Preventing psychosis and targeting people at risk:
From bright idea to NICE Guidelines

Paul French
Psychosis: The Early Course

Premorbid Phase

Very Early Symptoms

Psychotic Symptoms

1st treatment

The typical course of psychosis

Early Intervention in the at-risk phase ARMS

Early Intervention after onset of psychosis (EIS)

Tertiary Prevention

Adapted from Larsen et al., 2001

Psychosis

Psychosis
Buckingham Project UK
Falloon 1985

- GP’s trained to identify early psychosis symptoms
- Referred to specialist team for assessment
- Those with positive early symptoms treated with low dose medication, crisis and family intervention
- Outcome: 10 fold reduction in schizophrenia over 4 years
- But several methodological shortcomings (including small n)
Identification
Age of onset for schizophrenia

- Females %
- Males %

Percentage

Age

PACE referral criteria

• Age between 14 and 30 years
  AND
• Family history of DSM-IV psychotic disorder and reduction on GAF scale of $\geq 30$,
  AND/OR
• Attenuated symptoms, occurring several times during the week for at least one week
  AND/OR
• Brief, limited or intermittent psychotic symptoms (BLIPS) for less than one week and resolving spontaneously
Prediction of Psychosis

Yung et al 1998 British Journal of Psychiatry

40% made transition at six months, 50% at one year
Assessments for identification

• Brief Psychiatric Rating Scale (BPRS) Lukoff, Neuchterlein & Ventura (1993)

• Positive And Negative Syndromes Scale (PANSS) Kay, Fiszbein & Opler (1987)

• Comprehensive Assessment of At Risk Mental States (CAARMS) Pace clinic Yung et al 2002

• Structure Interview for Prodromal Symptoms (SIPS) Scale of Prodromal Symptoms (SOPS) Prime clinic McGlashen, Miller, Woods, Rosen, Hoffman & Davidson

• Bonn Scale for the Assessment of Basic Symptoms (BSABS) Klosterkoette, Schultze-Lutter

French, Owens, Parker, Dunn Psychiatric Research, 2012

- Preliminary analysis found that the simple checklist as originally conceived had excellent sensitivity (96%) but poor specificity (10%).

- The first retained the use of all 20 checklist items and achieved sensitivity of 89% and specificity of 60%.

- The second retained 6 checklist items and achieved sensitivity of 88% and specificity of 47%.
<table>
<thead>
<tr>
<th>Item</th>
<th>Scoring</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of street drugs (including cannabis)</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>Arguing with friends and family</td>
<td>+0.5</td>
<td></td>
</tr>
<tr>
<td>Spending more time alone</td>
<td>+1.5</td>
<td>+1.5</td>
</tr>
<tr>
<td>Sleep difficulties</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>Depressive mood</td>
<td>-3.0</td>
<td>-2.5</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>+1.0</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>Tension or nervousness</td>
<td>+1.0</td>
<td>+1.0</td>
</tr>
<tr>
<td>Less pleasure from things</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>Feel people are watching you or giving you a hard time for no reason</td>
<td>+1.0</td>
<td></td>
</tr>
<tr>
<td>Feeling, hearing or seeing things that others cant</td>
<td>+1.0</td>
<td></td>
</tr>
<tr>
<td>Feeling that everyday things have a special meaning just for you</td>
<td>+0.5</td>
<td></td>
</tr>
<tr>
<td>Odd behaviour or appearance</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>First degree family history of psychosis plus increased stress or deterioration in functioning</td>
<td>+0.5</td>
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If a total score of more than +1 then refer
Transition rates?

- Meta analysis on transition Fusar-Poli et al 2012 Archives
- Twenty-seven studies met the inclusion criteria, comprising a total of 2502 patients.
- There was a consistent transition risk, 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years.
- There was no publication bias, and a sensitivity analysis confirmed the robustness of the core findings.
Intervention
Mrazek and Haggerty (1994) have discussed the idea of preventative interventions and identified three prevention strategies. These are:

- **Universal** all of the population
- **Selective** specific risk factors
- **Indicated** minimal, but detectable, signs of psychosis
Early Detection: Problems

• Ethics of interventions in pre-psychotic phase

• Solution:
  – employ interventions with minimal risks / side effects
  – employ interventions that will be useful to those who will never become psychotic
  – informed choice

• Balancing the costs and benefits of treatment must be weighted in some way according to the ratio of people actually helped to those unnecessarily treated

- Why CT?
  - Effective for psychotic symptoms (AS)
  - Effective for relapse prevention (BLIPS)
  - Effective for mood disorders
    - very frequent in prodrome (Birchwood, 1996)
  - DSM IV outcomes of at-risk population
  - Session structure, problem list and goals useful for other difficulties
Prevention of psychosis

McGorry et al 2002 Archives of General Psychiatry

% making transition to psychosis

40%
35%
30%
25%
20%
15%
10%
5%
0%

6
12

Months

Needs based Tx
Specific interventions
n=58
Prime Study

- A double-blind comparison of olanzapine with placebo
- Prodromal symptoms were measured by the SOPS
- N=60, and the median age was 16 years
- 65% males
- 93% of the patients had mild but definable psychotic symptoms (attenuated symptoms)
- The average GAF was 42.
- The dose of olanzapine included 5, 10, and 15 mg strengths.
- At 1 year, 15 of the 60 patients developed a full psychotic syndrome.
- Of the converters, 8 of 15 converted within the first month from baseline.
A single blind randomised controlled trial Cognitive Therapy vs. Treatment As Usual
Preliminary Results from 12 months Follow-up
Morrison, French et al 2004

Transition rate in % per group

- PANSS P-scores
- Prescription of antipsychotics
- DSM-IV Diagnosis

CT (n=35) TAU (n=23)
A single blind randomised controlled trial
Cognitive Therapy vs. Treatment As Usual
Results from 36 months Follow-up
Morrison, French et al 2006
EDIE 2 MRC Funded Clinical Trial

- EDIE 2 - a randomised controlled trial of Cognitive Therapy compared to usual treatment for the prevention of transition to psychosis.
- 288 participants at ultra high risk across 4 centres in the United Kingdom.
- Centres are Manchester, Glasgow & Clyde, Birmingham/Worcester, East Anglia / Cambridge.
Consort Criteria

Referrals
634

Eligable, consenting patients

Baseline -1
Baseline 0

Randomize
N= 288

Follow up

CT up to 6 months
Monitoring
144

Exclusions

Month 1 Month 2 Month 3 Month 4 Month 5 Month 6
Month 9 Month 12 Month 15 Month 18 Month 21 Month 24
Consort Criteria

EXCLUDED (n=346)
- Did not meet entry criteria (n=321)
- Due to antipsychotic medication = 36
- Due to current psychosis at initial baseline = 91
- Due to current psychosis at second baseline = 29
- Due to being sub-threshold for ARMS = 110
- Due to not being help-seeking = 45
- Other = 10
- Lost contact before assessment complete (n=16)
- Declined involvement before assessment complete (n=9)
Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Whole Sample n=288</th>
<th>Ct plus monitoring n=144</th>
<th>Monitoring only n=144</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>20.74 (4.34)</td>
<td>20.73 (4.18)</td>
<td>20.75 (4.50)</td>
</tr>
<tr>
<td><strong>Male: Female ratio</strong></td>
<td>180:108</td>
<td>89::55</td>
<td>91:53</td>
</tr>
<tr>
<td><strong>CAARMS severity</strong></td>
<td>43.06 (18.87)</td>
<td>43.50 (17.65)</td>
<td>42.61 (20.07)</td>
</tr>
<tr>
<td><strong>CAARMS distress</strong></td>
<td>42.61 (20.03)</td>
<td>42.77 (20.51)</td>
<td>42.45 (19.62)</td>
</tr>
<tr>
<td><strong>GAF</strong></td>
<td>51.06 (10.60)</td>
<td>50.98 (10.98)</td>
<td>51.15 (10.25)</td>
</tr>
<tr>
<td><strong>BDI-PC Total</strong></td>
<td>9.73 (4.48)</td>
<td>10.41 (4.15)</td>
<td>9.02 (4.70)</td>
</tr>
<tr>
<td><strong>SIAS Total</strong></td>
<td>41.18 (16.98)</td>
<td>42.88 (16.92)</td>
<td>39.36 (16.93)</td>
</tr>
<tr>
<td><strong>MANSA Total</strong></td>
<td>47.70 (10.10)</td>
<td>46.33 (9.60)</td>
<td>49.10 (11.00)</td>
</tr>
</tbody>
</table>

Mean & SD’s for variables for total sample and each group.
Clinical features

• 53.8% endorsed feeling moderately anxious or depressed
• 33.6% endorsed feeling extremely anxious or depressed
• CAARMS subscale measuring suicidality and self harm 44.1% were experiencing “suicidal thoughts with vague plans” and 13.2% “Thoughts of suicide more frequent with associated plan”.

SCID

• 33% of the cohort did not receive a SCID diagnosis
• 33% received a diagnosis of Major Depressive Disorder
• 20% Panic Disorder
• 15% Social Anxiety Disorder
• 4% Post Traumatic Stress Disorder
• 9% Generalised Anxiety Disorder
• 2% Bipolar Disorder
SCID

- 61.5% of the cohort received one SCID diagnosis
- 27.7% of the cohort received 2 SCID diagnoses
- 12.9% 3 SCID diagnoses
- 4.6% 4 and 1.6% 5 SCID diagnoses.

It is important to remember that all of these are in addition to being considered as being at risk of psychosis.
Primary outcomes BMJ 2012

- Transition to psychosis
  - Effect of CT was non-significant (proportional odds ratio 0.73, 95% CI 0.32 to 1.68, p=0.45).

- Severity of psychotic symptoms (centred on month 12)
  - Difference between treatment arms at 12 months (CT minus Control) was estimated to be −5.05 (95% CI -9.11 to -0.99), which was statistically significant (p = 0.015)

- Distress from psychotic symptoms (centred on month 12)
  - Estimated difference at 12 months was −3.03 (95% CI -6.95 to +0.94; p=0.14).
Meta analyses
11 trials including 1246 participants and eight comparisons were included. Median sample size of included trials was 81 (range 51-288). Meta-analyses were performed for transition to psychosis, symptoms of psychosis, depression, and mania; quality of life; weight; and discontinuation of treatment. Evidence of moderate quality showed an effect for cognitive behavioural therapy on reducing transition to psychosis at 12 months (risk ratio 0.54 (95% confidence interval 0.34 to 0.86); risk difference −0.07 (−0.14 to −0.01). Very low quality evidence for omega-3 fatty acids and low to very low quality evidence for integrated psychotherapy also indicated that these interventions were associated with reductions in transition to psychosis at 12 months.
A search conducted according PRISMA guidelines found 10 studies that reported 12 month follow-up data, and 5 studies with medium-term follow-up varying from 24 to 48 months. 12 month and 24 - 48 month results on transition to psychosis were selected. The trials were assessed for quality. Random and fixed effects meta-analyses were conducted.
The quality of the papers varied from poor to excellent. Overall the risk reduction at 12 months was 54\% (RR=0.463 (95%CI:0.33-0.64)) with a Number Needed to Treat of 9 (95%CI:6-15). Although the interventions differed, there was only mild heterogeneity and publication bias was small. All sub analyses showed efficacy. Five studies with 24 to 48-month follow-up still showed a risk reduction of 37\% (RR=.635 (95%CI:0.44-0.92)) with a Number Needed to Treat of 12 (95%CI:7-59). Sensitivity analysis excluding the weakest study shows that the findings are quite robust.

Early detection and intervention in people with an ultra-high risk of developing psychosis prevents or postpones first episode psychosis. Antipsychotic medication showed efficacy, but more trials are needed. Omega-3 fatty acid needs replication. Integrated psychological interventions need replication with more methodologically sound studies. The findings regarding CBT seem robust, but the 95 percent confidence interval is still very large.
The relative risk (RR) of developing psychosis was reduced by more than 50% for those receiving CBT at every time point [RR at 6 months 0.47, 95% confidence interval (CI) 0.27–0.82, p=0.008 (fixed-effects only: six randomized controlled trials, n=800); RR at 12 months 0.45, 95% CI 0.28–0.73, p=0.001 (six RCTs, n=800); RR at 18–24 months 0.41, 95% CI 0.23–0.72, p=0.002 (four RCTs, n=452)].

Conclusions. CBT-informed treatment is associated with a reduced risk of transition to psychosis at 6, 12 and 18–24 months, and reduced symptoms at 12 months.
Addington
Morrison
Morrison
Van der Gaag
NICE Guidelines for Psychosis 2014
NICE 2014
Psychosis and schizophrenia in adults

• Preventing psychosis
• If a person is considered to be at increased risk of developing psychosis
  • offer individual cognitive behavioural therapy (CBT) with or without family intervention
  • offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. [new 2014]
Conclusion

- It is feasible to identify people at high risk of psychosis
- At risk of psychosis and definitely struggling
- CBT in ARMS reduces transition
- CBT in ARMS may reduce transition to multiple disorders or minimise long term disability

Thank you