Advances in the Treatment of Schizophrenia: New Approaches

A Satellite Symposium at the XXVII CINP Congress
The International College of Neuro-Psychopharmacology (CINP)
Welcome/Introductions

W. Wolfgang Fleischhacker, MD
Medical University Innsbruck
Disclosures

- Supported by an educational grant from Dainippon Sumitomo Pharma America, Inc.

- On April 1, 2010, DSPA merged with Sepracor Inc. creating one, united North American operation for our parent company, Dainippon Sumitomo Pharma Co., Ltd.
Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any use not approved by the US Food and Drug Administration) of products or devices.
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<td>Philip D. Harvey, PhD</td>
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<td>13.35 – 13.45</td>
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Antipsychotic Efficacy: Comparing First-Generation to New-Generation Antipsychotics

W. Wolfgang Fleischhacker, MD
Medical University Innsbruck
Disclosures

- **Grants/Research Support:** Alkermes, Inc.; Bristol-Myers Squibb Company/Otsuka Pharmaceutical Group; Eli Lilly and Company; Johnson & Johnson Pharmaceutical Research & Development, L.L.C.; Pfizer, Inc.

- **Consultant/Speaker’s Honoraria:** AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company/Otsuka Pharmaceutical Group; H. Lundbeck A/S; Johnson & Johnson Pharmaceutical Research & Development, L.L.C.; Merck & Co., Inc.; Pfizer, Inc.; United BioSource Corporation
Collectively, the meta-analytic comparisons indicate that SGAs are modestly (though not consistently) more effective than FGAs in the treatment of schizophrenia. Four of these drugs (amisulpride, clozapine, olanzapine, risperidone) were better than FGAs for overall efficacy, with small to medium effect sizes. The spurious invention of the atypicals can now be regarded as invention only, clearly manipulated by drug industry and only now being exposed. …even the low risk of tardive dyskinesia with atypical antipsychotics, the most serious neurological side effect, is not, by itself, likely to justify the greater expense of these drugs.

First- vs. Second-Generation Antipsychotics

Comparative Effectiveness/Efficacy Studies
CATIE Schizophrenia Trial Design

1,460 patients with chronic schizophrenia

Phase 1
- Double-blind, random treatment assignment
- Olanzapine: n = 330
- Quetiapine: n = 329
- Risperidone: n = 333
- Ziprasidone: n = 183
- Perphenazine: n = 257

Phase 2
- Participants who discontinue Phase 1 choose either the clozapine or the ziprasidone randomized pathway
- Clozapine (open-label)
- Olanzapine, quetiapine, or risperidone
- Ziprasidone
- Olanzapine, quetiapine, or risperidone

Phase 3
- Participants who discontinue Phase 2 choose one of the following open-label treatments
  - Aripiprazole
  - Clozapine
  - Fluphenazine decanoate
  - Olanzapine
  - Perphenazine
  - Quetiapine
  - Risperidone
  - Ziprasidone
  - 2 of the above antipsychotics

CATIE: Time to Discontinuation for Any Cause

- Proportion of Patients Without Event
- Time to Discontinuation for Any Cause (Months)

* Completed Phase I; $p < .0001$ for OLZ vs. QUE; $p = .002$ for OLZ vs. RIS

Clinician is considering changing a patient’s antipsychotic medication—contacts CUtLASS

CUtLASS 1
Change in medication due to inadequate response or side effects

Patient randomized

FGA including sulpiride

Eligible patient
DSM-IV Schizophrenia
Age 18-65 years

SGA
quetiapine
risperidone
amisulpride
olanzapine

Patient randomized

clozapine

CUtLASS 2
Change in medication due to poor response to 2 or more drugs

CUtLASS 1: Results

- CUtLASS 1: “SGA (non-clozapine) will outperform FGA drugs in patients with schizophrenia responding poorly to, or intolerant of, current treatment”
  - N = 227
  - FGA chosen: sulpiride 49%; SGA olanzapine 48%
  - 81% follow up at one year
  - Still on FGA: 54%; still on SGA 65% (ns)
    - 48% of the participants randomized to sulpiride and 74% of those randomized to olanzapine still on these drugs

- Trend to advantage for FGA on QLS and PANSS ($p = .15$)
  - No EPS difference overall
  - No patient preference for either class

QLS = quality of life scale; ns = not significant

The European First Episode Schizophrenia Trial$^{1,2}$

Effectiveness of Antipsychotic Drugs in First-Episode Schizophrenia and Schizoaffective Disorder

- Primary objective: To compare one-year retention on low doses of haloperidol as compared to amisulpride, olanzapine, quetiapine, and ziprasidone in patients with recent onset schizophrenia, schizoaffective, and schizoaffective disorder.
Haloperidol vs. Second-Generation Antipsychotic Drugs: Time to Treatment Discontinuation for Any Cause


HAL = haloperidol; AMI = amisulpride; OLZ = olanzapine; QUE = quetiapine; ZIP = ziprasidone

Second-Generation vs. First-Generation Antipsychotic Drugs for Schizophrenia Efficacy: Overall Symptoms

AMI = amisulpride; ARI = aripiprazole; CLO = clozapine; OLZ = olanzapine; QUE = quetiapine; RIS = risperidone; SER = sertindole; ZIP = ziprasidone; ZOT = zotepine

* Not approved by the US Food and Drug Administration

Four second-generation drugs (AMI, CLO, OLZ, and RIS) were more efficacious for the treatment of overall schizophrenia symptoms than first-generation drugs

Recently Approved Antipsychotics and Drugs in a Late Stage of Development

- Asenapine*

- Blonanserin†
  - Deeks ED, Keating GM. CNS Drugs 2010;24:65-84.

- Iloperidone*

- Lurasidone‡‡

*  Approved by the US Food and Drug Administration
†  Indicated for use in patients with schizophrenia in Japan and Korea; not approved by the US Food and Drug Administration
‡‡ Not approved by the US Food and Drug Administration or any other regulatory agencies
Asenapine

- Discovered by Organon
- Clinical profile
  - Efficacy shown in schizophrenia
  - Small EPS risk
  - Minimal effect on weight and lipid profile
  - ? Potential role in treatment of negative symptoms
  - Sublingual formulation requires BID dosing
- Approved in the United States for the acute treatment of schizophrenia in adults, and the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults
- In review for approval in Europe

1. Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
Asenapine vs. Placebo and Haloperidol: PANSS Total (LOCF)

Baseline means: PBO = 89.0; ASE 5 mg = 88.9; ASE 10 mg = 89.4; HAL = 88.5

Iloperidone

- Discovered by Hoechst Marion Roussel
- Clinical profile
  - Efficacy shown in schizophrenia
  - Less potent than risperidone?
  - Minimal EPS risk
  - Dose dependent weight and lipid impact
  - Genetic markers may be associated with efficacy
  - BID dosing; dose titration required
  - Prolongation of QT interval
- Approved in the United States for the acute treatment of schizophrenia in adults

1. Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
Iloperidone in Acute Schizophrenia: PANSS Total Score

Lurasidone*

- Discovered by Dainippon Sumitomo Pharma
- Clinical profile
  - Efficacy shown in schizophrenia
  - High affinity for 5-HT$_7$, 5-HT$_{1A}$, $\alpha_{2c}$ receptors (implicated in enhancement of cognitive function)
  - Minimal EPS risk
  - Minimal effect on weight and lipid profile
  - QD dosing; no dose titration required
- Current status—late phase III trials ongoing in schizophrenia. NDA has been submitted in United States only

* Not approved by the US Food and Drug Administration or any other regulatory agencies
PEARL 2: Study Design

**PEARL** = Program to Evaluate the Antipsychotic Response to Lurasidone

PEARL 2: PANSS Total (MMRM)


- PBO (n = 114)
- LUR 120 mg/day (n = 118)
- LUR 40 mg/day (n = 118)
- OLZ 15 mg/day (n = 121)

* p < .05; † p < .01; PBO = placebo; LUR = lurasidone; OLZ = olanzapine; MMRM = mixed method repeated measures
Blonanserin*

- Discovered by Dainippon Sumitomo Pharma
- Clinical profile\textsuperscript{1,2}
  - Effective in the treatment of patients with schizophrenia
  - Demonstrated efficacy in management of negative symptoms\textsuperscript{2}
  - Minimal effect on weight and lipid profile
- Indicated for use in patients with schizophrenia in Japan and Korea\textsuperscript{1}

* Not approved by the US Food and Drug Administration

1. Deeks ED, Keating GM. *CNS Drugs* 2010;24:65-84.
Blonanserin* in Acute Schizophrenia: PANSS Total Score

N = 307; BLO = blonanserin; HAL = haloperidol; PBO = placebo

* Indicated for use in patients with schizophrenia in Japan and Korea; not approved by the US Food and Drug Administration

Conclusions

- Neither first- nor new-generation antipsychotics represent a homogeneous class.
- Most new-generation antipsychotics are at least as effective as haloperidol.
- Specific drugs may have advantages over first-generation antipsychotics, e.g., certain subsyndromes of schizophrenia (positive symptoms, negative symptoms, suicidality, aggression, cognitive impairment, depression).
- Choice of treatment cannot be based on efficacy alone.
  - Safety/tolerability and subjective acceptance need to be accounted for as well.
- There is not, as of yet, a reliable way to predict efficacy in individual patients.
Q & A

W. Wolfgang Fleischhacker, MD
Disclosures

- **Grants:** GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Pfizer, Inc.

- **Consultant:** Biovail Pharmaceuticals, Inc.; Dainippon Sumitomo Pharma Co., Ltd.; Eli Lilly and Company; H. Lundbeck A/S; Hoffmann-La Roche Ltd.; Indevus Pharmaceuticals, Inc.; Otsuka America Pharmaceutical, Inc.; Schering-Plough Corporation; Solvay Pharmaceuticals, Inc.; Takeda Pharmaceuticals North America, Inc.
Schizophrenia Treatment Algorithm: Reasons for Switching

First-Line Antipsychotic

- Intolerant
- Unsafe
- Ineffective
The CATIE Study: Discontinuations Due to Intolerability

- N = 1,460
- Risperidone: lowest rate of discontinuation at 10% (mean dose 3.9 mg/day)
- Olanzapine: 9% dropouts due to weight gain
- Perphenazine: 8% dropouts due to EPS

PER = perphenazine; RIS = risperidone; OLZ = olanzapine; QUE = quetiapine; ZIP = ziprasidone

Adherence: A Difficult Balance

Perceived benefits

Side effects
Lack of insight
Disorganization
Subjective Well-Being Scale: Total Analysis

Mean Change from Baseline in SWN Total Score (n = 1,223) (n = 292) (n = 170) (n = 159) (n = 66) (n = 173) (n = 156)

OLZ 11.7 9.4 7.5 8.6 9.1 7.8 6.4
RIS 15.9 13.6 11.1 11.8 15.6 13.6 11.1
QUE 15.9 11.1 8.6 9.1 9.1 8.5 6.4
AMI 15.6
CLO 15.6
PO 7.8 8.5 6.4
Typical 7.8 8.5 6.4
Depot Typical 9.1

SWN = subjective well-being with neuroleptics; OLZ = olanzapine; RIS = risperidone; QUE = quetiapine; AMI = amisulpride; CLO = clozapine;
Scale = short form (20 items); range from 20 (worst) to 120 (best);
n = patients with evaluable differences from baseline to 6 months

## Medication Effects: Well-Being vs. Distressing Side Effects

<table>
<thead>
<tr>
<th>Well-Being</th>
<th>Distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeping pill</td>
<td>Sedation, fatigue</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>Sexual side effects</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>EPS</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Weight gain</td>
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### Sedation

<table>
<thead>
<tr>
<th>medication</th>
<th>sedation strength</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>++++</td>
</tr>
<tr>
<td>Low-potency conventionals</td>
<td>++++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
</tr>
<tr>
<td>High-potency conventionals</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
</tr>
</tbody>
</table>

- Sedation at bedtime is often welcome
- Difficulty arising and daytime sedation are perceived negatively

### EPS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rating</th>
</tr>
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<tbody>
<tr>
<td>High-potency conventionals</td>
<td>++++</td>
</tr>
<tr>
<td>Low-potency conventionals</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>–</td>
</tr>
<tr>
<td>Clozapine</td>
<td>–</td>
</tr>
</tbody>
</table>

- EPS is dose-related
- Early parkinsonism from conventional neuroleptics predicts TD
- Akathisia associated with nonadherence, poor outcomes

## Sexual Side Effects

- Related to prolactin, muscarinic, anticholinergic, and alpha-adrenergic effects
- Common reason for young males to stop medication
- Often not spontaneously reported

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<tbody>
<tr>
<td><strong>Risperidone/paliperidone</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Low-potency conventionals</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>High-potency conventionals</strong></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>++</td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
<td>+</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>+</td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td>+</td>
</tr>
<tr>
<td><strong>Clozapine</strong></td>
<td>+</td>
</tr>
</tbody>
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Weight Gain

- Weight gain is associated with:
  - Treatment discontinuation
  - Low self-esteem
  - Stigma
  - Medical morbidity
  - Criticism by family members and lack of support for treatment

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<tbody>
<tr>
<td>Clozapine</td>
<td>++++</td>
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<tr>
<td>Olanzapine</td>
<td>++++</td>
</tr>
<tr>
<td>Low-potency conventionals</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
</tr>
<tr>
<td>High-potency conventionals</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
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## Tolerability of New and Emerging Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Mean Wt Gain in 6-Wk Trials (kg)</th>
<th>QTc (mean change msec)</th>
<th>Prolactin (mean change from BL ng/mL)</th>
<th>EPS (%)</th>
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<tbody>
<tr>
<td></td>
<td>DRUG PBO</td>
<td>DRUG PBO</td>
<td>DRUG PBO</td>
<td>DRUG PBO</td>
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<tr>
<td>ASE</td>
<td>10-20</td>
<td>1.1</td>
<td>0.1</td>
<td>2-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td>ILO</td>
<td>20-24</td>
<td>2.0</td>
<td>-0.1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.6</td>
<td>-6.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>13.5</td>
<td>15.1</td>
</tr>
<tr>
<td>LUR</td>
<td>40-120</td>
<td>.67</td>
<td>0.36</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
<td>-0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>BLO</td>
<td>5-10</td>
<td>0.08-0.57</td>
<td>ND</td>
<td>ND</td>
</tr>
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<td></td>
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<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.3-26.6</td>
<td>9.4</td>
</tr>
</tbody>
</table>

ASE = asenapine; ILO = iloperidone; LUR = lurasidone; BLO = blonanserin; ND = No data

See supplemental bibliography for full references.
## Treatment-Emergent Adverse Events in Lurasidone Pooled Trials

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All LUR (n = 1,004)</th>
<th>HAL (n = 72)</th>
<th>OLZ (n = 122)</th>
<th>PBO (n = 455)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>15.0%</td>
<td>19.4%</td>
<td>7.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>12.0%</td>
<td>5.6%</td>
<td>4.9%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Sedation</td>
<td>11.9%</td>
<td>20.8%</td>
<td>14.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10.7%</td>
<td>12.5%</td>
<td>9.0%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.4%</td>
<td>16.7%</td>
<td>10.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.3%</td>
<td>13.9%</td>
<td>5.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Dystonia</td>
<td>3.5%</td>
<td>12.5%</td>
<td>0.8%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>2.4%</td>
<td>0%</td>
<td>20.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Extrapyramidal Disorder</td>
<td>2.0%</td>
<td>18.1%</td>
<td>0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>≥ 1 Adverse Event</td>
<td>78.9%</td>
<td>87.5%</td>
<td>82.8%</td>
<td>71.4%</td>
</tr>
</tbody>
</table>

AEs ≥ 10% and ≥ 2-times placebo; LUR = lurasidone; HAL = haloperidol; OLZ = olanzapine; PBO = placebo

CATIE: Weight Gain Per Month of Treatment

Mean Weight Gain/Month (lb)

- OLZ = olanzapine
- QUE = quetiapine
- RIS = risperidone
- PER = perphenazine
- ZIP = ziprasidone


\( p < .001 \)
CATIE: Metabolic Changes from Baseline

OLZ = olanzapine; QUE = quetiapine; RIS = risperidone; PER = perphenazine; ZIP = ziprasidone

Metabolic Profiles of Lurasidone and Olanzapine in PEARL 2
6-Week, Double-Blind, Placebo-Controlled Trial

Proportion of Patients with Clinically Significant Weight Gain
(≥ 7%)

LUR (n = 237) 7.2%
OLZ (n = 122) 40.2%*
PBO (n = 116) 8.7%

* p < .001; LUR = lurasidone; OLZ = olanzapine; PBO = placebo
Differential Metabolic Profiles of Lurasidone and Olanzapine 6-Week, Double-Blind, Placebo-Controlled Trial


* $p < .001$; † $p < .01$; LUR = lurasidone; OLZ = olanzapine; PBO = placebo
Recommendations for Monitoring Patients Starting Second-Generation Antipsychotics

More frequent assessments may be warranted based on clinical status
Lifestyle Intervention and Metformin for Treatment of Antipsychotic-Induced Weight Gain: A Randomized Controlled Trial

12-week placebo-controlled trial, metformin 750 mg/day

N = 128
Risk of Serious Events Within 30-Day Period in the Elderly by Medication Status

n = 241
Rates of Sudden Cardiac Death Among Antipsychotic Drugs

N = 26,749 person-years for current moderate-dose antipsychotic use
N = 1,186,501 person-years for no use

Baseline Correction: QTc Changes at Maximal Dose and with Metabolic Inhibitor (CI Testing)

SS = at steady state; +MI = with metabolic inhibitor; ZIP = ziprasidone; RIS = risperidone; OLZ = olanzapine; QUE = quetiapine; THIO = thioridazine; HAL = haloperidol

Study 054 Pfizer presentation to FDA Advisory Committee Meeting, July 2000.
### 11-Year Follow-Up Mortality in Schizophrenia Patients vs. Total Population of Finland

#### Any Cause

<table>
<thead>
<tr>
<th></th>
<th>Number of Deaths</th>
<th>Person-Years</th>
<th>Mortality</th>
<th>Adjusted HR (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLO</td>
<td>182</td>
<td>32,000</td>
<td>5.69</td>
<td>.74</td>
</tr>
<tr>
<td>PER</td>
<td>193</td>
<td>17,930</td>
<td>10.77</td>
<td>1.00</td>
</tr>
<tr>
<td>POLY</td>
<td>1,481</td>
<td>132,320</td>
<td>11.19</td>
<td>1.08</td>
</tr>
<tr>
<td>OLZ</td>
<td>264</td>
<td>25,130</td>
<td>10.50</td>
<td>1.13</td>
</tr>
<tr>
<td>THIO</td>
<td>227</td>
<td>18,420</td>
<td>12.32</td>
<td>1.14</td>
</tr>
<tr>
<td>RIS</td>
<td>295</td>
<td>19,410</td>
<td>15.20</td>
<td>1.34</td>
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<td>HAL</td>
<td>135</td>
<td>7,040</td>
<td>19.19</td>
<td>1.37</td>
</tr>
<tr>
<td>QUE</td>
<td>89</td>
<td>5,360</td>
<td>16.60</td>
<td>1.41</td>
</tr>
<tr>
<td>Other</td>
<td>1,234</td>
<td>70,520</td>
<td>17.50</td>
<td>1.45</td>
</tr>
</tbody>
</table>

N = 66,881; HR = Hazard Ratio;
CLO = clozapine; PER = perphenazine; POLY = polypharmacy; OLZ = olanzapine; THIO = thioridazine; RIS = risperidone; HAL = haloperidol; QUE = quetiapine

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>1.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>1.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.55</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SSRI</td>
<td>1.24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Estrogen</td>
<td>0.62</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.0</td>
<td>0.98</td>
</tr>
</tbody>
</table>

N = 16,341 and matched controls
Medication Selection

- Several trials may be needed to select the optimal drug
- Patients (and families) should be fully informed and participate in the decision
- Many factors contribute: efficacy, safety, tolerability, stigma (weight gain and TD)
- The decision should be revisited as indicated by safety monitoring
Antipsychotic Selection

Goal: The most effective and medically benign agent that the patient will take reliably
Setting the Bar Higher: Functional Remission in Schizophrenia

Philip D. Harvey, PhD
Emory University School of Medicine
Disclosures

- **Consultant:** Abbott Laboratories; Dainippon Sumitomo Pharma Co., Ltd.; Eli Lilly and Company; Shire Pharmaceuticals; Solvay Pharmaceuticals, Inc.; Wyeth Pharmaceuticals

- **Research Grants:** AstraZeneca Pharmaceuticals LP
Outcome of Schizophrenia in the 20th Century

Impact of Cognitive Dysfunction in Schizophrenia

- Cognitive dysfunctions are present in 80% of patients with schizophrenia
  - Deficits common in attention, memory, speed processing, and executive functioning
  - Well-known functional consequences on daily life, social functioning, and rehabilitation outcome
- Cognitive deficits, rather than the positive or negative symptoms of schizophrenia, predict poor performance in basic activities of daily living
- Family members caring for these patients have additional daily work burden, and suffer psychological anguish and anxiety
- Reducing cognitive deficits may decrease the economic burden to health care systems through lower numbers of hospital admissions and shorter hospitalization periods
Dimensions of Functional Impairment

- **Objective**
  - Occupational
  - Social
  - Self-care
  - Independent living

- **Subjective**
  - Subjective QoL
  - Perceived illness burden

QoL = quality of life
Rates of Real-World Functioning in Schizophrenia\textsuperscript{1,2}

90% of first-episode schizophrenia patients experience remission at the end of one year of treatment\textsuperscript{1}

At 5-year follow-up 18% had recovered\textsuperscript{1}

85% had relapsed at least once\textsuperscript{1}

50% are receiving disability compensation within 6 months of first admission\textsuperscript{2}

How Do You Assess Functional Disability?

- Self-report
- Informant report
- Direct observation
- Objective information
- Performance-based tests
Limitations of Assessment Domains

- **Objective information**
  - Availability, relevance, low rate of occurrence

- **Informant report**
  - Opportunities, situation specificity

- **Self-report**
  - Bias, cognitive limitations

- **Observation**
  - Situation specificity, low target frequency

- **Performance-based**
  - Practicality, content validity, difficulty
The UCSD Performance-Based Skills Assessment (UPSA)

- Performance-based assessment of skills in 5 functional domains
  - Finance, communication, planning, transportation, home activities
- Administered in a test-based format with real props and stimuli
- 30-minute assessment aimed at independent living

What Is Consistent Across Studies?

- UPSA is correlated to cognition
  - Twamley et al: $r = .64$
  - McKibbin et al: $r = .63$
  - Bowie et al: $r = .60$
  - Keefe et al: $r = .65$
  - Green et al: $r = .61$
  - Harvey et al: $r = .54^*$
  - MATRICS-CT $r = .67$

* UPSA-B administered in Swedish; 4-test neuropsychological assessment
See supplemental bibliography for full references.
Disability as a Cross-Cultural Central Illness Feature: Measuring Disability Across Different Countries

- Rural Sweden
- Urban New York
- Same outcomes measured:
  - NP performance; UPSA-B scores; rated RW outcomes (SLOF); RW milestones

UPSA Scores, NP Performance, and SLOF Everyday Functioning

NP = neuropsychological; UPSA-B = UCSD Performance-Based Skills Assessment-Brief Version; RW = real world; SLOF = Specific Levels of Functioning Scale

UPSA-B in China

- Large sample of Beijing residents
- Healthy comparison (n = 282), schizophrenia (n = 274), unipolar (n = 51), and bipolar (n = 60) subjects*
- Wide-ranging age and educational status
- UPSA-B translated and transliterated for use in China

* Some patients with bipolar disorder had history of psychosis

Some patients with bipolar disorder had history of psychosis

A Recovery Perspective

- This model has several features
  - Symptom control: achieving clinical remission
  - Improvement in functional status
  - A cooperative perspective on treatment
  - A focus on development of independence and autonomy

- One of the major determinants of recovery will be the use of functional abilities in the real world

Harvey PD. *Schizophr Bull* 2009;35:299.
Criteria for Clinical Remission

• Focus on clinical symptoms
• None of the main Criterion A symptoms are present:
  • Delusions (P1)
  • Hallucinations (P3)
  • Unusual Thought Content (G9)
  • Conceptual Disorganization (P2)
  • Mannerisms and Posturing (G5)
  • Blunted Affect (N1)
  • Social Withdrawal (N4)
  • Lack of Spontaneity (N6)
• Period is defined as 6 months or more

Functional Remission: A Developing Perspective

- Recovery includes both sustained symptomatic remission and functional improvements
- It is possible to define functional remission
- Such a definition should cover both the breadth of functional improvement and significance of improvement
- Domains of functioning include
  - Social
  - Vocational
  - Independent living

Harvey PD, Bellack AS. Schizophr Bull 2009;35:300-306.
Treatments Aimed at Functional Remission

- Psychosocial treatments, including rehabilitation interventions and cognitive remediation
- Pharmacological treatments
Three separate studies have shown that cognitive remediation leads to important functional improvements in patients who are attempting to achieve psychosocial gains. Some of these improvements are substantial.

Cognitive Training and Supported Employment: 1- and 3-Year Results from a Randomized Control Trial

Improvement in Cognitive Function: MCCB Effect Size for Lurasidone and Ziprasidone

3-week study in stable patients with schizophrenia

MCCB = MATRICS Consensus Cognitive Battery, www.matricsinc.org
Schizophrenia Cognition Rating Scale (SCoRS) Mean Change

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean Change from Baseline</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUR 120 mg (n = 116)</td>
<td><strong>0.6</strong></td>
<td>0.35</td>
</tr>
<tr>
<td>ZIP 160 mg (n = 121)</td>
<td>-0.2</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**p < .01 from baseline; NS (p = .161) between groups (ITT, LOCF); SCoRS = Schizophrenia Cognition Rating Scale

MK-801 Induced Passive Avoidance Deficit Model

training

naive rats

Inescapable shock

MK801

1 day later

MK801 + Lurasidone

do not enter the dark room

test

enter the dark room

1 day later

1 day later

MK-801 = dizocilpine

Evaluating Atypical Antipsychotic Ability to Reverse MK-801 Induced Impairment

Conclusions

- Disability is present across the course of schizophrenia, with similar impairments found in people with schizophrenia across different Western and Eastern cultures
- Current thinking about treatment focuses on remission and recovery
- Functional remission can be defined and measured
- Psychosocial and pharmacological treatments have shown potential for inducing some components of remission
- Integrated psychosocial and pharmacological treatments may be most important for advancing remission and promoting recovery
Q & A

Philip D. Harvey, PhD
Panel Questions and Answers

W. Wolfgang Fleischhacker, MD
Donald C. Goff, MD
Philip D. Harvey, PhD
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Prevention, Guidelines, and Early Recognition

Faculty: Larry Culpepper, MD, MPH; Keith P. Klugman, MD, PhD;
Kristin L. Nichol, MD, MPH, MBA

Wednesday, June 23, 2010
12.00–13.00 Eastern Time (USA)

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neuroscience CME

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August 26-29, 2010
Chicago, Illinois, USA

Visit neuroscienceCME.com/TV461 for current information
Presentation slides are available at neuroscienceCME.com/CINP442
This activity is being recorded, and will be available as a CE-certified on-demand webcast at neuroscienceCME.com/488 in approximately one month.
Advances in the Treatment of Schizophrenia: New Approaches

A Satellite Symposium at the XXVII CINP Congress
The International College of Neuro-Psychopharmacology (CINP)

Glossary of Terms and Bibliography
Advances in the Treatment of Schizophrenia: New Approaches

Glossary of Terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
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</thead>
<tbody>
<tr>
<td>AMI</td>
<td>Amisulpride</td>
</tr>
<tr>
<td>AN</td>
<td>Animal Naming test</td>
</tr>
<tr>
<td>ASE</td>
<td>Asenapine</td>
</tr>
<tr>
<td>BACS</td>
<td>Brief Assessment of Cognition in Schizophrenia</td>
</tr>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>BLO</td>
<td>Blonanserin</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BVMT</td>
<td>Brief Visuospatial Memory Test</td>
</tr>
<tr>
<td>CATIE</td>
<td>Clinical Antipsychotic Trials of Intervention Effectiveness</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CLO</td>
<td>Clozapine</td>
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<tr>
<td>COMP</td>
<td>Composite score</td>
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<tr>
<td>CUTFlass</td>
<td>Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DAI</td>
<td>Drug Attitude Inventory</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>EUFEST</td>
<td>European First Episode Schizophrenia Trial</td>
</tr>
<tr>
<td>FBS</td>
<td>Fasting blood sugar</td>
</tr>
<tr>
<td>FGA</td>
<td>First generation antipsychotic</td>
</tr>
<tr>
<td>HAL</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Depression Rating Scale</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>HVLT</td>
<td>Hopkins Verbal Learning Test</td>
</tr>
<tr>
<td>IGT</td>
<td>Iowa Gambling Task</td>
</tr>
<tr>
<td>ILO</td>
<td>Iloperidone</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LNS</td>
<td>Letter-Number Sequencing</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
</tr>
<tr>
<td>LS</td>
<td>Least squared</td>
</tr>
<tr>
<td>MATRICS-CT</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia-Cognitive Test Battery</td>
</tr>
<tr>
<td>MCCB</td>
<td>MATRICS Consensus Cognitive Battery</td>
</tr>
</tbody>
</table>
Glossary of Terms, continued

MI  Metabolic inhibitor
MK-801 Dizocilpine
MMRM Mixed-Effect Model Repeated Measure
NAB Neuropsychological Assessment Battery
NP Neuropsychological
NS Not significant
NYC New York City
OLZ Olanzapine
PANSS Positive and Negative Syndrome Scale
PEARL Program to Evaluate the Antipsychotic Response to Lurasidone
PER Perphenazine
PBO Placebo
PO Psychiatric-organic
QD Once daily
QLS Quality of Life Scale
QoL Quality of life
QTc Corrected QT interval
QUE Quetiapine
REAP Research on East Asia Psychotropic Prescription
RIS Risperidone
RW Real world
SCoRS Schizophrenia Cognition Rating Scale
SER Sertindole
SGA Second-generation antipsychotic
SLOF Specific Levels of Functioning Scale
SS Steady state
SSRI Selective serotonin reuptake inhibitor
SWN Subjective well-being with neuroleptics
TC Total cholesterol
TD Tardive dyskinesia
THIO Thioridazine
TMT Trail Making Test
UCSD University of California, San Diego
UPSA UCSD Performance-Based Skills Assessment
UPSA-B UCSD Performance-Based Skills Assessment–Brief Version
WCST Wisconsin Card Sorting Test
WMS Wechsler Memory Scale
ZIP Ziprasidone
ZOT Zotepine
Advances in the Treatment of Schizophrenia: New Approaches

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Supplemental Bibliography

Setting the Bar Higher: Functional Remission in Schizophrenia
Philip D. Harvey, PhD

Slide Title: Cognition, Functional Capacity, and Real-World Outcome

Slide Title: What Is Consistent Across Studies?
Supplemental Bibliography, continued

