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Atypical Antipsychotics and Cognitive Enhancement in Schizophrenia: The Current Status

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Atypical Antipsychotics and Cognitive Enhancement in Schizophrenia: The Current Status

Year 2007

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Regional Mental Health Care, St. Thomas.
From institutionalization to vocational independence

July 1992, Clozapine

Pierre Daniker
1917-1998
Chlorpromazine
1952
Progress in Cognition and cognitive neurosciences of schizophrenia

- Schizophrenia A Brain Disease
- ‘Mindless Brain’
- ‘Brainless Mind’
- Cognitive Theories; theories of Organization
- Cognitive Behavior Therapy in Schizophrenia
- Neuroimaging Correlates of Neuropsychological Deficits

Processing external stimuli, executive memory and cognition.
• Why are we talking so much about Cognition now a days.
• 85% prevalence of cognitive symptoms, while Delusions and hallucinations are seen in only 40%
• Fact that these are fairly stable, &
• Correlation to Outcome
<table>
<thead>
<tr>
<th>Kraepelin: adopted the term dementia praecox for a condition characterized by early psychosis and cognitive deterioration</th>
<th>The perceived importance of cognition in schizophrenia has since waxed and waned</th>
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<tbody>
<tr>
<td>Bluer though emphasized on disconnection between affect, thought and perception, still viewed cognitive deficit as integral to disorder</td>
<td>Kraepelin’s Cognitive and negative symptoms were overshadowed by positive symptoms</td>
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<td>RDC DSM iii &amp; iv all emphasized on PS and Cognition is still not included in criteria</td>
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Research in schizophrenia is at a stage where it has been irrefutably demonstrated by a host of workers that the key factor for social deficit, impairment, dysfunction and disability in schizophrenia is the problem particularly associated with cognitive set and consequences of neurodevelopmental process.

A renewed interest in cognition was seen recently, spurred by strong empirical relationship between cognition and real world functioning.

Outcome Status

- 10% of all patients with schizophrenia work full time
- Only 1/3 ever work part time
- Fewer than 10% of male patients have a child
- Self-care deficit is reflected in high rates of medical morbidity
‘Several studies have failed to demonstrate positive correlation between positive symptoms and functioning’

Change In QLS Total Score With Change in Memory Function - Positive Linear Correlation; Buchanan RW et al Biol.Psychiatry 1994;36
Impaired Cognition as a Core feature of schizophrenia and Cognitive symptoms lack Correlation with Positive symptoms and severity, suggesting its independence

- Individual reports that cognitive decline exists in schizophrenia started appearing early 1980; first was in 1977 by Cohen et al.

- The largest meta analysis for schizophrenia till date by Heinrichs and zakzanis 1998 established a performance lower by 0.46 to 1.46 SD.

- Explanation --- non disease factor, EPS, Medication etc.

- All these were done on chronic patients, severely de-compensated, institutionalized... reports were not taken seriously.
Magnitude of Cognitive Deficits 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.

Lar...ge number of studies consistently indicated benefit of Cognitive enhancement to outcome and continue to raise our expectation.
1994-Saykin et al, Philadelphia, Archives - the first reliable report for neuropsychological deficit in neuroleptic naive first episode patients

1996 Meltzer wrote about ‘cognition schizophrenia and atypical antipsychotics’

By 1998 a correlation was established by imaging studies between cognitive decline, N-P Dysfunction, behavioral measures and neuroanatomical changes

by 2000/2001 concept of cognitive dysfunction and its contents was fairly established and various thought disorders seen in schizophrenia were explained by this theory like: cognitive neuropsychiatric model of persecutory delusions by Backwood et al 2001 AJP
Prevalence: how many patients show this deficit

Distribution of Total Score onRepeatable Battery for Assessment of N-P status Randolph et al: Shift by 2 SD

left side shift by 20%
Where is the lesion and what is the deficiency

- 2002 hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. AJP Csernansky et al

- 2003 Neuronal correlates of episodic encoding and recognition of words in unmedicated patients during acute episode. Hofer et al, AJP

- 2003 Diagnostic specificity and neuroanatomical validity of neurological abnormality in first episode psychosis

- Memory and executive function
It has been further demonstrated that this cognitive change (dys-function or deficit) is the one which settles not only in early course of pathogenesis in adolescence and early adulthood, but may have originated during the prodromal phase of the illness in the individuals who are at-risk.
• Impaired Cognition is not an epiphenomenon of clinical symptoms.

• Some studies have reported normal cognition in a significant number of people.

• 80-90% of twins with schizophrenia scored below their unaffected twins on N-P tests.

• 98% of people with schizophrenia performed below the level predicted by estimates of their premorbid functioning.

• Several Studies have now demonstrated that Cognitive deficits occur in first episode of schizophrenia patients who have never taken antipsychotics.
Unlike Schneider’s first rank Symptoms
Cognitive symptoms Correlate highly with measures of functional outcome

Overwhelming evidence of cognitive deficit has spurred USA NIMH to target such deficits by pharmacological interventions (MATRICS)

Separate domain of deficit Vs generalized deficit
This debate has implication for etiology:

Whether the underlying brain abnormalities are local or global?
Antipsychotics and Cognitive Enhancement

Schizophrenia

Conventional APD
Diminish Cognition

Atypical brought the euphoria of enhancement

Latest Data: gain from atypical are marginal. For enhancement we need to look somewhere else

Conventional APD
Do not enhance cognition

Effect Sizes

Global cognitive index

0
0.125
0.250
0.375
0.500

clozapine

Olanzapine

Risperidone

Quetiapine

All AAPD Combined

A meta-analysis of 46 recent studies for N-P Change to clozapine, olanzapine, quetiapine, and Risperidone in schizophrenia; Woodward et al, Int J Neuropsychopharm.2005
CONCLUSION: Adjunctive treatment with risperidone for 6 weeks in patients with schizophrenia who had received chronic treatment with clozapine does not significantly improve cognitive function.

1985, Historical Clozapine Studies started bringing in the concept ‘reversibility’ of Cognition by H.Y.Meltzer et all and other groups.

- 2006 DB study of combination of clozapine with risperidone....: effects on cognition...J Cl. Psychiatry, Dec. 2006
Predictive Validity

Cognitive predictors of change in employment at 12 Month - clozapine study

*\(p < .05\), **\(p < .01\), ***\(p < .001\)

Remains Unemployed
None to Employed

Schizophrenia Bulletin 1999

Cognitive status and employment in schizophrenia
California Verbal Learning Test

CVLT

Long Delay - Free Recall (mean \(\pm\) SD)

\(\text{McGurk SR, Meltzer HY. Schizophrenia Res. 2000;45:174-184}\)
Cognitive Change and Symptom Correlations

- Symptoms e.g. thought disorder* & insight*
- Only negative symptoms***
- Global symptoms
- Duration of untreated psychosis***
- Severity dimension
- Chronicity dimension
- Demography

Correlations were established by sophisticated imaging, observing: neuronal loss, recovery, anatomical positions and functional pathways, establishing direct link between ‘brain-lesions’ and functional outcome, providing valid arguments to look into the brain more and more by pharmacological probes
Symptoms & Cognition as predictors of Community Functioning

Symptoms after optimal treatment are better predictors as compared to Symptoms during acute episode
Symptoms (disorganisation < psychomotor << reality distortion) were more predictive than neurocognition

Ross Norman, Ashok Malla, AJP, 1999

Some doubts were also raised.
Cognitive deficit and functional outcome

Effect Sizes (Cohen’s r) Strength of Relationship
Results from four different Meta-analysis

- Significant improvement in cognitive function
- Better work performance
- Better social function
- Better social skills
- Better coping with stress
- Hope!

Green MF et al, Schizophrenia Bull. 2000;26
Cognitive Enhancement

- Cognitive enhancement at different illness phases
- Comparison of Conventional and atypical antipsychotics effect on cognition - three different trials


Cognitive enhancement at different illness phases

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>6 months</th>
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<tr>
<td>Olanzapine</td>
<td></td>
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<tr>
<td>Ziprasidone</td>
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Normatively derived Effect Size units

Global Change in Effect Size

- Keefe
- Harvey
- Bilder

First Episode
Refractory
Three different trials
**The Evidence of Reversibility**

**Olanzapine better than Haloperidol**

*DB trial in the treatment of primary negative symptom and neurocognitive deficits in schizophrenia - JCP, J.P.Lindenmayer, 2007, March*

- Neuropsychological results: significant differences in change from baseline to end point for the olanzapine-treated group were seen for
  - A} declarative verbal learning memory (F= 11.499, df=1,14; p=0.021) &
  - B} Motor functioning domain (F= 4.405, df=1,31; p=0.044).

![Chart showing P-values for difference between treatments](chart.png)
The First Episode:  
the paradox and the new hope

- 90% of FEP experience remission at the end of one year of treatment
- At 5 years follow up 80% had a job
- 80% had a relapse, of that 80% most had second relapse
- Predictors of outcome do not correlate with psychotic/remitted status
Recent Studies

- RSP v QP, NS 6, 12 wk. EURAch. Psych 1 Ns, July 07. QP better. Reidel.
- OLN v QP, Acute 4, 8 wk. JCP. July 07. QP better.
- Keefe Study. July 07. OLN.RSP.QP.
- CATIE
- OLN v. HP. Lindermayer. JCP March 07. OL better.
- CLP+RSP. Meltzer, No benefit. JCP Dec 2006.
- QP v RSP. Harvey. 8 Wks. AJP Nov 06, both good.
- ZP v OLN. Harvey. 2003.
Strategies
1. Cognitive Enhancement
2. Cognitive Preservation

- Attempts were started to deal early and earliest and address more investigation.
- ‘Early Intervention and Prevention of Schizophrenia’
- Non-pharmacological and Pharmacological methods were employed to enhance cognition
- CBT, Cognitive Remediation Therapy
- Several molecules

Cognitive re-mediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial.................Schizophrenia Research August 2007
The Ultra High Risk Individuals

The course of neurocognition and social functioning in individuals at ultra high risk for psychosis

Schizophrenia Bulletin August 2007

- UHR subjects showed significant cognitive deficits at baseline and 2 distinct profiles of cognitive change over time.

- On average, 50% demonstrated improvement in social and role functioning over the follow-up period, while the other half showed either stability or decline in functioning.

- Functional improvement was associated with improved processing speed and visual memory, as well as improvement in clinical symptoms over the follow-up period.

- In contrast, patients who did not improve functionally showed stable clinical symptoms and cognitive performance over time.
Drugs- tried, tested, failed, & survived to improve cognition-outcome-depression-NS, complex. Every thing under the SUN

<table>
<thead>
<tr>
<th>Poly pharmacy</th>
<th>Dopamine antagonists</th>
</tr>
</thead>
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<tr>
<td>Many antipsychotics</td>
<td>Dopamine agonists</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>Serotoninine blockers</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Alpha-adrenergics</td>
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<tr>
<td>Conventional and atypical</td>
<td>Cholinesterase inhibitors</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>Herbal medicines</td>
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</tbody>
</table>
Effect of donepezil added to atypical antipsychotics on Cognition in schizophrenia......World J. Biol. Psychiatry

Conclusions: Adjunctive treatment with donepezil improves cognition in patients with schizophrenia who are stabilized on atypical antipsychotics.

- Despite the beneficial effects of atypical antipsychotics on cognition, many schizophrenic patients continue to suffer.
- Postmortem findings suggest that altered cholinergic activity is involved in cognitive impairment in schizophrenia.

Experience with Adjunctive Rivastigmine and AAPD on Cognitive deficits - negative results.
It was proposed that cognitive impairment: is a separate domain

- Cognitive symptoms correlate poorly with positive symptoms
- Cognitive symptoms are enduring whereas positive symptoms are phasic
- Improvement in cognition is independent of improvement in positive and negative symptoms and EPS in most but not all studies
Pharmacological and Non-pharmacological measures

- APD
- Cognition
- Functional outcome
- Social & Vocational outcome

Sequential Improvement
Model Building: Neurocognition, Interventions, Mediators, and Functional Outcome

Interventions
- Psychopharmacological
- Psychosocial

Promising Mediating Variables
- Neurocognitive Capacities
- Learning Potential
- Social Cognition
- Volition

Other Factors
- Clinical Symptoms
- Environmental

Functional Outcome Domains
- Social
- Occupational
- Independent Living
- Rehabilitation Success

Green, Meltzer, Newcomer & Bellack, APA 2000
Tools for measuring cognition: Depends upon the research questions

1. Neuropsych.Batteries, manual or Computerized
2. Psycho-physiological Tests

<table>
<thead>
<tr>
<th>Validity</th>
<th>CATIE battery</th>
</tr>
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<tr>
<td>Time required</td>
<td>MATRICS battery</td>
</tr>
<tr>
<td>Domain specificity</td>
<td>BCA</td>
</tr>
<tr>
<td>Correlation with functional outcomes</td>
<td>BACS</td>
</tr>
<tr>
<td>Statistical convertibility</td>
<td>RBANS, WAIR-III, WMS, VCST</td>
</tr>
<tr>
<td>Culture neutrality</td>
<td>UPSA, MCCB</td>
</tr>
</tbody>
</table>
The study was completed at 57 US centers, 18-65, Schizophrenia.

Randomized to receive olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine. Dosing flexible and based on clinicians' judgment. Participants and assessors were blind.

Neurocognitive testing was performed using 11 different tests. Testing was completed at baseline and then at 2, 6, and 18 months of study treatment.

The primary study outcome was the change in cognition from baseline to 2 months in each treatment group.
• Current status - CATIE Trial

2 Months, N=467 without TD

• Improvement from base
• No significant inter-group differences
• Perphenazine as good as other atypical.
• When group with TD added, improvements sustained
• Patients with TD had less over all improvement
• Ziprasidone showed less improvement when TD group was excluded

![Graph showing LSM Improvement in Neurocognition with data points for Olanzapine, Perphenazine, Quetiapine, Risperidone, and Ziprasidone with p-values]
• **Current status-CATIE Trial, 2 Months, individual NC domains across treatments**

- No significant disparity between the groups in improvement across the individual NC domains
- Change in the individual measures were small but consistently positive
• Current status, CATIE Trial, at 6 Months, N= 523

• The NC composite score improved (p < 0.001) for each of the treatment groups from base to 6 months

• There was no difference between the groups on the change in the NC composite score (p=0.35), or any of the NC domains (all p values < 0.01)
• **Current status - CATIE Trial, at 18 Months, N=303**

- 37% patients were from 2 months analysis
- 21% of original pool
- Sample was found representative of entire pool on NC domains,
- the improvement in composite score from month 2 to month 18 was 0.11, suggesting that most of the cognitive improvement occurred in first 2 months of treatment
- Perphenazine group had better improvement than Olanzapine group or Risperidone group
- Ziprasidone and Quetiapine

![Graph showing improvement in neurocognition for different medications](image-url)
The relationships between change in cognition and change in social and vocational outcome?

- **Current status: Keefe Study, AJP 2007 July**

- **Unaffected siblings show premorbid cognitive decline**

- The team concludes: “To our knowledge, this is the first study demonstrating that unaffected siblings of people with familial schizophrenia have poor academic functioning during adolescence and deterioration in academic performance between childhood and adolescence compared with controls.

- Familial liability to schizophrenia and premorbid adjustment British J Psychiatry 2007; 191: 260–261
There were small differences between groups

- Pooled across treatments, the partial correlations (controlling for baseline cognition and clinical symptoms) were small (0.14 and 0.18, respectively) at 12 weeks and roughly medium (0.22 and 0.36, respectively) at 52 weeks.

- Associations are relatively small -- for two reasons.
• One is that we do not have a clear pre-cognitive treatment effect in this study.

• Second, there is no psychosocial treatment component as part of this design that would facilitate translation of any cognitive benefits to the level of community functioning.

Enhancement basically occurs at 2 months and sustains at 52 months.

Week 52

-0.700
-0.525
-0.350
-0.175
0

CGI-S
PS
NS
GP
PANSS-Total

Olanzapine
Risperidone
Quetiapine
PANSS-Total
Quetiapine’s superiority at week 12 also is not very robust and it does not sustain up to week 52.

The discussion and explanation is lacking on this point.

- The explanation for superiority of quetiapine based upon blocking of muscarinic receptor by quetiapine is insufficient as there is a complex biological process for cognition.
Conclusion - that we should not plan to address our unmet need for cognition enhancement with antipsychotic medications

- The improvements seen with the second-generation medications are within the range of expectation. For this reason,

- It is not known whether all three drugs have modest beneficial effects on cognition or whether they are all cognitively neutral

- The cognitive effects - 52 weeks were not significant, because of a slight reduction in effect size and reduced statistical power from attrition.

- We need to look elsewhere
Cognition, Drug Treatment, and Functional Outcome in Schizophrenia: A Tale of Two Transitions


- Optimism that second-generation antipsychotics would yield cognitive improvements has progressively been tempered as treatment effect sizes have progressively dwindled, possibly as a result of dosing factors (as doses of comparators became lower) or patient selection factors (as more patients received second-generation medications)
2. Atypical neuroleptics stimulate neurogenesis in adult rat brain

Wakade & Mahadik. Journal Neuroscience Res.

1. Unlike conventional antipsychotics, atypicals have been shown to be neuroprotective i.e., atypicals can prevent brain tissue loss associated with psychosis and stimulate neurite extension, neurogenesis, and cell survival.

3. Nerve growth factor (NGF) in Plasma schizophrenia subjects; Schizophrenia Bull. 2003

- Normal NGF (pg/ml)
- Never medicated FEP patients
- Chronic patients treated with typicals
- Chronic patients treated with atypicals

How to Explain cognitive enhancement by atypicals
Functional neuro-anatomy of cognitive deficits in schizophrenia - temporal lobe model

Studies of Cognitive activation and fMRI Studies of working memory and cognitive controls Reveal

• Temporal Sagital Gyres (TSG)
• Dorsolateral Pre-frontal Cortex
• Hippocampal Formation (LTM)
• Corpus Callosum
New treatments for cognition in schizophrenia

- Muscarnic antagonist: N-desmethyl clozapine
- Glutamate enhancers: Org 24448, LY 451 395
- GABA-A partial agonist: NGD 97-1
- Histamine antagonist : BF2-649
- Adrenergic modulators : c105
- 5-HT-1A antagonists : AV 965
- Nicotine partial agonist : Tc -1734
- Nk-3 antagonist : Sr 42801
The concept of neuronal plasticity and conditioning for memory

The Nobel Prize in Physiology or Medicine 2000

Arvid Carlsson, Paul Greengard and Eric Kandel
for their discoveries concerning
"signal transduction in the nervous system"
The COMT Gene

- Future Direction, New Molecules or New Genes??

COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia...Schizophrenia Research, 2007 Feb

The path from here to there...

Genes: multiple susceptibility alleles each of small effect

Cells: subtle molecular abnormalities

Systems: abnormal information processing

Behavior: complex functional interactions and emergent phenomena

psychiatric illness

temperament

cognition

The Wisconsin Card Sorting Test
Molecular targets for treating Cognitive Dysfunction in Schizophrenia. Schizophrenia Bull. 2007 July

- Cholinergic : Cholinesterases, Muscarinic, Nicotinic Receptors
- Glutaminergic: NMDA AMPA/Kainate, Glycine, Glutamate Receptors
- Dopaminergic: D1, D4
- Serotonergic : 5-HT2A, 5HT-1A, 5HT4, 5HT6, 5HT7
- Others: Alpha2, GABAA, Neurosteroid & Sigma,
- Potential Future Targets: Neuregulin 1, COMT, DISC1 and Neurotrophic Factors

Comment by: Amresh Shrivastava

Submitted 17 September 2007
Posted 17 September 2007

Molecular targets for cognitive improvement are a desirable context. This may lead to some improvement in a few dimensions of outcome in schizophrenia, assuming that cognitive deficits are a key component in its pathology. However we need not forget that they are neither universal nor unchallenged. It has been rightly pointed out that cognitive deficits may be the final result of many complex causations and pathways. No doubt succeeding in developing a molecule for working on molecular targets may give some benefit.

This entire research effort needs much appreciation. However, it opens other vistas of debate as well. E.g., cognition is a complex bio-behavioral psychological function. Believing that there are exclusive molecular targets suggests that 'Cognitive deficits have molecular pathology.' That they are driven by dopaminergic, cholinergic, and glutaminergic neurotransmitter systems. Available data only shows association of dysfunction of these systems of neurotransmission in various areas of brain with cognitive deficits. It does not indicate what preceded and what is the causal relationship. In that sense it would be quite premature to assume that molecular target medication development will provide any significant change in the scenario of outcome.
CONCLUSION:

- Cognition is integral to schizophrenia
- A criteria in DSM/ICD expected
- Deficits are related to global & social functioning, and can enhance outcome
- Measurement batteries would be simple and reliable
- Amongst various enhancing measures newer pharmacological molecules are expected
- Hope that practice of such therapy would be simple and cost-effective
- Hope that this would make a difference to life of patients
“Of all the things I’ve lost, I miss my mind the most”

MissMind