Is there a case for earlier use of antipsychotic LAIs in schizophrenia?
If not us, then who?
If not now, when?

Attributed at different times to:
  Hillel the Elder,
  John F Kennedy
  Robert F Kennedy
  George W Romney
  Ronald Reagan
  Mikhail Gorbachev
  Barak Obama
Question

If earlier use of antipsychotic LAIs in schizophrenia could reduce the burden of relapse and improve long-term outcome, at what point in the lifetime course of the illness should they be offered to patients?

– During first-episode of psychosis (FEP)?
– After the first relapse?
– After 3 relapses?
– After 6 relapses?
Synopsis

• NICE schizophrenia guideline

• The trajectory of schizophrenia and the burden of relapse

• Pros & cons of antipsychotic LAIs

• What evidence supports wider use of antipsychotic LAIs?

• How early should patients be offered antipsychotic LAIs?
When are antipsychotic LAIs usually offered?

Psychosis and schizophrenia in adults: treatment and management

1.5.5.3 Consider offering depot / long-acting injectable antipsychotic medication to people with psychosis or schizophrenia:

- who would prefer such treatment after an acute episode
- where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. [2009]
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Why do outcomes in schizophrenia remain stubbornly poor?

Despite . . .

– Early intervention
– Innovative models of community-based care
– Access to effective treatments (including LAIs)
Poor outcomes in patients with schizophrenia include:

- Poor engagement in on-going care
- Lack of involvement in on-going care
- Substance misuse
- Comorbid psychiatric disorders
- Poor adherence to treatment
- Poor response to antipsychotic treatment
- Cognitive deficits
- Poor access to general health care
Response & recovery following a first episode of schizophrenia

- Rate of remission in 1st year of treatment
  - 70% - 80%\textsuperscript{1-3}

- If treatment is maintained, at 9-year follow-up:
  - Patients in remission 78% of the time\textsuperscript{4}

- Rate of relapse within 12 months of stopping medication
  - 77%
  - (3% if treatment maintained)\textsuperscript{5}

- 82% of responders relapse within 5 years\textsuperscript{6}

What would be predicted annual relapse / admission rates?

If:
- 50% of patients don’t take treatment regularly
- Relapse rates in these patients are about 50% in 1 year

Schizophrenia: 2-year Outcomes in UK

% of patients (N=1,015)

Hunter R, Cameron R, Norrie J.
Using patient-reported outcomes in schizophrenia: The Scottish Schizophrenia Outcomes Study
Psychiatric Services 2009;60:240-245

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Revolving door = vicious cycle

Delay in treating first episode

Treatment response but subsequent poor adherence to treatment

Progression to chronic illness and/or treatment resistance

Relapse & need to re-establish treatment
Deteriorating course, brain tissue loss and treatment resistance with repeated relapses after a first episode of schizophrenia

Relapse: a focal point for better outcomes

- In-patient admissions
- Physical health
- Family
- Substance misuse
- Contact with criminal justice system
- Cognitive impairment increased
- Homelessness
- Unemployment

Valenstein M, Ganoczy D, McCarthy JF et al.
Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review
J Clin Psychiatry 2006;67:1542-50
Why are LAIs not prescribed for more patients?

Reasons given by psychiatrists for NOT prescribing LAIs

% of psychiatrists

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence on oral is adequate</td>
<td>86%</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>80%</td>
</tr>
<tr>
<td>Drug not available as LAI</td>
<td>75%</td>
</tr>
<tr>
<td>Cost</td>
<td>71%</td>
</tr>
<tr>
<td>Not appropriate</td>
<td>68%</td>
</tr>
<tr>
<td>Oral drug better control of effect</td>
<td>58%</td>
</tr>
<tr>
<td>EPS risk higher with LAI</td>
<td>31%</td>
</tr>
</tbody>
</table>

In a survey of patients with no experience of LAIs, 79% stated they had never been given the option by their psychiatrist.

Jaeger M, Rossler W. Psychiatry Res 2010; 175: 58-62

Synopsis

• NICE schizophrenia guideline
• The trajectory of schizophrenia and the burden of relapse

• Pros & cons of antipsychotic LAIs

• What evidence supports wider use of antipsychotic LAIs?
• How early should patients be offered antipsychotic LAIs?
Pros & Cons of LAIs vs oral antipsychotics

**Pros**
- Minimal fluctuations in drug plasma concentration
- Improved adherence?
- Certainty over antipsychotic administration
- Fewer relapses?
- Better outcomes?
  - QoL
- Cost-effective?

**Cons**
- Invasive / painful
- Stigma of injection
- Patient reluctance / refusal
- Uncertainty of diagnosis
  - (1st episode)
- High cost of newer LAIs
- AEs – if experienced, may be prolonged
- Evidence of better outcomes is limited

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Synopsis

• NICE schizophrenia guideline
• The trajectory of schizophrenia and the burden of relapse
• Pros & cons of antipsychotic LAIs
• What evidence supports wider use of antipsychotic LAIs?
• How early should patients be offered antipsychotic LAIs?
Is the evidence for better outcomes with LAIs limited?

1st-generation antipsychotics only

- LAI antipsychotic vs placebo depot
  - LAI superior in reducing relapse (NNT=2)
  - Significantly more movement disorders with LAIs (NNH=3, 95% CI 2-6.5)

- LAIs vs oral antipsychotic
  - LAIs superior on global improvement (NNT=4, 95% CI 2-9)
  - No differences in relapse, drop-out or adverse effects

- LAI vs LAI
  - Lower relapse rate with Zuclopenthixol (NNT=8, 95% CI 5-53)

- High dose LAI vs standard dose LAI
  - No advantage to higher dose
Is the evidence for better outcomes with LAIs limited?

Abstract
Non-adherence is a major problem in the treatment of schizophrenia. Depot antipsychotics reduce relapse rates by improving adherence, but a systematic review of long-term trials is limited.

Method
We searched the Cochrane Schizophrenia Group's register, ClinicalTrials.gov, Cochrane medication, and the reference sections of included studies for randomised controlled trials in outpatients that compared depot with oral antipsychotics in schizophrenia. We included 10 trials, 1700 patients, 6 RCTs of Fluphenazine, 2 RCTs of Risperidone, 1 RCT each of Haloperidol, Zuclopenthixol, Fluphenazine (4 RCTs), Pimozide (2 RCTs), Zuclopenthixol (1 RCT), Olanzapine, Quetiapine, 1 RCT each. Relapse rates were 21.6% for LAIs and 33.3% for oral antipsychotics. The NNT was 10 (95% CI 6-25).

Discussion
Depot antipsychotic drugs significantly reduced relapse. Due to a number of methodological issues, the evidence is, nonetheless, subject to possible bias.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone LAI vs oral risperidone</td>
<td>- Relapse rates not reported</td>
</tr>
<tr>
<td></td>
<td>- No differences between treatment groups</td>
</tr>
<tr>
<td>Risperidone LAI vs oral quetiapine</td>
<td>- Relapse rates &amp; improvement in mental state not reported</td>
</tr>
<tr>
<td></td>
<td>- Risperidone-treated patients experienced more EPS, weight gain, prolactin-related AEs</td>
</tr>
<tr>
<td>Risperidone LAI vs oral aripiprazole</td>
<td>- Relapse rates &amp; PANSS improvements similar in both groups</td>
</tr>
<tr>
<td></td>
<td>- More prolactin-related AEs with risperidone</td>
</tr>
<tr>
<td>Risperidone LAI vs oral olanzapine</td>
<td>- Relapse rates not reported</td>
</tr>
<tr>
<td></td>
<td>- PANSS improvements similar in both groups</td>
</tr>
<tr>
<td></td>
<td>- More EPS with risperidone</td>
</tr>
<tr>
<td></td>
<td>- More weight gain with olanzapine</td>
</tr>
<tr>
<td>Risperidone LAI vs Paliperidone LAI</td>
<td>- Relapse rates not reported</td>
</tr>
<tr>
<td></td>
<td>- PANSS response rates &amp; AEs similar in both groups</td>
</tr>
<tr>
<td></td>
<td>- Paliperidone-treated patients less likely to use anticholinergic medication</td>
</tr>
<tr>
<td>Risperidone LAI vs 1st-generation LAI</td>
<td>- Relapse rates &amp; movement disorders not reported</td>
</tr>
<tr>
<td></td>
<td>- More risperidone-treated patients left the study early</td>
</tr>
</tbody>
</table>
Is the evidence for better outcomes with LAIs limited?

- **Paliperidone LAI vs placebo**
  - 5 studies, 2215 patients
  - Lower relapse rate with paliperidone (NNT=5, 95% CI 4-6)
  - Where recurrence of psychosis recorded as an AE:
    - Fewer recurrences with paliperidone (NNT=10, 95% CI 8-14)
  - Consistent, significant elevation of prolactin with paliperidone
  - Significantly greater weight increase with paliperidone

- **Paliperidone LAI vs Risperidone LAI**
  - 2 studies, 1969 patients
  - No differences on measures of efficacy
  - Paliperidone-treated patients less likely to use anticholinergic medication
  - No data on service use, quality of life, patient behaviour or satisfaction, cognitive functioning
**2nd Generation Antipsychotic LAI Registration Studies**

### Risperidone
- **Vs Placebo**
  - 12-week RCT
  - RIS > PBO
- **Non-inferiority**
  - 12-week RCT
  - Vs oral risperidone
  - LAI not inferior to oral
- **Long-term**
  - Tolerability only

### Paliperidone
- **Maintenance of effect**
  - Vs Placebo
    - Relapse rates
      - PAL 17.6%
      - PBO 47.8%
  - Non-inferiority vs risperidone LAI
    - Response rates
      - PAL 44.3%
      - RIS 54.4%

### Aripiprazole
- **Maintenance of effect**
  - Vs Placebo
    - 4.7-fold greater risk of relapse with placebo
  - Non-inferiority vs oral aripiprazole
    - Relapse rates
      - LAI 7.1%
      - ORAL 7.8%
Real-world studies show significant advantages for LAIs compared with oral antipsychotics

LAI=long-acting injection; RR=risk ratio.

Kirson NY, Wong B, Yermakov S, et al. The impact of study design in comparative effectiveness research in schizophrenia. Presented at: 52nd Annual Meeting of New Research Approaches for Mental Health Interventions; May 29-June 1, 2012; Phoenix, AZ.
Risperidone LAI vs oral antipsychotics in clinical practice

- Patients with schizophrenia hospitalised in last 2 years or at imminent risk of hospitalisation
- Randomised to risperidone LAI or psychiatrist’s choice of oral antipsychotic
- 2 years follow-up
- Primary outcome:
  - new admission to hospital

Paliperidone LAI vs oral antipsychotics: real-world outcomes

- Patients with schizophrenia arrested at least twice in last 2 years & incarcerated at least once
- Randomised to Paliperidone LAI or choice of 1 of 7 oral antipsychotics
- 15 months follow-up
- Primary outcome:
  - Time to first treatment failure

Alpsh L, Benson C, Cheshire-Kinney K et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15 month study J Clin Psychiatry 2015;76:554-61
Aripiprazole LAI vs oral antipsychotics: mirror-image naturalistic study

- Open-label, mirror-image study
- Patients requiring a change of antipsychotic for any reason
- 6 months prior standard care with oral antipsychotics
  - Data collected retrospectively
- 6 months prospective treatment with aripiprazole LAI
- Primary outcome:
  - Admission to hospital
Aripiprazole LAI vs oral antipsychotics: mirror-image naturalistic study

**Phase A:** standard care with oral antipsychotic
Data collected retrospectively

**Phase B:** Aripiprazole LAI 400mg once-monthly
Data collected prospectively

- 1 month period: Patient must be stable out-patient

- 6-month hospital admission data N=433

- 6-month hospital admission data N=433

Kane JM, Zhao C, Johnson BR et al.
Hospitalization rates in patients switched from oral antipsychotics to aripiprazole once-monthly: final efficacy analysis

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Total psychiatric hospitalisation rates

Usual care 6-month period vs Aripiprazole LAI 6-month period

% of patients with ≥1 psychiatric hospitalisation

Usual care
N=433
38.1%
P<0.0001

Aripiprazole LAI
N=433
8.8%
NNT=3
95% C.I. 3-4

All patients who entered Phase B treatment with Aripiprazole LAI


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Aripiprazole LAI vs Paliperidone LAI
The ‘QUALIFY’ Study

Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia

Dieter Naber a, Karina Hansen b, Carlos Forray c, Ross A. Baker d, Christophe Sapin b, Maud Beillat b, Timothy Peters-Strickland d, Anna-Greta Nylander e, Peter Hertel e, Henrik Steen Andersen e, Anna Eramo f, Jean-Yves Loze g, Steven G. Potkin h,*
Aripiprazole LAI vs Paliperidone LAI

- Randomised, open-label, rater-blinded
- DSM-IV-TR schizophrenia 18 – 60 years
- Mentally stable patients needing change of treatment
- No LAI in previous 6 months

Randomised to:
- Aripiprazole LAI 400mg monthly
- Paliperidone LAI 50 – 100 mg monthly
- 28 weeks
- Primary outcome Change from baseline on QLS score

Aripiprazole LAI vs Paliperidone LAI

Study design

<table>
<thead>
<tr>
<th>Screening (&lt;2 weeks)</th>
<th>Oral conversion (3 weeks)</th>
<th>LAI initiation (5 weeks)</th>
<th>LAI continuation, once-monthly (20 weeks)</th>
<th>Safety follow-up (4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral aripiprazole 5–30 mg/day</td>
<td>Oral paliperidone 3–12 mg/day</td>
<td>AOM 400</td>
<td>AOM 400</td>
<td>67.6% Completed 28 weeks</td>
</tr>
</tbody>
</table>

148 patients

Assessments at weeks 2 & 3

Assessments at weeks 4 & 8

5 monthly assessments starting week 12

Injection 1 (day 28): AOM 400, with 2 weeks oral aripiprazole (10–20 mg/day)

Injection 1 (day 21) 150mg
Injection 2 (day 28) 100mg

5 injections

50mg – 150mg per month

Mean doses at 24 weeks:
Aripiprazole 387mg
Paliperidone 110mg

Patients randomised 1:1

Baseline

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Naber D, Hansen K, Forray C et al.
Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia
Schiz Res 2015;168:498-504
Primary outcome

- Change from baseline on Heinrichs-Carpenter Quality of Life Scale (QLS)
- 21 items in 4 domains
  - Interpersonal relations
  - Instrumental role
  - Intrapsychic foundations
  - Common objects & activities
- Score for each item
  - From 0 (severe impairment) to 6 (unimpaired)
- Change of ≥5 points in total score clinically important

Secondary outcomes

- CGI-S
- Investigator’s Assessment Questionnaire (IAQ)
  - Symptom assessment
  - AEs / tolerability

Aripiprazole LAI vs Paliperidone LAI: RESULTS

1: Change in QLS total score

Mean doses at 24 weeks:
- Aripiprazole 387mg
- Paliperidone 110mg

Naber D, Hansen K, Forray C et al.
Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia
Schiz Res 2015;168:498-504
Aripiprazole LAI vs Paliperidone LAI: RESULTS

2: Change in CGI-S score


Mean doses at 24 weeks:
Aripiprazole 387mg
Paliperidone 110mg

Difference = -0.28
P=0.004

* p<0.05; ** p<0.01
### Aripiprazole LAI vs Paliperidone LAI: RESULTS

#### 3: Other secondary outcomes

<table>
<thead>
<tr>
<th>IAQ total scores at endpoint</th>
<th>Aripiprazole</th>
<th>Paliperidone</th>
<th>Difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>n=133</td>
<td>n=131</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>32.32</td>
<td>33.81</td>
<td>-1.49</td>
<td>-2.94;-0.05</td>
<td>0.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Differences in outcomes (Arip-Pali) in patients ≤ 35 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome measure</td>
</tr>
<tr>
<td>QLS</td>
</tr>
<tr>
<td>CGI-S</td>
</tr>
<tr>
<td>IAQ</td>
</tr>
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Naber D, Hansen K, Forray C et al.
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Schiz Res 2015;168:498-504

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• What evidence supports wider use of antipsychotic LAIs?

• How early should patients be offered antipsychotic LAIs?
TIPS Study:
Early Treatment and Intervention in Psychosis

RESEARCH QUESTIONS

- Does neurocognitive functioning change over the 10-year period from start of treatment in FEP patients?
- Does relapse (early relapse vs no early relapse) determine the longitudinal neurocognitive trajectory in FEP patients?
- Does evidence support global or specific neurocognitive change related to illness severity over a 10-year follow-up period, and is verbal memory especially sensitive?

- 213 FEP patients
- DSM-IV criteria for non-organic psychosis
- Follow-up evaluations – 1, 2, 5, & 10 years
- Symptoms assessed with PANSS & GAF scale
- Battery of neurocognitive tests

Barder HE, Sundet K, Rund BR et al.
Ten year neurocognitive trajectories in first-episode psychosis
**Relationship between neurocognition and relapse in 1\textsuperscript{st} episode psychosis**

- Significant associations between relapse and all cognitive measures except executive function
- Verbal fluency
  - The *no-relapse* group performed better than the *relapse* group at all time points
- Significant associations between relapses in 1\textsuperscript{st} year and working memory & verbal learning at 1- & 2-years
  - Confirmed at 5- and 10-year follow-up
- Verbal learning
  - *no-relapse* group performed better than the *relapse* group at 1- and 2-years

Barder HE, Sundet K, Rund BR et al.
Ten year neurocognitive trajectories in first-episode psychosis
Verbal fluency from baseline to 10-year follow-up

Verbal fluency index

Baseline 1 year 2 year 5 year 10 year

No relapse first year
Relapse(s) first year
Antipsychotic discontinuation in 1st episode schizophrenia leads to rapid relapse

- Patients stable for 1 year after recovery from first episode of schizophrenia or schizoaffective disorder
- Randomly assigned to continue antipsychotic or gradual withdrawal
- Primary outcome:
  - Relapse-free survival at 9 months
- Study terminated prematurely for ethical reasons

Rates (%) of relapse-free survival at 9 months

- Continuation group
  - N=9
  - 88%
  - P=0.001
  - NNT=1
  - 95% C.I. 1-3
- Discontinuation group
  - N=11
  - 18%

Boonstra G, Burger H, Grobbee DE, Kahn RS
Antipsychotic prophylaxis is needed after remission from a first psychotic episode in schizophrenia patients: results from an aborted randomised trial.
Poor adherence in 1st episode schizophrenia leads to high rates of relapse

Systematic review:
Relapse rate on medication discontinuation after FEP = 77%
Zipursky RB, Menezes NM, Streiner DL.
Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review.
Schizophr Res. 2014;152:408–414

antipsychotic medication increased risk of relapse almost 5-fold

Robinson D, Woerner MG, Alvir JMJ et al.
Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder
Arch Gen Psychiatry 1999;56:241-47
Deteriorating course, brain tissue loss and treatment resistance with repeated relapses after a first episode of schizophrenia

Long-term maintenance of antipsychotic in FEP is reflected in remission

Clozapine v. chlorpromazine in treatment-naive, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial*†

Ragy R. Girgis, Michael R. Phillips, Xiaodong Li, Kejin Li, Huiping Jiang, Chengjing Wang, Naihuan Duan, Yajuan Niu and Jeffrey A. Lieberman

Background
The differential effects of so-called ‘first- and second-generation’ antipsychotic medications, when given in the first episode, on the long-term outcome of schizophrenia remain to be elucidated.

Aims
We compared the 9-year outcomes of individuals initially randomised to clozapine or chlorpromazine.

Method
One-hundred and sixty individuals with treatment-naive, first-episode schizophrenia or schizophreniform disorder in a mental health centre in Beijing, China were randomised to clozapine or chlorpromazine treatment for up to 2 years, followed by up to an additional 7 years of naturalistic treatment. The primary outcome was remission status for individuals in each group.

Results
Individuals in both groups spent essentially equal amounts of time in each clinical state over the follow-up time period (remission, 78%; intermediate, 8%; relapse, 14%). There were no significant differences on other measures of illness severity. The clozapine group was more likely than the chlorpromazine group to remain on the medication to which they were originally assigned (26% v. 10%, P = 0.01). There were no significant differences between the two groups for other secondary efficacy outcomes.

Conclusions
These findings support the comparability between antipsychotic medications but not the tolerability of clozapine in the treatment of psychosis.

Declaration of interest
R.R.G. has received research support from Janssen, AstraZeneca, Bristol-Myers Squibb, and several pharmaceutical companies. He is a consultant to AstraZeneca and Janssen. M.R.P. has received research support from Janssen, AstraZeneca, Bristol-Myers Squibb, and several pharmaceutical companies. He is a consultant to AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck, Organon, Pfizer, and Wyeth. N.D. has received research support from Pfizer. J.A.L. has received research support from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, and Pfizer. He has been a consultant for Johnson & Johnson and Novartis; an advisory board member for Bioline, Forest Labs, Lundbeck, Organon and Wyeth; and a DSMB member for Solvay. J.A.L. has received no direct financial compensation or salary support for participation in the study.

Antipsychotic treatment was maintained in nearly 80% of patients over the entire study period (9 years)

These patients were in remission for 78% of the time
If earlier use of antipsychotic LAIs in schizophrenia could reduce the burden of relapse and improve long-term outcome, at what point in the lifetime course of the illness should they be offered to patients?

– During first-episode of psychosis?
– After the first relapse?
– After 3 relapses?
– After 6 relapses?
Final questions

Is there a case for earlier use of antipsychotic long-acting injections?

Does the burden of relapse outweigh the burden of LAIs?
Improving the use of medicines in severe mental illness

Medicines in Mental Health Ltd offers a range of services designed to obtain maximum benefit from medicines in the treatment of severe mental illness.

Thank you

www.mentalmeds.co.uk