Biomarkers in psychiatric drug development: an update

DISCUSSION

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• I am an employee of F. Hoffmann – La Roche Ltd and own stocks of this company
## Summary

<table>
<thead>
<tr>
<th>Galatzer-Levy</th>
<th>New computational approaches for characterizing clinic phenotypes and analyzing biomarkers</th>
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<tbody>
<tr>
<td></td>
<td>• Machine learning provides new, not necessarily intuitive ways to slice your data</td>
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<td>• Revelation of ‘hidden’ patterns that may have biological meaning</td>
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<td></td>
<td>➢ Identification and classification of specific subgroups (diagnoses, treatment response, illness course, neurobiologic underpinnings)</td>
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<tr>
<td>Etkin</td>
<td>Machine learning approaches to identify imaging markers predicting antidepressant response</td>
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<td>• Patients with better conflict regulation show response to AD treatment</td>
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<td>• Machine learning applied to fMRI and EEG data can predict response to active treatment</td>
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<td>➢ Behavioral and fMRI ‘endophenotypes’ relevant to treatment response</td>
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## Summary

<table>
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<tr>
<th>Javitt</th>
<th>NMDA receptor-based neuroimaging biomarkers for schizophrenia research</th>
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<tr>
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<td>• Ketamine-induced BOLD response as ‘biomarker’ to test drugs that inhibit excessive Glu release</td>
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<td>• PoM study demonstrates potentially relevant effect at high, but not low dose of pomeglumetad</td>
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<td>➢ Biomarker driven dose finding studies should be implemented before conducting studies in patients</td>
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<th>Anderson</th>
<th>Imaging biomarkers for the assessment of placebo response</th>
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<td>• The observed changes in placebo treated patients consists of</td>
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<td>• A true placebo response that can be demonstrated with fMRI and PET</td>
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<td>• A ‘temporal statistical effect’ or placebo ‘effect’ that is driven by regression to the mean, expectations of patients and clinician and other factors</td>
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<td>➢ The latter is the nemesis of drug trials</td>
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For whom does an antidepressant work?

**EMBARC** (PIs: Trivedi, Weissman, McGrath, Parsey):
309 depressed patients -> sertraline vs placebo

All patients taken together:

\[ d = 0.27 \]

\[ NNT = 8.4 \]

Etkin, Fonzo, Zhang, under review
Emotional conflict task

Task: identify facial expression, ignore word

Emotional conflict is biologically salient

Etkin, *Neuron* 2006

Implicit regulation: across-trial adjustments in behavior (RT)

Subjects unaware of pattern
Emotional conflict regulation circuit

- **reactivity**
- **regulation**

- dACC/dmPFC
- insula
- amygdala
- vACC/vmPFC

Etkin, *Neuron* 2006
Egner, *Cer Cort* 2008
Etkin, *TICS*, 2011
For whom does an antidepressant work?

Example result:

**Symptoms:**
- below median (better regulation)
- above median (worse regulation)

**Depression severity (HAM-D17):**
- d=0.76

**Remission:**
- NNT=3.4
- d=0.76
- PBO
- SER

Etkin, Fonzo, Zhang, under review
Challenges in the search for biomarkers
• **Strength:**
  - Possibility to reveal patterns in large data sets that are not observable with classical approaches which may point to critical biological underpinnings
  - Highly useful in classification schemes where understanding of the biology may not be critical

• **Weakness:**
  - Despite impressive results, «back-translation» to useful classification schemes or biologically relevant subgroups remains a challenge

• **Critical for drug development:**
  - Solutions of ML approaches (i.e. Responder analyses) can only be starting points to drill down to relevant «points of engagement» (similar to genetics where points of convergence need to be defined)
• How can the findings presented by Etkin and Javitt inform drug development?
  • Phase 1
  • Phase 2
  • (Phase 3)
Framework for early clinical development in psychiatry

Exploratory studies to characterise target engagement, physiological modulation of circuits and disease relevant pharmacology

- **MAD (Safety)**
  - Incorporating behavioral assays/imaging readouts

- **PoM Study (Healthy volunteers/Patients)**
  - Target engagement
  - Behavioural assays/imaging readouts
  - Physiological activity
  - Circuit engagement

- **PoC Study (Patients)**
  - Evidence of effects on clinical endpoint
  - Efficacy in disease domains

**MAD** = Multiple Ascending Dose; **PoM** = Proof of Mechanism; **PoC** = Proof of Concept
Importance of proof of target engagement

• Phase 1b POM studies
  • Target engagement:
    • PET = «structural» target engagement
Importance of proof of target engagement

• Phase 1b POM studies
  • Target engagement:
    • Pharmacodynamic endpoint or assays = «functional» target engagement
    ➢ **Mechanistic understanding to target critical** (i.e. NMDA receptor blockade leads to Glu release)
    ➢ **Relationship to target symptom dimension or indication desirable but not required** (relevance of excessive Glu release to schizophrenia unclear)

<table>
<thead>
<tr>
<th>Pharmacological challenges</th>
<th>Depletion studies</th>
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<tr>
<td>• NMDA Antagonist (Ketamine) Challenges</td>
<td>Tryptophan depletion</td>
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<tr>
<td>• Amphetamine induced DA release and raclopride displacement</td>
<td>Alpha-methyl-para-tyrosine (AMPT),</td>
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<td>• Methylphenidate Challenges</td>
<td></td>
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<td>• Fenfluramine induced prolactin increase</td>
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<td>• CCK Challenge (panic disorder)</td>
<td></td>
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<tr>
<td>• Lidocaine (Hippocampal excitability)</td>
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• Critical aspects
  ➢ Mechanistic Understanding, Validation and Reproducability!!!
  ➢ Issues is the dosing of the challenge compound: The magnitude of effect may overwhelm the potential therapeutic effect of a novel compound >> titration?
  ➢ Caution advised when assuming that positive effects will garantuee clinical effects
Importance of patient and endpoint selection

• Phase 1b POC studies
  • Providing initial evidence of relevant effect related to clinical target dimension
  • Evaluation of potential effects of a novel compound on relevant imaging readout or behavioral assay
  • Ideally, patients who are responsive to treatment and/or may have the behavioral abnormality that drives the target symptomatology
  • Genetics and omics not helpful in common CNS disorders because too distant from symptoms and behaviors (example IMI-NEWMEDS data)
Importance of patient and endpoint selection

• Phase 1b POC studies
  • Use of imaging and behavioral endophenotypes that allow
    • Reliable selection of treatment responsive patients?
      • Example
        • Conflict resolution
        • Imaging ‘profile’ associated with response in prior studies
    • Reliable selection of patients with regard to diagnosis and/or target symptom dimension
      • Example:
        • Patients with characteristically enhanced perception of negative emotions (MDD)
        • Patients with deficits in mismatch negatitivity (schizophrenia)
        • Patients with abnormal reward functioning (negative symptoms, schizophrenia)
        • Patients with hippocampal hyperactivity (schizophrenia)
        • AD patients with positive amyloid scans

➢ Challenges:
  ➢ Specificity often not established
  ➢ Link to clinical dimensions tenuous and not validated
  ➢ Normative data often not available for classification of patient
  ➢ Generalizability may be restricted
Patients with negative symptoms show deficits in effortful behavior (Effort choice task)

Gold et al, 2013

Patients with high negative symptoms (blue line) are less willing to work hard for a high reward
PDE10 Inhibitor worsens effortful behavior in patients with negative symptoms (Effort choice task)

**Placebo condition: Patient show performance consistent with reported deficits**
PDE10 Inhibitor worsens effortful behavior in patients with negative symptoms (Effort choice task)

*Placebo condition: Patient show performance consistent with reported deficits*

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**Figure Description:**

The figure illustrates the probability of selecting a difficult option across different reward magnitudes for various conditions: Placebo, 15 mg, and 5 mg. The x-axis represents the reward magnitude, while the y-axis shows the probability of selecting a difficult option. The data points are accompanied by error bars, indicating the variability. Significant differences are indicated by asterisks: 
- **1** = p<0.05
- **2** = p<0.01
- **3** = p<0.001

Golden et al., 2013
Enhancing chance of success

• Phase 2
  • Heterogeneity often mentioned but rarely addressed in clinical trials
  • Use of imaging not feasible
    • However, use of behavioral assays or other disease relevant assessments possible
  • Selection or stratification:
    • Emotion perception
    • Reward functioning
    • Cognitive ‘subtypes’ in schizophrenia
    • Amyloid load
  • Lack of normative data may make stratification difficult. May have to use ‘dynamic’ stratification

<table>
<thead>
<tr>
<th>Premorbid IQ</th>
<th>Current IQ</th>
<th>Aetiology</th>
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<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Neurodevelopmental aetiology</td>
</tr>
<tr>
<td>Normal</td>
<td>Low</td>
<td>Perionset worsening</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
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• If a go/nogo decision is tied to outcome, then the relevance of these behavioral biomarkers to symptomatic dimensions or diagnosis has to be convincingly established
Development of behavioral biomarkers

- Development of behavioral and imaging biomarkers as exemplified by Etikin and Javitt critical for future drug development
- Academic research and/or consortia
  - Define potentially useful behavioral biomarkers
- Precompetitive consortia
  - Psychometric characterization and validation of biomarkers
  - Example
    - ECNP sponsored consortium developing assays to assess motivated behavior and reward based learning
- Key Challenge: Reproducability, Validation,.....
Key drivers of placebo response

- Number of study sites
- Quality of assessments
- Number of study arms
Clinical effects of pomaglumetad (LY21400230)

Initial positive result

Subsequent failures to replicate


Downing et al., BMC psychiatry. 14:351, 2014
Placebo response

- Is the ability to generate a true ‘biological’ placebo response a prerequisite for a pharmacological treatment effect?
  - Should such patients be targeted in early PoC trials?
  - Or conversely, should they be excluded?

- Are there any other methods to identify placebo responders?

- Could we use the knowledge about factors underlying a true placebo response in patient selection$stratification?
Summary

• Example of promising approaches that should help define assays to identify patient subgroups, responders and factors associated with placebo response

• Importance of dilitent target and dose-finding studies

• Collaborations between academia and pharma required to develop such methods to a industry-level standard
Questions to Panel and Audience

• Questions to Isaac R. Galatzer-Levy:
  • What are the biggest challenges and pitfalls for ML approaches?
  • How do you differentiate between different solutions? i.e one phenotype (negative symptoms) but underlying heterogeneity? Validation?

• Questions to A. Etkin:
  • Should we include assessments of conflict resolution/response in AD trials?
  • Which other behavioral assays would you recommend for inclusion and/or assessment of treatment responsivity?

• Question to D. Javitt:
  • Are there any other measures short of MRS that we could use to assess Glu system?

• Question to A. Anderson:
  • What would you recommend to identify placebo responders?
  • How would you incorporate findings on placebo response in a clinical trial?
Questions to Panel and Audience

• How can such findings inform drug development?
• How can they be implanted in larger studies?
• Would additional work be needed to implement them?
• What are the pitfalls?

Questions to regulators:
• If patient selection were based not only on diagnosis but also a behavioral phenotype, how would that affect potential registration?
• If we could identify placebo responders and would exclude them from a trial, how would that been seen by regulators?
Thank you for your attention!