Challenges and Issues in Designing Poc Trials for Autism Spectrum Disorders:

More questions than answers

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Premise

- **RG7314, a potent antagonist of the V1A vasopressin receptor, being developed as treatment for the deficit of social communication in ASD**
- **Task: Design a PoC trial**

Challenges

- **Inclusion criteria; patient population**
- **Outcome measures**
- **Trial Duration**
- **Placebo reponse**
- **Combination with psychosocial intervention**

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Inclusion criteria

- **Diagnosis**
  - ASD
- **Should Inclusion criteria set a threshold for symptom severity similar to trials in schizophrenia or major depression?**
  - Enrichment for pronounced deficit in social communication?
  - CGI for specific symptom domains, i.e. social communication?

Inclusion criteria

- **What has been done in previous trials?**

Trial	N	Compound	Target Indication	Symptom Threshold
Unis et al, 2002	85	Secretin	'Symptoms of Autism'	No
Levy et al, 2003	62	Secretin	'Symptoms of Autism'	No
King et al, 2009	149	Citalopram	Repetitive Behavior	Yes
Remington et al, 2001	37	Haloperidol, Clomipramin	Stereotypy	No
Hollander et al, 2005	45	Fluoxetine	Repetitive Behavior	No
McCracken et al, 2002	101	Risperidone	Irritability	yes
Marcus et al 2009	218	Aripiprazole	Irritability	Yes

- **Our Solution**
  - ADOS score according to diagnostic criteria
  - CGI ≥ 4, SRS ≥ 75

Autism Diagnostic Observation Schedule (ADOS)

- **A semi-structured, standardized assessment of social interaction, communication, and imagination for individuals suspected of having ASD**
- **Classification is made on the basis of exceeding 3 thresholds :**
  - Social behavior domain +
  - Communication domain +
  - Combined social-communication total.

Domain thresholds (module 4 example; fluent speech, adolescent adult)	Autistic Disorder	ASD
Communication	3	2
Social Interaction	6	4
Communication + Social Interaction	10	7

Lord et al (2000)

Social Responsiveness Scale (SRS)

- **A 65-item informant-based rating scale designed specifically for use in ASD to quantitatively measure an individual's ability to engage in emotionally appropriate reciprocal social behavior in a naturalistic social setting**

- **Social skill levels are assessed over five domains:**
  - Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms

- **The total score generated serves as an index of severity of social deficits in the autism spectrum**

- **T-score (standardized score)**
  - 60-75 = mild to moderate range
  - >75 = severe range

Constantino (2005)

Issue: Patient population

Are treatment effects in adults or lack thereof predictive of treatment effects in adolescents and children?

1. Most programs will first test compound in a population (adults) which is **not the final target population** (children, adolescents)
2. Developmental stage, CNS plasticity and other factor may affect treatment response
3. Combination with behavioral intervention may yield different results at earlier compared to later stages

Answer: Results in adult patients with ASD may not be predictive

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Outcome measures

DSM-V definition of criterion A of ASD diagnosis:

Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1.Deficits in social-emotional reciprocity

- Ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction,

2.Deficits in nonverbal communicative behaviors used for social interaction

- Ranging from poorly integrated- verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

3.Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers)

- Ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people

➢ **No scale assesses all three aspects**

Outcome measures: Assessment of potential effects on deficits in social communication

- **Challenge:**
  - FDA (Autism Speaks Outcomes Meeting Mar 2012): 2/3 domains within social communication (DSM-V) should be assessed
    1. Social-emotional reciprocity
    2. Nonverbal communicative behaviors
    3. Developing and maintaining relationships

- For PoC study , targeting just 1 might be acceptable
- May not be the case for Phase 3 enabling and phase 3 studies

Outcome measures considered

- **ABC Social Withdrawal Score**
  - *"Appropriate for use as a measure of social withdrawal. Demonstrated measure of change. Could be enhanced by additional factor analyses studies based on ASD participants."*
- **CGI (global impression); *alternatively, CGI for social communication only***
  - *"Psychometric data are lacking, but commonly used as a global measure. It can be rated by a blinded independent evaluator"*
  - *"Can be weighted in favor of particular domain of behavior."*
- ***VABS (adaptive functioning) ?***
  - *"Mixed evidence demonstrating that it is a measure of behavioral change in both pharmacological and behavioral intervention trials. Not appropriate for short-term trial"*
  - *Unknown if we will we see an effect in 12 weeks?*
- **SRS**
  - *"Provides measures of general symptoms associated with autism but not specifically finer domains of social communication"*

SOURCE: Autism Speaks Outcomes Meeting Mar 2012

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Trial duration

- **Trajectory of potential improvement of deficit in social communication due to pharmacological intervention unkown**
- **PoC trials usually 6 to max 12 weeks, but is such treatment duration sufficient to show an effect at the behavioral level?**
- **Need for surrogate (proxy) clinical readouts, i.e. biomarkers of response**
  - **Eye tracking?**
  - **Social reward functions?**
  - **Issues: No established assessment available, i.e. implementation of measures used in academic trials in multisite clinical trials challenging if not impossible**

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“Placebo” Response

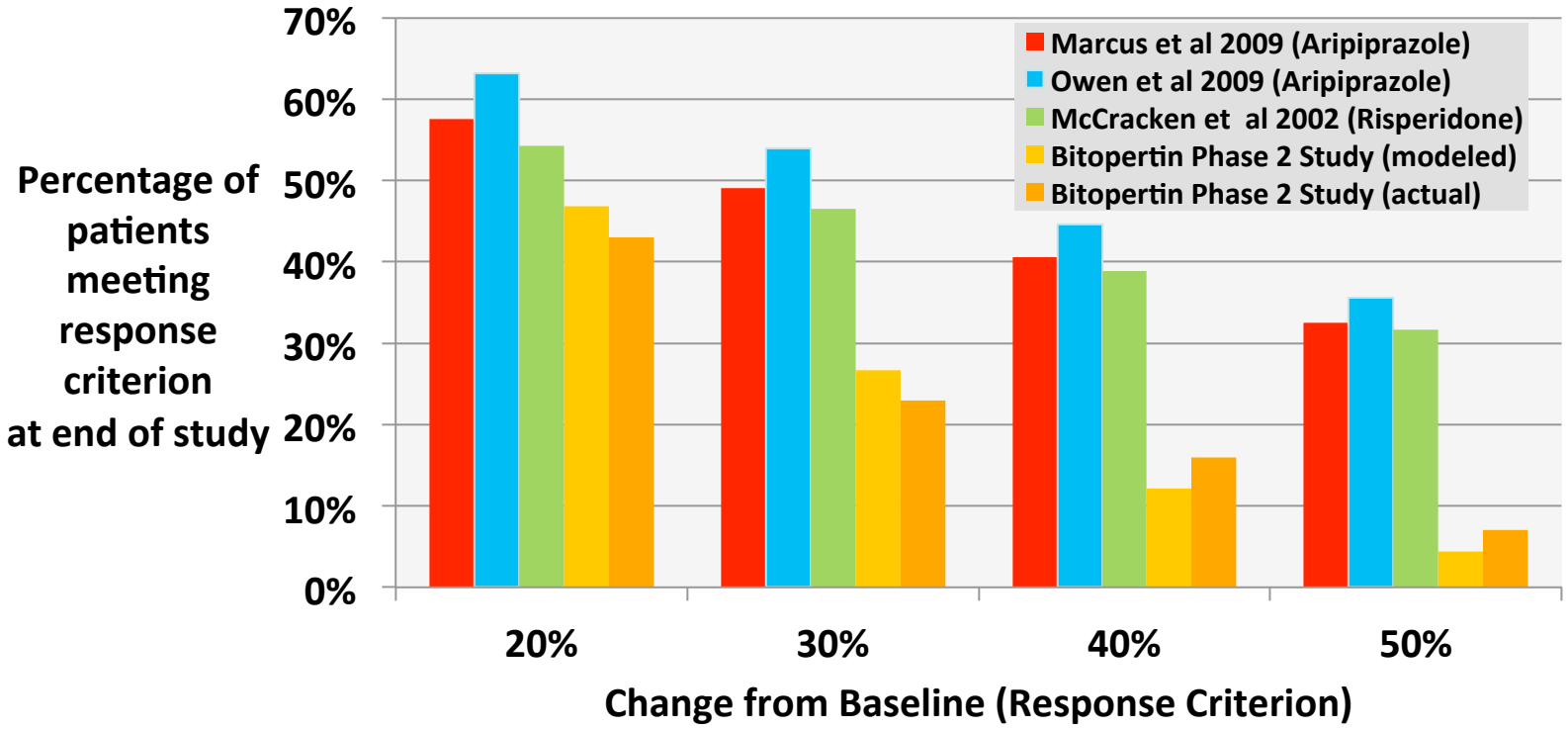
- **«Placebo» response = Improvement in group treated with placebo**
- **Knowledge of this placebo response desirable when designing trial, particularly for defininining a priori response criteria**
- **Not well known for ASD**

"Placebo" Response in ABC Social Withdrawal Factor in previous studies targeting irritability or repetitive behavior

				ABS S/W Score						
Drug/Study	**Duration**	**Age**	**N (Placebo)**	**Bsl**	**SD Bsl**	**Δ**	**SDΔ**	**%Δ**	**ES***	**ES****
Aripiprazole										
Marcus et al 2009	8 w	6-17	49	18.0	10.5	5.2	8.4	29%	**0.62**	**0.50**
Owen et al 2009	8 w	6-17	49	18.1	1.2	6.2	7.7	34%	**0.81**	**0.55**
Risperidone										
McCracken et al 2002	8 w	5-17	52	16.1	8.7	4.1	--	25%	**--**	**0.49**
Citalopram										
King et al 2009	12 w	5-17	76	11.1	8.0	2.9	5.0	26%	**0.36**	**0.58**
Bitopertin				----------PANSS----------						
Phase 2 neg sx trial	8 w	18-60	61	25.9	3.7	5.8	4.8	19%	**1.00**	**1.28**

* Using SD change ** Using SD Baseline

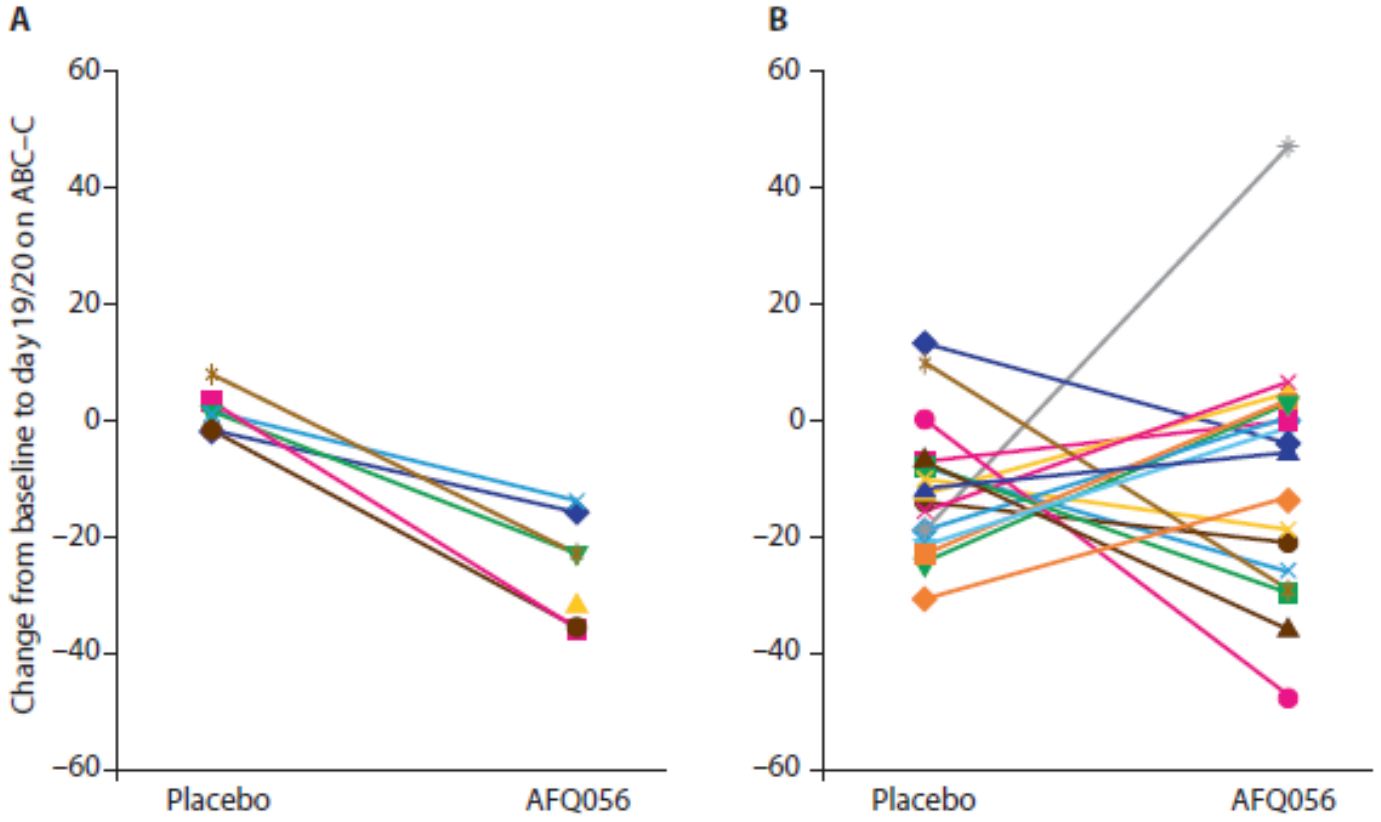
Estimates of response rates* in Social Withdrawal** in placebo groups in studies of aripiprazole and risperidone targeting irritability/impulsivity associated with autistic disorder



* Calculated under assumption of normal distribution of observed change in placebo group

** Social Withdrawal Factor of ABC Scale

Effect of mGluR5 antagonist AFQ056 on ABC total score in Fragile X patients by methylation status of the FMR1 promoter region



Effect driven by presence/absence of placebo response?

“Placebo” response

- **Expectation bias of informants driving “placebo” response?**
- **Need for development of more objective assessments for drug trials**
  - Clinical Assessment based on scripted interactions
  - Videotaping and blinded review of assessments?

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Issue:Combination with standardized behavioral treatment

1. Chance higher to observe a "prosocial" effect of investigatonal compound if combined with targeted behavioral intervention? Needed to observe effect?
2. Is this feasible given only short term study?
3. FDA (Meeting Washington Mar 2012): Still want to see effect of drug alone

Conclusion

- **Clinical Development of drugs that target deficit in social communication in ASD very challenging and high risk due to**
  - **Little knowledge of optimal inclusion criteria**
  - **Initial test of drugs in adult patients**
  - **Lack of outcome measures that have been developed to capture change over time and assess all three aspects of deficits in social communication**
  - **Expectation bias of informants that provide basis of currently used assessment confounding observation of true pharmacological effects**
  - **Unclear if psychosocial intervention should be combined with drug treatment**

Thank you for your attention

Backup

Inclusion criteria

- **Stratification?**
  - Previous response to psychosocial treatment
  - Developmental trajectory?
  1. Using biomarkers to stratify along dimension of social reward and salience functions? *(comment: idea to stratify into groups with more versus less impairment in system that compound x assumed to target)*
     a) Social reward functioning; social salience
     b) Other learning assays (eg. emotional word list learning)
     c) Cyber ball
  2. History? *(comment: idea that developmental trajectory could help identify relevant impairment in system that our compound is assumed to target; i.e. patients with pronounced delay in speech acquisition)*
  3. Previous treatment response? *(comment: idea to identify patients with generally higher propensity to respond to any intervention, that is exclude patients with obvious "treatment resistance")*