Switching and Selecting Atypical Antipsychotic Drugs: Paliperidone

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Switching and selecting atypical antipsychotic drugs:
Paliperidone

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Disclosure

• Research, education & travel grant. Speakers group & advisory panels:
  • Janssen Cilag
  • Janssen Ortho
  • Astra Zeneca. Canada & UK
  • Pfizer

• Roche Pharmaceuticals
  • Nicolus Pharmaceuticals
  • SUN Pharma
  • Prempharma
  • Elli Lily
Learning objectives

• Needs and problems of switch
• Evidence about efficacy of switch
• Paliperidone
• Clinical practice of switching antipsychotics
Pharmacokinetics vs. Pharmacodynamics

Variability is the major determinant of the dose-effect relationship in patients
D$_2$-Receptor Occupancy Fluctuation with Simulated Repeated Dosing

IR 3 mg/d: Fluctuation = 64 – 83%
ER 6 mg/d: Fluctuation = 75 – 78%
What is the prescribing pattern

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

Case
Q2 To which APD
Switch to Paliperidone
Switch to Paliperidone

Switch:
when do we change APD?
How to select new APD

Selecting Antipsychotics

Acute Episode
Relapse
Why do patients discontinue medication?

CATIE 1

Weiden PJ. J.Clin Psychiatry 2007;68 [suppl 1]:12-19
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>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS – 3 months</td>
<td>0.506</td>
<td>0.002</td>
<td>✔</td>
<td>0.002</td>
<td>✔</td>
<td>0.005</td>
<td>✔</td>
<td>0.002</td>
<td>✔</td>
<td>0.084</td>
</tr>
<tr>
<td>PANSS-6</td>
<td>✔✔</td>
<td>✔</td>
<td>&lt;0.001</td>
<td>✔</td>
<td>0.43</td>
<td>✔</td>
<td>0.003</td>
<td>✔</td>
<td>0.018</td>
<td>0.100</td>
</tr>
</tbody>
</table>

• Outcome of switch is dependent upon
  – Medication switched to
  – Medication switched from.
Model of factors that influence decision

Weiden PJ, J.Clin.Psychiatry, 2007;68(suppl 1)
Criteria's for Response

- Considerable divergence of expert opinion
- One survey of experts indicated that a period of 2.6 to 5.5 weeks was required.
- Lack of minimal response after 1 or 2 weeks is a powerful predictor of subsequent poor response.

**Reviews and Overviews**

**Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus**

Nancy C. Andreasen, M.D., Ph.D. New advances in the understanding of schizophrenia etiology, course, and treatment have increased interest in the need for group reviewed available definitions and assessment instruments to provide a conceptual framework for a meaningful, func
<table>
<thead>
<tr>
<th>Dimension of Psychopathology</th>
<th>DSM-IV Criterion</th>
<th>Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) Items</th>
<th>Proposed Remission Criteria Items</th>
<th>Positive and Negative Syndrome Scale Items</th>
<th>Brief Psychiatric Rating Scale (BPRS) Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoticism (reality distortion)</td>
<td>Delusions</td>
<td>Delusions (SAPS) 20</td>
<td>Delusions P1</td>
<td>Grandiosity 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hallucinations</td>
<td>Hallucinations (SAPS) 7</td>
<td>Unusual thought content G9</td>
<td>Suspiciousness 11</td>
<td></td>
</tr>
<tr>
<td>Disorganization</td>
<td>Disorganized speech</td>
<td>Positive formal thought disorder (SAPS) 34</td>
<td>Hallucinatory behavior P3</td>
<td>Unusual thought content 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grossly disorganized or catatonic behavior</td>
<td>Bizarre behavior (SAPS) 25</td>
<td>Conceptual disorganization P2</td>
<td>Hallucinatory behavior 12</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms (psychomotor poverty)</td>
<td>Affective flattening (SANS)</td>
<td>Affective flattening 7</td>
<td>Blunted affect N1</td>
<td>Mannerisms/posturing 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avolition-apathy (SANS)</td>
<td>Avolition-apathy 17</td>
<td>Social withdrawal N4</td>
<td>No clearly related symptom</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anhedonia-asociality (SANS)</td>
<td>Anhedonia-asociality 22</td>
<td>Lack of spontaneity N6</td>
<td>No clearly related symptom</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alogia (SANS)</td>
<td>Alogia 13</td>
<td>Lack of spontaneity N6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required. Rating scale items are listed by item number.

^b Use of BPRS criteria may be complemented by use of the SANS criteria for evaluating overall remission.
Efficacy and safety of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 52-week open-label studies.

Int Clin Psychopharmacol. 2008

This analysis shows that paliperidone extended-release can maintain improvements in symptoms and functioning and is generally well tolerated for up to 52 weeks in schizophrenia patients.


Does the remission sustain??

Paliperidone: Delayed Symptom Recurrence

![Graph showing delayed symptom recurrence with p < 0.001 paliperidone vs. placebo](image)
Is paliperidone better than other AAPD?

For which symptom domain it works best?


Path analysis indicated that up to 33% of negative symptom improvement was a direct treatment effect.

Negative symptom improvement also was indirectly mediated via changes in positive and depressive symptoms.


Is it same or better than Risperidone
KW, 20 years, FES admitted 3 weeks, discharged in ‘good remission’ Olan 10 mg BID, April 2008
Texas Algorithm, 2006

What are evidence-based recommendations for selecting Antipsychotic medication?

Partial or No Response

Consider earlier trial of clozapine in patients with a H/O recurrent suicidality, violence, or comorbid substance abuse. Persistence of positive symptoms > 2 years warrants & > 5 years requires a clozapine trial, independent of number of antipsychotic trials.
## Benefits of switching

*Figure 2. Potential Side Effect Benefits When Switching Between Antipsychotic Medications*

<table>
<thead>
<tr>
<th>Preswitch Antipsychotic</th>
<th>Postswitch Antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haloperidol</strong></td>
<td></td>
</tr>
<tr>
<td>↓ EPS</td>
<td>↓ Prolactin</td>
</tr>
<tr>
<td>↓ Akathisia</td>
<td>↓ EPS</td>
</tr>
<tr>
<td>↓ Sedation</td>
<td></td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Akathisia</td>
<td>↓ EPS</td>
</tr>
<tr>
<td>↓ Insomnia</td>
<td></td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Dyslipidemia</td>
<td>↓ Weight</td>
</tr>
<tr>
<td>↓ Sedation</td>
<td></td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Sedation</td>
<td>↓ Dyslipidemia</td>
</tr>
<tr>
<td>↓ Weight</td>
<td></td>
</tr>
<tr>
<td><strong>Risperidone</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Prolactin</td>
<td>↓ Dyslipidemia</td>
</tr>
<tr>
<td>↓ Weight</td>
<td></td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Prolactin</td>
<td></td>
</tr>
<tr>
<td>↓ Sedation</td>
<td></td>
</tr>
</tbody>
</table>

*Reprinted with permission from Weiden.*
Figure 1. Time Course of Side Effects: Withdrawal, Early, and Persistent

- "Withdrawal" Side Effects
- "Early" Side Effects
- "Persistent" Side Effects

Time: Days, Weeks, Months

Previous Antipsychotic

New Antipsychotic
Antihistaminic Effects of Antipsychotics

*Sedation is dose-related and usually abates after several weeks.
†Sedation also possible; insomnia usually abates after several weeks.

Adapted from Weiden, P. J., 2007
Incidence of Cardiac Adverse Events Occurring in $\geq 5\%$ of Patients, n (%)

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo N=355</th>
<th>3 mg N=127</th>
<th>6mg N=235</th>
<th>9mg N=246</th>
<th>12mg N=242</th>
<th>15mg N=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>10 (3)</td>
<td>3 (2)</td>
<td>17 (7)</td>
<td>18 (7)</td>
<td>18 (7)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Sinus Tachycardia</td>
<td>15 (4)</td>
<td>11 (9)</td>
<td>9 (4)</td>
<td>10 (4)</td>
<td>17 (7)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>QTc Prolongation</td>
<td>9 (3)</td>
<td>4 (3)</td>
<td>9 (4)</td>
<td>7 (3)</td>
<td>12 (5)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

No clinically relevant difference between proportions of QTc in pali vs. placebo groups (1.6% vs. 1.4%)
## EPS-Related Adverse Events

<table>
<thead>
<tr>
<th>Percent</th>
<th>Placebo</th>
<th>3mg</th>
<th>6mg</th>
<th>9mg</th>
<th>12mg</th>
<th>15mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>13</td>
<td>10</td>
<td>25</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>
P-01-246
PLASMA LEVELS OF PALIPERIDONE IN A NATURALISTIC SETTING

INSTITUTIONS
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2. Hygiene-Institut des Ruhrgebiets, Gelsenkirchen, Germany

AUTHORS
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2. Matthias Weber², Dr., MD
3. Ralf Kudling¹, Dr., MD
4. Eckhard Klieser¹, Prof. Dr., MD

Aims: Paliperidone is a new compound with a special extended release formulation, which was introduced in Germany in 2007. Aim of our examination was to search for a correlation between plasma levels of the compound and efficacy and tolerability in a naturalistic setting.

Methods: Of all inpatients at the evangelical clinics in Gelsenkirchen with the diagnosis of a paranoid schizophrenia according to ICD-10, who received a pharmacological treatment with paliperidone in 2007, 21 patients (14 female/7 male, mean age 42 +/- 14.7 years) underwent blood testing for paliperidone-plasma-concentration. Paliperidone / 9-hydroxyrisperidone was detected by a validated method using liquid chromatography/tandem mass spectrometry (LC/ESI-MS/MS) after protein precipitation and dilution. In the linear range of 2 - 200 µg/l (r = 0.9996) the LLOQ was 2 ng/ml and the inter-day-precision at 20 µg/l was 6.6%.

Results: Severity of illness before treatment was overall 4.4 with a range of 1.2 on the CGI. Treatment outcome was 2.3 with a range of 0.9 on the CGI. Side-effects were not observed. The mean paliperidone-dose was 7.7 ( +/- 2.7) mg/day, 6 patients received 12 mg daily. Plasma-concentrations of paliperidone were 36.25 +/− 20.13 µg/l for all patients, 54.73 +/− 12.84 µg/l for the 12-mg-group and 28.86 +/− 17.76 µg/l for the 6-mg-group. The correlation between dose and plasma-concentration was 0.59, there were no correlations observed for severity of illness, outcome or side-effects.

Conclusions: In our sample, treatment with paliperidone was safe and effective. We could establish a dose-plasma-level-correlation in a naturalistic setting with a mean plasma concentration for 9-hydroxyrisperidone of 36.25 µg/l.
Switching to a new medication yielded no advantage over staying on the previous medication. Staying on olanzapine was associated with greater weight gain.
Outcome switching: CATIE, 2009
Clinical benefit in switching antipsychotics

- Previous CATIE demonstrated equal efficacy in Head-head trial
- This study reiterates equal benefit in switching

**Limitations**

- Subjects were not ‘unresponsive’ dose, duration of previous APD was not known, so ‘mirror-image’ comparison was not possible
Weight Gain Comparision of Atypical Antipsychotics

Incidence of ≥7% Increase in Body Weight in Short-Term Trials*

*Based on United States Product Inserts
**Error bars reflect reporting of weight gain in PI by baseline BMI
***confirmation of US PI
Metabolic profiles of second-generation antipsychotics in early psychosis: Findings from the CATIE study. 2009

WHO IS A CANDIDATE FOR SWITCHING?

Expert Consensus Guidelines recommend the combination of psychosocial interventions plus a trial switch to an antipsychotic with less weight gain liability.

(J Clin Psychiatry 2007;68[suppl 4]:34–39)

### Table 2. Screening and Monitoring for Patients With Schizophrenia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Every 4 Weeks</th>
<th>Every 8 Weeks</th>
<th>Every 12 Weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/family history</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Weight (body mass index)</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

*aReprinted with permission from the American Diabetes Association.*

*bMore frequent assessments may be warranted based on clinical status.*
Side effects of Antipsychotics

Seizure, Arrhythmias, Blood count, Prolactin, Weight, & Metabolic

- Atypical antipsychotic drugs and the risk of sudden cardiac Death,

- [Hematological adverse effects] caused by psychiatric drugs
  - Mazaira S. Vertex. 2008 Nov-Dec;19(82):378-86

- Akathisia and second-generation antipsychotic drugs

- Antipsychotic agents and cardiometabolic morbidity in youth.

- Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol.

- Association between antipsychotic drugs, antidepressant drugs, and venous thromboembolism.

- Antipsychotic-induced hyperprolactinemia.
SWITCHING STRATEGIES FOR ANTIPSYCHOTIC MEDICATION

Figure 4. Antipsychotic Switching Strategies

- **Switching Strategies**: Various methods shown for switching antipsychotic therapy, including Abrupt Switch, Taper Switch, Cross-Taper Switch, and Plateau Cross-Taper Switch.

- **Legend**:
  - Current Antipsychotic
  - New Antipsychotic
  - Overlap of Current and New Antipsychotic

**Abrupt Switch**
- Immediate Discontinuation of Previous Antipsychotic
- Immediate Start of New Antipsychotic

**Taper Switch**
- Immediate Start of New Antipsychotic
- Gradual Discontinuation of Current Antipsychotic

**Cross-Taper Switch**
- Taper Current Antipsychotic
- Gradually Start New Antipsychotic

**Plateau Cross-Taper Switch**
- At Plateau, Treat With Both Current and New Antipsychotic
- Gradual Start of New Antipsychotic
- Taper Current Antipsychotic

Switching only changes nature of Problem

• Do’s (check list)
  – Measuring clinical condition
  – Physical health
  – Base line investigation (EKG, Blood work)
  – Explain
  – Review all medications
  – Attention to D-D-I (take help from Pharmacist)
  – Read new information
  – Monitor
  – Frequent appointment

• Quantification and measurement in psychosis
  – SAPS-SANS
  – PANSS
  – BPRS
  – HDRS
  – ADL
  – GAF
  – QOL
Clinical Consequences of switching

• Good experience for every one
  – Do not reduce the level of monitoring
  – Late consequences and Risk of non-compliance.

• Into bigger problem
  – Withdrawal symptoms of antipsychotic
  – Increase in secondary symptoms (anxiety-insomnia)
  – Persisting side effects of prior APD
  – Emergence of new psychiatric symptoms
    – Side effects of newer APD
    – Break-through Psychosis
    – Fall, giddiness, fainting,
    – Emergency situation (Seizure, low blood count, Cardiac event, Steven-Johnston)
Differences in effects on fasting triglyceride levels were also found between agents in a short, open-label, parallel-group switching strategies.

Figure 3. Changes in Fasting Triglyceride Levels After Switching Antipsychotic Medications

Data from Pfizer FDA Briefing Document. Change from baseline to peak exposure at end of study (15–25 days).

* p < .01.
** p < .001.
Determinants of outcome in schizophrenia
Relapse

Drug Discontinuation

Relapse
Non-adherence is a sign of Partial or Complete Non-response

All Cause Discontinuation rate (%)

All Treatment Groups, CATIE I

74%
Non-adherence or discontinuation is associated (marker) of poor efficacy.
Final message

- Switching should be NOT be a priority situation.
- It does not give any superiority in terms of efficacy amongst SGA except clozapine
- Outcome of switch depends upon both the previous and the new molecule
- The first clinical option should be optimization of dose, schedule, education & non-drug therapies.
- It should be opted only if clinical conditions are compelling
- Whenever switch, due consideration should be given to all denominators of its outcome.
- Not to compromise efficacy
- Not to continue with side effects