Targeting Ventral Striatal Activation and Anhedonia in Early Phase Clinical Trials of Mood and Anxiety Spectrum Disorders: The NIMH FAST-MAS Perspective

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Financial Relationships

• Consultant/Advisory Board:
  – Abbott, Astra-Zeneca, Attentiv, Bristol Myers-Squibb, Eisai, GSK, Lilly, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Purdue, Roche, Sanofi-Aventis, Somaxon, Sunovion, Takeda, Transcept

• Grant Funding:
  – Grant support specifically related to this talk: NIMH Contract: HHS-N271-2012-000006-I
  – Abbott, ANS-St. Jude, Astellas,Brainsway, Duke Institute for Genome Sciences and Policy (IGSP), Duke Institute for Brain Sciences (DIBS), Lundbeck, Neosync, NIH, Novartis, Johnson and Johnson, Otsuka, Pfizer, Sunovion, Takeda, Teva, Transcept
Overview

• Proposed solutions to the challenges facing CNS drug development:
  – Transform early phase study methodology (“Quick Win/Fast Fail”)
  – Revolutionize how we think about mental illness (RDoC vs DSM)

• Example of Attempt at Implementing This Approach:
  – NIMH FAST-MAS: Study targeting anhedonia in terms of the ventral striatal response to reward
Problems with Phase 2: Gate to Most Expensive Phase of Development

- Phase 2a clinical trial design\methodology thought to be biggest contributor to problems
  - Key Information relating to a drug candidate obtained from Phase 2a trials:
    - Likelihood of improving FDA-accepted endpoints
    - Information for designing pivotal trials such as dose
    - Likelihood of commercial potential
  - Phase IIa trials are frequently underpowered, “mini” phase 3 trials which are not long enough to demonstrate change
  - Usual Clinical endpoints too variable to test potential in Phase IIa study with sufficient power at limited cost
    - Vulnerable to bias problems
    - Basing go-no-go decision on getting statistical significance on a single clinical endpoint in such a study is highly risky
Problems with DSM Diagnostic System

• Diagnostic categories based on consensus not science:
  – Based on clinician observation and patient symptom reports
    • Not informed by recent scientific developments
      – Fails to align with neuroscience and genetics findings
  – Not predictive of treatment response.
  – Does not capture fundamental underlying mechanisms.
  – Slow the development of new treatments targeted to underlying pathophysiological mechanisms.
    • Contribute to study failures:
      – Unlikely to be successful developing a drug for a condition that:
        » Doesn’t have a unique pathophysiology
        » Is not reliably distinguishable from other conditions
        » May subsume more than 1 condition

Failure to Establish POC and Target Engagement at Doses Studied

• Companies often go to Phase III prior to establishing Proof of Concept (POC) in terms of efficacy/safety profile in Phase I-II

• Generally fail to establish target engagement with doses studied and that engaging target has effect on brain mechanisms relevant to clinical outcome
  – Leads to studies that do not test specific a priori hypotheses ("all I care about is if it works and if it works I don’t care how")
    • Makes outcomes vulnerable to non-specific effects and bias
    • Greatly diminishes likelihood of replication

Paul et al., Nature Reviews. 2010
Proposed Solution: “Quick-Win/Fast-Fail” Approach

• Since vast majority of candidates fail can we find a way to fail them faster and less expensively?
  – Requires shift of R&D investment from later to earlier stages
  – Design Phase I/IIa studies to definitively indicate potential
  – Pursue POC studies with biomarkers/surrogate endpoints early
    • Must establish early on whether or not a molecule engages its target and has desired pharmacological activity in humans
      – Biomarkers: Closer than clinical endpoints to pathophysiology and therapeutic mechanisms; thereby decrease variability and increase power
        » Makes assessing efficacy potential possible in smaller/cheaper Phase IIa study which better predict Phase 3 results; decrease vulnerability to bias
      – Developing reliable biomarkers of both efficacy and safety for a variety of diseases will be necessary to make early ‘go/no-go’ decisions;

Paul et al., Nature Reviews. 2010
Addressing Diagnostic Problems: NIMH Research Domain Criteria (RDoC) project

• Meant to replace DSM as new way of classifying psychopathology based on dimensions of observable behavior and neurobiological measures
  – Dimensional system: spans range from normal to abnormal
  – New framework for research on pathophysiology, especially genomics/neuroscience
    • Shift focus from refining clinically based classification to incorporating data on pathophysiology
  – Ultimately will inform future classification schemes.
    • Will help identify new treatment targets, detect treatment subgroups, improve match of research findings and clinical decision making.
    • Aimed at ensuring reliable and valid diagnosis.

Insel et al., Am J Psych. 2010
RDoC Constructs

• Identified key dimensions of function called “constructs”
  – Concept summarizing data about a specified functional dimension of behavior (and implementing genes and circuits) subject to continual refinement with advances in science.
  – Represent the fundamental unit of RDoC analysis
  – Central to psychiatric conditions, linked to underlying brain circuitry, and cut across current diagnostic boundaries
  – Constructs defined by associated:
    • Genes; Molecules Cells; Circuits; Physiology Behavior; Self-Reports; Paradigms

Insel et al., Am J Psych. 2010
## Example Domain: Positive Valence Systems – Approach Motivation

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Established networks for carrying out early phase trials of molecules engaging promising new **targets** embodying principles just discussed

- Unique NIMH/private/academic partnership

Meant to:

- Provide a path for promising compounds currently not being developed
- Establish a new standard for early phase drug development that will improve the cost/benefit of CNS drug development and rekindle pharma interest
- Improve our understanding of mechanisms of psychopathology, treatments for psychiatric disorders, and optimal trial methodologies

Awarded Grants in 3 Areas:

- Mood and Anxiety Spectrum Disorders (FAST-MAS)
  - Grant Awarded to Duke (PI: A Krystal) HHS-N271-2012-000006-I
- Psychotic Spectrum Disorders (FAST-PS)
  - Grant Awarded to Columbia (PI: J Lieberman)
- Autism Spectrum Disorders (FAST-AS)
  - Grant Awarded to UCLA (PI: J McCracken)
Key Steps in Implementing this Approach in Designing FAST-MAS Phase 2a Trial

- Choosing:
  - target
  - molecule which engages that target
  - dose of the molecule to study
  - appropriate RDoC construct(s)
  - outcome measures
  - patient population to study and how to select for that population
  - number of subjects to include in the trial
• Working with committee including NIMH Program Officers and consultants to identify most promising targets to study and how to study them
  – Design trials based on the principles outlined earlier to optimize capacity to make a **definitive go/no-go decision** at end of Phase IIa.
• Go/No-Go decision made based on whether **molecule engages target** not on whether have significant effect on a clinical scale
  – If we don’t engage the circuitry it would not make sense to move forward even if there is a therapeutic effect on a clinical or self-report endpoint
  – This would be a setup for a failed phase III trial.
FAST-MAS Target Selection

Process: Qualification Criteria

- Promising Pre-clinical/Clinical data
- Target of interest to the field
- Available means of assessing **target engagement**
- Available molecule for testing target hypothesis
  - Have to convince industry partner of the value of this approach
- Far along enough so that IND exists or IND-ready
- Not too far along in development
  - Phase II underway or beyond
- Established efficacy but target engagement not established
- Has not been found to lack efficacy in relevant clinical trial(s) or have prohibitive AE/tox profile
  - Or problem is molecule specific
• Target engagement might mean demonstrating:

  – **Receptor occupancy with PET ligand**
  – That treatment affects a specific brain circuit with fMRI, or EEG measure
  – That treatment changes some relevant aspect of behavior in a laboratory task
  – That treatment leads to change in symptoms or behavior
Process of Target Selection

- Exhaustive search led to identification of a target of interest
  - molecule was available that engaged that target and was at appropriate point in development
  - Means of establishing target engagement with PET available
    - Prior PET study allowed choice of dose that definitively engaged target
      - If PET study had not been available we would first have done a PET receptor occupancy vs dose study
  - Industry-partner willing to collaborate
  - Means of establishing POC in terms of effect on brain circuit during trial available
Choice of RDoC Construct(s):
We Chose to Study Anhedonia

• Because pre-clinical data strongly suggest that pharmacologically engaging the receptor target of interest should measurably affect key brain circuit so as to increase reward.
  – The inability to experience pleasure is a core symptom of major depression but also cuts across traditional diagnosis (anxiety disorders and schizophrenia)

Treadyway et al., 2009; Pizzagalli et al., 2005, 2009; Joiner et al., Psych Res. 2003; Snaith et al., BJP, 1995
Choice of RDoC Construct(s): Challenge - Where in RDoC is the Function I want to Study?

• Need to find equivalent of anhedonia in RDoC and identify associated circuitry, behavior tests, clinical scales to employ in study

• The relevant RDoC Domain is Positive Valence Systems. There are a number of relevant RDoC Constructs related to reward:
  – Reward valuation, Expending Effort for Reward, Reward prediction/expectancy, Reward Responsivity, Effect of Reward on Learning
    • Reflects current best understanding of relevant neurobiology
  – Had to choose which is of primary interest but also decided to include measures to allow us to assess outcomes related to all of the key components
    • Circuits and measures overlap to a degree across Constructs of interest
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Establishing POC in Terms of Effect on Brain Circuit

• Link to neural circuitry
  – Proof of Mechanism/Neural circuitry target engagement can be assessed with:
    • Task-associated fMRI Activation in ventral striatum during Monetary Incentive Delay Task
    • Resting state delta EEG current density in the rostral anterior cingulate

Wacker et al., 2009; Pizzagalli et al., 2004, 2009; Stoy et al., 2012; Ossewaarde et al., 2011
Choice of Outcomes: Reverse of Traditional Approach

• **Primary**
  – Circuit measure of expected effect of drug on the brain. Primary outcome is measure of engaging circuitry related to hedonic experience/response

• **Key Secondary**
  – Behavioral intermediate phenotype assessment (more closely linked to neural circuitry than clinical outcome but also linked to clinical outcome)
    • Probabilistic Reward Task assesses capacity to learn based on reward
  – Clinical Outcome: Measured with a clinical scale that has been demonstrated to be sensitive to treatment effects in depressed patients treated SSRI/SNRI
    • Snaith-Hamilton Pleasure Scale (SHAPS)

• **Exploratory**
  – Additional circuit measure
    • QEEG measure of cingulate activity
  – Additional Behavioral Measure
    • Effort Expenditure for Rewards Task assesses the degree to which one is motivated by reward as demonstrated by effort
  – Additional Self-report scale
    • Temporal Experience of Pleasure Scale (TEPS)
  – HAM-D, HAM-A
Challenges in Process of Choosing Outcomes

• Started with clinical outcome
  – Agonizingly hard to give up:
    • HAM-D/HAM-A, DSM approach
    • Approach of seeking to find significant placebo vs drug effect on HAM-D/HAM-A or equivalent
  – Moved to Snaith-Hamilton
    • Clearly underpowered and risky
    • Hard to give up clinical outcome

• Finally settled on circuit outcome which was really the original intent and where we started
  • Go/No-Go decision will be made based on whether molecule engages target not on whether have significant effect on a clinical scale
    – If we don’t engage the circuitry it would not make sense to move forward even if there is a therapeutic effect on a clinical or self-report endpoint;
    – This would be a setup for a failed phase III trial.
Choice of Subject Population

• Dx mix:
  – DSM Dx mood and anxiety spectrum
    • One third must meet anxiety disorder criteria and not MDD
  – Anhedonia entry criteria (Snaith-Hamilton)
    • Circuit measure work insufficient to allow screening
      – This would ultimately be the goal.
Challenges to Choice of Subject Population

- Novel endpoints may be unsuitable/unstudied for screening subjects
- Population choice affects regulatory (FDA) viability and clinical market potential
  - NIMH is having discussion with FDA about how RDoC approach can be applied to drug development/approval
  - Some FAST-MAS consultants have deep FDA experience
  - FDA approval will only be possible if can show that improvement of the RDOC endpoint does not represent improvement of one of the symptoms of a disorder; With anhedonia need to demonstrate:
    1) Treatment improves anhedonia but NOT depression scale (HAM-D/MADRS)
    2) Treatment improves anhedonia cross-diagnostically:
       - major depression; anxiety disorder who do not meet major depression criteria; and/or schizophrenia who do not meet major depression criteria.
Challenges to Subject Population: Market Potential/Clinical Application

- “People don’t have RDoC Constructs they have disorders.”
  - MDD criteria (5/9) identifies heterogeneous population (insomnia/sleepiness, weight loss/gain, etc)
    - No way to tell how useful/valid it is as it is its own “gold standard”; links to neurobiology suggest it is poor
  - We are treating symptoms now
    - No evidence or belief that treatments for schizophrenia address the entire syndrome. They address specific symptoms.
    - Treatment of depression is often similar. Outcome improved by targeting treatment to what we referred to as symptoms of MDD along antidepressants: insomnia (sleep aids), anergia (stimulants)

- “Won’t everyone end up on multiple medications?”
  - People are on multiple medications now!
    - In clinical practice 60% of visits with 2 or more medications; 33% visits with 3 or more medications
    - Single agent therapy often fails across multiple disorders

- “Doesn’t the DSM diagnosis matter?”
  - No data on whether MDD/anhedonia needs different treatment than schizophrenia/anhedonia
  - Our drugs are currently broad spectrum and dx really doesn’t matter.
    - There is almost no disorder for which an “antipsychotic” is not used

Zigman and Blier, J Psychopharm. 2012; Mojtabai and Olfson, Arch Gen Psych. 2010;
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<th>Target DSM-5 Diagnosis and Field Site</th>
<th>Intraclass Kappa</th>
<th>95% CI</th>
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<tr>
<td>Dallas VA</td>
<td>0.27</td>
<td>0.11–0.43</td>
<td>Questionable</td>
<td>0.49</td>
<td>0.37 (0.31–0.44)</td>
</tr>
<tr>
<td>Houston VA/Menninger</td>
<td>0.25</td>
<td>0.13–0.36</td>
<td>Questionable</td>
<td>0.34</td>
<td>0.36 (0.31–0.40)</td>
</tr>
<tr>
<td>UCLA</td>
<td>0.42</td>
<td>0.26–0.55</td>
<td>Good</td>
<td>0.26</td>
<td>0.28 (0.23–0.33)</td>
</tr>
<tr>
<td>UTS</td>
<td>0.13</td>
<td>−0.06 to 0.30</td>
<td>Unacceptable</td>
<td>0.21</td>
<td>0.19 (0.15–0.24)</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.28</td>
<td>0.20–0.35</td>
<td>Questionable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mixed anxiety-depressive disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penn</td>
<td>0.19</td>
<td>−0.07 to 0.42</td>
<td>Unacceptable</td>
<td>n/ac^c</td>
<td>0.07 (0.05–0.10)</td>
</tr>
<tr>
<td>UCLA</td>
<td>−0.04</td>
<td>−0.13 to 0.08</td>
<td>Unacceptable</td>
<td>n/ac^c</td>
<td>0.10 (0.07–0.13)</td>
</tr>
<tr>
<td>Pooled</td>
<td>−0.004</td>
<td>−0.10 to 0.09</td>
<td>Unacceptable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generalized anxiety disorder</strong></td>
<td>0.20</td>
<td>0.02–0.36</td>
<td>Questionable</td>
<td>0.34</td>
<td>0.20 (0.16–0.24)</td>
</tr>
<tr>
<td><strong>Posttraumatic stress disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dallas</td>
<td>0.63</td>
<td>0.48–0.75</td>
<td>Very good</td>
<td>0.50</td>
<td>0.46 (0.40–0.54)</td>
</tr>
<tr>
<td>Houston VA/Menninger</td>
<td>0.69</td>
<td>0.59–0.78</td>
<td>Very good</td>
<td>0.47</td>
<td>0.42 (0.37–0.46)</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.67</td>
<td>0.59–0.75</td>
<td>Very good</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complex somatic symptom disorder revised (Mayo)</strong></td>
<td>0.61</td>
<td>0.40–0.77</td>
<td>Very good</td>
<td>0.10^d</td>
<td>0.08 (0.06–0.11)</td>
</tr>
<tr>
<td><strong>Binge eating disorder (Penn)</strong></td>
<td>0.56</td>
<td>0.32–0.77</td>
<td>Good</td>
<td>n/ac^c</td>
<td>0.05 (0.03–0.07)</td>
</tr>
<tr>
<td><strong>Alcohol use disorder (Houston VA/Menninger)</strong></td>
<td>0.40</td>
<td>0.27–0.54</td>
<td>Good</td>
<td>0.26^e</td>
<td>0.29 (0.24–0.33)</td>
</tr>
</tbody>
</table>

Regier et al., Am J Psychiatry. 2013
Challenges in Determining Number of Subjects

- N=90; Parallel-group; 2 arms: Study drug/Placebo
  - Study powered to detect effect size of 0.5
  - Capacity to estimate effect size on primary outcome limited by very few treatment studies carried out with MID fMRI
    - Roughly estimated effect size of 0.88
- We had to resist the tendency to power the study for clinical endpoints; it took several revisions before settled on smaller study with circuit outcome
General Limitations/Risks of “Fast-Fail” We Faced

• Can only study a limited set of targets
  – Requires developing means of establishing target engagement prior to proceeding into Phase Ib studies
• False-negative POC data (type 2 errors) could offset some or all of the cost savings generated by shifting attrition earlier
• Puts pressure on need for additional studies that form the basis for the early decision to have a relatively low uncertainty, which is not always possible.
• Cannot prevent Phase 3 failures due to relatively uncommon unanticipated adverse effects

Paul et al., Nature Reviews 2010
Summary

• The solution to the current crisis is that early phase drug development has to become biomarker/RDoC-based, though methods not currently fully worked out
  – New biomarker-based/technology intensive studies have to be carried out
  – RDoC needs to be more fully developed
  – Trials need to be carried out to test the utility of this approach