Promising Treatments for Cognitive Impairment

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The Promise of Drugs for Cognitive Impairment
Several pro-cognitive drugs are being developed, and are currently in various review stages by the FDA.
These new drugs have the potential to alter the outcome of many psychiatric disorders. They will offer new choices but also raise new challenges for the patient, their families and clinician, and our society.
Historically Speaking

- In the sixties, outcome in schizophrenia was thought to correlate with the severity of positive symptoms.
- In the seventies and eighties, researchers recognized the importance of negative symptoms, and felt that outcome correlated much more with negative symptoms than positive symptoms.
Since the nineties, and progressively more in the last decade research has outlined the magnitude of cognitive impairment in schizophrenia and its huge impact on functional outcomes.

However it’s not a panacea!
Neurocognitive Impairment in Schizophrenia
Why don’t we readily see the neurocognitive impairment in schizophrenia?

A: Use the cardiac stress test analogy.
Coronary Ischemia – Inadequate Oxygen Supply to the Heart - Silent at Rest but Noticeable During High Demand
Is the neurocognitive impairment of schizophrenia global or selective?

A: Mostly global but some areas appear to be affected more than others.
Is there a single specific neurocognitive impairment specific to schizophrenia?

A: No
Cognition in Schizophrenia: Core Feature of the Illness

• Present before onset of clinical symptoms
• Seen in unaffected first-degree relatives
• Relatively stable across clinical state; life span until late adulthood
• Low cross sectional correlations w/ psychotic symptoms
• Discrepancy between clinical and cognitive effects of antipsychotic meds
• Schizophrenia profile of deficits (w/ variation)
Cognitive Impairment Magnitude in Schizophrenia

Meta-Analysis; 204 studies, 7420 patients and 5865 controls

Characteristic profile in schizophrenia: maximal impairment in memory, attention, and executive function; relative preservation of old learning and visual perceptual skills.

- SD Units:
  - Dig Span
  - Vocab
  - Block Des
  - WCST
  - Trails B
  - CPT
  - Fluency
  - Vis Mem
  - Verb Mem

Healthy Comparison Mean

Heinrichs & Zakzanis
Neuropsychology 1998
Alzheimer’s Dementia compared with Schizophrenia Neuropsychological Deficit Scores

Alzheimer’s Disease: substantial impairment in memory retention relative to schizophrenia

From Heaton et al. (1994)
Key Cognitive Domains for Schizophrenia
From NIMH-MATRICS Consensus Process

1) Speed of Processing
2) Attention / Vigilance
3) Working Memory
4) Verbal Memory
5) Visual Memory
6) Reasoning and Problem Solving
7) Social Cognition
Cognitive Domain: Verbal Learning

**Definition:** Ability to acquire, store, and retrieve verbal information for more than a few minutes.

**Example:**
Hopkins Verbal Learning Test – Revised

**Activities of daily living:**
remembering information from a rehabilitation program, class, vocational setting, clinic visit

- CANARY
- SHOES
- EAGLE
- BLOUSE
- NAILS
- CROW
- BLUEBIRD
- SCREWDRIVER
- PANTS
- CHISEL
- SKIRT
- WRENCH
Cognitive Domain: Working memory

**Definition**: Ability to hold information “on line” in a temporary store and/or to manipulate the information

**Example:**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Number</th>
<th>Span</th>
</tr>
</thead>
<tbody>
<tr>
<td>K3B4</td>
<td>_ _ _ _</td>
<td></td>
</tr>
<tr>
<td>R8C3G5</td>
<td>_ _ _ _ _</td>
<td></td>
</tr>
</tbody>
</table>

**Activities of daily living**: carrying on a social conversation; switching between different tasks
Cognitive Domain: Attention / Vigilance

**Definition:** Ability to respond to targets, not respond to non-targets, over a period of time

**Example:** Continuous Performance Test – Identical Pairs

"Press when you see the same number twice in a row"

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Response</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>254</td>
<td>hold</td>
<td>1 sec</td>
</tr>
<tr>
<td>364</td>
<td>hold</td>
<td>100 ms</td>
</tr>
<tr>
<td>743</td>
<td>hold</td>
<td></td>
</tr>
<tr>
<td>743</td>
<td>press</td>
<td></td>
</tr>
</tbody>
</table>

**Activities of daily living:** identifying relevant information in a social interaction; discussion with a doctor
We mortals cannot read other people’s minds directly. But we make good guesses from what they say, what we read between the lines, what they show in their faces and eyes, and what best explains their behavior.

*It is our species’ most remarkable talent.*

Steven Pinker
Measurement for Social Cognition in Schizophrenia

1. Still Faces affect perception
2. Filmed vignettes identifying social situations or emotions
3. Written vignettes
   - Theory of Mind, social knowledge, attributional bias, emotion management
4. Other methods: e.g., jumping to conclusions, role plays
Cognition and Functional Outcome in Schizophrenia

- Cognitive deficits are reliable correlates and predictors of functional outcome (disability)
- Functional outcome includes: work outcome, social outcome, independent living, & skills acquisition
- Magnitude of associations: medium for specific domains; large for summary scores
- Relationships are stronger than between psychotic symptoms & functional outcome
- Cognitive deficits are linked to success in psychiatric rehabilitation
NIMH – MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia)

Goals and Products

• Create Standardized Measure for use in Clinical Trials
• Define Optimal Experimental Designs
• Establish path to FDA Approval
• Attract large pharmaceutical companies to focus efforts on this important clinical target
• Success required involvement of: NIMH, FDA, pharmaceutical industry, and academia

www.matrics.ucla.edu
In Summary

• Functional outcome in schizophrenia is generally poor and the level of disability is generally high.

• Cognitive impairments are key determinants of poor functional outcome in schizophrenia.

• The cognitive impairments of schizophrenia:
  - Are core features of the illness
  - Can be reliably measured
  - Are not well-treated by any current medications

• There is considerable activity to develop new treatments for cognitive impairment and recovery-focused approaches -- but for now, outcome remains disappointing.
Is there clear evidence that novel antipsychotic medications improve neurocognitive functioning in schizophrenia?

A: No, usually several confounding variables prevent any reliable conclusions from available studies.
Confounding Variables

- Pharmacological Status at baseline
- Multiple Study Arms
- Double-Blind Methodology
- Duration of Trial
- Dosing Strategies
- Neurocognitive Test Batteries
- Discrimination Between Cognitive Enhancement and Other Clinical Changes
Cognitive Impairment is Present Across Various Psychiatric Conditions

- Schizophrenia
- Bipolar Disorder
- Major Depression
- Alzheimer's Disease
Effect Sizes of Cognitive Deficits in Schizophrenia, Affective Psychoses, and Euthymic BD.

Bora E et al. Schizophr Bull 2009;36:36-42

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Figure 1. Significant differences between groups in social cognition tasks.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0057664
Prevalence of Cognitive Impairment in Schizophrenia, Affective Psychoses, and Euthymic BD.

Percentage of patients with cognitive impairment

Bora E et al. Schizophr Bull 2009;36:36-42
The MATRICS Consensus Cognitive Battery:

- What We Know 6 Years Later

- Michael F. Green, Ph.D.; Josette G. Harris, Ph.D.; Keith H. Nuechterlein, Ph.D.
The MCCB tests were selected for high test-retest reliability (reliability of the overall composite score was 0.90 in the initial validation study). This value has been consistently found in multisite clinical trials. For example, the reliability was 0.88 in the 29-site study mentioned above (8) and has been even higher (0.93, 0.95) in other published clinical trials (9, 10).
After 2 years of large consensus meetings, a five-site psychometric and validation study, complex intellectual property agreements, and an endorsement by NIMH and the U.S. Food and Drug Administration (FDA), the MATRICS Consensus Cognitive Battery (MCCB) was initially presented in a series of three articles in 2008 (1–3).
Since then, the MCCB has been evaluated and scrutinized in a way that few test assessment batteries have been. Over time its strengths and limitations have come into sharper focus, and we believe it is a good time to review what we know about the MCCB 6 years later.
The MATRICS initiative was designed to address a particular issue—the FDA was previously unwilling to approve a drug for enhancing cognition in schizophrenia without consensus on domains, measurement, and study design (4, 5).
The overarching goal of MATRICS was to construct a pathway for drug approval in this area. Identifying consensus cognitive domains and developing a consensus battery were part of the broader MATRICS agenda that included agreement on study design, subject selection, neuropharmacological targets, and government-industry interactions.
The first step was to agree on cognitive domains that should be represented in schizophrenia treatment trials (7) and then to select tests at the domain level on the basis of a priori criteria. It was hoped that the MCCB would behave well in clinical trials, but that was an educated guess at the time.
Research conducted since then supported the test qualities of the MCCB when used in multisite clinical trials, its sensitivity to treatment effects, and its covariation with biomarkers.
The MCCB tests were selected for high test-retest reliability (reliability of the overall composite score was 0.90 in the initial validation study). This value has been consistently found in multisite clinical trials. For example, the reliability was 0.88 in the 29-site study mentioned above (8) and has been even higher (0.93, 0.95) in other published clinical trials (9, 10).
Numerous studies have examined the MCCB’s sensitivity to treatment effects. The published results have been most impressive for the cognitive training interventions, and results are now also emerging for psychopharmacological interventions.
The MCCB was sensitive to the cognition-enhancing effects of 50 hours of neuroplasticity-based auditory training when compared with a control condition (11).

A more recent publication with 40 hours of neuroplasticity-based training in recent-onset patients similarly found improvements in the MCCB (12).
The MCCB was sensitive to the effects of a cognitive remediation program in a multisite feasibility study. The effects were significant at the midpoint assessment, relative to the effects of a control condition, and showed a nonsignificant tendency at the end of the study, when the sample size was smaller (13).
A clinical trial with patients in a partial hospital program showed that the MCCB reflected improvements with attention-shaping procedures versus a control condition in these low-functioning patients (16).
Transcranial direct current stimulation showed significant improvement on the MCCB composite, when compared with a sham control condition (17).
In a study with an α7 nicotinic partial agonist, beneficial results were at the trend level on the MCCB composite for the entire sample, and effects were significant for patients who were retested at the same time of day as they were tested at baseline and for patients who were age 45 years or less (18).
The MCCB showed significant beneficial effects of add-on sodium benzoate therapy (a d-amino acid oxidase inhibitor) when compared with placebo. This study focused on the MCCB neurocognitive composite (composite of all of the domains except social cognition) (19).
A study with an α7 nicotinic agonist demonstrated a significant group-by-smoking interaction, in that nonsmoking patients showed a significant improvement on the MCCB neurocognitive composite that was larger than the effect in smoking patients (20).
Biomarkers of MCCB Performance

- Therapeutic development for cognitive deficits in schizophrenia is greatly facilitated if we can identify biomarkers to determine whether the therapeutic candidates elicit their targeted biological effects. Two studies illustrate the utility of the MCCB in this regard.
In a study using magnetic resonance spectroscopy, NAA/Cr correlated with the composite MCCB score (r=0.52), as well as with scores for the domains of attention/vigilance, verbal learning, and social cognition (21).
Right hippocampal fMRI hyperactivity identified in patients with schizophrenia was associated with lower MCCB composite scores ($r=0.53$). Exploratory analyses revealed the effect was driven by associations between activity and attention/vigilance, working memory, and visual learning (22).
Summary: Cognitive difficulties experienced by people with schizophrenia

- Speed
- Memory
- Attention
- Reasoning
- Tact/Social cognition
- Synthesis
Pharmacological Treatments for Cognition

Effect Size (Cohen's $d$)

- Antipsychotics (Keefe et al., 2007)
- d-Cycloserine (Buchanan et al., 2007)
- Glycine (Buchanan et al., 2007)
- Galantamine (Buchanan et al., 2008)
- Practice Effect (Goldberg et al., 2007)

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Rate of accumulation of information on therapies

Cumulative information on psychological therapies

- Family Therapy
- CBTp
- CRT
The DRUGS

Because the etiology of schizophrenia is not clearly decoded, the treatments for schizophrenia are to some a long sequence of trial and error based on many different theories regarding the underlying mechanisms.
The DRUGS

Table 1. Agents Studied as Adjuncts to Antipsychotics for Negative Symptoms and/or Cognitive Impairment in Patients With Schizophrenia

<table>
<thead>
<tr>
<th>Acetylsalicylic acid and nonsteroidal anti-inflammatory agents</th>
<th>Anticonvulsants and lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Antiglucocorticoids</td>
</tr>
<tr>
<td>Agents used to treat attention-deficit/hyperactivity disorder</td>
<td>β blockers</td>
</tr>
<tr>
<td>Cholinesterase inhibitors and other agents used to treat Alzheimer’s disease</td>
<td>Experimental agents that act on glutamate receptors</td>
</tr>
<tr>
<td>GABAₐ receptor drugs</td>
<td>Neurosteroids and hormones</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Opioid system agents</td>
</tr>
<tr>
<td>Peptides</td>
<td>Purinergic agents</td>
</tr>
<tr>
<td>Serotonin 5-HT₁ₐ receptor agonants</td>
<td>Serotonin 5-HT₃ receptor antagonants</td>
</tr>
<tr>
<td>Wakefulness promoting agents</td>
<td></td>
</tr>
</tbody>
</table>

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Abbreviation: GABA = γ-aminobutyric acid.
Acetylcholine Receptors

- Acetylcholine receptors comprise two major families, nicotinic and muscarinic receptors; evidence implicates deficits of both families in schizophrenia.\(^{10}\)

- Following up on epidemiological studies\(^{11}\) of the high percentage of schizophrenia patients who smoke tobacco (60% to 90%), the role of alpha-7 nicotinic acetylcholine receptors (\(\alpha_7\) nAchR) has been explored. Nicotine itself might normalize some disrupted auditory processes, as measured by electroencephalography.\(^{12}\)
EVP-6124 and TC-5619

Several clinical trials of partial α7 nAChR agonists have been conducted, with EVP-6124 and TC-5619 furthest along in development.
Encenicline (EVP-6124)

• EVP-6124 is hypothesized to work through a completely different mechanism of action than discussed here so far. Encenicline is a selective α-7 nicotinic acetylcholine receptor (N-A7A) agonist. N-A7A receptors are located in several brain areas involved in cognitive domains including attention and long-term and working memory.

• The procognitive effects of encenicline (0.3 mg/d or 1 mg/d) were tested in an 84-day, phase 2 randomized controlled trial in 319 patients with chronic stable schizophrenia taking antipsychotics other than clozapine. The 0.3-mg/d dose of EVP-6124 had a positive effect on global cognitive function and on functionality, as well as on the PANSS negative symptom subscale.
EVP-6124 was well tolerated with no clinically significant findings on electrocardiograms, vital signs, hematology, and serum chemistry evaluations. The most commonly reported adverse events were headache, nausea, and nasopharyngitis.32
This partial α7 nAchR also showed positive results recently in a Phase II trial. Significant ($P < .05$) improvement was demonstrated in executive function in the Groton Maze Learning Task of the CogState Schizophrenia Battery and the Scale for Assessment of Negative Symptoms.\textsuperscript{14}

Strong anatomic links also exist between muscarinic acetylcholine receptors and the brain dopaminergic system, especially muscarinic type-1 and type-4 (M1 and M4) receptors. The potential utility of an M1, M4, or combined M/M4 agonist is also supported by studies of M1 and M4 knockout mice, with particular evidence of cognitive enhancement with the use of M1 agonists.\textsuperscript{15}
Administration of the M1 allosteric agonist GSK1034702 to healthy human smokers, using the nicotine abstinence model of cognitive dysfunction, resulted in improvements in immediate recall.\textsuperscript{16}
In a small pilot study of 20 schizophrenia patients, xanomeline, a mixed M1/M4 agonist, demonstrated significant improvements in verbal learning, short-term memory, and overall symptoms.\textsuperscript{17}
Dopamine Receptors

- All marketed antipsychotics block the dopamine type-2 (D2) receptor\textsuperscript{18}; they are primarily effective on positive symptoms.\textsuperscript{4} In contrast, a role for the dopamine type-1 (D1) receptor in cognition is suggested by studies that demonstrate reduced D1 and $N$-methyl-d-aspartate (NMDA) glutamate receptor function in the prefrontal cortex.\textsuperscript{19-22}
Glutamatergic receptors

- Intoxication with NMDA antagonists (such as phencyclidine and ketamine) yields a phenotype with similarity to schizophrenia.\(^\text{25}\) More than 20 years of research has provided evidence for the role of glutamatergic NMDA receptors in the pathophysiology of schizophrenia.\(^\text{26,27}\)
NMDA receptors are distributed widely in the brain, but specific glutamatergic processes are localized to areas that are associated with cognition. This relative distribution provides a convenient framework from which to view the pattern of cognitive dysfunction associated with schizophrenia:
• NMDA receptors in the prefrontal cortex contribute to development of executive processing
• NMDA receptors in the hippocampus are involved in learning and memory acquisition
• NMDA receptors in the visual cortex and auditory cortex are fundamental for auditory and visual sensory memory.

• Previous reviews of ketamine administration have described cognitive deficits in healthy control subjects, comparable to what is seen in schizophrenia. The deficits are noted primarily in measures of executive functioning, attention/vigilance, verbal fluency, and visual and verbal working memory.
Ionotropic Glutamate Receptors as Treatment Targets
Instead of providing exogenous glycine or an analog of glycine, an alternative therapeutic option is to increase the availability of endogenous glycine through glycine reuptake pump inhibition. The glycine transporter type 1 (GLYT1) reuptake pump is the major root of inactivation of synaptic glycine. Several GLYT1 pump inhibitors exist, such as the natural agent N-methyl-glycine, also called sarcosine, as well as drugs in clinical development.
The action of GLYT1 inhibitors is analogous to that of drugs that inhibit reuptake of other neurotransmitters, such as selective serotonin reuptake inhibitors. Glycine is not known to be synthesized by glutamate neurons, meaning that glutamate neurons must obtain glycine from glycine neurons or from glial cells. When the reuptake pump on the glial cell is blocked, more glycine is available in the synapse, increasing the potential activity of the NMDA receptor.
D-Serine

- A meta-analysis\textsuperscript{24} showed that glycine and d-serine adjunctive to antipsychotics demonstrated improvements in multiple symptom domains in patients with schizophrenia, while d-cycloserine did not. In particular, adjunctive d-serine with risperidone or olanzapine was statistically superior to placebo for negative symptoms. Of note, those receiving clozapine did not improve with these adjunctive treatments.\textsuperscript{24}
Sarcosine

- Sarcosine, a GLYT1 inhibitor, has been tested as monotherapy in antipsychotic-naive patients with schizophrenia and appeared to reduce symptoms with minimal side effects.\(^{25}\) In a meta-analysis,\(^ {24}\) sarcosine augmentation with antipsychotics improved multiple symptom domains compared with placebo, with the exception of patients who were receiving clozapine.
Bitopertin.

- A novel glycine-transport inhibitor, bitopertin, showed significant improvement in negative symptoms as an adjunctive treatment in a large Phase II trial. In the “per protocol” population (ie, patients who completed 8 weeks of treatment without any major protocol violations [n = 231]), negative symptoms diminished to a significantly ($P < .05$) greater degree from baseline in the 10 mg/d and 30 mg/d dosage groups, compared with placebo. Phase III studies of bitopertin are ongoing (www.clinicaltrials.gov/ct2/show/NCT01192906).
Bitopertin

- Is a highly selective and potent glycine transporter type 1 reuptake inhibitor that increases synaptic glycine levels and thereby facilitates NMDA-channel opening. Excessive calcium influx through the NMDA-gated channel can be neuroxotic—a risk that is counterbalanced by several safeguards that may complicate this therapeutic approach. For example, activation of the glycine site results in downregulation of the NMDA receptor by endocytosis.\(^7\) In addition, an endogenous antagonist at the glycine site, kynurenic acid, competes with glycine and D-serine in the modulation of glutamatergic signaling.
Bitopertin Disappoints as Schizophrenia Treatment

Medscape

Jun 16, 2014 - News for bitopertin as a possible treatment for schizophrenia is disappointing, as 5 of 6 phase 3 studies have been discontinued for not .
D-serine

Direct evidence of a cognitive benefit of glutamatergic-based drugs is limited. In a recent large, multicenter study, low dosage D-serine (~30 mg/kg/d) did not separate from placebo, but an open-label study suggests increased efficacy with dosages >30 mg/kg/d. In addition to symptomatic improvements, a highly significant, large effect-size improvement was seen for overall cognition for dosages ≥60 mg/kg/d, leading to a significant dose-by-time interaction (P < .01).
25 Currently Open, Placebo Controlled Registered Trials

- Anti-inflammatory Combination Therapy | Drug: Placebo
- Interventions: Cannabidiol CR
- Amisulpride | Drug: Olanzapine | Drug: Quetiapine | Drug: Risperidone
- Interventions: Drug: Curcumin
- Interventions: Drug: DAR-0100A
- Interventions: Drug: Donepezil
- Interventions: Drug: D-serine
- Interventions: Drug: Eltoprazine
Eltoprazine

Eltoprazine is a 5HT1a/1b partial agonist small molecule drug candidate originally developed by Solvay, S.A. (now Abbvie) with positive human clinical data produced in a Phase 2a trial for the treatment of LID associated with PD, Attention Deficit Hyperactivity Disorder and Cognition. Eltoprazine has been evaluated in a number of neurology-focused indications and has a well-established safety profile, having been administered to over 700 patients to date.
Drug: EVP-6124
Drug: EVP-6124 | Drug: Placebo
Drug: EVP-6124 | Drug: Placebo
Drug: Galantamine | Drug: Galantamine or Placebo
Drug: iomazenil
Drug: LY500307
Drug: Memantine
- Ondansetron
- Simvastatin
- Galantamine
- Roflumilast
Varenicline
Varenicline|Drug:
Vitamin D3|Drug:
Gluten Free Flour|Other:
Wheat Flour
Caveat !!!!!!!!!!!!!!!!

- ACE- Inhibitors for AD
- Cost a lot
- Provide little relief
- Delayed progress