





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Oxytocin vs. placebo in adult autism: A pilot study

- Intranasal oxytocin imported from Switzerland with FDA IND-waiver
- 6-week randomized placebo controlled trial
  - Sample : 20 adults with ASD
    - *Ages 18-45*
    - *Diagnosis confirmed with ADI / ADOS*
- BID dosing of 24 IU / dose

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Oxytocin vs. placebo in autism
Pilot study

- Child faces: 12 F, 12 M, equal numbers of emotions and high vs. low intensity
- Instructions: I AM GOING TO SHOW YOU SOME PEOPLES' FACES AND I WANT YOU TO TELL ME HOW THEY FEEL. I WANT YOU TO TELL ME IF THEY ARE HAPPY, SAD, ANGRY, OR FEARFUL (SCARED).

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Oxytocin vs. placebo in autism
Pilot study

- Child paralanguage test
  - 32 trials, 16F, 16 M, and equal number of high vs. low intensity emotions
  - Instructions: I AM GOING TO PLAY AN AUDIO TAPE IN WHICH YOU WILL HEAR SOMEONE SAY THE SENTENCE: “I’M GOING OUT OF THE ROOM NOW, BUT I’LL BE BACK LATER.” I WANT YOU TO LISTEN TO THE SENTENCE AND TELL ME IF THE PERSON SAYING THE SENTENCE IS HAPPY, SAD, ANGRY, OR FEARFUL (SCARED).

Oxytocin vs. placebo in autism Pilot study

- Statistically significant improvements in
  - Social cognition (Reading the mind in the eyes test)
  - Quality of life (WHOQOL – emotional subtest)
  - Low order repetitive behaviors

- Promising trends
  - Social function (SRS)

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Oxytocin vs. placebo in autism
Pilot study

- Safety Profile

Table 2 Safety: OXT vs. Placebo	
IN-OXT	**Placebo**
Irritability-mild	Fatigue
Irritability-moderate	Increasing mood lability
Increasing allergy symptoms	Cough
?seizures	Worsening tics-severe
	Worsening social withdrawal-mild
	Panic attack in response to first IN spray-severe

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Future directions

- Health Canada approval for adolescent clinical trial –
  - Funded by DOD
    - *3 years, 2 phases*
    - *Phase 1: dose finding, outcome measure exploration*
    - *Phase 2: randomized placebo-controlled trial*
- Larger scale clinical trials with IN Oxytocin in adults
  - CIHR application pending

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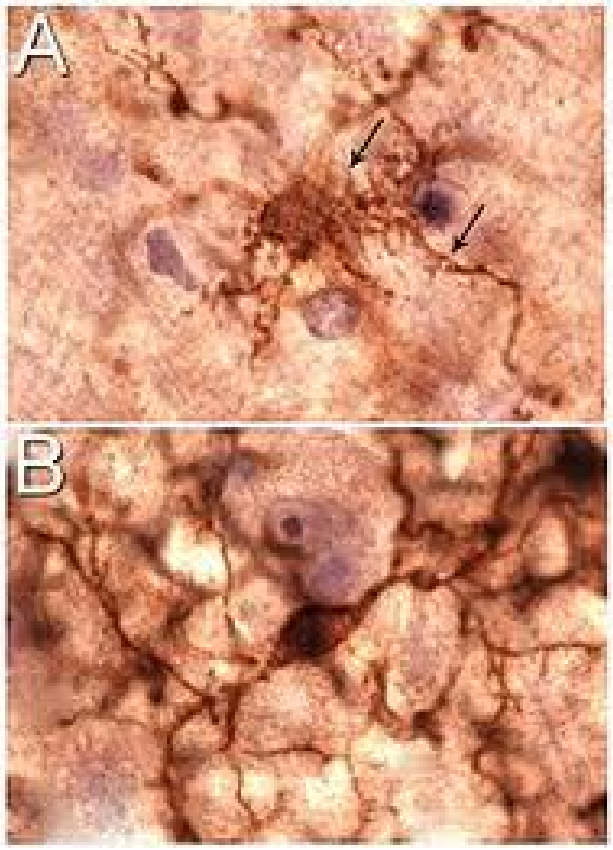
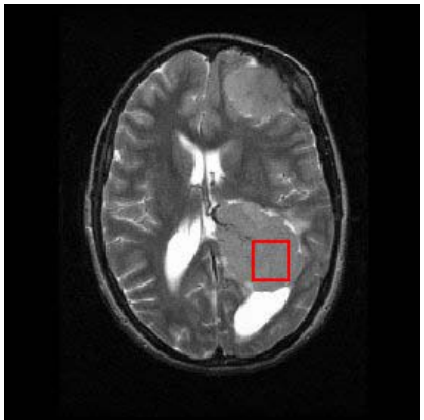
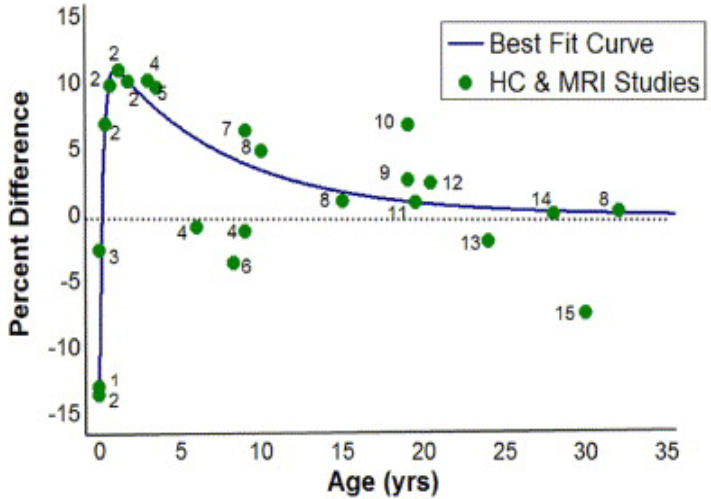
Omega 3 fatty acids and the immune hypothesis



- Postmortem studies:
  - Activated microglia in brains of children with ASD
    - *?inflammation*
- Most replicated imaging finding in ASD:
  - Early overgrowth, WM>GM
- Is it possible that inflammation accounts for early overgrowth?





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Omega 3 fatty acids and the immune hypothesis

- Possible medications targeting microglia activation (innate immune response of the brain)

- Pioglitazone (PSI foundation)
- Omega -3 fatty acids (ALVA foundation)
  - 40 kids, ages 2-5
  - randomized 1:1 to omega-3 vs. placebo
  - 6 month study

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Memantine

- Glutamate / Gaba balance
  - i.e. noise to signal ratio

Unfortunately: regulatory issues delay recruitment in Canada

60 kids, 6-12 years old

Currently we manage the recruitment in the US

Hope to start recruitment in Canada in 1 year

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Acknowledgments

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