Lurasidone
Lurasidone In Vitro Receptor Binding

Log of Ki Values (nM)

HIGH AFFINITY
- Dopamine D<sub>2</sub> Antagonist
- Serotonin 5-HT<sub>2A</sub> Antagonist
- Serotonin 5-HT<sub>7</sub> Antagonist

MODERATE AFFINITY
- Adrenergic α<sub>2C</sub> Antagonist
- Serotonin 5-HT<sub>1A</sub> Partial Agonist
- Adrenergic α<sub>2A</sub> Antagonist

LITTLE or NO AFFINITY
- Muscarinic M<sub>1</sub> IC<sub>50</sub>&gt;1000 nM*
- Histamine H<sub>1</sub> IC<sub>50</sub>&gt;1000 nM*

*IC<sub>50</sub>: half maximal inhibitory concentration.

<table>
<thead>
<tr>
<th>EU Doses (mg, active moiety) Lurasidone</th>
<th>US Doses (mg, HCl salt) Lurasidone HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5</td>
<td>20</td>
</tr>
<tr>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>74</td>
<td>80</td>
</tr>
</tbody>
</table>
Vs Olanzapine - CGI-S

Placebo (n=114)
Lurasidone 37 mg/day (n=119)
Lurasidone 111 mg/day (n=118)
Olanzapine 15 mg/day (n=122)

*P<0.05; **P<0.01; ***P<0.001.

Time to Relapse for Lurasidone Versus Quetiapine XR

CI, confidence interval; HR, hazard ratio; LUR, lurasidone; QXR, quetiapine XR.
Kaplan-Meier Survival Curve up to 365 days.
Study 234 demonstrated that lurasidone was noninferior to quetiapine XR for risk of relapse. The study was not designed to demonstrate superiority of lurasidone over quetiapine XR.

Total Efficacy: SMD±95% CI.

CI, confidence interval; SMD, standardised mean differences.

Mean Weight Changes With Lurasidone (OC) Versus Olanzapine

Mean weight change from open-label baseline to end of open-label extension was:
- Lurasidone/Lurasidone: 0.41 kg
- Olanzapine/Lurasidone: -1.88 kg
- Placebo/Lurasidone: 0.87 kg

8 months = 6-week double-blind + 26-week open-label extension.
BL, baseline; DB, double-blind; OC, observed case.

Median Change in Prolactin With Short-term Lurasidone Treatment

Lurasidone*  Placebo
(n=929)  (n=411)

Median Change From Baseline to Week 6 (ng/mL)

0.00  -1.92

Lurasidone dose, 18.5-148 mg/day.
*May elevate prolactin levels.

### Total Cholesterol and Triglycerides: Change From Baseline at Week 6 (LOCF)

**Total Cholesterol**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Change From Baseline (mg/dL)</th>
<th>Baseline Mean (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=659)</td>
<td>-5.0</td>
<td>191.9</td>
</tr>
<tr>
<td>Lurasidone 18.5-148 mg/day (n=1417)</td>
<td>-5.0</td>
<td>191.1</td>
</tr>
<tr>
<td>Olanzapine 15 mg/day (n=115)</td>
<td>7.7</td>
<td>194.2</td>
</tr>
<tr>
<td>Quetiapine XR 600 mg/day (n=106)</td>
<td>6.2</td>
<td>181.4</td>
</tr>
<tr>
<td>Risperidone 4 mg/day (n=64)</td>
<td>6.6</td>
<td>180.7</td>
</tr>
<tr>
<td>Haloperidol 10 mg/day (n=70)</td>
<td>-8.1</td>
<td>198.0</td>
</tr>
</tbody>
</table>

**Triglycerides**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Change From Baseline (mg/dL)</th>
<th>Baseline Mean (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=659)</td>
<td>-6.2</td>
<td>151.3</td>
</tr>
<tr>
<td>Lurasidone 18.5-148 mg/day (n=1417)</td>
<td>-4.4</td>
<td>148.7</td>
</tr>
<tr>
<td>Olanzapine 15 mg/day (n=115)</td>
<td>24.8</td>
<td>132.7</td>
</tr>
<tr>
<td>Quetiapine XR 600 mg/day (n=106)</td>
<td>9.7</td>
<td>138.1</td>
</tr>
<tr>
<td>Risperidone 4 mg/day (n=64)</td>
<td>3.5</td>
<td>115.9</td>
</tr>
<tr>
<td>Haloperidol 10 mg/day (n=70)</td>
<td>-2.7</td>
<td>185.0</td>
</tr>
</tbody>
</table>

***P≤0.001 versus lurasidone.

Data on file. Sunovion Pharmaceuticals Inc.
Glucose: Change From Baseline at Week 6 (LOCF)

Baseline mean = 97.5 96.9 94.2 92.6 92.6 97.7

*P≤0.05 ; ***P≤0.001 versus lurasidone.

Data on file. Sunovion Pharmaceuticals Inc.
QTc Prolongation of Antipsychotic Drugs Versus Placebo

Lurasidone -0.1 (-0.21 to 0.01)
Aripiprazole 0.01 (-0.13 to 0.15)
Paliperidone 0.05 (-0.18 to 0.26)
Haloperidol 0.11 (0.03 to 0.19)
Quetiapine 0.17 (0.06 to 0.29)
Olanzapine 0.22 (0.11 to 0.31)
Risperidone 0.25 (0.15 to 0.36)
Amilsulpride 0.66 (0.39 to 0.91)
Clozapine NA*
Chlorpromazine NA*

NA, not applicable.
*Insufficient data.
Mean Change in PANSS Total Score: Aripiprazole Versus Olanzapine

Lurasidone

• As good as olanzapine
• Better than quetiapine
• No effect on:
  – Weight
  – Prolactin
  – Glucose
  – Lipids
  – QT
Depots
Conventional long-acting injectables
Survivorship curves for patients who received long-acting fluphenazine decanoate and oral fluphenazine hydrochloride

Hogarty et al. Arch Gen Psychiatry 1979;36:1283–1294
Please note, we have aligned this graph to Figure 1 within the Hogarty et al., 1979 publication. Please confirm that you are happy with this?
Michelle Pelling-West, 17/09/2014

Could skip this slide
Allan Bundgaard Jakobsen, 30/09/2014

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Jenny Muiry, 06/10/2014
### Pairwise comparisons for risk of all-cause discontinuation of the initial antipsychotic treatment and risk of rehospitalisation after a first hospitalisation for schizophrenia\(^a\)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>All-cause discontinuation</th>
<th></th>
<th></th>
<th>Rehospitalisation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted hazard ratio(^b)</td>
<td>95% CI</td>
<td>p</td>
<td>Adjusted hazard ratio(^b)</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Any depot injection compared with equivalent oral formulation</td>
<td>0.41</td>
<td>0.27–0.61</td>
<td>&lt;0.0001</td>
<td>0.36</td>
<td>0.17–0.75</td>
<td>0.007</td>
</tr>
<tr>
<td>Haloperidol depot injection compared with oral haloperidol</td>
<td>0.27</td>
<td>0.08–0.88</td>
<td>0.03</td>
<td>0.12</td>
<td>0.01–1.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Perphenazine depot injection compared with oral perphenazine</td>
<td>0.32</td>
<td>0.19–0.53</td>
<td>&lt;0.0001</td>
<td>0.53</td>
<td>0.22–1.28</td>
<td>0.16</td>
</tr>
<tr>
<td>Risperidone depot injection compared with oral risperidone</td>
<td>0.44</td>
<td>0.31–0.62</td>
<td>&lt;0.0001</td>
<td>0.57</td>
<td>0.30–1.08</td>
<td>0.09</td>
</tr>
<tr>
<td>Zuclopenthixol depot injection compared with oral zuclopenthixol</td>
<td>0.75</td>
<td>0.29–1.89</td>
<td>0.54</td>
<td>0.49</td>
<td>0.11–2.14</td>
<td>0.35</td>
</tr>
</tbody>
</table>

\(^a\)All-cause discontinuation was analysed among those patients who had started their initial antipsychotic treatment during the first 30 days after the index hospitalisation (1,507 patients had started any antipsychotic, and 587 patients had started haloperidol, perphenazine, risperidone, or zuclopenthixol); in the analysis of risk of rehospitalisation, those patients in the total cohort (n=2,588) who had used haloperidol, perphenazine, risperidone, or zuclopenthixol at any time during follow-up were included in the analysis; \(^b\)the hazard ratios are adjusted by using the following as covariates: age at diagnosis, sex, duration of first hospital episode, and current and previous use of anxiolytics, hypnotics and sedatives, antidepressants, drugs used in addictive disorders, analgesics, antiparkinsonian drugs, blood glucose-lowering drugs, and lipid-modifying agents; for risk of rehospitalisation, covariates also included previous use of antipsychotics during the follow-up and the choice of initial antipsychotic. If pooled estimates were weighted using the person-years of each monotherapy category, the adjusted hazard ratios would have been 0.43 (95% CI=0.32–0.58, p<0.0001) for all-cause discontinuation and 0.53 (95% CI=0.32–0.88, p=0.0139) for rehospitalisation; CI=confidence interval

JM90  Proposal to use next slide instead of this one
This slide hidden, to be considered for deletion
Jenny Muir, 06/10/2014
# Licensed LAI doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupentixol (Depixol®)¹</td>
<td>50 mg/4 weeks</td>
<td>400 mg/week</td>
<td>x32</td>
</tr>
<tr>
<td>Fluphenazine (Modecate®)²</td>
<td>12.5 mg/5 weeks</td>
<td>100 mg/2 weeks</td>
<td>x20</td>
</tr>
<tr>
<td>Haloperidol (Haldol®)³</td>
<td>50 mg/4 weeks</td>
<td>300 mg/4 weeks</td>
<td>x6</td>
</tr>
<tr>
<td>Pipotiazine (Piportil®)⁴</td>
<td>50 mg/4 weeks</td>
<td>200 mg/4 weeks</td>
<td>x4</td>
</tr>
<tr>
<td>Zuclopenthixol (Clopixol®)⁵</td>
<td>200 mg/4 weeks</td>
<td>600 mg/week</td>
<td>x12</td>
</tr>
<tr>
<td>Olanzapine (Zypadhera®)⁶</td>
<td>150 mg/2 weeks</td>
<td>300 mg/2 weeks</td>
<td>x2</td>
</tr>
<tr>
<td>Paliperidone (Xeplion®)⁷</td>
<td>50 mg/month</td>
<td>150 mg/month</td>
<td>x3</td>
</tr>
<tr>
<td>Risperidone (Risperdal Consta®)⁸</td>
<td>25 mg/2 weeks</td>
<td>50 mg/2 weeks</td>
<td>x2</td>
</tr>
<tr>
<td>Aripiprazole (Abilify Maintena®)⁹</td>
<td>300 mg/4 weeks</td>
<td>400 mg/4 weeks</td>
<td>x1.3</td>
</tr>
</tbody>
</table>

LAI=long-acting injectable

We have included the SmPC for each drug to support the minimum and maximum doses. Additionally, we have updated the aripiprazole factor to x1.3. Please confirm if this is acceptable?
Michelle Pelling-West, 25/09/2014

This slide seem not to fit in this section as it includes both typical and atypical APs
Allan Bundgaard Jakobsen, 30/09/2014

Slide hidden, to be considered for deletion
Jenny Muiry, 06/10/2014
Attainment of steady-state – classical depots

Time at which efficacy and tolerability are evaluated

Steady state level

Plasma level

Time

Doses
Please provide a reference for this slide.
Michelle Pelling-West, 17/09/2014

Not sure that is the message here. It is not so that efficacy and tolerability of LAIs are evaluated during the first injection interval, only?
I think the slide can be omitted since PK graphs are presented for the various LAIs
Allan Bundgaard Jakobsen, 30/09/2014

Slide hidden, to be considered for deletion
Jenny Muiry, 06/10/2014
Dose-response curve for haloperidol decanoate dose versus relapse

Proportion of patients who developed tardive dyskinesia at some point during 3 years of follow-up

n=6,921 without tardive dyskinesia at baseline; Schizophrenia Outpatients Health Outcomes (SOHO) study
Please note, some of these data (i.e., the range of patients who develop TD) have been published by Novick in J Clin Psychopharmacol 2010. However, not all of these data are supported in the publication. Please provide the 2006 poster for checking and compliance reference mark-up.

Jenny Muiry, 06/10/2014

Slide hidden, to be considered for deletion.
Replace with next slide providing a broader perspective.

Jenny Muiry, 08/10/2014
‘Atypical’ ‘long-acting injectables’
Risperidone LAI
Comparison of oral risperidone versus IM plasma concentrations (simulation)

Active moiety=risperidone plus 9-OH risperidone; IM=intramuscular
Please provide a reference for this slide.
Due to the colours used in the original slide (i.e., yellow), we have traced this graph. Please can you confirm this is acceptable?
Additionally, please can you indicate what the red dashed line represents?
Michelle Pelling-West, 26/09/2014

Slide hidden, to be considered for deletion
Jenny Muiry, 08/10/2014
Serum concentrations of risperidone plus 9-OH risperidone following IM injection of long-acting risperidone or oral risperidone medication

Black line=median value; box=25–75 quartile; error bars=extreme values of the distribution; separate points beyond the error bars represent values considered to be statistical outliers; IM=intramuscular

Slide hidden, to be considered for deletion
Jenny Muir, 08/10/2014
Effect on bed-stay
– mirror-image study of risperidone LAI

Mean number of days spent in hospital
(per patient/year) – total cohort (n=211)

Mean number of days spent in hospital
(per patient/year) – continuers and discontinuers

LAI=long-acting injection
Olanzapine pamoate
Olanzapine pamoate (OP): unique pharmacokinetic profile

Olanzapine plasma concentrations after a single 405 mg OP depot dose, study LOBS (n=129)

Early release of olanzapine allows possibility of no oral supplementation and early onset of effect

Vertical bar=standard deviation; OP=olanzapine pamoate

We have been unable to find any olanzapine data within the Gefvert et al., 2005, or Eerdekens et al., 2004 publications. All data presented is supported by the FDA website. Therefore, should be delete these additional references, please advise?

Please can you indicate what the red dashed line represents?

Michelle Pelling-West, 26/09/2014

Slide hidden, to be considered for deletion

Jenny Muir, 08/10/2014
Post-injection syndrome: possible mechanism

- Mechanism probably related to higher solubility of olanzapine pamoate in blood than in muscle

- Contact with substantial volume of blood results in more ‘rapid release’ of a portion of the dose

- Results in higher than expected systemic olanzapine concentrations

1. McDonnell et al. Presented at CINP, 2008, Munich, Germany;
Please provide McDonnell et al., 2008 for checking. Please note, the Gulliver et al., 2008 abstract (P-02-82), does not support the bullet points or graph on this slide, please advise.

Michelle Pelling-West, 23/09/2014
Paliperidone palmitate
Pharmacokinetic projection for the recommended paliperidone palmitate initiation and maintenance dosing regimen shows considerable overlap with once-daily paliperidone 6 mg

The strengths, expressed are 25, 50, 75, 100, and 150 mg eq paliperidone, equate to 39, 78, 117, 156, and 234 mg paliperidone palmitate, respectively; ER=extended release; mg eq=milligrams equivalent

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Jenny Muir, 08/10/2014
All patients received 150 mg eq on Day 1; the doses expressed as paliperidone palmitate 25, 100, and 150 mg eq equate to 39, 156, and 234 mg of paliperidone palmitate, respectively; on the day of injection (Days 1, 8, 36, and 64), the samples were taken predose; the 25th and 75th quartiles are depicted in the graph; mg eq=milligrams equivalent

Please can you clarify what the red dashed line represents?
Michelle Pelling-West, 25/09/2014

Slide hidden, to be considered for deletion
Jenny Muiry, 08/10/2014
Log-rank test, p<0.0001; intent-to-treat final analysis set; fewer paliperidone palmitate patients (18% [36/205]) than placebo patients (48% [97/203]) experienced a relapse event in the final analysis.

What dose?

Approximate dose equivalence

<table>
<thead>
<tr>
<th>Risperidone oral (mg/day) (bioavailability=70%)</th>
<th>Paliperidone oral (mg/day) (bioavailability=28%)</th>
<th>Risperidone LAI (mg/2 weeks)</th>
<th>Paliperidone palmitate (mg/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2</strong></td>
<td><strong>4</strong></td>
<td><strong>25</strong></td>
<td><strong>50</strong></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td><strong>6</strong></td>
<td><strong>37.5</strong></td>
<td><strong>75</strong></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td><strong>9</strong></td>
<td><strong>50</strong></td>
<td><strong>100</strong></td>
</tr>
<tr>
<td><strong>6</strong></td>
<td><strong>12</strong></td>
<td><strong>-</strong></td>
<td><strong>150</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ID</th>
<th>Comment</th>
<th>User</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP43</td>
<td>We have added references to this slide, please confirm that this is acceptable.</td>
<td>Michelle Pelling-West</td>
<td>25/09/2014</td>
</tr>
<tr>
<td>ABJ11</td>
<td>This slide could be skipped</td>
<td>Allan Bundgaard Jakobsen</td>
<td>30/09/2014</td>
</tr>
<tr>
<td>JM78</td>
<td>Slide hidden, to be considered for deletion</td>
<td>Jenny Muiry</td>
<td>06/10/2014</td>
</tr>
</tbody>
</table>
Paliperidone palmitate long-acting injection – prospective year-long follow-up of use in clinical practice


Objective: To follow-up patients prescribed paliperidone palmitate long-acting injection (PP) over 1 year to determine factors predicting continuation with PP treatment.

Method: Naturalistic observation of patients registered as starting PP in a single healthcare unit in London, UK. Monovariate and multivariate (Cox regression) analysis of factors predicting continuation at 1 year.

Results: Data were available for 210 patients consecutively prescribed PP of whom 10 were lost to follow-up. At 1 year, 65% of 200 patients (176 with a diagnosis of schizophrenia or schizoaffective disorder) started on PP were still receiving it. The main reason for discontinuation was perceived ineffectiveness (52% of discontinuers); only 10 subjects (5% of total) discontinued because of adverse effects. Initiation as an out-patient [hazard ratio (HR) 0.39, 95% CI 0.20, 0.67, \( P = 0.001 \)]; being switched from risperidone (HR 0.56, 95% CI 0.32, 0.94, \( P = 0.026 \)) and correct initiation (HR 0.56, 95% CI 0.34, 0.93, \( P = 0.024 \)) were significantly associated with a lower likelihood of discontinuation.

Conclusion: Paliperidone palmitate was effective and well tolerated in this naturalistic cohort. Optimising treatment by targeting PP for patients identified as having lower risk of discontinuation can give rise to continuation rates approaching 80% at 1 year.
Kaplan Meier plot showing proportion of patients (95% CI) prescribed paliperidone palmitate by time

65% continued

70% discontinued risperidone LAI at this point

Number at risk

| No. on drug | 200 | 180 | 164 | 151 | 142 | 131 | 131 |

CI=confidence interval; LAI=long-acting injectable

A hazard ratio of <1 indicates that the group is more likely to continue on paliperidone palmitate at 1 year; CI=confidence interval; SPC=summary of product characteristics


<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (cessation before one year)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>0.78</td>
<td>0.47, 1.28</td>
<td>0.324</td>
</tr>
<tr>
<td>Initiated as out-patient</td>
<td>0.39</td>
<td>0.20, 0.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Previously responsive to treatment</td>
<td>0.58</td>
<td>0.32, 1.02</td>
<td>0.060</td>
</tr>
<tr>
<td>Switched from risperidone in any form</td>
<td>0.56</td>
<td>0.32, 0.94</td>
<td>0.026</td>
</tr>
<tr>
<td>Correctly dosed according to SPC</td>
<td>0.56</td>
<td>0.34, 0.93</td>
<td>0.024</td>
</tr>
</tbody>
</table>
This slide could be skipped
Allan Bundgaard Jakobsen, 30/09/2014

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Jenny Muiry, 06/10/2014
Dose prescribed (n=194\textsuperscript{a})

\textbf{Mean dose of paliperidone palmitate at 1 year, or at time of discontinuation=99.1 mg/month (risperidone=80 mg/month)}

\begin{itemize}
  \item 50 mg: 10\%
  \item 75 mg: 18\%
  \item 100 mg: 54\%
  \item 150 mg: 18\%
\end{itemize}

\textsuperscript{a}Six patients did not receive the first maintenance dose

We have aligned the data presented in the graph to that presented in Table 5 within the publication (i.e., originally, 10% of patients were reported as being on the 150 mg maintenance dose - we have changed this to 18%). Please note, we have been unable to find, within the publication, the reported mean dose of risperidone. Please provide a reference to support this.

Michelle Pelling-West, 25/09/2014

This slide could be skipped

Allan Bundgaard Jakobsen, 30/09/2014

Slide hidden, to be considered for deletion

Jenny Muiry, 06/10/2014
Mirror study – hospital admissions and number of days spent in hospital before and after paliperidone palmitate LAI

Mean number of hospitalisations per patient/year (p=0.0001)

<table>
<thead>
<tr>
<th>Period prior to initiation of PP</th>
<th>Period following initiation of PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of hospital admissions</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Mean number of hospital bed days per patient/year (p=0.0001)

<table>
<thead>
<tr>
<th>Period prior to initiation of PP</th>
<th>Period following initiation of PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of hospital bed days</td>
<td>38.8</td>
</tr>
</tbody>
</table>

Mean number of hospital admissions and hospital bed days for 3 years before starting PP were compared with the mean yearly figure with the year following discharge from hospital having started PP (inpatients) or from the date of PP initiation (outpatients). 200 consecutive patients initiated on PP for 1 year; PP=paliperidone palmitate

Allan and Ross, we have prepared this new slide based on the Taylor & Olofinjana. Int Clin Psychopharmacol 2014;29:229–234 publication. Is this what you were looking for, Ross?

Jenny Muiry, 08/10/2014
Bed days – number of bed days spent in hospital (per patient/year)

Data indicate that paliperidone palmitate is likely to be cost-effective: its purchase cost (close to £5,000/year at maximum dose) is outweighed by savings made on reduced hospitalisations (estimated cost/day of UK psychiatric inpatient care is £338; 16 days is £5,408)

The data values are not presented in the publication. Therefore, should we also state 'Data on file'? Alternatively, we should remove the data values, please advise?

A saving of £5,200/year is not stated in the publication. Please can you clarify how this was calculated?

Michelle Pelling-West, 26/09/2014

Slide hidden, to be considered for deletion

Jenny Muiry, 08/10/2014
Effectiveness of paliperidone palmitate versus haloperidol decanoate for maintenance treatment of schizophrenia – a randomised clinical trial

Joseph P. McEvoy, MD; Matthew Byerly, MD; Robert M. Hamer, PhD; Rosalie Dominik, DrPH; Marvin S. Swartz, MD; Robert A. Rosenheck; Neepa Ray, MS; J. Steven Lambert, MD; Peter F. Buckley, MD; Tania M. Wilkins, MS; T. Scott Stroup, MD, MPH

IMPORTANCE Long-acting injectable antipsychotics are used to reduce medication nonadherence and relapse in schizophrenia-spectrum disorders. The relative effectiveness of long-acting injectable versions of second-generation and older antipsychotics has not been assessed.

OBJECTIVE To compare the effectiveness of the second-generation long-acting injectable antipsychotic paliperidone palmitate with the older long-acting injectable antipsychotic haloperidol decanoate.

DESIGN, SETTING, AND PARTICIPANTS Multisite, double-blind, randomized clinical trial conducted from March 2011 to July 2013 at 22 US clinical research sites. Randomized patients (n = 311) were adults diagnosed with schizophrenia or schizoaffective disorder who were clinically assessed to be at risk of relapse and likely to benefit from a long-acting injectable antipsychotic.

INTERVENTIONS Intramuscular injections of haloperidol decanoate 25 to 200 mg or paliperidone palmitate 39 to 234 mg every month for as long as 24 months.

MAIN OUTCOME MEASURES Efficacy failure, defined as a psychiatric hospitalization, a need for crisis stabilization, a substantial increase in frequency of outpatient visits, a clinician’s decision that oral antipsychotic could not be discontinued within 8 weeks after starting the long-acting injectable antipsychotics, or a clinician’s decision to discontinue the assigned long-acting injectable due to inadequate therapeutic benefit. Key secondary outcomes were common adverse effects of antipsychotic medications.

RESULTS There was no statistically significant difference in the rate of efficacy failure for paliperidone palmitate compared with haloperidol decanoate (adjusted hazard ratio, 0.98; 95% CI, 0.65-1.47). The number of participants who experienced efficacy failure was 49 (33.8%) in the paliperidone palmitate group and 47 (32.4%) in the haloperidol decanoate group. On average, participants in the paliperidone palmitate group gained weight and those in the haloperidol decanoate group lost weight; after 6 months, the least-squares mean weight change for those taking paliperidone palmitate was increased by 2.17 kg (95% CI, 1.25-3.09) and was decreased for those taking haloperidol decanoate (−0.96 kg; 95% CI, −1.88 to −0.04). Patients taking paliperidone palmitate had significantly higher maximum mean levels of serum prolactin (men, 34.56 µg/L [95% CI, 29.75-39.37] vs 15.41 µg/L [95% CI, 10.73-20.08]; P < .001, and for women, 75.19 [95% CI, 63.03-87.36] vs 26.84 [95% CI, 13.29-40.40]; P < .001). Patients taking haloperidol decanoate had significantly larger increases in global ratings of akathisia (0.73 [95% CI, 0.59-0.87] vs 0.45 [95% CI, 0.31-0.59]; P < .001).

CONCLUSIONS AND RELEVANCE In adults with schizophrenia or schizoaffective disorder, use of paliperidone palmitate vs haloperidol decanoate did not result in a statistically significant difference in efficacy failure, but was associated with more weight gain and greater increases in serum prolactin, whereas haloperidol decanoate was associated with more akathisia. However, the CIs do not rule out the possibility of a clinically meaningful advantage with paliperidone palmitate.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01136772
**Study design – loading strategy**

**Oral risperidone**
2 mg/day (Day -1 & -2)  
Then 4 mg/day (Days -3 to -7)

- Paliperidone palmitate  
  234 mg intramuscularly, Day 1

- Paliperidone palmitate  
  156 mg intramuscularly, Day 8

- Paliperidone palmitate  
  117 mg intramuscularly, Day 28

**Oral haloperidol**
2 mg/day (Day 1 & 2)  
Then 4 mg/day (Days -3 to -7)

- Haloperidol decanoate  
  50 mg intramuscularly, Day 1

- Haloperidol decanoate  
  50 mg intramuscularly, Day 8

- Haloperidol decanoate  
  75 mg intramuscularly, Day 28

311 patients were randomised to treatment: 157 randomised to receive paliperidone; 154 randomised to receive haloperidol

We have included the dosing schedule for paliperidone. Please advise if this is acceptable?
Michelle Pelling-West, 25/09/2014

This slide could be skipped
Allan Bundgaard Jakobsen, 30/09/2014

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Jenny Muiry, 06/10/2014
Adjusted hazard ratio for paliperidone palmitate versus haloperidol decanoate, 0.98 (95% CI, 0.65–1.47); efficacy failure, determined by an outcome adjudication committee, reflected inadequate control of psychopathology; CI=confidence interval

## Outcome measures of safety in the modified intent-to-treat population (1)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Paliperidone palmitate (n=147)</th>
<th>Haloperidol decanoate (n=147)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (LS mean) from baseline, mean (95% CI), kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>2.17 (1.25 to 3.09)</td>
<td>-0.96 (-1.88 to -0.04)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 12</td>
<td>3.46 (1.83 to 5.09)</td>
<td>-1.93 (-3.56 to -0.31)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 18</td>
<td>4.75 (2.36 to 7.14)</td>
<td>-2.91 (-5.28 to -0.53)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 24</td>
<td>6.04 (2.88 to 9.20)</td>
<td>-3.88 (-7.02 to -0.73)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ever gained ≥15 lbs from baseline, No. (%)</td>
<td>48 (33.1)</td>
<td>32 (22.4)</td>
<td>0.03&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>At least 1 laboratory assessment after first injection, No. of patients</td>
<td>129</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Laboratory values, worst change from baseline; results LS mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1C&lt;/sub&gt;, %</td>
<td>0.34 (0.17 to 0.52)</td>
<td>0.23 (0.06 to 0.41)</td>
<td>0.38&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>21.13 (12.59 to 29.67)</td>
<td>20.96 (12.38 to 29.54)</td>
<td>0.98&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>12.42 (7.20 to 17.63)</td>
<td>16.82 (11.56 to 22.07)</td>
<td>0.25&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>11.70 (7.06 to 16.34)</td>
<td>13.49 (8.85 to 18.14)</td>
<td>0.59&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>36.91 (22.40 to 51.43)</td>
<td>46.57 (31.93 to 61.21)</td>
<td>0.36&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>-5.28 (-6.74 to -3.83)</td>
<td>-4.52 (-5.98 to -3.05)</td>
<td>0.47&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neurologic effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS global severity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of AIMS ≥2, No. (%)</td>
<td>28 (21.4)</td>
<td>30 (23.8)</td>
<td>0.57&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Worst change from baseline, LS mean (95% CI)</td>
<td>0.43 (0.31 to 0.55)</td>
<td>0.50 (0.38 to 0.62)</td>
<td>0.39&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>BARS global score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of BARS ≥3, No. (%)</td>
<td>4 (2.8)</td>
<td>15 (10.6)</td>
<td>0.006&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Worst change from baseline, LS mean (95% CI)</td>
<td>0.45 (0.31 to 0.59)</td>
<td>0.73 (0.59 to 0.87)</td>
<td>0.006&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>SAS mean score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of SAS ≥1, No. (%)</td>
<td>109 (79.0)</td>
<td>101 (74.8)</td>
<td>0.45&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Worst change from baseline, LS mean (95% CI)</td>
<td>0.21 (0.16 to 0.27)</td>
<td>0.25 (0.20 to 0.30)</td>
<td>0.34&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Comparison of paliperidone palmitate versus haloperidol decanoate; <sup>b</sup>test of time-by-treatment interaction; <sup>c</sup>comparison of binary outcomes is from a Cochran-Mantel-Haenszel test stratified by grouped site; <sup>d</sup>overall comparison between treatment groups obtained from ANCOVA, adjusting for baseline value and pooled site. The least-squares mean and standard error are from the corresponding ANCOVA model; LS=least squares; CI=confidence interval

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Jenny Muiry, 08/10/2014
Outcome measures of safety in the modified intent-to-treat population (2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Paliperidone palmitate (n=147)</th>
<th>Haloperidol decanoate (n=147)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum prolactin levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among men only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest level after baseline, LS mean (95% CI), µg/L</td>
<td>34.56 (29.75 to 39.37)</td>
<td>15.41 (10.73 to 20.08)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Worst ASEX after baseline, LS mean (95% CI)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17.68 (16.36 to 19.00)</td>
<td>17.95 (16.66 to 19.25)</td>
<td>0.77&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ASEX score ≥19, No. (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>34 (37.8)</td>
<td>37 (39.4)</td>
<td>0.72&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incidence of gynecomastia or galactorrhoea, No. (%)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>5 (4.7)</td>
<td>3 (2.8)</td>
<td>0.46&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Among women only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest level after baseline, LS mean (95% CI), µg/L</td>
<td>75.19 (63.03 to 87.36)</td>
<td>26.84 (13.29 to 40.40)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Worst ASEX after baseline, LS mean (95% CI)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23.41 (21.01 to 25.80)</td>
<td>22.83 (20.12 to 25.54)</td>
<td>0.75&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ASEX score ≥19, No. (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24 (72.7)</td>
<td>19 (73.1)</td>
<td>0.88&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incidence of gynecomastia, menstrual irregularities, or galactorrhoea, No. (%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>10 (38.5)</td>
<td>5 (29.4)</td>
<td>0.13&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Comparison of paliperidone palmitate versus haloperidol decanoate; <sup>b</sup>overall comparison between treatment groups obtained from ANOVA, adjusting for pooled site. The least-squares mean and standard error are from the corresponding ANOVA model; <sup>c</sup>comparison of binary outcomes is from a Cochran-Mantel-Haenszel test stratified by grouped site; <sup>d</sup>ASEX range is 6 to 30, with higher scores representing worse sexual functioning; <sup>e</sup>from the Barnard exact test, due to low event counts in men; <sup>f</sup>incidence is among premenopausal women only and includes only moderate or severe effects (n=26 for the paliperidone group, and n=17 for the haloperidol group); LS=least squares; CI=confidence interval

Is tardive dyskinesia worse with haloperidol?

There was no statistically significant difference in the incidence of probable tardive dyskinesia (p=0.24)

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Jenny Muir, 08/10/2014
But...

Significantly more patients taking haloperidol decanoate than paliperidone palmitate started on a medication to treat parkinsonism (p=0.007)

Slide hidden, to be considered for deletion
Jenny Muir, 08/10/2014
Dose-response curve for haloperidol decanoate dose versus relapse

This slide could be skipped
Alan Bundgaard Jakobsen, 30/09/2014

Slide hidden, to be considered for deletion
Jenny Muiry, 06/10/2014
Aripiprazole once-monthly LAI
## Tolerability

<table>
<thead>
<tr>
<th>Weight gain (SMD)</th>
<th>EPS (OR)</th>
<th>Prolactin (SMD)</th>
<th>QTc (SMD)</th>
<th>Sedation (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAL</td>
<td>CLO</td>
<td>ARI</td>
<td>LUR</td>
<td>AMI</td>
</tr>
<tr>
<td>ZIP</td>
<td>SER</td>
<td>QUE</td>
<td>ARI</td>
<td>PAL</td>
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<tr>
<td>LUR</td>
<td>OLA</td>
<td>ASE</td>
<td>PAL</td>
<td>SER</td>
</tr>
<tr>
<td>ARI</td>
<td>QUE</td>
<td>ASE</td>
<td>QUE</td>
<td>ILO</td>
</tr>
<tr>
<td>AMI</td>
<td>ILO</td>
<td>OLA</td>
<td>ZIP</td>
<td>RIS</td>
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<tr>
<td>ASE</td>
<td>AMI</td>
<td>CHL</td>
<td>LUR</td>
<td>ASE</td>
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<tr>
<td>PAL</td>
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<td>ILO</td>
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<tr>
<td>RIS</td>
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<td>RIS</td>
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<tr>
<td>OLA</td>
<td></td>
<td>ZOT</td>
<td></td>
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</tr>
</tbody>
</table>

**Favours drug**

**Favours placebo**

**Drug better**

**Placebo better**

SMD = standardised mean differences; OR = odds ratio

Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: an open-label, parallel-arm, multiple-dose study

Phase 1b open-label study in patients with schizophrenia (n=41)

Concomitant oral aripiprazole 10 mg/day x 14 days

Mean aripiprazole concentration, ng/ml

Time, weeks

0 4 8 12 16 20 24 28

Aripiprazole once-monthly injections

Concomitant oral aripiprazole 10 mg/day x 14 days

400 mg (n=12)

300 mg (n=8)

200 mg (n=4)

aAfter the first aripiprazole once-monthly injection, continue treatment with oral aripiprazole for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy

Slide hidden, to be considered for deletion
Jenny Muir, 08/10/2014
Time from randomisation to impending relapse during double-blind treatment

Relapse rates at final analysis
Aripiprazole-OM: 10.0%
Placebo-OM: 39.6%

Hazard ratio: 5.03
95% CI: 3.15–8.02
Log-rank test: p<0.0001

Number of patients at risk
Aripiprazole-OM: 269 244 201 186 153 130 104 76 63 54 44 36 30 23
Placebo-OM: 134 118 85 68 53 45 37 27 22 14 12 9 5 3

CI=confidence interval; OM=once-monthly
We have split your original slide into two, so that each graph is more visible. Please advise if this is acceptable?

Michelle Pelling-West, 26/09/2014
Mirror study
– total psychiatric hospitalisation rates before and after prospective treatment with aripiprazole-OM

Total psychiatric hospitalisation rate between retrospective period (Months -4 to -1) and prospective period (Months 4 to 6) (p<0.0001)

Total psychiatric hospitalisation rate between retrospective 6-month period and prospective 6-month period (p<0.0001)

<table>
<thead>
<tr>
<th>Patients who completed 3 months treatment on aripiprazole-OM (n=336)</th>
<th>All patients who entered Phase B treatment with aripiprazole-OM (n=433)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with ≥1 psychiatric hospitalisation</td>
<td>Percentage of patients with ≥1 psychiatric hospitalisation</td>
</tr>
<tr>
<td>27.1%</td>
<td>38.1%</td>
</tr>
<tr>
<td>2.7%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

OM=once-monthly
Kane et al. J Med Econ 2014 (Provisionally accepted)
Conclusions

• Long-acting injectables improve outcomes

• Typical depots are difficult to use

• Optimally dosed typical depots may be near equivalent in some respects

• Atypical depots – varied outcomes

• Paliperidone LAI/aripiprazole-OM probably cost-effective

• Aripiprazole-OM lacks significant metabolic, cardiac, and prolactin-related effects

LAI=long-acting injectable; OM=once-monthly
Conclusions slide will need to be updated once final deck is decided upon.

The bullet, "Paliperidone LAI/arianiprazole-OM probably cost-effective" will need to be deleted.

Jenny Muir, 08/10/2014