Do we really need depot antipsychotics?

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Disclosure statement
Höschl, 2011-2012

Paid consultant:
— Lundbeck (LINF faculty member)
— Servier (research)

Lectures abroad:
— Eli Lilly
— ECNP
— Lupin/EPA

Lectures in the Czech Rep. Eli Lilly, others (Janssen-Cilag, Krka, BMS, GSK, EGIS) for: Academia Medica Pragensis
Disclosure statement

This lecture is sponsored by:

The presentation reflects only the speaker's points of view, and not necessarily those of the meeting sponsor (Eli Lilly and Company).

The registered indication for different drugs may vary across different countries, for further information see the SPC recommendations specific to your country.
Reasons to administer depot antipsychotics

- Comfort of both doctor and patient
- Belief in a higher efficiency
- Tradition (AP1G)
- Pressure of a family
- In general **LAI as a solution of non-adherence**
- other (economics etc.)

\[ \text{LAI} = \text{long acting injections} \]
Reasons against administration of depot AP

- Rather invasive way of administration
- Irreversibility of applied dose
- Less flexibility
- Worries of major side-effects
- In general LAI as a tool of doctor’s dominance
- Other (price etc.)

AP=antipsychotics
## Non-adherence

<table>
<thead>
<tr>
<th>Dg:</th>
<th>non-adherence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>55-71</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19-80</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>53</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>20-80</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>54-82</td>
</tr>
</tbody>
</table>

*Lacro et al., 2002, Fenton et al., 1997*
Non-adherence

Schizophrenia and its specifics:
1) Loss of insight
2) Disorganization and cognitive deficit
3) Often lifelong treatment
4) Stigma

Average p.o. nonadherence in schizophrenia: 41.2-49.5%

<table>
<thead>
<tr>
<th>Psychiatry</th>
<th>20-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>54-82</td>
</tr>
</tbody>
</table>

Lacro et al., 2002, Fenton et al., 1997

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Consequences of non-adherence

2. Lage & Hassan. *Ann Gen Psychiatry* 2009;8:7;

- Higher health care costs
- Relapse
- Rehospitalization
- Low satisfaction with own life
- Suicides
- Impaired cognitive & psycho-social functioning
- Non-adherence

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Proportion of hospitalized patients by the number of days of omitted medication within 1 year

Weiden et al., 2004
Continual/intermittent treatment & relapses

Cerpenet et al., 1990
Herz et al., 1991
Jolley et al., 1989, 1990
Pietzcker et al., 1993
Schooler et al. 1993

Proportion of relapses (%)

Modified from: Haddad, 2011
The consequences of relapses?

1) Primarily health and social
2) Economical
Health consequences of relapses

• Higher prevalence of residual symptoms
  Shepherd et al. 1989

• Deepening social impairment
  Hogarty et al. 1989

• Lower response to following treatment
  Wiersma et al. 1998, Lieberman 1996

• Increasing doses of antipsychotics
  Ohmori et al., 1999
Relapses and structural brain changes

Focal decreases in gray matter density (MRI) in patients with schizophrenia (N=96) as compared to healthy individuals (N=113) at baseline (left) and 5 years follow-up (right).

van Haren, 2007
Psychotic condition and brain changes

Cahn et al., 2008
The consequences of relapses?
1) Primarily health and social
2) Economical
Cost of relapses of schizophrenia

Ratio of annual costs - relapses/no relapses is 3 :1

Hong et al., 2009; Ascher-Svanum et al., 2010
RELAPSE

IMPACT ON A PATIENT:
- Functional impairment
- Brain structure changes
- Reduced quality of life
- Aggression
- Drug abuse
- Self-harm
- Self-care degradation

IMPACT ON HEALTH CARE SYSTEM:
A) Higher treatment costs
   - Hospitalization
   - Outpatient
   - Crisis intervention
B) Unrecognized nonadherence
   - Unnecessary medication changes (switch, increase dd., combinations)
   - Wrong diagnosis of pharmacoresistance

PARTIAL/TOTAL NONADHERENCE

PERSISTENT SYMPTOMS

From: Haddad, 2011
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How to improve adherence?

Psychosocial and program interventions

- CBT
- „Compliance therapy“
- Cognitive adaptation
- More frequent and/or longer visits
- Psychoeducation of a patient/family
- Monitoring of symptoms/side-effects

Adherence

Pharmacological interventions

- Dose adjustment to correct adverse effects
- Simpler dosing regime
- Long-acting injections of antipsychotics

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Nonadherence

Non-adherence in LAI:
- **9%** (Shi et al., 2007)
- **5%** (Heyscue et al., 1998)
- **7%** (Lambert et al., 2007)

Average p.o. non-adherence in schizophrenia: 41.2-49.5%

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## Overview of depot antipsychotics

<table>
<thead>
<tr>
<th>Group</th>
<th>Form</th>
<th>Active substance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGA</strong></td>
<td>oil base</td>
<td>Fluphenazine decanoate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>haloperidol decanoate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(flu/zuclo)pentixol decanoate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pipothiazine palmitate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>perphenazine decanoate</td>
</tr>
<tr>
<td><strong>SGA</strong></td>
<td>microspheres</td>
<td>risperidone LAI</td>
</tr>
<tr>
<td></td>
<td>crystal form</td>
<td>olanzapine pamoat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>paliperidone palmitate</td>
</tr>
</tbody>
</table>

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• Esters of active substance with fatty acids: Decanoic acid (C10), enanthic acid (C8), undecylenic (C11) and palmitic acid.

• Esters are fat-soluble, and thus in oil base of depots (sesame and coconut oil or Visceoleo = syntetic vegetable oil).

• Slow release from depot. In plasma ester hydrolysis and release of the active substance happens.
SGA-LAI

• The active substance is contained in polymer mikrospheres (poly D,L lactide-co-glycolide: PLG) subject to biodegradation.
• Active substance is released after 2-3 wks!
• The release culminates about 28th day
• Steady-state is reached after 8 weeks
• Ratio $C_{\text{max}}/C_{\text{min}}=3$
• Dosage à 2 weeks
Olanzapine LAI (OLAI)

- **LAI on crystal base** = salt of pamoic acid and olanzapine in water solution.
- **Slow release** from muscle starts immediately after application.
- **CAVE:** faster dissolution in blood ⇒ postinjection sy
- Release culminates about 2-4 days.
- **Dosage 1 inj. in 2-4 weeks**

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Paliperidonon LAI

- LAI on crystal base = nanocrystals of salt of palmitic acid and paliperidone in water solution.
- Slow release from muscle starts immediately after application.
- Release culminates about 13th day.
- Dosage 1 inj. in 2-4 weeks

Note: Paliperidone palmitate may not be equally effective as RLAI (Fleischhacker et al. 2011)

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## LAI: Practical aspects

<table>
<thead>
<tr>
<th>Substance</th>
<th>Site of application</th>
<th>Form/storage</th>
<th>Preparation and application</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGA LAI</td>
<td>m. gluteus</td>
<td>oil in the ampoule</td>
<td>Z-tracking, need to change the site of inj., lumps</td>
</tr>
<tr>
<td>Risperidone</td>
<td>m. gluteus or m. deltoideus</td>
<td>powder, special kit</td>
<td>Needed to be refrigerated, need of special kits and training; need to apply the whole dose of prepared medicament Z-tracking=0</td>
</tr>
<tr>
<td>Paliperidone LAI</td>
<td>m. gluteus or m. deltoideus</td>
<td>Injections with prepared solution</td>
<td>Choose a needle by weight. Deltoid=faster uptake. Z-tracking=0</td>
</tr>
<tr>
<td>Olanzapine OLAI</td>
<td>m. gluteus</td>
<td>powder, special kit</td>
<td>Needs special kits and training; suspension preparation is time consuming, Higher doses are more voluminous. Z tracking=0. CAVE: 3 hours observation!</td>
</tr>
</tbody>
</table>
## Dosing equivalents - SGA p.o. vs SGA-LAI

<table>
<thead>
<tr>
<th>SGA-LAI</th>
<th>Equivalent of target p.o. dose</th>
<th>Dose/Frequency of LAI</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone</td>
<td>&lt;3 mg p.o.</td>
<td>25 mg/2 weeks</td>
<td>Bai et al., 2007</td>
</tr>
<tr>
<td></td>
<td>3-5 mg p.o.</td>
<td>37.5 mg/2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5 mg p.o.</td>
<td>50 mg/2 weeks</td>
<td></td>
</tr>
<tr>
<td>paliperidone</td>
<td>6 mg</td>
<td>117 mg/4 weeks</td>
<td>Citrome 2010; Janssen 2009; Samtani et al 2009</td>
</tr>
<tr>
<td></td>
<td>9 mg</td>
<td>156 mg/4 weeks</td>
<td></td>
</tr>
<tr>
<td>olanzapine</td>
<td>10 mg</td>
<td>150 mg/2 weeks</td>
<td>Citrome 2009; Eli Lilly 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg/4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 mg</td>
<td>210 mg/2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>405 mg/4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>300 mg/2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 4 weeks equivalent</td>
<td></td>
</tr>
</tbody>
</table>

Modified from: **Haddad, 2011**

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Efficacy of LAI vs. oral antipsychotics
RCT meta-analysis: Efficacy of FGA-LAI vs. oral AP

- Total: **848 patients**
- LAI: **fluphenazine** decanoate, **fluspirilene** decanoate, **pipothiazine** palmitate.
- p.o.: **chlorpromazine**, **haloperidol**, **penfluridol**, **trifluoperazine**.
- **No difference** in risk of relapse (RR=0.96; 95% CI: 0.8-1.1).
- Global improvement, however, more often on FGA-LAI (**NNT=4**, 95% CI: 2-9).

*Adams 2001*
RCT meta-analysis: Efficacy of FGA-LAI vs. oral AP

- Total: **848 patients**
- LAI: fluphenazine decanoate, fluspirilene decanoate, pipotiazine palmitate.
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*Adams 2001*
Prospective observational study: Efficacy of FGA-LAI vs. oral AP

1. LAI more effective  
   Tiihonen et al. 2006; Zhu et al., 2008

2. Less effective than olanzapine p.o.  
   SOHO, Haro et al., 2006, 2007

3. More effective in fluphenazine decanoate, less effective in haloperidole decanoate  
   Conley et al., 2003

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Observational prospective cohort study

- Finnish population with 1\textsuperscript{st} episode of \textit{schizophrenia} (n=2230) observed 1995-2005.
- Relative risk of \textit{rehospitalization} in 10 AP (9 \textit{p.o.}+ perphenazine depot) vs haloperidol \textit{p.o.}
- Lowest risk in \textit{perphenazine depot} (adjusted relative risk = 0.41; 95\% CI = 0.29–0.59).

\textit{Tiihonen et al., 2006}
Results:

1. Initial use of clozapine (RR 0.17; [95%CI 0.1-0.29]), perphenazine depot (0.24[0.13-0.47]) and olanzapine (0.35[0.18-0.71]) led to the lowest rate of discontinuation compared to haloperidol p.o.

2. In average 3.6 years → 4640 rehospitalizations

3. Lowest incidence of rehospitalizations was on perphenazine depot (RR 0.32[95%CI 0.22-0.49]), olanzapine (0.54[0.41 -0.71]) and clozapine (0.64; [0.48-0.85])
Tiihonen J, Wahlbeck K, Lönnquist J, Klaukka T, Ioannidis JPA, Volavka J, Haukka J:

Perphenazine depot

Olanzapine
Clozapine
Chlorprothixen
Thioridazine
Perphenazine
Risperidone
Combination etc.
Haloperidol
Chlorpromazine
Levomepromazine
Without medication

Rehospitalizations

Adj.RR(95%CI)

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Results-cont.: 

4. Haloperidol was associated with a poor outcome among women

5. Mortality was markedly raised in patients with no antipsychotics (RR 12.3; [95%CI 6-24.1]) and risk of suicide was high (RR 37.4; [5.1-276])
Mirror studies: Distribution (%) of a total length of hospitalization BEFORE and AFTER onset of FGA-LAI (podle Haddad, 2011)

BEFORE (p.o.)  AFTER FGA LAI

Denham a Adamson 1971
Gottfries a Green 1974
Morritt 1974
Johnson 1979
Lindholm 1975
Marriott a Hiep 1976
Polonowita a James 1976
Devito et al. 1978
Freeman 1980
Tan et al. 1981
Tegeler a Lehmann 1981

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Efficacy of LAI (FGA+SGA) vs. oral AP- Summary
Oral versus depot antipsychotic drugs for schizophrenia—A critical systematic review and meta-analysis of randomised long-term trials

Claudia Leucht, Stephan Heres, John M. Kane, Werner Kissling, John M. Davis, Stefan Leucht

Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar der Technischen Universität München, Ismaningerstr. 22, 81675 München, Germany
Department of Psychiatry, University of Chicago at Illinois, Chicago, USA
The Zucker Hillside Hospital, Psychiatry Research, North Shore—Long Island Jewish Health System, Glen Oaks, New York, NY, USA

Meta-analysis of 10 randomized, controlled studies of oral vs depot antipsychotics

n=1700 patients

LAI (FGA+SGA) vs. oral AP RCT Metaanalysis (I)

- RCT > 12 m. Only outpatient studies included. Therefore: pragmatic conditions closer to clinical reality.
- 10 studies (1975-2010), N=1700.
- **LAI:** Fluphenazine depot (6 studies), RLAI (2 studies), haloperidol-decanoat (1), zuclopenthixol-depot (1)
- **Oral:** fluphenazine (N=4), pimozid (N=2), zuclopenthixol (N=1), quetiapine (N=1), olanzapine (N=1) any other AP (N=1).
- Followed variables: Relapse (primary variable), rehospitalisation, non-adherence, drop-out.
**Depot formulas significantly decrease risk of relapse**

**Results**: Ten studies with 1700 patients met inclusion criteria. **Depot formulations significantly reduced relapses** with relative and absolute risk reductions of 30% and 10% respectively (RR 0.70; CI 0.57–0.87; NNT 10; CI 6–25, \( P=.0009 \)), and **dropout due to inefficacy** (RR 0.71, CI 0.57–0.89). Limited data on non-adherence, rehospitalisation, dropout due to any reason, and adverse events revealed no significant differences. There were several potential sources of bias such as limited information on randomisation methods, problems of blinding and different medications in depot and oral groups. Moreover, other studies reduced the potential superiority of depot by excluding non-adherent patients.
Depot formulas significantly decrease risk of relapse

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Depot Events</th>
<th>Oral Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arango 2005</td>
<td>10</td>
<td>6</td>
<td>1.28 [0.56, 2.93]</td>
</tr>
<tr>
<td>Barnes 1983</td>
<td>3</td>
<td>3</td>
<td>0.89 [0.21, 3.85]</td>
</tr>
<tr>
<td>Del Guidice 1975</td>
<td>21</td>
<td>30</td>
<td>0.80 [0.65, 0.99]</td>
</tr>
<tr>
<td>Falloon 1978</td>
<td>8</td>
<td>5</td>
<td>1.92 [0.74, 4.95]</td>
</tr>
<tr>
<td>Gaebel 2010</td>
<td>54</td>
<td>102</td>
<td>0.53 [0.39, 0.71]</td>
</tr>
<tr>
<td>Hogarty 1979</td>
<td>22</td>
<td>32</td>
<td>0.63 [0.43, 0.92]</td>
</tr>
<tr>
<td>Li 1996</td>
<td>32</td>
<td>52</td>
<td>0.54 [0.37, 0.79]</td>
</tr>
<tr>
<td>Potapov 2008</td>
<td>4</td>
<td>8</td>
<td>0.50 [0.18, 1.40]</td>
</tr>
<tr>
<td>Rifkin 1977</td>
<td>2</td>
<td>3</td>
<td>0.81 [0.15, 4.45]</td>
</tr>
<tr>
<td>Schooler 1979</td>
<td>26</td>
<td>35</td>
<td>0.76 [0.49, 1.20]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>843</strong></td>
<td><strong>829</strong></td>
<td><strong>0.70 [0.57, 0.87]</strong></td>
</tr>
</tbody>
</table>

**Total events**
- Depot: 182
- Oral: 276

Heterogeneity: Tau^2 = 0.04; Chi^2 = 15.35, df = 9 (P = 0.08); I^2 = 41%

Test for overall effect: Z = 3.32 (P = 0.0009)

**DIFFERENCE IS ROBUST** (just to compare: absolute difference in the proportion of responders to antidepressants vs. placebo = 10%).

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…but there are new RCTs with SGA LAI (>1y)

- **No** difference between RLAI and **oral aripiprazole** in loss of retention, duration of remission or time to relapse. N=355
  
  *MacFadden et al., 2010*

- **RLAI no** more efficient than oral antipsychotics in the prevention of hospitalisation. N= 369.
  
  *Rosenheck et al., 2011*

- **No** difference between OLAI and olanzapine *p.o.* in time and number of **discontinuation** or in **relapse prevention**. N=525.
  
  *Detke et al., 2011*

- There was significantly **longer time to relapse** in RLAI compared to quetiapine *p.o*. N=666.
  
  *Gaebel et al., 2010*
...but there are new RCTs with SGA LAI (>1y)

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+ There was significantly longer time to relapse in RLAI compared to quetiapine p.o. N=666.
  Gaebel et al., 2010
• **OBJECTIVE:** …long-term treatment effectiveness of monthly injections of olanzapine long-acting injection (LAI) compared with that of daily oral olanzapine.

• **METHODS:** …outpatients ≥ 2 episodes of worsening of schizophrenia in the past 24 months resulting in hospitalization or an increased level of care, and with a PANSS total score <70 at study entry. Patients were randomized to **405 mg/4 weeks of olanzapine LAI (N=264)** or **10mg/day oral olanzapine (N=260)** for < 2 years of open-label treatment. After the first 4 weeks dosing was flexible, 150-405 mg/4 weeks OLAI or 5-20 mg/day oral olanzapine. Investigators could taper the previous oral AP (first 2 weeks only) and then supplement with oral olanzapine 5 mg/day (during the subsequent 6 weeks only). The primary outcome measure was **time to all-cause discontinuation.** It should be noted that halfway through study enrollment, a 3-hour post-injection observation period and other precautionary procedures related to the risk of post-injection syndrome were added to the protocol and applied only to the LAI group.
• **RESULTS:** The two groups did not significantly differ on median time to all-cause discontinuation (645 days LAI, 678 days oral; p=.61), study completion rates (45.1% LAI; 47.7% oral; p=.60), time to relapse (p=.56), or relapse rates (31.1% LAI; 29.2% oral; p=.70). There were no clinically significant differences in adverse events or other safety measures between treatment groups. Mean weight gain was 2.0±7.2 and 2.2±7.3 kg for LAI and oral-treated patients, respectively (p=.78). No incidents of post-injection syndrome occurred in LAI-treated patients throughout the 2-year trial.

Because the 405 mg/4 weeks LAI dose provided approximately 15 mg/day of olanzapine, whereas the oral group could be dosed to 20 mg/day, an exploratory post hoc analysis was conducted to test the impact of this difference. When dose increases to 20 mg/day after the initial 8 weeks of treatment were treated statistically as a sub-acute relapse, the LAI group had a longer median time to relapse (379 days LAI, 213 days oral; p<.001) and a lower relapse rate (31.1% LAI, 45.8% oral; p<.001) than the oral group.

• **CONCLUSIONS:** OLAI was found to be as effective, well tolerated, and safe as oral olanzapine for pts with schizophrenia. Discontinuation rate for OLAI was similar to that of oral olanzapine, despite the 3-hour post-injection observation period and other precautionary procedures.

Detke et al., 2011
...but there are new RCTs with SGA LAI (>1y)

- Double-blind RCT: OLAI vs. olanzapine p.o. Equally low relapse rate in both forms of the same compound. N=1065. Length of study: 12T. 
  Kane et al., 2010

...while observational studies are unambiguous

+ Mirror studies show consistently reduction of hospitalisation days on RLAI after onset of treatment
  Taylor et al. 2008; Chang et al. 2009; Fuller et al. 2009; Olivares et al. 2009; Willis et al., 2010
Comparison of oral and depot antipsychotics

Finnish observational prospective cohort study (I)

- Direct comparison of LAI with its oral counterpart (haloperidol, perphenazine, risperidone, zuclopenthixol)
- N=2.588
- Finnish register (Finnish National Hospital Discharge Register)
  - Patients with dg. F20, after first hospitalisation
- Depot vs. Oral antipsychotics; outcome measures:
  - drop-outs
  - rehospitalisations
  - mortality

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A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia

_Tiihonen J et al._

Conclusions: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.

(Am J Psychiatry Tiihonen et al.; 1–7)
Depot AP exert lower risk of drop-outs (-59%) and rehospitalisations (-64%)

<table>
<thead>
<tr>
<th></th>
<th>DROP-OUTS</th>
<th>REHOSPITALISATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Depot vs oral</td>
<td>0.41</td>
<td>0.27–0.61</td>
</tr>
<tr>
<td>Haloperidol depot vs oral</td>
<td>0.27</td>
<td>0.08–0.88</td>
</tr>
<tr>
<td>Risperidone RLAI vs oral</td>
<td>0.44</td>
<td>0.31–0.62</td>
</tr>
<tr>
<td>Perphenazine depot vs perphenazine oral</td>
<td>0.32</td>
<td>0.19–0.53</td>
</tr>
</tbody>
</table>

HR=hazard ratio
Zuclopenthixol NS

Patients on any antipsychotic have lower mortality risk

- 160 deaths out of 2,588 followed patients
- AP+ (64†/6260 person-years)
- AP- (96†/4509 person-years)
- Hazard ratio = 0.45 (95% CI = 0.31–0.67)

using AP vs non-using AP

Where can it be wrong?

**RCT:**

- Strict protocol constraints
- Demanding procedures
- Special approach to a patient
- Therefore: **Selection of adherent patients**

LAI, however, are in practice used and recommended to non-adherent patients!


*Höschl 2012*
RANDOMIZED CLINICAL STUDIES

PROSPECTIVE COHORT STUDIES

OBSERVATIONAL STUDIES

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Comparison LAI vs. oral AP:

**Meta-analysis RCT** *(Leucht et al. 2011)*

- In LAI the **risk of relapse** is by 30% **lower** (RR 0.70, CI 0.57–0.87, NNT 10, CI 6–25, P=0.0009) compared to oral meds.

**Finnish observational prospective cohort study** *(Tiihonen et al. 2011)*

- **Risk of rehospitalisation** is in LAI by two thirds **lower** than in oral meds (adjusted RR = 0.36; 95% CI=0.17–0.75).

In clinical practice, where non-adherence is higher, the efficiency of LAI is markedly higher than that of oral antipsychotics. In this aspect observational studies are closer to everyday clinical care than RCT.

*Haddad 2011*
LAI and adverse effects
Do LAI exert more adverse effects?

Patel et al., 2003, 2009
RCT: LAI and AE incidence

- Meta-analysis FGA vs. oral antipsychotics: no difference in extrapyramidal symptoms or tardive dyskinesias
  
  Adams et al., 2001

- Even reduction of serum prolactin found after randomisation from risperidone p.o. to adequate dose of RLAI.
  
  Bai et al.; 2006, Chue et al., 2005

- Double blind RCT: no changes in adverse effects in randomization from olanzapine p.o. to corresponding dose of OLAI.
  
  Kane et al., 2010
RCT: LAI and AE incidence

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The idea that compared to oral equivalents LAI show higher incidence of AE is not supported by evidence and can be regarded as a myth.

Haddad 2011
LAI and tardive dyskinesia

- **Rule of „three“**: The risk of TD is three times higher in patients with more than three discontinuations of AP medication for more than 3 months (adjusted OR=3.29; 95%CI: 1.27–8.49).

- Cumulative exposition to AP and/or anticholinergics does not predict TD.

  *van Harten et al., 1998*

- **Do LAI give a chance to change for better?**

*Höschl 2012*
# Receptor profile of 2\textsuperscript{nd} generation antipsychotics

<table>
<thead>
<tr>
<th>Group</th>
<th>Blockade of receptors</th>
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<tbody>
<tr>
<td></td>
<td>D2</td>
</tr>
<tr>
<td><strong>Selective D2/3 antagonists</strong></td>
<td></td>
</tr>
<tr>
<td>sulpiride</td>
<td>+</td>
</tr>
<tr>
<td>amisulpride</td>
<td>+</td>
</tr>
<tr>
<td><strong>5HT/D antagonists-SDA</strong></td>
<td></td>
</tr>
<tr>
<td>ziprasidone</td>
<td>+</td>
</tr>
<tr>
<td>iloperidone</td>
<td>+</td>
</tr>
<tr>
<td>sertindole</td>
<td>+</td>
</tr>
<tr>
<td>risperidone</td>
<td>+</td>
</tr>
<tr>
<td><strong>Multireceptor antagonists-MARTA</strong></td>
<td></td>
</tr>
<tr>
<td>quetiapine</td>
<td>+</td>
</tr>
<tr>
<td>zotepine</td>
<td>+</td>
</tr>
<tr>
<td>olanzapine</td>
<td>+</td>
</tr>
<tr>
<td>clozapine</td>
<td>+</td>
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</tbody>
</table>

Prof. MUDr. Jaromír Švestka, DrSc.
EUFEST: Time to Treatment Discontinuation Different Between SGAs and Haloperidol

**Study Design:** RCT of haloperidol vs SGAs over 12 mo in pts with first-episode schizophrenia

**Graphs:**
- **Discontinuation For Any Cause, %**
  - Haloperidol (n = 103): 72%
  - Quetiapine (n = 104): 53%
  - Ziprasidone (n = 82): 45%
  - Amisulpride (n = 104): 40%
  - Olanzapine (n = 105): 33%

- **Average Time to Discontinuation, mo**
  - Haloperidol (n = 103): 0.5 mo
  - Quetiapine (n = 104): 1.2 mo
  - Ziprasidone (n = 82): 1.1 mo
  - Amisulpride (n = 104): 5.3 mo
  - Olanzapine (n = 105): 6.3 mo

*Kahn R.S. Lancet 2008; 371: 1085-97*
1. Prevailing „outcome measure“ is time to treatment discontinuation (due to …)

2. Neuroleptics are as effective as „atypicals“

3. AP2G are not significantly more effective on QOL

4. AP2G are ≈ equally effective with slight predominance of clozapine, olanzapine and amisulpride. Higher efficacy of olanzapine, however, is repeatedly confirmed in studies with different design.

5. AP2G differ each from other by side effects profile

6. AP2G do not exert any specific group characteristics
Zypadhera - Summary

**Advantages**

- Proven efficacy in schizophrenia
- Onset already first week
- No oral medication needed
- Flexible 2 - 4 week application

**Risks**

- Adverse effects similar to p.o. olanzapine, except post-injection syndrome
- Post-injection syndrome
- Caution and observation required (3 hours)

Global safety profile should be considered in light of potential benefit in a patient with schizophrenia who is indicated for long-term injection treatment.
Do we really need depot antipsychotics?

Cyril Höschl

Acknowledgement: Filip Šťániel (PCP)