Early Clinical Research in Mental Health: Working with the US TURNS Consortium

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Clinical Development is Evolving

Traditional Paradigm: Phased Approach

- Scarcity of molecules from discovery
- Pre-Clinical
- Phase I
- Phase II
- Phase IIb
- Phase III
- Test each scarce molecule thoroughly

Emerging Paradigm: POC / Confirmation Approach

- Abundance of molecules from discovery
- Pre-Clinical
- Hypothesis Generating (Proof of Concept)
- Hypothesis Confirmation
- Shift attrition earlier
Why patients in early clinical research?

- **Cost to get a drug to market**
  - Estimated at $1.2 billion (!)
  - Cost of failure (less than 1 success for every 10 tries?)

- **Time to get to market**
  - 12 to 15 years
  - Patent clock ticking…

- **Late-stage failures**
  - Many high-profile drugs failing in Phase III up from 30% in 2011 to 35% in 2012
  - In 2012 alone, BMS-094 (hepC) is estimated to have cost $1.7 billion; Bapineuzumab (Pfizer, J&J, AD), Dalcetrapib (Roche, cholesterol)
Elements of Early Clinical Research

- Primary objective
  - Safety
  - Pharmacokinetics (drug exposure)

- Secondary-Exploratory objective
  - Efficacy

- No or limited potential for clinical benefit
Challenges with patients

- More difficult to recruit
  - Early clinical research: no potential benefit, motivation to participate?
- Can be more fragile population
  - Concomitant medications: Potential for drug-drug interactions
  - Disease progression
  - Adverse events related to disease
Example of a US Clinical Research Consortium
What is TURNS?

- Created in 2004
- $9 US million, 4 year contract
- National Institute of Mental Health (NIMH)
- The project directed by Stephen R. Marder, MD at UCLA
- Seven academic institutions
- Core resources (trial & data management, stats, site coordination, scientific operations)
The TURNS mission

- The NIMH approach is built on the assumption that progress in developing new treatments will require collaboration between the best academic, government, and industry scientists.

- TURNS is one component of a multipronged NIMH effort to stimulate academic and industry sponsored research focused on cognitive deficits in schizophrenia.
TURNS objectives

- Developed a tool to measure cognitive impairment in schizophrenia
  - Measurement and Treatment Research for Cognition in Schizophrenia (MATRICS)
- Fund and run multiple, exploratory Phase 2a studies
  - Grant application from academia and industry (large or small companies)
  - PIs from each institution
  - Clinical conduct at TURNS institutions
Davunetide in Schizophrenia Cognitive Impairment

- Randomized, double blind, placebo controlled
- 60 patients clinically stable, on any anti-psychotic medication
- Placebo, 5 mg QD or 15 mg BID for 12 weeks
- 7 US sites
- TURNS / NIMH funded
- Clinical endpoints: safety, cognition, function
- Clinicaltrials.gov NCT00505765
- Magnetic Resonance Imaging (MRI) Sub-study
Key Inclusion Criteria

- Men and women between 18 and 60 years of age (inclusive) with a DSM-IV/DSM-IV-TR diagnosis of schizophrenia
- On stable dose of second generation antipsychotic
- Performance less than the maximum cutoff for one MCCB tests

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=22)</th>
<th>Davunetide 5 mg (N=20)</th>
<th>Davunetide 15 mg BID (N=21)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>Age, years</td>
<td>41.4</td>
<td>10.4</td>
<td>43.2</td>
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<tr>
<td>Education, years</td>
<td>12.1</td>
<td>2.7</td>
<td>12.6</td>
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<tr>
<td>WTAR reading score</td>
<td>26.1</td>
<td>13.1</td>
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Demographics and Safety

<table>
<thead>
<tr>
<th>Sex</th>
<th>Placebo</th>
<th>Davunetide 5 mg</th>
<th>Davunetide 15 mg BID</th>
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<tbody>
<tr>
<td>Female</td>
<td>8</td>
<td>36.4</td>
<td>7</td>
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<tr>
<td></td>
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<td>35.0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.3</td>
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</table>

Antipsychotic Medication:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo</th>
<th>Davunetide 5 mg</th>
<th>Davunetide 15 mg BID</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td>4</td>
<td>18.2</td>
<td>6</td>
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<tr>
<td></td>
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<td>30.0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>Depot fluphenazine</td>
<td>2</td>
<td>9.1</td>
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<tr>
<td>Depot haloperidol</td>
<td>1</td>
<td>4.6</td>
<td>0</td>
</tr>
<tr>
<td>Olanzapine</td>
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<td>18.2</td>
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<td>7</td>
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<td></td>
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<td>33.3</td>
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<tr>
<td>Paliperidone</td>
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<td>13.6</td>
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<td></td>
<td></td>
<td>5.0</td>
<td>0</td>
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<tr>
<td></td>
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<td>0.0</td>
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<tr>
<td>Quetiapine</td>
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<td>3</td>
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<td></td>
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<td>9.5</td>
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<td>Risperidone*</td>
<td>6</td>
<td>27.3</td>
<td>1</td>
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<td>4</td>
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<td>Ziprasidone</td>
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<tr>
<td></td>
<td></td>
<td>9.5</td>
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</tbody>
</table>

Safety

- Well tolerated
- Good compliance
- Transient nasal irritation in all groups
- No effect on extrapyramidal symptoms
MATRICS Composite Score

- MATRICS Domains
  - Attention/Vigilance
  - Reasoning/Problem solving
  - Social Cognition
  - Visual Learning
  - Verbal Learning
  - Working Memory
  - Processing Speed

Mixed Model ANCOVA
- 5 mg vs placebo: p=0.174 (Week 6)
MATRICS Sub-Domain Scores

Conclusions
- Moderate (0.5 SD) to large (0.8 SD) treatment effect, although not statistically significant
- Visual Learning and Working Memory, same domains that improved in aMCI study
UCSD Performance-based Skills Assessment (UPSA)

- Measure of functional capacity to manage everyday tasks:
  - Household chores
  - Communication
  - Finance
  - Transportation
  - Planning recreational activities
  - Medication management
**UCSD Performance-Based Skills Assessment**

Effect size (sd units)

### ANCOVA (corrected for baseline)

<table>
<thead>
<tr>
<th>Effect</th>
<th>F</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>3.26</td>
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<tr>
<td>Week</td>
<td>0.91</td>
<td>0.35</td>
</tr>
<tr>
<td>Treatment x week</td>
<td>0.17</td>
<td>0.85</td>
</tr>
</tbody>
</table>

**Conclusions**
- 5 mg BL was lower than placebo, ANCOVA should correct but still possibility of regression to mean
- Large (>0.8 SD) treatment effect size, should constitute a clinically meaningful change—something a family member would notice
Exploratory Imaging Biomarker
Hypothesis
Davunetide can increase the metabolic integrity as measured by the NAA/Cr ratio compared to baseline

- NAA (N-acetyl-aspartate): a marker of neuronal integrity and function
- Cr (creatine): a marker of energy metabolism
- Ch (choline): a marker of membrane density and integrity
Non-parametric analysis shows strong trend towards significant treatment effect versus placebo.

Statistically significant increase in NAA levels found in patients treated with *davunetide* relative to baseline (p=0.017).

- Placebo was showed no change (p=0.928)
Lessons Learned (Sponsor’s perspective)

- Partnering and collaboration key to scientific success!
- Access to leading schizophrenia KOLs
- Subdomains of MATRICS may be informative
- Imaging biomarkers (like MRS) in early clinical research can be valuable
  - Can gain mechanistic information on drug action
  - Technical challenges with multi-site data acquisition and integration
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Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia. Schizophr Res. 2012 Apr;136(1-3):25-31

Questions?

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