Clinical Trials of New Medications Targeting Disease Mechanisms in Fragile X Syndrome

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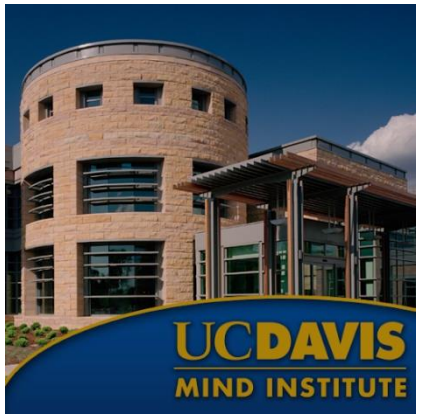
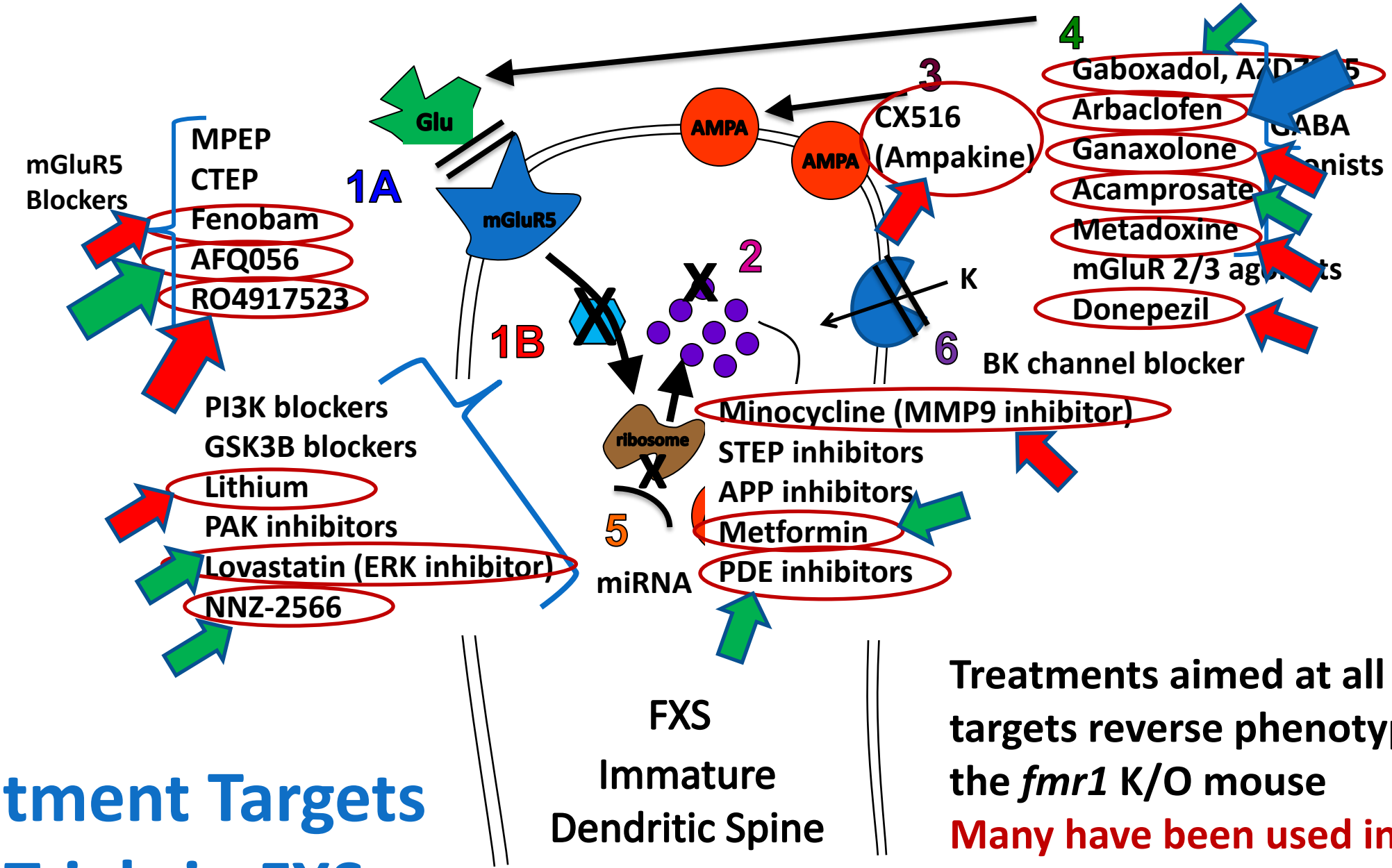
17TH nfxf FRAGILE X CONFERENCE VIRTUAL SERIES

RUSH UNIVERSITY MEDICAL CENTER



Cincinnati Children's™
changing the outcome together

Treatment Targets and Trials in FXS



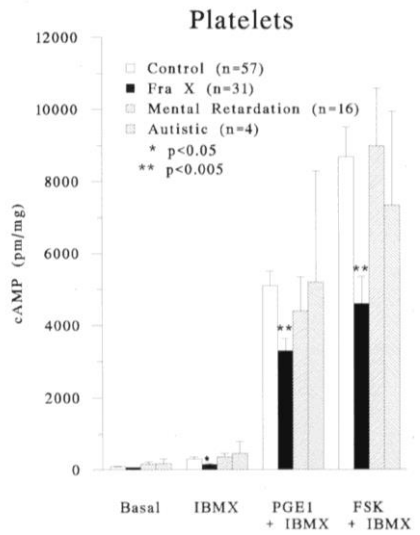
Treatments aimed at all of these targets reverse phenotypes in the *fmr1* K/O mouse

Many have been used in early human trials in FXS

Fragile X and Cyclic AMP

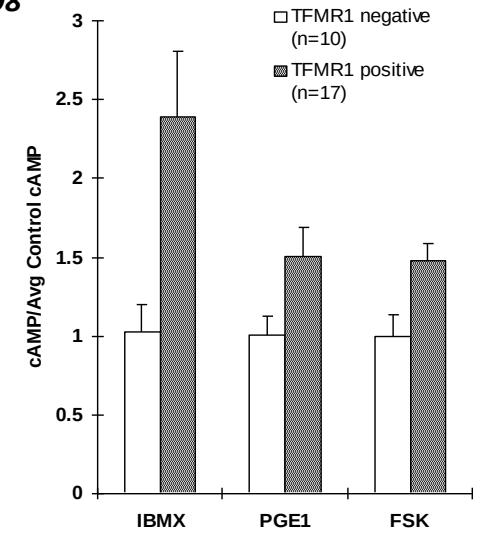
(A Life Story)

Berry-Kravis and Huttenlocher, Ann Neurol, 1992



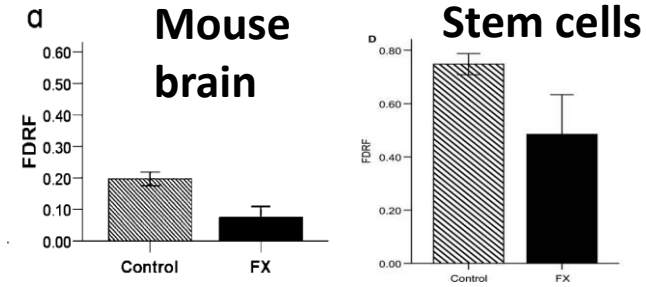
1990: cAMP signaling reduced in FXS cells

Berry-Kravis and Ciurlionis, J Neurosci Res 1998



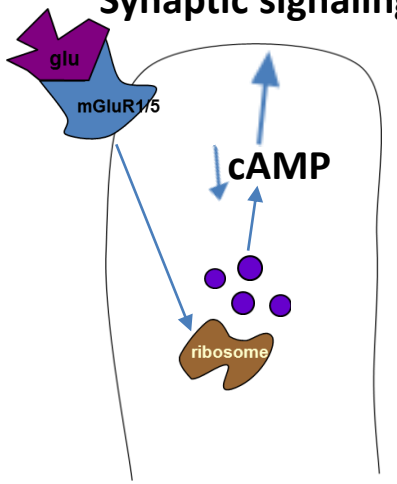
1996: Overexpression of FMRP in neural cells increases cAMP

Kelley et al. Plos 1 2007



2006: Bhattacharya – cAMP production decreased in FXS mouse brain, fly head, stem cells

Synaptic signaling deficits



[Kanellopoulos](#) et al. [J Neurosci](#) 2012

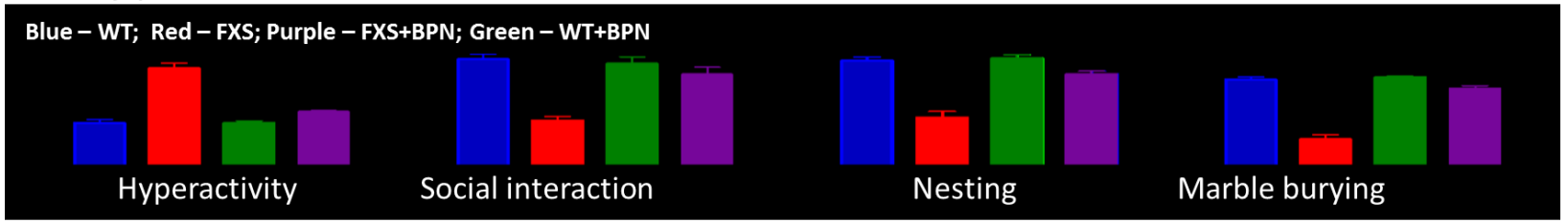
2012: Learning/memory deficits in absence of FMRP result from mGluR-mediated inhibition of cAMP signaling in Drosophila.

Phosphodieterase inhibitors reduce degradation of cAMP, raise levels – more normal in FXS

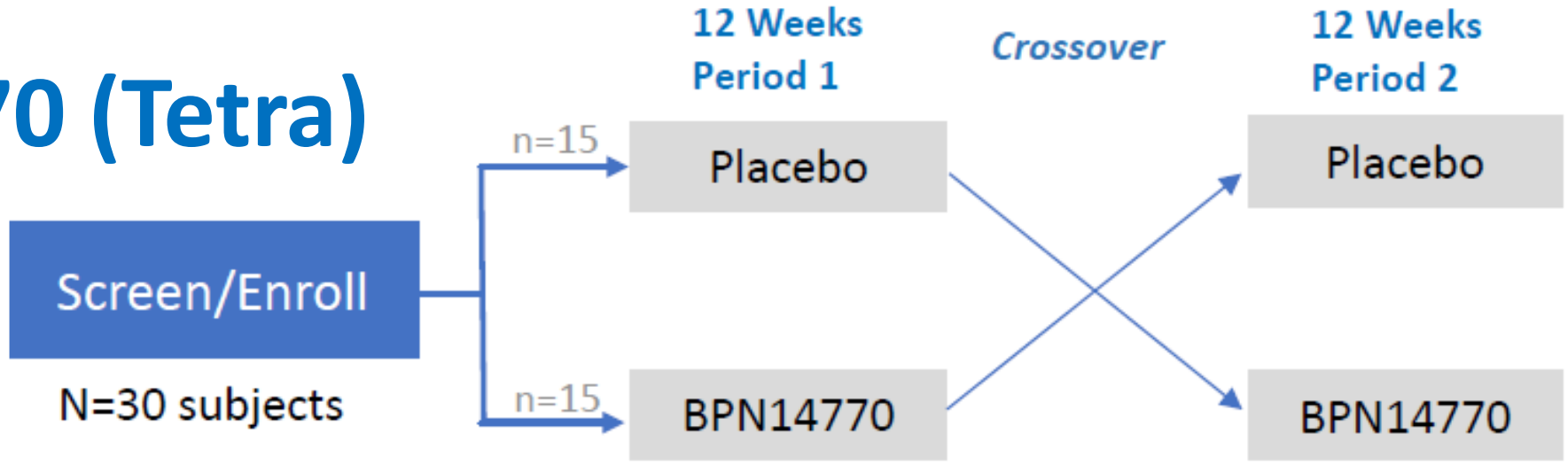
Type 4D brain selective - BPN14770

Normalize phenotypes in FXS mouse in 2 labs

Gurney et al. Sci Reports 2018



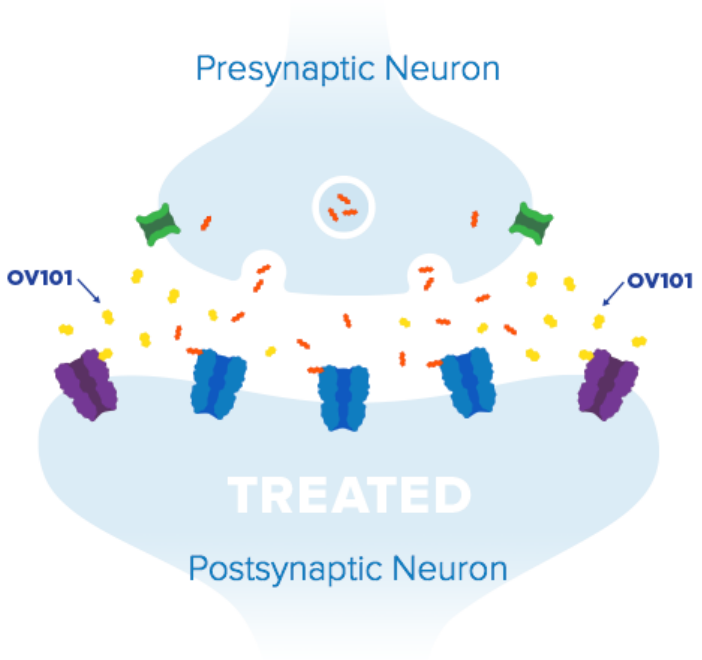
BPN14770 (Tetra)



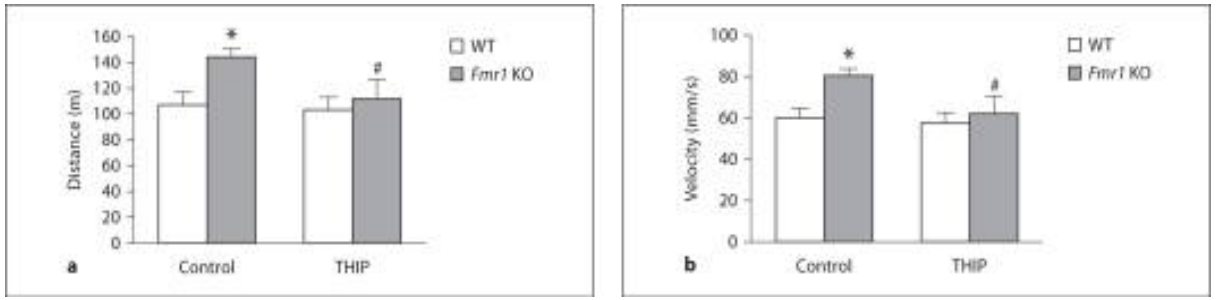
- **Early phase 2 trial in adults with FXS, June 2018, Berry-Kravis/Tetra/FRAXA partnership**
- **30 adult FXS males, crossover design**
- **Primary safety**
- **Many exploratory outcomes, target cognition and focus on new cognitive and biomarkers, PK/PD design that should be the type of trial to initiate all disease targeted new drugs – to see if it should "go" and if there is a responder population that should be targeted for enrollment in subsequent trials**
- **Assessments – Biomarkers, NIH Toolbox, KiTAP, ERP, Eye tracking, PK/safety labs, Vineland**
- **Filled and will finish in July with results August or September – no safety problems**

Gaboxadol

- Targets extrasynaptic GABA(A) receptors
- Increases GABA (inhibitory) tone – decrease excessive neural activity
- Could help with sleep, hyperactivity, sensory oversensitivity
- PK phase 1 done – collected a few pre- and post-dose ERP studies

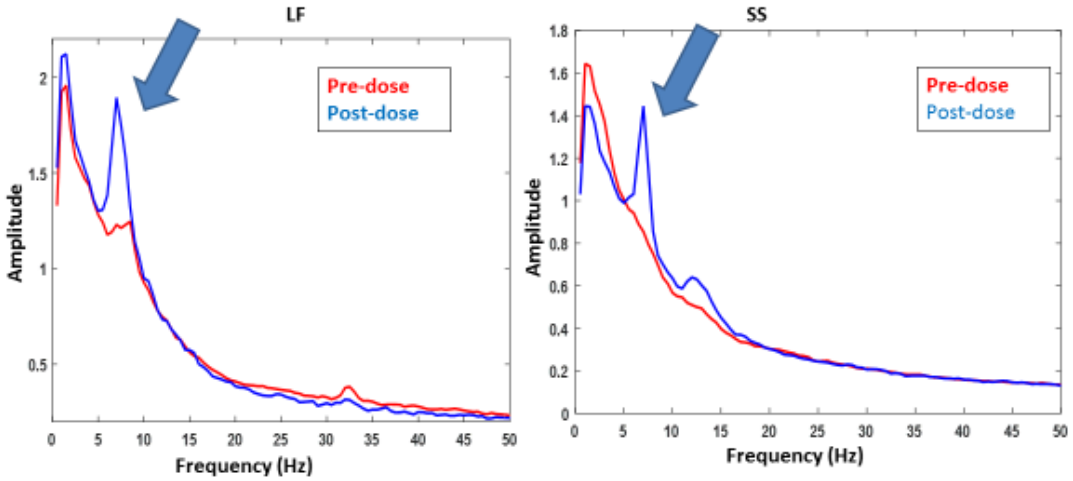


Decreases hyperactivity in FXS mouse



Olmos-Serrano et al., 2011

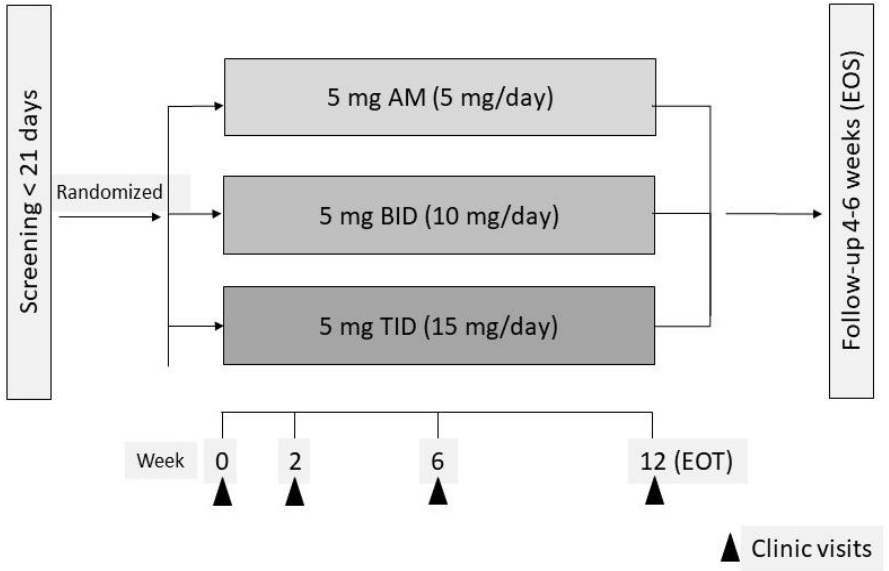
Gaboxadol – ERP from PK Study



Resting EEG spectrum – post dose large increase in alpha and maybe some slight gamma decrease (more like normal post-dose)

Gaboxadol – Phase 2 Study PK/PD

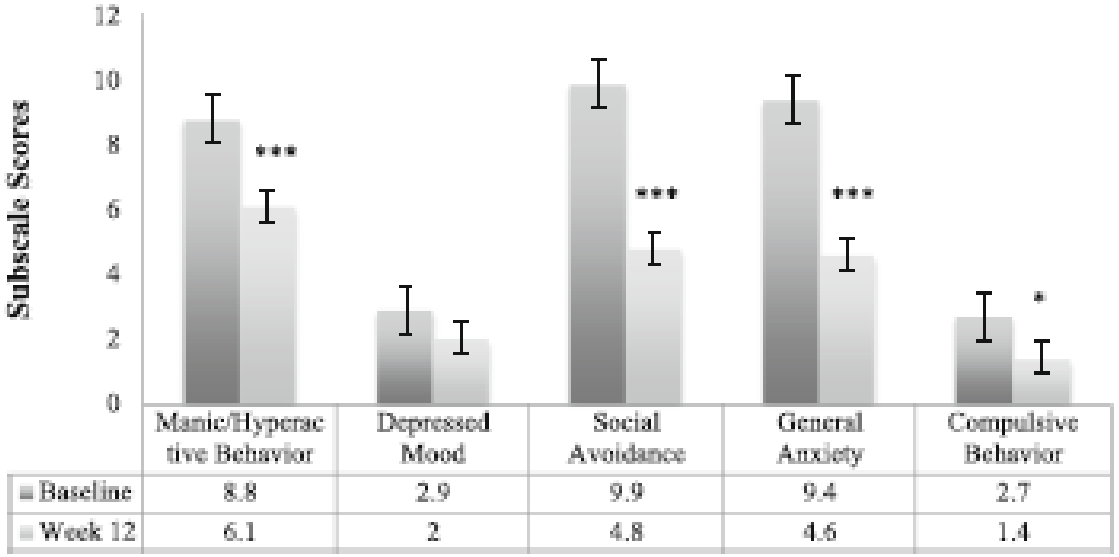
- Participants: FXS Males age 12-22, IQ<75
  - 3 or less stable con-meds
  - no GABA drugs, no CBD
- Assessments – behavior questionnaires, safety labs, KiTAP, RBANS, ERP, Actigraphy
- Plan to use ERP for PK/PD for early phase trial "go-no go" decision
- Results
  - No safety problems
  - Questionnaires improve
  - Lowest dose may be best
- Improvement in range of prior placebo effects
- Probably subpopulation of responders ~40%
- Need placebo-controlled study
- Need ERP analyses



Scale	Improvement	p
ABC Irritability	20%	0.03
ABC Hyperactivity	29%	0.005
ABC Lethargy/Social Withdrawal	38%	0.001
ABC Stereotypic Behavior	21%	0.01
ADAMS Total	22%	0.004
CGI-S	0.4	0.002

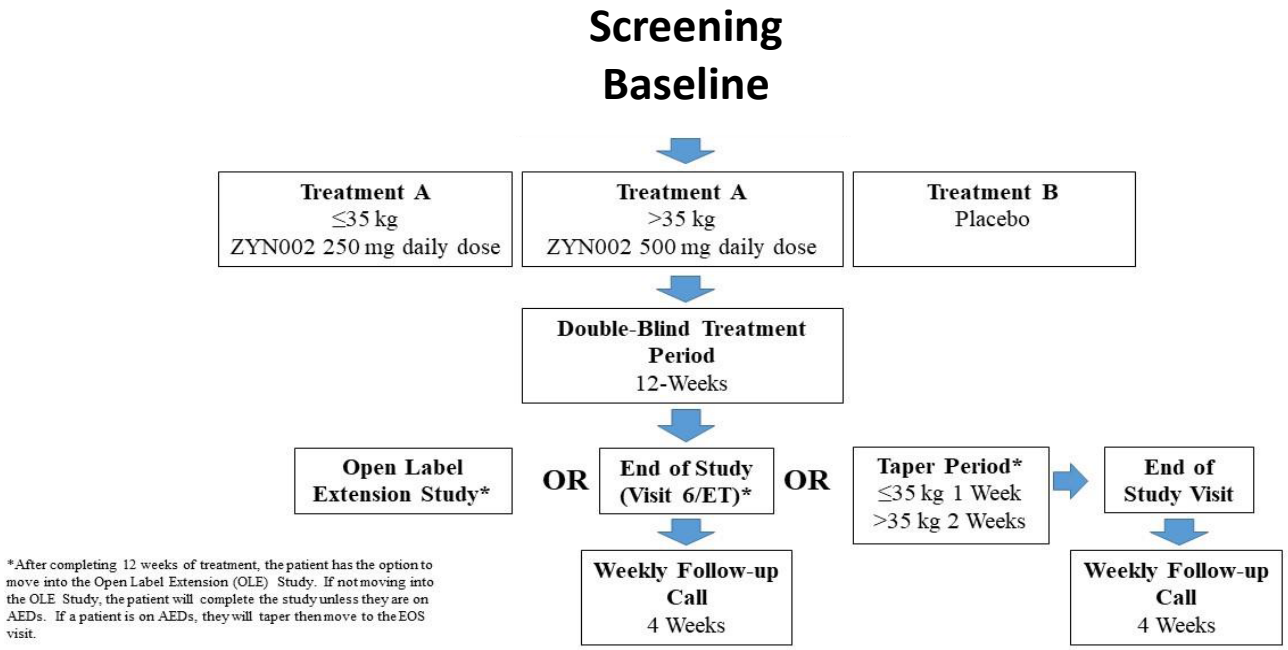
Cannabadiol (CBD) Zynerba

- Marijuana plant product synthesized by Zynerba, no THC so no “high”
- Probably best targeted to anxiety
- Targets endocannabinoid system - abnormal and both overactive and underactive in FXS mouse
  - mechanism not clear but could provide behavioral support
- Zynerba (ZYN002 cream) open label trial, Australia, 20 FXS patients, age 5-17, 50-250 mg, 12 weeks open label, improved scores on ADAMS (Anxiety) and ABC-FX (Aberrant behavior), no major side effects

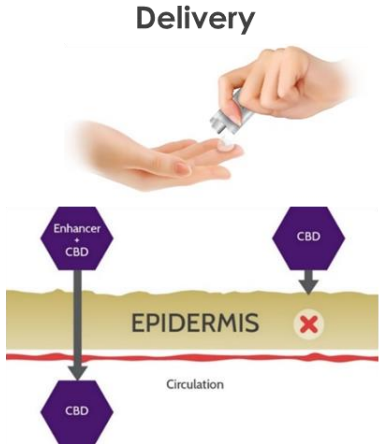


	Manic/Hyperactive Behavior	Depressed Mood	Social Avoidance	General Anxiety	Compulsive Behavior
Baseline	8.8	2.9	9.9	9.4	2.7
Week 12	6.1	2	4.8	4.6	1.4

Cannabadiol (CBD) Zynerba



Placebo-controlled phase 3 trial with extension – 200 patients: USA, Australia, New Zealand



- Opened Winter 2019 in USA
- Target behavior/social anxiety
- Inclusion/Exclusion:
  - Age 3-<18
  - BMI 12-30
  - Male or female
  - Allowed 2 stable con-meds
  - No minocycline or GABA drugs
- Behavior forms, blood tests, exams
- Open label extension ongoing
- Trial filled as of end January 2020
- Database lock this month – results perhaps in July

Example of Changing the Paradigm for Drug Development in NDDs: NeuroNext Pilot Trial (NN107)

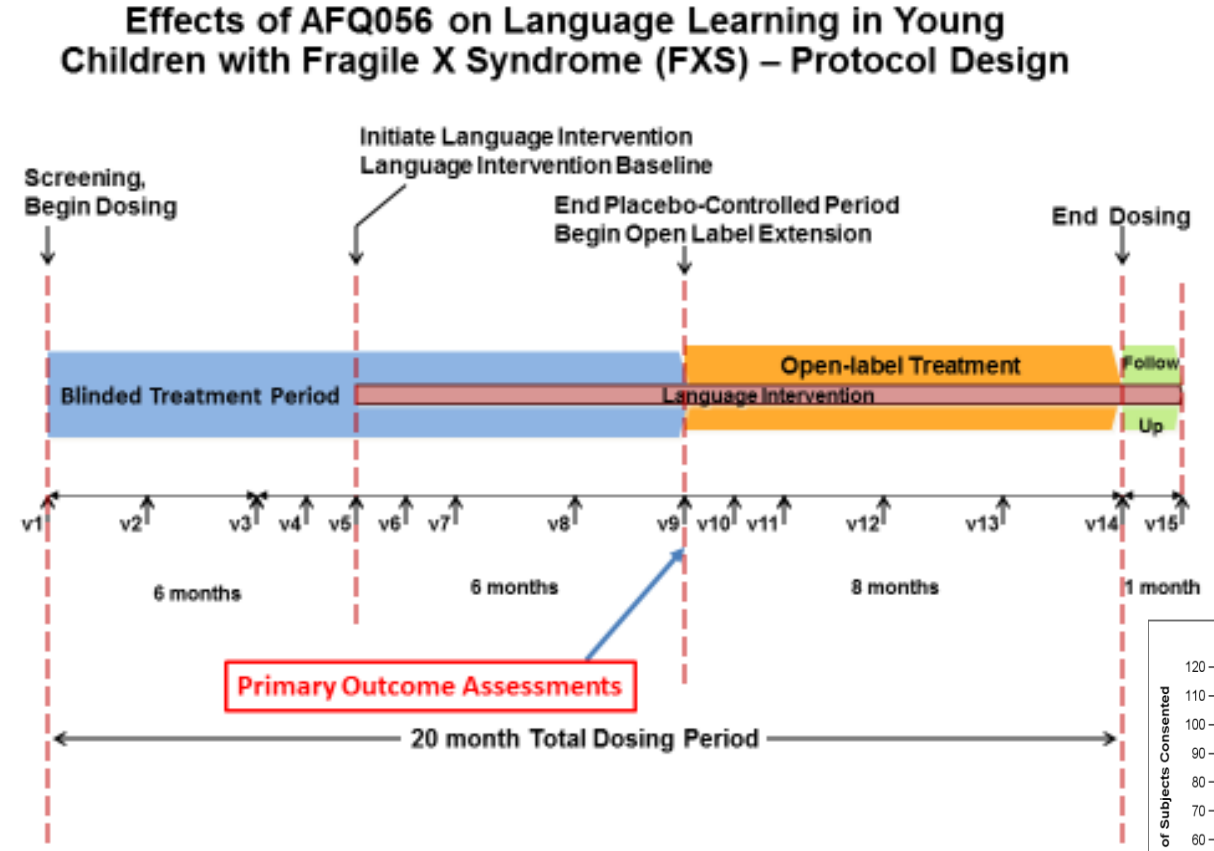
Effects of AFQ056 on Language Learning in Young Children with Fragile X Syndrome (PI EBK)

- Create model for development of mechanism targeted pharmacotherapy in NDDs, study effects of drug on "plasticity", really test mGluR theory in FXS (funding: NIH, NeuroNext network, Novartis IIT program grant for drug)
- Address many problems with prior trials:
  - Incorporate young age (3-6y)
  - Long trial to study learning
  - Embed parent-implemented language learning intervention (PILI) to amplify and focus learning
  - Objective language/cognition measures, observational communication measure (WCS) primary outcome – targeted to measure type of language learning from PILI
  - Biomarkers (ERP, eye tracking, blood) of target engagement

First Ever Large Multi-Site Trial Studying Effects of a Targeted Drug Treatment on LEARNING!

NeuroNEXT

NN107 Design, Sites, Progress



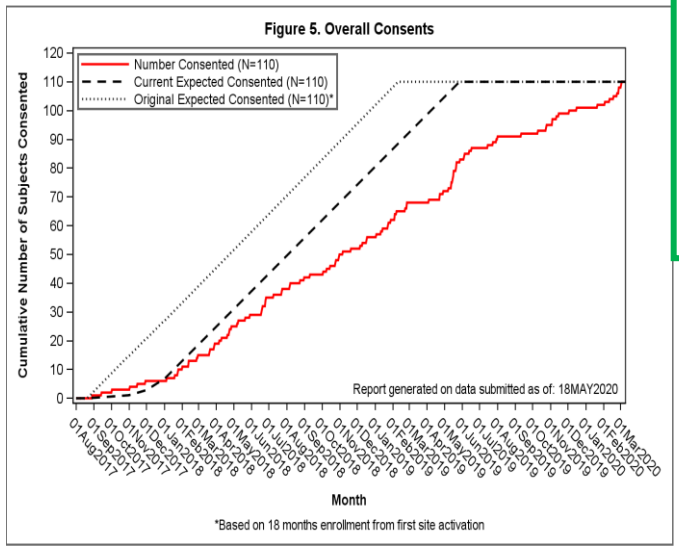
110 FXS Kids (to complete 100)

- Age 32 months to 6 years
- *FMR1* full mutation
- DQ<75
- English primary language
- Has intentional communication
- Stable meds/therapies

Training Completed:

28 psychologists/SLPs WCS
15 SLPs PILI
4 central SLPs
9 sites ERP
11 sites eye tracking

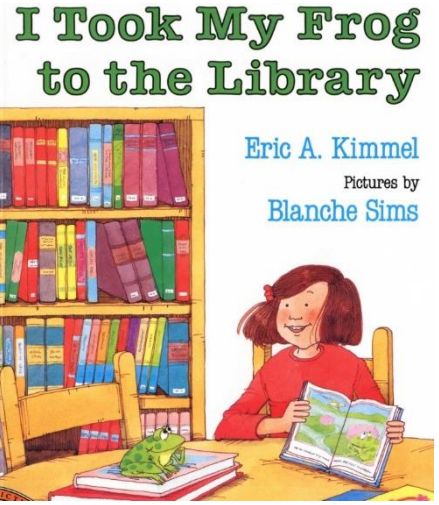
110 patients enrolled, 91 randomized
67 completed PC period
34 completed study



Controlled trial of lovastatin in 10 to 18yo combined with Parent Implemented Language Intervention (PILI)

- **Lovastatin** is an inhibitor of the rate-limiting enzyme in cholesterol biosynthesis and an FDA-approved treatment for hyperlipidemia (Acosta et al 2011).
- Lovastatin down-regulates the RAS-ERK1/2 pathway and lowers the excessive protein synthesis in FXS
- In FX KO mice lovastatin rescues seizures and lowers excess protein production in KO mouse (Osterweil et al 2013)
- Lovastatin was beneficial in open label trial in FXS (Cantu et al 2014)
- Randomized controlled of 10 to 40 mg of lovastatin lasting 20 weeks in 32 patients with FXS carried out at the MIND Institute, UC Davis

What is Parent Implemented Language Intervention (PILI)

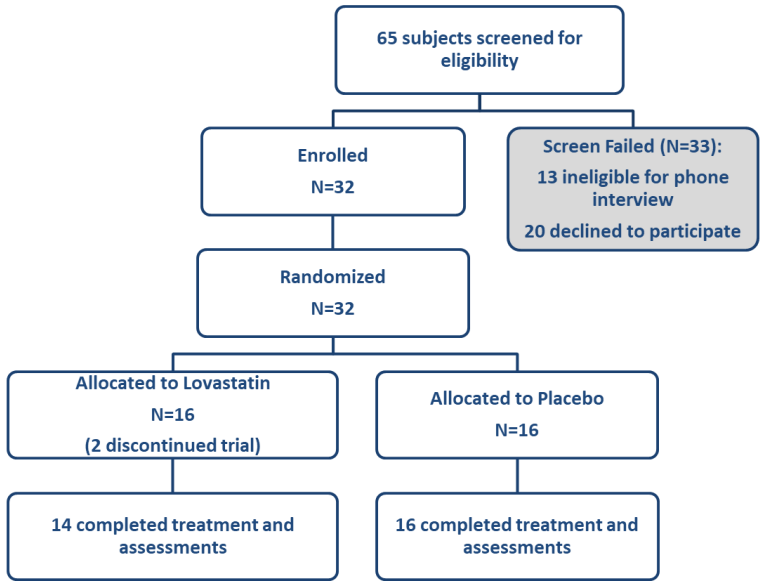


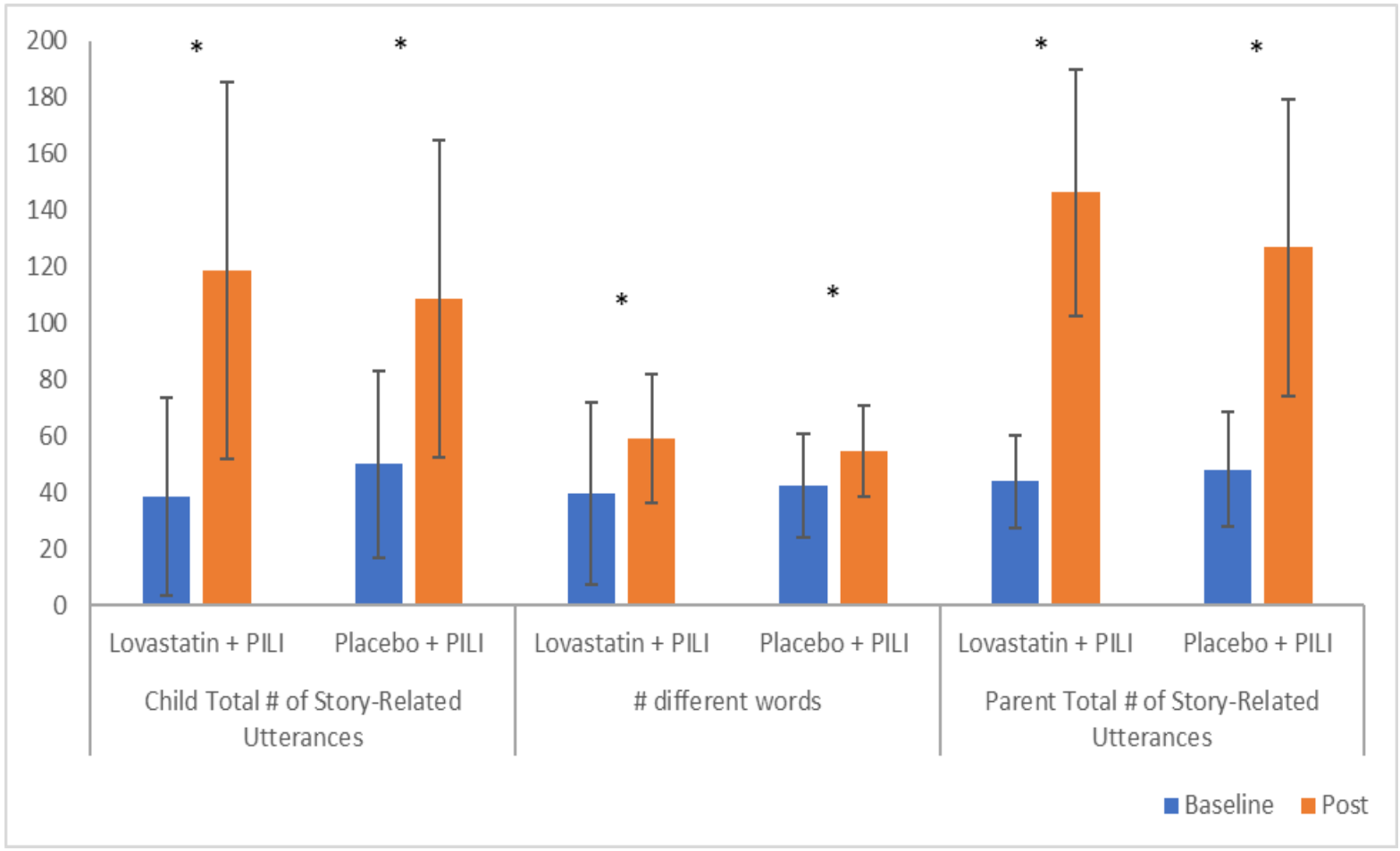
Parents choose12 wordless picture books

- Parent and child looked at the picture book together
- Parent introduced/told the story
- Parent used targeted intervention strategies to provide models of vocabulary and grammar and to prompt the child to take a turn (guided by SL therapist via Skype and ear phones)
- With repeated exposure to a book, child gradually played a greater role in retelling the story and thus practiced new vocabulary and grammar
- Efficacy of PILI alone previously shown (McDuffie et al 2016;2019)

Means of Primary Outcome Measures (Expressive Language Sampling)

Consort Diagram





Secondary outcome measures including CGI-I and CGI-S and VAS for Spoken language and Social impairment had equal improvements in each group.

Thurman et al 2020 JND

Correlations between Parent Sum Strategies Used with Child outcomes

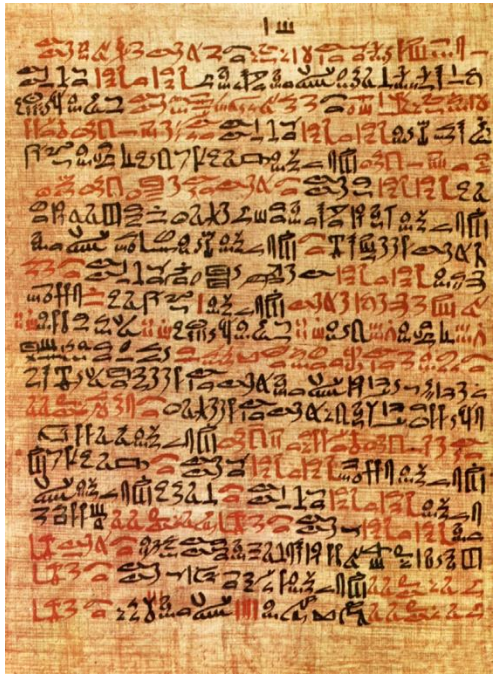
with Placebo: child outcome correlated with goodness of parent intervention but not with lovastatin; so one interpretation is lovastatin appeared to compensate for the deficits of the parent intervention

Table 4. Correlation coeffcients (p-values) of Parent Sum Strategies used with a given child outcome				
	All	Lovastatin	Placebo	P-value (LOVA vs. Placebo)
Child total # of Utterance	0.587 (p=0.0010)	-0.095 (p=0.7682)	0.647 (p=0.0067)	0.0455
Child # different words	0.569 (p=0.0016)	-0.194 (p=0.5464)	0.704 (p=0.0023)	0.0135
1. Correlation analyses were based on % changes of the variables from its corresponding baseline value.				
2. Correlation analyses were performed using logarithmically transformed values of all variables.				

Conclusions (Thurman et al 2020 JND)

- PILI is an efficacious intervention for children with FXS
- Lovastatin plus PILI was equally effective as placebo plus PILI for 10 to 18yo, so no significant additive effect of the medicine but it may have compensated for poor parent intervention on PILI
- There were no significant differences in AEs
- Laboratory changes demonstrated lowered cholesterol (134 to 104) on lovastatin vs placebo (132 to 134)

Metformin a type 2 diabetes med



Used by the Pharaohs Ebers papyrus 1500 BC

- Known to help overeating and obesity and prevent cognitive deficits in diabetics
- Helpful in several patients with Prader-Willi Phenotype of FXS and others in open label study of 7 patients (Dy et al 2017)
- Drosophila FX model: elevated insulin signaling and enhanced PI3K/Akt/mTOR pathway; metformin lowered this and improved circadian rhythm defect and memory problems (Monyak et al 2016)
- Rescues phenotype in KO mouse (Gantois et al 2017 Nature Med)

Controlled trial of metformin in FXS

- Ages 6 to 25yo with FXS funded by Azrieli Foundation at 3 sites; Currently at end of 2nd year of a 3 year study (60 with FXS to enroll at each site)
- Randomized, double blind controlled trial lasting 4 months so baseline, 2 month and 4 month visits to the MIND or 2 sites in Canada (Edmonton –Dr Bolduc and Montreal –Dr Jacquemont) and then open label with clinical follow-up with PCP
- Baseline and outcome measures with language sampling, NIH toolbox for cognition, behavior measures, ERP, eye tracking with Tobii eye tracker, molecular biomarkers (MMP9, S6 kinase)

Metformin in Children Ages 2-7 treated clinically

(Biag et al 2019)

	1		2		3		4		5	
	Baseline	After 4 mos.	Baseline	After 4 mos.	Baseline	After 3 mos.	Baseline	After 3 mos.	Baseline	After 7 mos.
ABC Composite Score	15	7	109	39	29	20	32	28	113	59
I. Irritability	8	3	32	12	12	8	4	6	40	19
II. Lethargy	1	0	20	4	1	0	4	3	23	12
III. Stereotypy	2	0	11	5	0	0	4	4	10	5
IV. Hyperactivity	4	4	29	13	13	9	16	12	29	14
V. Inappropriate Speech	0	0	6	2	2	2	0	0	9	8
VI. Social Avoidance	0	0	11	3	1	1	4	3	2	1

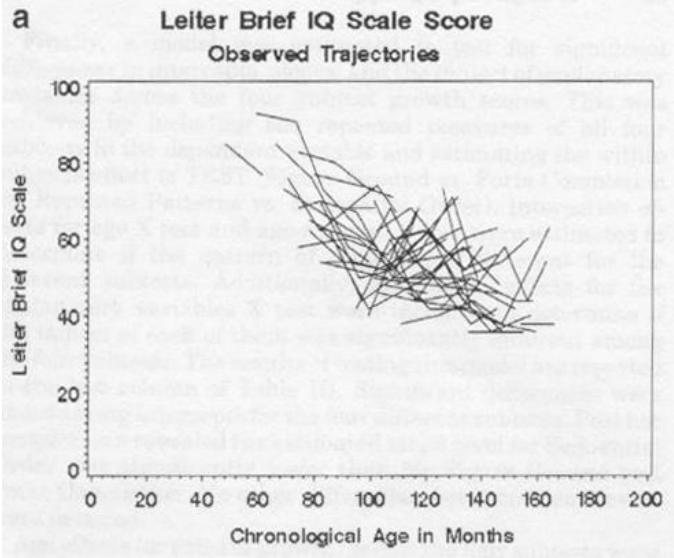
	6		7		8		9	
	Baseline	After 1 mos.	Baseline	After 8 mos.	Baseline	After 7 mos.	Baseline	After 6 mos.
ABC Composite Score	22	20	33	48	67	59	62	51
I. Irritability	5	3	14	17	21	25	29	22
II. Lethargy	0	0	0	1	11	5	0	0
III. Stereotypy	2	0	2	1	9	6	9	8
IV. Hyperactivity	12	11	17	27	22	16	17	14
V. Inappropriate Speech	3	6	0	2	4	6	7	7
VI. Social Avoidance	0	0	0	0	0	1	0	0

Improvements seen on the Aberrant Behavior Checklist and in Mullen Scales of Early Learning

Mullen subscale	Pre-metformin[a]	Post-metformin[a]	Slope[a,b]	*p*-value*
Visual reception[c]	30 (18–38)	40 (29–40)	0.52	.04
Fine motor	20 (18–26)	25 (21–27)	0.34	.02
Receptive language	27 (19–32)	34 (27–36)	0.56	.03
Expressive language	19 (16–22)	28 (17–48)	0.77	.02
Early learning composite score	61 (54–63)	61 (55–62)	NA	.5
Global developmental age[c,d]	30 (21.2–31.2)	34.2 (33.7–35.5)	0.52	.04

[a]All values measured in median and interquartile range.
[b]Rate of Growth.
[c]Analysis with $n = 5$, all others were calculated with $n = 6$.
[d]Global developmental age was calculated based on the average age equivalents of the Mullen subscales.
*A pre-specified significance level of $p < .05$ was assumed.

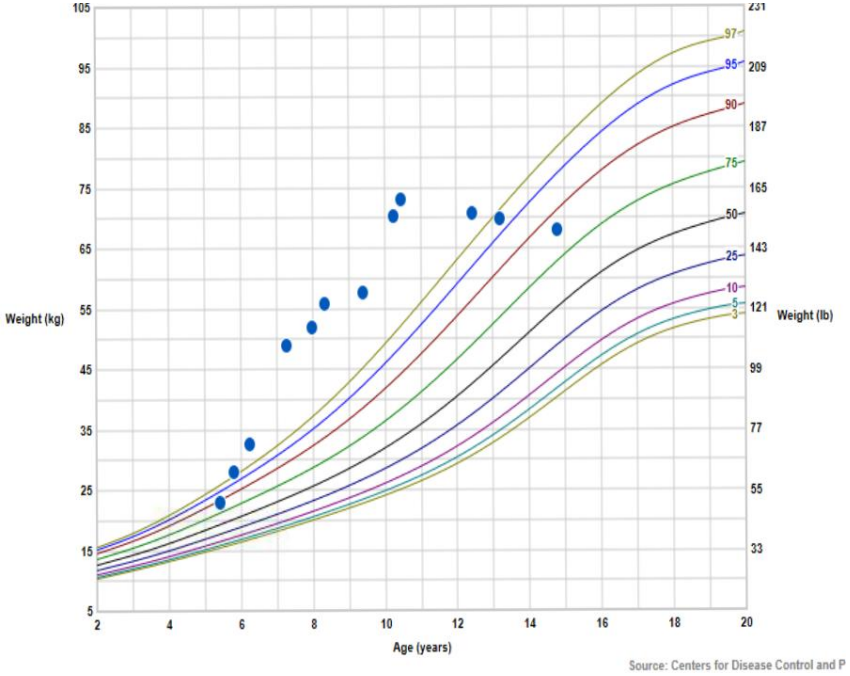
Metformin improved IQ (2 pts) and prevented macroorchidism in one case of FXS



Metformin for 1 year
improved IQ in 2 adult males
(Protic et al 2019)

Case	Time of testing	Nonverbal IQ	Verbal IQ	Full-Scale IQ
Case 1	Baseline	50	61	53
	Follow up	52	66	57
Case 2	Baseline	47	58	50
	Follow up	51	68	58

A 12yo boy with PWP of FXS was
treated for 2 years with metformin
- his weight percentiles normalized
- at 14yo he was Tanner stage 3
with normal sized testicles (Protic et al 2019)



Double-Blind Placebo-Controlled 10 week study of acamprosate in 5-22 year olds with FXS

- Drug is FDA approved for the treatment of alcoholism in adults
- 10 week flexible dosing, parallel groups study at Cincinnati and Rush
- Funded by the John Merck Fund
- To facilitate use of placebo, over encapsulation of acamprosate required a very larger study drug (1 inch long)
- Max dosing 666mg three times a day, two capsules three times a day

Double-Blind Placebo-Controlled 10 week study of acamprosate in 5-22 year olds with FXS

- 46 persons enrolled
- Mean final acamprosate drug dosing at Week 10 was 1,612.4 mg/day +/- 535.4 mg/day (range 333-1,998 mg/day).

	Acamprosate Treatment	Placebo Treatment
Mean Age	15.37 +/- 4.4 years (range 7.54-21.29)	15.03 +/- 4.1 years (range 6.5-22)
Number of males	N=18	N=19
Number of Females	N=5	N=4
Ethnicity/Race: White	N=20	N=21
Ethnicity/Race: Black	N=2	N=1
Ethnicity/Race: Hispanic	N=1	N=1
Mean Full Scale IQ	47.8 +/- 11.9 (range 36-80)	45.67 +/- 10.2 (range 40-75)

Adverse Event	Acamprosate	Placebo	Total
1 Dizziness/faintness	2	1	3
100 Restlessness	2	3	5
101 Sadness	2	0	2
102 Sedation/Drowsiness	1	1	2
103 Self injurious Behavior	0	2	2
106 Suicidal Ideas	0	1	1
109 Fever	0	3	3
2 Headache (including sinus headache)	3	0	3
20 upper respiratory infection	4	2	6
23 Sinus condition	1	0	1
37 Appetite decrease	1	3	4
39 Change in Stool	1	0	1
41 Diarrhea	11	5	16
44 Indigestion	1	0	1
45 Nausea	0	1	1
46 Stomach or abdominal discomfort	6	2	8
49 Vomiting	2	3	5
7 Ear ache	1	0	1
76 Generalized rash	1	0	1
78 Localized rash	0	1	1
82 Aggression	1	1	2
83 Anxiety/Nervousness/Worry	1	1	2
88 Difficulty falling asleep	0	1	1
96 Interrupted sleep/ other sleep proble	0	1	1
97 Irritability (including agitation)	2	4	6
Total	43	36	79

Clinical Results: Large Placebo Response, No Drug-Associated Improvements

	Acamprosate Group				Placebo Group				Week 10				
	Baseline		Week 10		Baseline		Week 10		Acamprosate-Placebo Difference				
Outcome Measure	LS Mean	SEM	LS Mean	SEM	LS Mean	SEM	LS Mean	SEM	LS Mean	SEM	DF	tValue	Probt
ADAMS, depressed mood	3.53	0.70	2.20	0.74	5.41	0.72	3.16	0.73	-0.96	1.05	82	-0.92	0.36
ADAMS, generalized anxiety	9.46	0.91	6.55	0.95	8.69	0.93	6.75	0.94	-0.20	1.35	82	-0.15	0.88
ADAMS, manic/hyperactive behavior	8.70	0.75	6.62	0.79	8.84	0.77	7.10	0.78	-0.48	1.13	82	-0.43	0.67
ADAMS, compulsive behavior	4.30	0.49	3.14	0.51	3.92	0.50	2.06	0.53	1.09	0.74	81	1.46	0.15
ADAMS, social avoidance	9.69	1.01	6.90	1.05	10.33	1.03	7.36	1.05	-0.46	1.50	82	-0.31	0.76
ABC-Irritability Subscale	19.84	2.81	15.84	2.79	18.36	2.72	12.89	2.72	2.96	3.93	85	0.75	0.45
ABC-Lethargy/Social Withdrawal**	**10.30**	**1.12**	**5.88**	**1.12**	**11.66**	**1.09**	**5.79**	**1.09**	**0.09**	**1.57**	**85**	**0.06**	**0.95**
ABC-Stereotypy	7.23	1.10	5.75	1.09	8.47	1.06	6.42	1.06	-0.67	1.53	85	-0.44	0.66
ABC-Hyperactivity Subscale	13.50	1.56	10.50	1.55	13.04	1.51	10.22	1.51	0.28	2.18	85	0.13	0.90
ABC-Inappropriate Speech	7.01	0.81	5.79	0.80	6.30	0.78	4.35	0.78	1.45	1.13	85	1.28	0.20
ABC-Social Avoidance	6.91	0.66	4.07	0.65	6.82	0.64	3.42	0.64	0.64	0.92	85	0.70	0.49
ADHD-RS Hyperactivity Subscale	12.90	1.38	10.04	1.38	12.23	1.34	7.96	1.48	2.07	2.04	81	1.02	0.31
ADHD-RS Inattention Subscale	17.53	1.09	12.75	1.09	15.87	1.06	12.21	1.17	0.54	1.61	81	0.34	0.74
SRS Restricted/Repetitive Behavior Subscale	21.18	1.49	17.92	1.52	20.51	1.48	16.72	1.52	1.20	2.17	85	0.55	0.58
SRS Social Awareness Treatment Subscale	12.52	0.90	11.79	0.91	13.32	0.89	11.35	0.91	0.44	1.30	85	0.34	0.74
SRS Social Cognition Treatment Subscale	21.41	1.34	18.83	1.36	19.44	1.33	17.31	1.36	1.52	1.94	85	0.78	0.44
SRS Social Communication Treatment Subscale	35.84	2.42	30.75	2.47	34.01	2.41	28.97	2.47	1.78	3.52	85	0.50	0.62
SRS Social Motivation Treatment Subscale	17.94	1.23	14.28	1.26	17.32	1.23	13.04	1.26	1.24	1.80	85	0.69	0.49
SRS Total Raw Score	108.85	6.62	93.53	6.75	104.18	6.58	87.24	6.75	6.29	9.63	85	0.65	0.52
VABS	59.10	4.12	58.81	4.77	61.44	4.28	57.90	4.56	0.91	6.55	63	0.14	0.89

LS Mean= Least Squares Mean SEM= Standard Error of the Mean DF=degrees of freedom P=Probability P value

**Denotes a priori specified primary outcome

ADAMS= Anxiety, Depression, and Mood Scale ABC=Aberrant Behavior Checklist, factored for FXS, Sansone et al. 2012

ADHD-RS= Attention Deficit Hyperactivity Rating Scale SRS= Social Responsiveness Scale

VABS= Vineland Adaptive Behavior Scale, Adaptive Behavior Composite Score

Next Steps

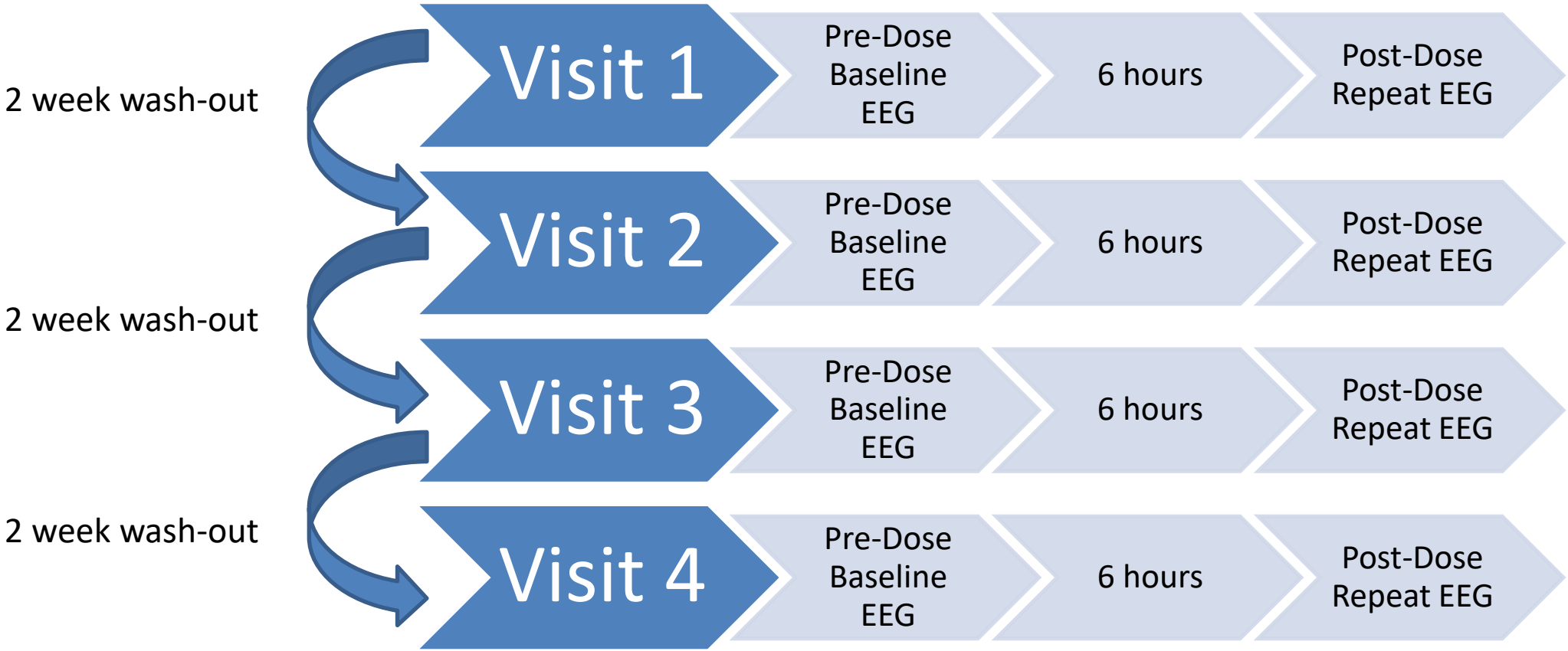
- Analyze quantitative data
  - Eye tracking results
  - Expressive language sampling
  - Molecular blood assay data
    - Plasma amyloid precursor protein
    - Lymphocytic extracellular signal related kinase activation

Single Dose Probe Study

- Can we see single-dose effects of drugs under study in FXS?
  - Effects on EEG and performance based/quantitative measures
  - Drugs under study: baclofen 30mg, lovastatin 20mg, minocycline XR 270mg

Current Study Design

During each visit, randomized to one of four drug conditions:
Acamprosate, Lovastatin, Minocycline, Placebo



Results

No significant EEG or clinical impact of single-dose minocycline or lovastatin

Baclofen had EEG effects and eye tracking effects

Mean(SD)	FXS (n=16)
Age	26.3 (8.9) 16 – 43
% male (n)	69 (11)
Stanford-Binet 5 Abbreviated IQ (SS)	57.5 (17.0) 47 – 88
Stanford-Binet 5 Deviation IQ	55.9 (29.5) 11 – 91
Social-Communication Questionnaire Total Score	10.8 (7.0) 0 – 24

Baclofen

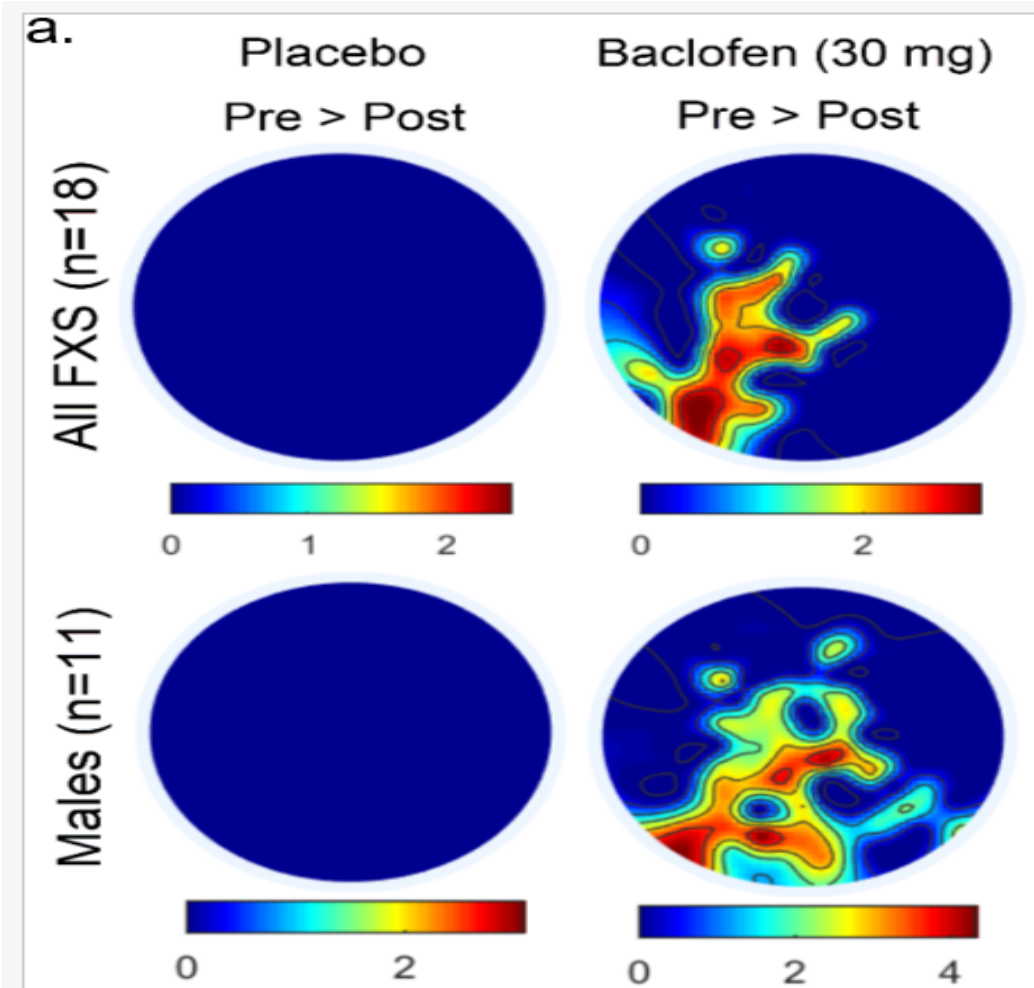
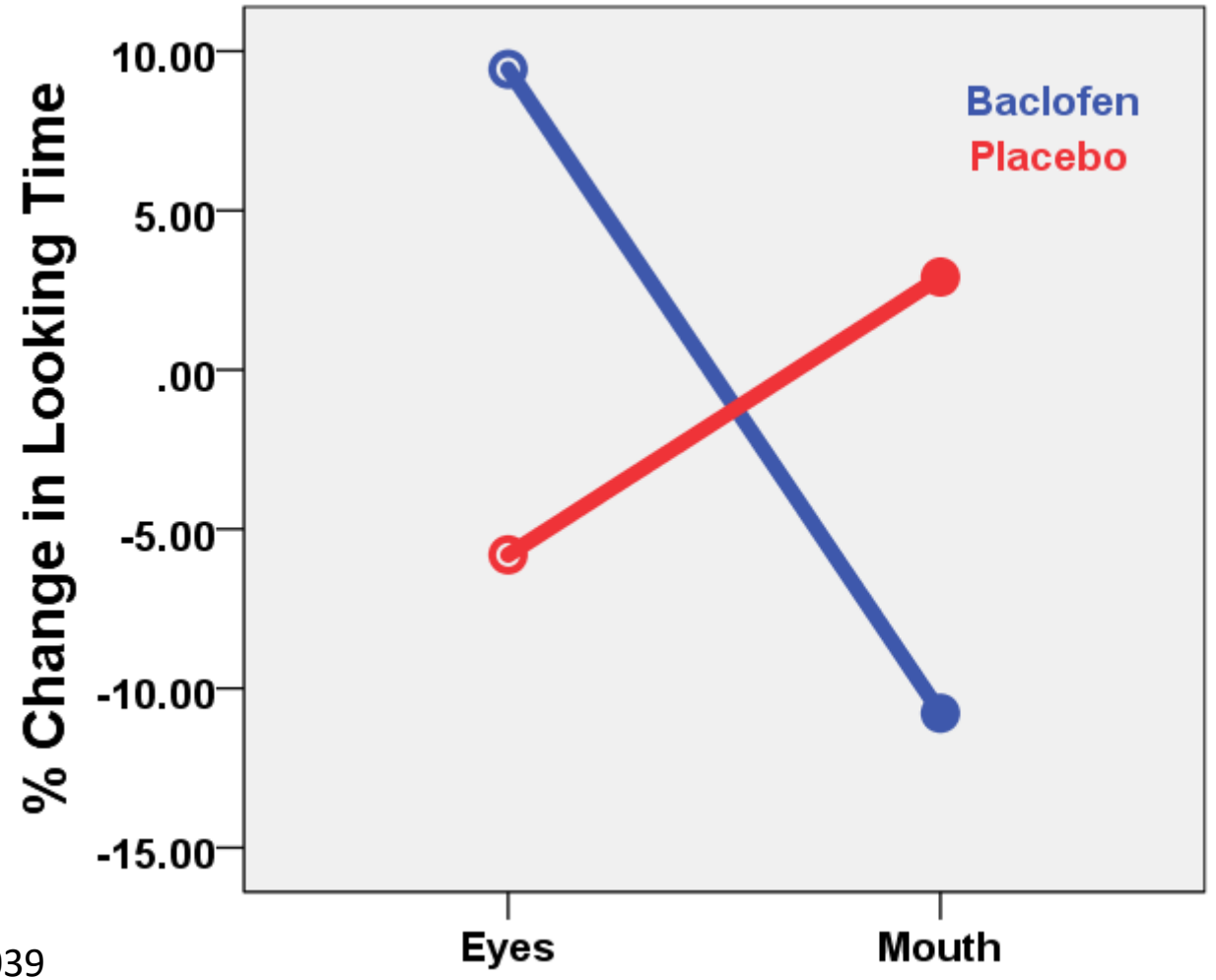


Figure 5: Baclofen, but not placebo, significantly decreases gamma power by cluster permutation testing in full mutation FXS males. Warmer colors: Significant reduction in Gamma activity post-dose.

Baclofen Significantly Increases % Time Looking at Eyes vs. Mouth Compared to Placebo (Calm Only)



FacialFeature*Drug Interaction, p=.039

Next Steps

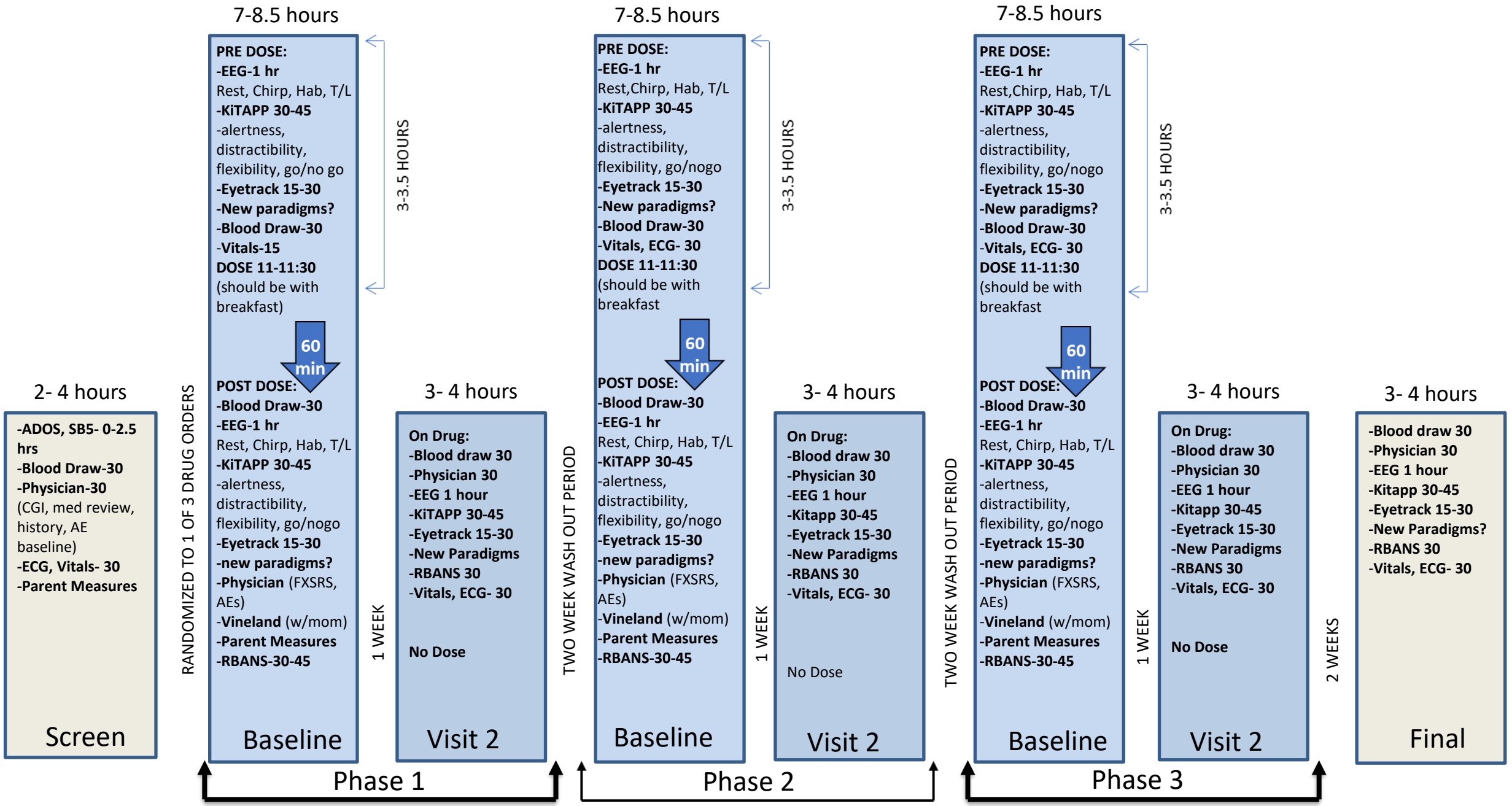
Evaluate potential correlations with EEG findings and clinical measures

Evaluate impact of medication on higher-level EEG parameters such as phase amplitude coupling and connectivity measures

Evaluate in the future how single-dose results may be predictive of chronic dosing impact

AZD7325, now BAER-101 in Young Adults with Fragile X

- Selective GABA A alpha 2,3 agonist
- Initially studied for the treatment of anxiety without the potential sedating and tolerance inducing side-effects of benzodiazepines
- Using pre- post-test EEG and performance based measures design
- Include pre- post-dosing after first dose and after two weeks of chronic low or high drug dosing or placebo dosing
- Goal N=15, stopping after #13 completes due to Covid delays and concerns; Early results expected end July 2020


2- 4 hours
-ADOS, SB5- 0-2.5 hrs
-Blood Draw-30
-Physician-30
(CGI, med review, history, AE baseline)
-ECG, Vitals- 30
-Parent Measures
Screen
RANDOMIZED TO 1 OF 3 DRUG ORDERS
7-8.5 hours
PRE DOSE:
-EEG-1 hr
Rest, Chirp, Hab, T/L
-KiTAPP 30-45
-alertness, distractibility, flexibility, go/no go
-Eyetrack 15-30
-New paradigms?
-Blood Draw-30
-Vitals-15
DOSE 11-11:30
(should be with breakfast)
3-3.5 HOURS
60 min
POST DOSE:
-Blood Draw-30
-EEG-1 hr
Rest, Chirp, Hab, T/L
-KiTAPP 30-45
-alertness, distractibility, flexibility, go/nogo
-Eyetrack 15-30
-new paradigms?
-Physician (FXSRS, AEs)
-Vineland (w/mom)
-Parent Measures
-RBANS-30-45
Baseline
1 WEEK
3- 4 hours
On Drug:
-Blood draw 30
-Physician 30
-EEG 1 hour
-KiTAPP 30-45
-Eyetrack 15-30
-New Paradigms
-RBANS 30
-Vitals, ECG- 30
No Dose
Visit 2
Phase 1
TWO WEEK WASH OUT PERIOD
7-8.5 hours
PRE DOSE:
-EEG-1 hr
Rest,Chirp, Hab, T/L
-KiTAPP 30-45
-alertness, distractibility, flexibility, go/nogo
-Eyetrack 15-30
-New paradigms?
-Blood Draw-30
-Vitals, ECG- 30
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1 WEEK
3- 4 hours
On Drug:
-Blood draw 30
-Physician 30
-EEG 1 hour
-Kitapp 30-45
-Eyetrack 15-30
-New Paradigms
-RBANS 30
-Vitals, ECG- 30
No Dose
Visit 2
Phase 3
2 WEEKS
3- 4 hours
-Blood draw 30
-Physician 30
-EEG 1 hour
-Kitapp 30-45
-Eyetrack 15-30
-New Paradigms?
-RBANS 30
-Vitals, ECG- 30
Final

Acknowledgements

- Industry partners: Tetra, Zynerba, Ovid
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- FXS trial sites
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