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Antipsychotics and Outcome in Schizophrenia

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International pilot study of schizophrenia (IPSS): Agra centre, India

- Multicentre, WHO at 2 and 5 years
- 76% followed at 2 years (n=1,202)
- Consistent finding at 2 and 5 years was that schizophrenia in developing countries has better outcome
### Government of India multicentre study on course and outcome of schizophrenia

- **Time spent in psychotic state**
  - 15% or less: 62%; 75% or more: 4%
- **Best pattern of course**: 45%; **worst course**: 10%
- **Impairment of occupational functioning**
  - nil: 40%; **severe**: 18%
- **Social impairment**
  - nil: 34%; **severe**: 12%
- **Overall outcome**
  - **favourable**: 66%; intermediate: 30%; unfavourable: 4%

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![Functional Outcome Since 1895](image-url)


- **Change in QLS Total Score with Change in Memory Function - positive linear correlation**;
  Buchanan RW et al Biol. Psychiatry 1994;36
Complete Remission as Outcome status in Schizophrenia

'Real World' Comparison of First- and Second-Generation Antipsychotics in Regard to Length of Inpatient Hospitalization and Number of Re-hospitalizations (2008)

Antipsychotics

Whether to treat schizophrenia with antipsychotic? Banglore Study

- OBJECTIVE: To compare disability in schizophrenia patients receiving antipsychotics and untreated
- Untreated: unchanged Mean disability scores
- Continued to receive and initiated APD: showed a significant decline disability.
- The proportion of patients classified as 'disabled' declined significantly in the treated group (P < 0.01), but remained the same in the untreated group

**Treatment effectiveness in Schizophrenia** (World Health report 2001, WHO)

% of relapse after 1 Year

- Chlorpromazine + family Therapy- Max: 23
- Chlorpromazine + family Therapy- Min: 2
- Chlorpromazine- Max: 25
- Chlorpromazine- Minimum: 20
- Placebo: 55


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**CATIE – Phase 3, Symptom response**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ARIP</th>
<th>CLOZ</th>
<th>COMB</th>
<th>FLU-D</th>
<th>OLAN</th>
<th>PERP</th>
<th>QUET</th>
<th>RISP</th>
<th>ZIPR</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PANSS-3</td>
<td>0.506</td>
<td>0.002</td>
<td>0.002</td>
<td>0.005</td>
<td>0.002</td>
<td>0.084</td>
<td>0.013</td>
<td>0.044</td>
<td>0.045</td>
<td>0.832</td>
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<tr>
<td>PANSS-6</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>&lt;0.001</td>
<td>0.43</td>
<td>0.003</td>
<td>0.018</td>
<td>0.100</td>
<td>0.009</td>
<td>0.371</td>
<td>0.515</td>
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</table>
What is the prescribing pattern

SGAs have become the first-line treatment for psychiatric disorders.


'Real World' Comparison of First- and Second-Generation Antipsychotics in Regard to Length of Inpatient Hospitalization and Number of Re-hospitalizations (2008)

- % reduction in days before hospitalization
- % reduction in LOS
- days before readmission 2004
- % readmitted 2004
- LOS 2004
- 

1994 & 2004

- % reduction for SGA in number of days before relapse was significantly more impressive
- During both time periods, patients on FGAs had significantly shorter LOS than those receiving SGAs
- Inpatients receiving SGAs were hospitalized longer than those receiving FGAs.
- Conversely, patients receiving SGAs were significantly less likely to be re-admitted

**Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis**

Stefan Leucht, Caroline Corvan, Dieter Arntz, Hajo R Engel, Chamber L, John M Clark

**Summary**

Background: Because of the debate about whether second-generation antipsychotic drugs are better than first-generation antipsychotic drugs, we did a meta-analysis of randomised controlled trials to compare the effects of those two types of drugs in patients with schizophrenia.

150 DB, N= 21 533,

4 Drugs amisulpride, clozapine, olanzapine, risperidone were better than FGA, with small to medium ES:

The other SGA were not more efficacious than the FGA, even for negative symptoms.

With the exception of aripiprazole and ziprasidone, SGA drugs induced more weight gain

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**The CATIE and CULTASS studies in schizophrenia: results and implications for clinicians.**

- CATIE and CULTASS suggest that SGAs do not live up to all the previous expectations.
- However, even if most of these advantages are debatable, the lower risk of Tardive dyskinesia and the better subjective effects should be strong enough reasons to favour these drugs.
- There is no single antipsychotic that is best for every schizophrenia patient, as individual responses differ markedly.
- For successfully individualized treatment, a multitude of antipsychotic options are needed.

Naber D, Lambert M. The CATIE and CULTASS studies in schizophrenia: results and implications for clinicians.

CNS Drugs. 2009 Aug 1;23(8):649-59.
Lessons to take home from CATIE.

- Rather than selecting drugs on the basis of unfounded expectations of superior efficacy, clinicians can focus on selecting drugs and optimizing dosages to minimize adverse effects without sacrificing efficacy.
- Tardive dyskinesia may be a good reason to avoid a high dosage of first-generation antipsychotics.
- Although the evidence for differential risk is less compelling for a modest dosage of low-affinity first-generation antipsychotics.
- Similarly, the metabolic effects of some second-generation antipsychotics can be decisive in considering risks.
- In either case, the clinician should detect earliest signs and take action while dyskinetic or metabolic effects are most reversible.

Carpenter WT, Buchanan RW. Lessons to take home from CATIE. Psychiatr Serv. 2008 May;59(5):523-5.

Bottom line: the dichotomy between first- and second-generation antipsychotics was not supported by efficacy data (and now, is not supported effectiveness data).

Only clozapine has documented superiority in treatment-resistant cases.

Lessons to take home from CATIE.

Carpenter WT, Buchanan RW. Lessons to take home from CATIE. Psychiatr Serv. 2008 May;59(5):523-5.
Do Atypical Antipsychotics Differ in Determining Long-term Outcome of First Episode Schizophrenia? A Naturalistic Outcome Study in India

Amresh Srivastava¹, Nilesh Shah², Megan Johnston³, Larry Stitt⁴, Meghana Thakar⁵, Gurusamy Chinnasamy⁶, & Anukant Mital⁷

INTRODUCTION

• Antipsychotic medications form the mainstream of treatment in schizophrenia

• These drugs have several short term as well long term advantages

• It is not known if atypical antipsychotics have the long-term effect of improving outcome and meeting expectations (1,2,3)
The present study examined the usage of antipsychotics drugs and their associations with clinical outcome in a long-term naturalistic study

METHODS AND MATERIALS

- First episode hospitalized schizophrenia patients (diagnosed according to DSM-IIIR criteria) were followed for ten years
- After ten years, diagnosis was re-confirmed (using DSM-IV criteria) and outcome was assessed
- Outcome was assessed using Clinical Global Impression Scale (CGIS)
- CGIS scores were correlated with key antipsychotic drugs used in the preceding 12 months
Multiple outcome criteria in schizophrenia

Thirteen criteria

- Psychopathology (positive symptoms, negative symptoms and disorganisation)
- Cognitive function (attention, executive function, working memory, recall memory, semantic memory, storage memory)
- Interpersonal social function
- Work–school function
- Extrapyramidal function (parkinsonism, akathisia, tardive dyskinesia)

Meltzer HY. Eur Psychiatry 1995;10(Suppl. 1):19S–25S

Multiple outcome criteria in schizophrenia (cont’d)

- Independent living
- Aggression
- Quality of life
- Compliance
- Hospitalisation
- Family burden
- Social burden
- Suicidality

Meltzer HY. Eur Psychiatry 1995;10(Suppl. 1):19S–25S
Re-assessed outcome at 10 years

Clinical recovery, CGIS, N=107
Social recovery, 3 Criteria, N=107

Global Social outcome
RESULTS

- Only 62.6% improved significantly in a cohort of 101 patients after ten years
- 85% patients were maintained on atypical antipsychotics
Percentage usage pattern and per day mean dosage in mg at end point:

- **Cognition**
  - Significant decrease in visuo-spatial function.
  - (p=.002, Paired t).
  - % of patients with abnormal value on BG increased but not significantly (p=.114, McNemar’s Chi-square test)
  - Memory decreased (WMS) significantly (p=.003, Paired t)
  - % of patient with abnormal values increased but not significantly (p=.144, McNemar’s Chi-square test)
Correlation between BG & WMS (Cognition) at Baseline and other Baseline Variables

<table>
<thead>
<tr>
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<th>BG</th>
<th></th>
<th>WMS</th>
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<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
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<tr>
<td>PANSS</td>
<td>-0.210</td>
<td>.104</td>
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<td>.115</td>
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<tr>
<td>NS</td>
<td>0.070</td>
<td>.593</td>
<td>-0.164</td>
<td>.206</td>
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<tr>
<td>PS</td>
<td>-0.006</td>
<td>.966</td>
<td>-0.150</td>
<td>.249</td>
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<tr>
<td>Duration</td>
<td>-0.051</td>
<td>.695</td>
<td>0.350</td>
<td>.006</td>
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<tr>
<td>Age at Intake</td>
<td>-0.014</td>
<td>.918</td>
<td>-0.088</td>
<td>.504</td>
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<tr>
<td>Sex</td>
<td>.243</td>
<td>.059</td>
<td>-0.047</td>
<td>.717</td>
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Association between Baseline Cognition (BG/WMS) and outcome parameters at 10 Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>BG</th>
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<th>WMS</th>
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<tr>
<td></td>
<td>Parameter Estimate (se)</td>
<td>P value</td>
<td>Parameter Estimate (se)</td>
<td>P value</td>
</tr>
<tr>
<td>10 Year Outcomes</td>
<td>PS</td>
<td>-0.042 (0.037)</td>
<td>.260</td>
<td>0.012 (0.039)</td>
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<tr>
<td></td>
<td>NS</td>
<td>-0.052 (0.072)</td>
<td>.474</td>
<td>-0.029 (0.076)</td>
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<tr>
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<td>GP</td>
<td>0.133 (0.122)</td>
<td>.279</td>
<td>0.087 (0.129)</td>
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<tr>
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<td>HDRS</td>
<td>0.071 (0.054)</td>
<td>.196</td>
<td>-0.079 (0.054)</td>
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<tr>
<td></td>
<td>GAF</td>
<td>0.176 (0.117)</td>
<td>.137</td>
<td>0.045 (0.124)</td>
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<tr>
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<td>QOL</td>
<td>-0.203 (0.109)</td>
<td>.067</td>
<td>0.112 (0.116)</td>
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<tr>
<td></td>
<td>CGIS-I</td>
<td>0.0005 (0.0048)</td>
<td>.913</td>
<td>0.004 (0.005)</td>
</tr>
</tbody>
</table>
Conclusion

Long-term Outcome of first episode schizophrenia does NOT differ across atypical antipsychotics
Pathway for poor Outcome

Cognitive dysfunction

Poor Social Functioning and Integration

Loss Of Insight

Relapse

Drug Discontinuation

Poor awareness

Weiden et al. Psych Services, 2004

Determinants of outcome in schizophrenia

Outcome

Patient

Illness

Nature of Treatment

Setting of treatment

Family

environment
Illness Related

- illness loses its intensity [Dube K.C]
- definitions did not reveal significant variability [Kulhara P]
- Short duration of illness [Verghese et al]
- longer time spent in psychosis [Thara R]
- short-term course [Varma V.K.]
- Sexual, religious and grandiose delusions and flat affect [Thara, R]
- DUP. [Tirupati, Yanos PT]
- Relapse [Yanos PT]
- Comorbidity
- negative syndrome
- cognitive functioning [Altamura AC]
- Premorbid level of functioning
- violence,
- severity of illness [Wittorf A]

Patient related

- absence of economic difficulties, Verghese A
- increase in religious activities Verghese A
- a non-schizoid pre-morbid personality [Verghese A]
- Male [Dube K.C.]
**Family related**

- Positive attitudes of relatives and neighbours, [Verghese A]
- EE
- Psycho-education [Kulhara P.]

**Treatment related (nature)**

- Consistent compliance
- Reduced levels of membrane essential polyunsaturated fatty acids (EPUFAs), [Arvindakshan M]
- Rehabilitation [Chatterjee S]
- Limited efficacy for specific domains of psychopathology of current treatments; [Yanos PT]
Treatment settings

- Rural background, (Verghese A)

Environment related

- Mean environmental temperature [Gupta,S]
- Bias [Thirthalli J]
- Transcultural factors [Kulhara.P]
Measures to maximise the outcome

- Early psychosis programme
- Cognitive enhancement and preservation
- Improvising insight, awareness and compliance
- Minimising EPS
- Minimising drop-outs and discontinuation
- Psycho-education
- Psychosocial intervention
- Cognitive behavioural
- Minimising hospital stay
- Relapse prevention

References

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7. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. [Int Clin Psychopharmacol. 2007 Nov;22(5-6):284-97.]
9. Controlling the combination of omega-3 fatty acids and vitamin D improves the outcome of schizophrenia. [Schizophrenia Res. 2003 Aug;59(3):180-90.]