Specific Therapeutic Strategies for Preventing Disease Progression in Schizophrenia

Herbert Y Meltzer
Depts of Psychiatry and Behavioral Sciences, Physiology and Pharmacology
Northwestern Feinberg School of Medicine
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Specific Therapeutic Strategies for Developing Treatments for Preventing Disease Progression in Schizophrenia?

• Disease progression in schizophrenia
• What are potential targets to stop the progression?
• Agents and modalities
• What design paradigms should be employed?
• How are they to be analyzed?
Schizophrenia as a Disorder of Synaptic Spines - A Spinopathy

- The core deficit in schizophrenia: loss of dendritic spines, neuronal connectivity, and circuit integration
- Evidence of progression: decreasing brain volume from prodrome to chronic state in hippocampus as well as cortex. Reduction in gray matter underlies the smaller cortical and hippocampal volumes. Present in high risk individuals.
- Pyramidal cell volume is ~10% smaller in layer 3 of the DLPFC, auditory cortex.
- Treatment target is to preserve or restore spine number, function, and neurocircuitry dependent upon their integrity

Glausier and Lewis, Neuroscience 2013 215: 90-107 IBRO
Penzes et al. Nature Neuroscience 2011

干预
DLPFC Spine Density is Decreased in Some But Not All Patients with Schizophrenia

Atypical APDs, e.g. olanzapine, have been shown to restore cortical spines in scPCP-treated rats (Elsworth et al. Neuropsychopharmacology, 2011)

Heterogeneity in treatment response to atypical APDs is to be expected: critical issue is to identify treatment related improvement in subgroups of patients that could reflect disease modification

Fig. 2. (B) Scatter plot demonstrating lower layer deep 3 spine density in schizophrenia subjects relative to healthy comparison and psychiatrically ill subjects. (C) Within the same subjects, lower DLPFC spine density is specific to layer deep 3. Scale bar = 10 μm in A. Adapted from Lewis and Gonzalez-Burgos (2008).
The Glutamatergic Hypothesis of Schizophrenia: PCP or Ketamine Models

• Subchronic or acute phencyclidine and ketamine - better model for full schizophrenia syndrome than DA or 5-HT alone, especially cognitive impairment, positive and negative symptoms
  – Both are NMDA non-competitive antagonists
  – Given pre- or post-natally, or to adults, induce behaviors that are analogous to psychosis and cognitive impairment

• Potential cause of theta and gamma rhythm abnormalities in schizophrenia which are putative biomarkers for treatment response

• Collective genetic evidence that NMDA and AMPA receptors and signaling systems are risk factors is strong: e.g. SLC1A6, SLC1A2, GRIN1, GRIN2A, KAL-7, NRG1, ErbB4, DTNBP1, DAAO, G72/30, GRM3

• These proteins may be the required targets for improving CIAS
Phencyclidine-induced Loss of Asymmetric Spine Synapses in Rodent Prefrontal Cortex is Reversed by Acute and Chronic Treatment with Olanzapine

John D Elsworth*, Bret A Morrow†, Tibor Hajszen‡, Csaba Leranth‡ and Robert H Roth

1Laboratory of Neuropsychopharmacology, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; 2Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT, USA; 3Department of Biophysics, Biological Research Center, Hungarian Academy of Sciences, Szeged, Hungary

Figure 2

Loss of spines is persistent

Figure 3

Loss of spines can be prevented

Figure 4

Recovery of spines within 90 minutes

Figure 5

Neuropsychopharmacology (2011) 36, 2054–2061
Shaping synaptic plasticity: The role of activity-mediated epigenetic regulation on gene transcription

Javier Cortés-Mendoza, Sol Díaz de León-Guerrero, Gustavo Pedraza-Alva, Leopold Pérez-Martínez

The Psychosis Domain is Progressive In Some but Not All Who Meet Current Criteria

- Pre-prodrome
- Prodrome
  - 1st episode treatment-resistant
  - Chronic treatment-resistant
    - Chronic clozapine dependent
    - Remission, recovery
    - *(50-70% of 30%)*
  - 1st episode-DA dependent
  - Chronic DA dependent
    - *(10-20% of 30%)*
- Stable, recovery
  - *(70%)*

*(30%)*

*(10%)*
The Cognition Domain is Partially Progressive and Partially Responsive to Treatment with Atypical APDs

Direct and indirect (increased efflux of DA, NE, ACh, glutamate, BDNF) pharmacology of atypical APDs provides targets to ameliorate and prevent CIAS: 5-HT\textsubscript{1A}, 2A, 6,7, D1, D2, alpha 7, alpha 4 beta 2, M1, M4, BDNF
Atypical Antipsychotic Drugs Are Effective in Some Patients with Schizophrenia! or maybe not?

• Atypical antipsychotic drugs have been shown to have disease-modifying properties in some patients with schizophrenia.
• This hotly debated issue is critical because if it can be shown that they have this effect, we have a basis for going forward.
• If they are not effective, than the animal models we have which show their efficacy should be avoided.
• The basis for their heterogeneity, if they are effective, becomes a key target of research for novel treatments. Such heterogeneity has led to novel treatment for HIV infections and cancers.
Risperidone-induced Improvement in In Hallucinations and Delusions after 10 Years of Refractory Schizophrenia

Improvement in Working Memory During Risperidone

GAF Score doubled from 25 to 50

Recovery on Atypical APD: Case Report

Improvement in Executive Function During Risperidone

Improvement in Grey Matter Density in Subthalamic Nucleus and Anterior Cingulate after 6 Months Risperidone Const.

Meltzer et al. ACNP meeting 2012. Remission has lasted 3+ years

Anderson et al. ACNP 2011
Partial Improvement in Cognitive Impairment with Clozapine

Hagger et al. Biological Psychiatry 1994
# Improvement in Cognition With Clozapine, Olanzapine, Risperidone and Quetiapine: 20 Studies Summarized

<table>
<thead>
<tr>
<th>COGNITIVE CONSTRUCT</th>
<th>EFFECT SIZE</th>
<th>H&amp;K*</th>
<th>W,P,M,Z**</th>
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<tbody>
<tr>
<td>Verbal fluency</td>
<td>0.43</td>
<td>0.30</td>
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<tr>
<td>Secondary memory</td>
<td>0.39</td>
<td>0.46</td>
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<tr>
<td>Vigilance</td>
<td>0.39</td>
<td>0.34</td>
<td></td>
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<tr>
<td>Visuomotor skills</td>
<td>0.27</td>
<td>0.38</td>
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<tr>
<td>Spatial memory</td>
<td>0.20</td>
<td>0.35</td>
<td></td>
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<tr>
<td>Executive function</td>
<td>0.18</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Immediate memory</td>
<td>0.13</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

*Harvey and Keefe, Amer J Psychiatry 2001

**Woodward et al. Intl J Neuropsychopharmacology 2005
≥0.5SD Improvement in Speeded Motor Pursuit > Working Memory with Clozapine > Typical Neuroleptic Drugs

% Improvement From Baseline ≥ 0.05SD in DSST

% Improvement From Baseline ≥ 0.05SD in PRIM

Implications for future CIAS trials: Specific domains selected from POC studies should be primary end point(s) rather than composite scores
Adjunctive Varenicline Treatment with Antipsychotic Medications for Cognitive Impairments in People with Schizophrenia: A Randomized Double-Blind Placebo-Controlled Trial

Joo-Cheol Shim*1,2, Do-Un Jung1, Sung-Soo Jung3, Young-Soo Seo3, Deuk-Man Cho4, Ji-Heon Lee5, Sae-Woom Lee5, Bo-Geum Kong1, Je-Wook Kang1, Min-Kyung Oh2,6, Sang-Duk Kim7, Robert P. McMahon8 and Deanna L. Kelly8

*Corresponding author.

No overall significant differences between varenicline and placebo in 8 week trial in comprehensive neurocognitive battery

However, varenicline was superior to PBO in the DSST and WCST non-perseverative errors

Some CPT measures and Stroop interenence measures were superior for varenicline for smoker but not non-smokers.

Varenicline, an alpha 4 beta2 and alpha 7 nicotine AChR agonist, is able to acutely reverse the effect of scPCP in rats (Oyamada et al., unpublished)
Tardive Dyskinesia; A Cause of Cognitive Impairment which Minimized response to Atypical APDs

• **A disease modifying aspect of schizophrenia**

• After treatment with typical APDs, TD develops and with it cognitive impairment worsens
  – impairs response to atypical APDs and may occur with suppressed TD or subclinical TD

• Preventing TD by minimizing $D_2$ receptor blockade, prevents iatrogenic disease progression, by preventing damage to basal ganglia and preserving $D_2$ receptor stimulation in cortex and hippocampus
Treatment Outcomes of Patients With Tardive Dyskinesia and Chronic Schizophrenia

Stanley N. Caroff, MD; Vicki G. Davis, DrPH; Del D. Miller, PharmD, MD; Sonia M. Davis, DrPH; Robert A. Rosenheck, MD; Joseph P. McEvoy, MD; E. Cabrina Campbell, MD; Bruce L. Saltz, MD; Silvana Riggio, MD; Miranda H. Chakos, MD; Marvin S. Swartz, MD; Richard S. E. Keefe, PhD; T. Scott Stroup, MD, MPH; and Jeffrey A. Lieberman, MD, for the CATIE Investigators

**Results:** Changes in PANSS scores were not significantly different ($F_{1,974} = 0.82, P = .360$), but patients with TD showed less improvement in neurocognitive scores ($F_{1,359} = 6.53, P = .011$). Among patients with TD, there were no significant differences between drugs in the decline in AIMS scores ($F_{1,151} = 0.32, P = .811$); 55% met criteria for TD at 2 consecutive visits postbaseline, 76% met criteria for TD at some or all postbaseline visits, 24% did not meet criteria for TD at any subsequent visit, 32% showed a ≥50% decrease in AIMS score, and 7% showed a ≥50% increase in AIMS score.

<table>
<thead>
<tr>
<th>Measure</th>
<th>TD (n = 64)</th>
<th>Non-TD (n = 353)</th>
<th>TD vs Non-TD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Mean (SE)</td>
<td>Adjusted Mean (SE)</td>
<td>$F$</td>
</tr>
<tr>
<td>Cognitive composite (Z-score) change from baseline</td>
<td>0.06 (0.08)</td>
<td>0.27 (0.04)</td>
<td>6.53</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>-0.17 (0.12)</td>
<td>0.10 (0.06)</td>
<td>4.17</td>
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<tr>
<td>Working memory</td>
<td>0.14 (0.10)</td>
<td>0.18 (0.05)</td>
<td>0.14</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.10 (0.08)</td>
<td>0.26 (0.04)</td>
<td>3.69</td>
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<tr>
<td>Vigilance</td>
<td>0.10 (0.12)</td>
<td>0.31 (0.06)</td>
<td>2.47</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.09 (0.10)</td>
<td>0.22 (0.05)</td>
<td>1.41</td>
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</table>
Another Confound in the Literature on Cognitive Impairment with APDs: Concomitant Medication Effects

- Fluoxetine, but not venlafaxine, downregulates MAPK/ERK expression in the hippocampus, a key target for the NMDAR antagonists.
- Chronic fluoxetine but not venlafaxine decreased the activity of the phospho-ERK-2 pathway
- May be related to differences in enhancement of synaptic DA and NE levels
- DA may enhance memory through D_1 receptor stimulation which enhances glutamate release (Bouron and Retuer, 1999)
- D1 agonism is one of the mechanisms which restores cognition in scPCP-treated rodents
- CIAS trials should avoid polypharmacy and test augmentation with most promising combinations based upon NMDAR antagonist preclinical trials.

Benoit et al. Schiz Res 2014 (on line)
Lurasidone and clozapine reverse NMDAR hypofunction in the PCP model of schizophrenia

Yuen et al (Mol Pharmacol 2012 Feb;81(2):113-9s)
The enhancing effect of lurasidone on NMDAR-EPSC is mimicked by antagonism of 5-HT\textsubscript{7} receptors but not haloperidol.

Yuen et al. (Mol Pharmacol 2012 Feb;81(2):113-9)
SB269970 Prevents the Impairment in LTP Produced by Subchronic PCP-Disease Modification of a Spinopathy

No significant difference in LTP between WT (n=8 slices) & SB269970 + PCP (n=11)
- WT: 163 +/- 18%
- SB269970: 157 +/- 11%
- PCP: 114 +/- 6%

Significantly lower LTP in PCP (n=9) vs. WT or SB269970 + PCP
P<0.05, 1-way ANOVA with Tukey’s Post-Hoc test

TBS = Theta Burst Stimulation to induce LTP
10 bursts, delivered @ 5 Hz
5 stimuli/burst delivered at 100 Hz
Sub-chronic PCP Impairs Novel Object Recognition (NOR) in Female Rats

Discrimination Index (DI) = (Novel – Familiar times) / Total exploration time

Snigdah et al. JPET 2010
Microdialysis+NOR study in Mice

**NOR (N=7)**

<table>
<thead>
<tr>
<th>NOR (N=7)</th>
<th><strong>Left</strong></th>
<th><strong>Right</strong></th>
<th><strong>Familiar</strong></th>
<th><strong>Novel</strong></th>
</tr>
</thead>
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<td><img src="image1.png" alt="Graph" /></td>
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<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
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</tbody>
</table>

**ACH**

**DA**

**5-HT**

**Glu**

**NE**

**GABA**

**mPFC (N=7)**

**HIP (N=7)**

**Microdialysis+NOR**

**Housing baseline**

**AE**

**Housing**

**Test**

**Housing**
Lurasidone, an Atypical Anti-psychotic Drug, and Tandospirone, A Selective 5-HT$_{1A}$ Partial Agonist, Restore Novel Object Recognition in Sub-Chronic PCP-Treated Female Long-Evans Rats

1: Vehicle + Vehicle
2: Subchronic PCP + Vehicle
3: Subchronic PCP + Lurasidone (0.1)
4: Subchronic PCP + Tandospirone (0.6)
5: Subchronic PCP + Haloperidol (0.1)

The Triple Combination of Pimavanserin, A 5-HT$_{2A}$ Inverse Agonist, A Subeffective Dose of Tandospirone, A Selective 5-HT$_{1A}$ Partial Agonist, and Haloperidol, a D$_2$ Antagonist Restore Novel Object Recognition in Sub-Chronic PCP-Treated Female Long-Evans Rats

1: Vehicle + Vehicle
2: Subchronic PCP + Vehicle
3: Subchronic PCP + PIM (3) + TAN (0.2) + HAL (0.03)
4: Subchronic PCP + PIM (3) + TAN (0.2) + HAL

Oyamada, Horiguchi and Meltzer, in preparation
The Triple Combination of Pimavanserin, A 5–HT$_{2A}$ Inverse Agonist, A Subeffective Dose of Tandospirone, A Selective 5–HT$_{1A}$ Partial Agonist, and Haloperidol, a D$_2$ Antagonist PREVENT IMPAIRMENT IN Novel Object Recognition in Sub–Chronic PCP–Treated Female Long–Evans Rats

**Discrimination Index**

1: Vehicle + Vehicle
2: Subchronic PCP + Vehicle
3: Subchronic PCP + LUR (1)
4: Subchronic PCP + HAL (1)
5: Subchronic PCP + PIM (3) + TAN (0.6) HAL (0.1)

DI **p<0.01  ###p<0.001  ##p<0.01  p<0.05 vs subchronic PCP

Horiguchi et al. 2011; Oyamada et al. in preparation
Epigenetics and Experience

• Stress exacerbates effect of PCP on rodent models of CIAS while environmental enrichment ameliorates the PCP-induced deficit
• May be model for cognitive remediation, social support, assisted work
• May enhance epigenetic mechanisms which affect gene expression
Agents and Modalities

• Targeting synaptic proteins: pre- and post-synaptic, especially post-synaptic density
• Specific mechanisms that fine tune key neurotransmitters and growth factors
• Glutamate, GABA, serotonin, acetylcholine, dopamine, trace amines,
• Growth factors: BDNF, VGF, etc
• Signaling mechanisms: e.g. ERK, Map-kinase
Reasons Why Clinical Trials For Cognitive Enhancement after Sometimes Failed or Shown Small Effect Sizes

- Adjunctive treatments added to patients treated with the full range of psychotropic drugs except clozapine
- Exclusion of clozapine
- Inclusion of patients regardless of duration of illness and tardive dyskinesia – manifest, masked, latent
- Use of composite scores for primary endpoint
- Insufficient duration of treatment
- Failure to appreciate inverted U-shape dose response curve
- Absence of pharmacogenetic markers
- No consideration of interaction with epigenetics-experience
- Primary focus on group means rather than response at a rate beyond practice effect
- Absence of withdrawal studies to show efficacy
What Design Paradigms Are to Be Employed-

• Test presumptive treatments to prevent progression of high risk, mildly cognitively impaired prodromal individuals, preferably drug free and prior to psychosis
  – Blinded, randomized RCT with one or more putative treatments and placebo arm

• Non-D2 antagonist, based drugs which prevent the development of subchronic PCP-induced impairment in rodent or primate cognitive domains.

• E.g. TPA023, tandospirone, 5-HT7, 5-HT6 antagonists amisulpride
What Design Paradigms Are to Be Employed-II

• Prevention of development of neuroleptic resistance
  – Failure of positive symptoms to respond to typical neuroleptics develops in ~20% of schizophrenic patients
  – No comparable information is available for patients treated solely with atypical antipsychotic drugs
  – Assuming it occurs at the same rate or less, it would be of interest to set a goal of preventing the development of treatment resistance in patients treated with atypical antipsychotic drugs.
  – Epidemiologic evidence in a country such as Finland might yield information that would lead to controlled studies
Specific Therapeutic Strategies for Developing Treatments for Disease Progression in Schizophrenia

• How are efficacy results to be analyzed and what might an indication look like?

  Validate within subject improvement by on-off blinded studies, being sensitive to the possibility that restoring efficacy once lost may be difficult to achieve

  Obtain genetic, biochemical, EEG, imaging markers for efficacy.

  For augmentation agents, consider approval of use with specific antipsychotic drugs
Conclusions

• Schizophrenia is progressive and heterogeneous
• The focus of treatment should be on CIAS, and CIAS, may best be treated early in life. However, limited, later in life improvement is possible.
• Tardive dyskinesia and concomitant meds may reduce response to putative antipsychotics, including atypical APDs.
• Subchronic effects of NMDAR antagonists, e.g. PCP, may be the best model we have for developing treatments for, or prevention of, CIAS, because it targets spines and circuits involved in CIAS.