Preventing relapse in schizophrenia: a real priority or only a tick-box exercise?

“L’imagination est plus important que le savoir”

Albert Einstein
“These practices signify serious risk to patients due to a crippling lack of resources. The fact that psychiatrists are having to consider sectioning patients to secure something as basic as a bed is a huge warning sign of extreme under provision.”
QUESTIONS

• How important is schizophrenia?

• How important is it to prevent relapse in schizophrenia?

• Is it important enough to do anything meaningful about it?

• What can be done to support relapse prevention?
Schizophrenia

• Most common form of psychotic disorder
• Lifetime prevalence 0.4% to 1.4%
• Over 80% of adults have persistent problems with social functioning
• Premature mortality approx 50% above that of the general population

National Collaborating Centre for Mental Health
Core interventions in the management of schizophrenia in primary and secondary care (update).
National Clinical Practice Guideline Number 82, Full Guideline
Outcomes of public concern

VIOLENCE

SUBSTANCE MISUSE

SELF-HARM & SUICIDE

HOMELESSNESS

UNEMPLOYMENT

VICTIMISATION

SCHIZOPHRENIA

Kooymann I, Dean K, Harvey S & Walsh E
Outcomes of public concern in schizophrenia
Br J Psychiatry 2007;191:29-36

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“Schizophrenia is arguably the worst disease affecting mankind, even AIDS not excepted”

QUESTIONS

• How important is schizophrenia?

• How important is it to prevent relapse in schizophrenia?

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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
What is the impact of relapse?

Relapse

- In-patient admissions
- Unemployment
- Homelessness
- Disrupted education
- Contact with criminal justice system
- Physical health
- Family
- Substance misuse

Andrew A, Knapp M, McCrone P et al. Effective interventions in schizophrenia: the economic case
QUESTIONS

• How important is schizophrenia?

• How important is it to prevent relapse in schizophrenia?

• Is it important enough to do anything meaningful about it?

• What can be done to support relapse prevention?
What does relapse and subsequent admission to an acute psychiatric unit cost your service?
Hospital Admissions for Schizophrenia in Wales

Data from NHS Wales Informatics Service for 2012-13 (Patient Episode Database for Wales PEDW)

- Number of admissions
- Length of stay
- Average cost/admission
- Total cost
LHBs in Wales

- Betsi Cadwaladr
- Powys
- Hywel Dda
- Abertawe Bro-Morgannwg
- Cwm Taf
- Aneurin Bevan
- Cardiff & Vale

Data available

- Betsi Cadwaladr
- Abertawe Bro-Morgannwg
- Cwm Taf
- Aneurin Bevan
- Cardiff & Vale

No data

- Powys
- Hywel Dda
LHBs in Wales:
Schizophrenia Hospital Admissions 2012-13

Betsi Cadwaladr
Hywel Dda
Cwm Taf
Aneurin Bevan
Abertawe Bro Morgannwg

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LHBs in Wales: Schizophrenia Admissions 2012-13

AVERAGE LENGTH OF INPATIENT STAY

DAYS

<table>
<thead>
<tr>
<th>Area</th>
<th>Length (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betsi Cadwaladr</td>
<td>70</td>
</tr>
<tr>
<td>Hywel Dda</td>
<td>105</td>
</tr>
<tr>
<td>Cwm Taf</td>
<td>80</td>
</tr>
<tr>
<td>Aneurin Bevan</td>
<td>76</td>
</tr>
<tr>
<td>Abertawe Bro Morgannwg</td>
<td>163</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>99</td>
</tr>
</tbody>
</table>

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LHBs in Wales: Schizophrenia Admissions 2012-13

AVERAGE COST OF SINGLE INPATIENT EPISODE

Cost calculations based on: £374/day
Department of Health Reference Costs 2012-13

Betsi Cadwaladr: £26,180
Hywel Dda: £39,270
Cwm Taf: £29,920
Aneurin Bevan: £28,424
Abertawe Bro Morgannwg: £60,962
AVERAGE: £36,951

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LHBs in Wales: Schizophrenia Admissions 2012-13
TOTAL ANNUAL COST OF INPATIENT EPISODES

£ MILLION

TOTAL = £ 39.2 MILLION

Betsi Cadwaladr: 8.5
Hywel Dda: 4.0
Cwm Taf: 2.7
Aneurin Bevan: 8.3
Abertawe Bro Morgannwg: 15.7

Cost calculations based on: £374/day
Department of Health Reference Costs 2012-13
Downward pressure on costs

✓ Reduce length of stay
✓ Reduce total number of admissions
QUESTIONS

• How important is schizophrenia?

• How important is it to prevent relapse in schizophrenia?

• Is it important enough to do anything meaningful about it?

• What can be done to support relapse prevention?

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Chronic schizophrenia: Poor adherence leads to high relapse rates

• Pooled analysis of 66 studies with 4365 patients with chronic schizophrenia

• Relapse rates over 10 month period

• Number needed to harm for antipsychotic withdrawal

NNH = 3 (95% CI 2-3)

* Data from 29 of the 66 studies where there were matched withdrawal and treatment maintenance groups


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Poor adherence in schizophrenia: a large and persistent problem

Systematic review of literature

- 39 studies from 1980 onwards
  - 10 retrospective, 15 cross-sectional, 14 prospective
- Mean duration of illness 9-24 years
- Range of adherence measures
- “Taking medication as prescribed at least 75% of the time”

49.5% of patients non-adherent

What would be predicted annual relapse / admission rates?

If:

50% of patients don't take treatment regularly and
Relapse rates in these patients are about 50% in 1st year

Schizophrenia: 2-year Outcomes in UK

% of patients (N=1,015)

Hospital admission
Self-harm
Suicide attempt
Civil detention in past 12 months
CPA

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Adherence is influenced by multiple factors

**Patient**
- Concerns about side effects
- Few perceived benefits
- Stigma
- Daily routine
- Concerns about dependence
- Lack of involvement

**Illness**
- Severity of illness
- Depression / psychosis
- Cognitive impairment

**Clinician / Service**
- Poor therapeutic relationship
- Poor explanation / communication
- Inadequate follow-up

**General**
- Complexity of treatment
- Duration of treatment
- Lack of support

Mitchell AJ, Selmes T
Why don’t patients take their medicines? Reasons and solutions in psychiatry.
Advances in Psychiatric Treatment 2007;13:336-346

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A strategy for preventing relapse

Medicines management

Individualise antipsychotic treatment
The choice of antipsychotic medication should be made by the service user and healthcare professional together. Provide information and discuss the likely benefits and possible side effects of each drug, including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences)
Individualising treatment

Antipsychotic
Oral? LAI?

Which side-effects does the patient most want to avoid?

Which treatments are least likely to cause these side-effects?

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3.6 Individuals with schizophrenia consider the most troublesome side effects to be EPS, weight gain, sexual dysfunction and sedation.
Leucht S, Cipriani A, Spineli L et al
Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis
Lancet 2013;382:951-62

C Extrapiramidal side-effects OR (95% Crl)

<table>
<thead>
<tr>
<th>Drug</th>
<th>OR (95% Crl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>0.3 (0.12 to 0.62)</td>
</tr>
<tr>
<td>Sertindole</td>
<td>0.81 (0.47 to 1.3)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.00 (0.73 to 1.33)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.01 (0.68 to 1.44)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1.20 (0.73 to 1.85)</td>
</tr>
<tr>
<td>Lloperidone</td>
<td>1.58 (0.55 to 3.65)</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>1.60 (0.88 to 2.65)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1.61 (1.05 to 2.37)</td>
</tr>
<tr>
<td>Asenapine</td>
<td>1.66 (0.85 to 2.93)</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>1.81 (1.17 to 2.69)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.09 (1.54 to 2.78)</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>2.46 (1.55 to 3.72)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>2.65 (1.33 to 4.76)</td>
</tr>
<tr>
<td>Zotepine</td>
<td>3.01 (1.38 to 5.77)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4.76 (3.70 to 6.04)</td>
</tr>
</tbody>
</table>

More extrapyramidal side-effects with placebo

More extrapyramidal side-effects with active drug
Leucht S, Cipriani A, Spineli L et al.
Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis
Lancet 2013;382:951-62
Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis
Lancet 2013;382:951-62
A strategy for preventing relapse

Medicines management

- Individualise antipsychotic treatment
- Engage patient by improving communication & information
MINIMUM INFORMATION REQUIREMENTS?

• Benefits of treatment vs no treatment
• How likely is it to work?
• How does it compare with other options?
  – Side effects
• Risks associated with poor adherence to treatment
58 MH Trusts; >13,000 patients

**Medicines:**

- 32% - views taken into account ‘only to some extent’
- Only 43% definitely told of possible side-effects
- 48% not given information in a way they could understand
- 23% - medicines not reviewed in past 12 months

A strategy for preventing relapse

Medicines management

- Individualise antipsychotic treatment
- Engage patient by improving communication & information
- Avoid complex treatment regimens
A strategy for preventing relapse

Medicines management

- Individualise antipsychotic treatment
- Engage patient by improving communication & information
- Avoid complex treatment regimens
- Adjust to daily routine
- Ensure patient understands treatment regimen
- Ensure easy access to repeat prescription
- Consider depot antipsychotic

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Questions

- How effective are LAIs at preventing relapse?
- How early should LAIs be offered?

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]
2nd Generation antipsychotic LAI 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**
- Relapse prevention study
  - Vs Placebo
    - Relapse rates
      - PAL 17.6%
      - PBO 47.8%
- Maintenance of effect
  - Non-inferiority vs risperidone LAI
    - Response rates
      - PAL 44.3%
      - RIS 54.4%

**Aripiprazole**
- Relapse prevention study
  - Vs Placebo
    - Placebo treatment had 4.7-fold greater risk of relapse
- Relapse prevention study
  - Non-inferiority vs oral aripiprazole
    - Relapse rates
      - LAI 7.1%
      - ORAL 7.8%

US FDA Dossier for Risperdal Consta NDA 21-346 2001
CHMP Assessment Report: Xeplion EMA/60983/2011
CHMP Assessment Report: Abilify Maintena EMA/737723/2013
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

Aripiprazole LAI vs usual care

- Open-label, mirror-image study
- Comparison of hospital admission rates
- 6 months retrospective standard care with oral antipsychotics
- 6 months prospective treatment with aripiprazole LAI

Patients admitted to hospital (%)

Usual care N=183
- 41.5%
- P<0.0001

Aripiprazole LAI N=183
- 14.2%

Poor adherence in 1\textsuperscript{st} episode schizophrenia leads to high rates of relapse

- 5-year follow-up study after initial recovery from first episode of schizophrenia or schizoaffective disorder
- Discontinuation of 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
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

<table>
<thead>
<tr>
<th></th>
<th>Continuation group</th>
<th>Discontinuation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=9</td>
<td>88</td>
<td>18</td>
</tr>
<tr>
<td>P=0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
Summary

• Poor adherence in schizophrenia is common and results in
  – Severe psychiatric morbidity
  – High cost burden for the NHS

• Pragmatic interventions could remove barriers to adherence and prevent relapse
  – Individualising treatment
  – Improving patient engagement
  – Reducing complexity of regimens
  – Earlier / wider use of antipsychotic LAI
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.

Medicines in Mental Health Ltd is an independent health sector provider dedicated to improving outcomes from the use of medicines in mental health. We have worked with many stakeholders in mental health including the NHS, professional organizations, academic institutions, the voluntary sector and the pharmaceutical industry. We offer a number of services: