A Brand New Day: 
Preventing Psychotic Disorders by Early Detection and Intervention

William R. McFarlane, M.D.

Maine Medical Center Research Institute
Portland, Maine
USA

Tufts University
University of Vermont
Early detection and prevention in another illness

“If you catch cancer at Stage 1 or 2, almost everybody lives. If you catch it at Stage 3 or 4, almost everybody dies.

We know from cervical cancer that by screening you can reduce cancer up to 70 percent. We’re just not spending enough of our resources working to find markers for early detection.”

--Lee Hartwell, MD
Nobel Laureate, Medicine
President and Director,
Hutchinson Center
New York Times Magazine
December 4, 2005, p. 56

Early detection and prevention in psychotic illness

“The psychiatrist sees too many end states and deals professionally with too few of the pre-psychotic.”

--Harry Stack Sullivan, 1927
Shortened productive lives

Cardiovascular disease
Mental illness
Cancer
Respiratory disease
Alcohol use
Infectious disease
Drug abuse

$10 million

Lifetime costs for each new case of schizophrenia

Source: Mental Health Report of the Surgeon General
75% Proportion of people who have one psychotic episode and schizophrenia and then develop disability

10% Proportion of people with schizophrenia who are gainfully employed
2-3%  
Proportion of youth who develop schizophrenia or a severe, psychotic mood disorder

12-15%  
Proportion of people with schizophrenia or a psychotic mood disorder who commit suicide
>33 : 1

Odds that a person with vs. without psychotic symptoms will attempt or commit suicide

25

Years of life lost by people with schizophrenia due to all causes, including heart disease, cancer and suicide
Functioning as an effect of number of psychotic episodes

Effects of untreated initial psychosis

- Being psychotic is a personal disaster and the longer it lasts, the more it can become traumatic and stigmatizing.
- Being psychotic reduces cognitive and social function. They may lose contact with family and friends, fail school, or drop out of work.
- Neurobiological deficit processes linked to symptom formation may possibly proceed unlimited as long as the patient is untreated.
- The longer the psychosis lasts, the more difficult it may be for the therapist to establish a good therapeutic relationship with the patient.
Cognitive Deficits

Affective Sx: Depression

Social Isolation

School Failure

Biological Vulnerability: CASIS

Brain Abnormalities

Structural Biochemical Functional

Early Insults

e.g. Disease
Genes, Possibly
Viral Infections,
Environmental
Toxins

Social and
Environmental
Triggers

Disability

Increasing Positive Symptoms

Early Insults

e.g. Disease
Genes, Possibly
Viral Infections,
Environmental
Toxins

Brain Abnormalities

Structural Biochemical Functional

Cortical volume reduction in childhood-onset schizophrenia, ages 14-19

After Cornblatt, et al., 2005

Cortical volume reduction in childhood-onset schizophrenia, ages 14-19

p-value
Biosocial causal interactions in late schizophrenic prodrome

- Early prodrome: Social & performance deficits, Perceptual distortions, Critical comments, CD, EOI, Anxiety
- Acute onset: Panic, Misattribution, High EE

Is early intervention indicated prevention of psychotic disorders?
Risk of psychosis over 10 years

Trials of Indicated Prevention

- Buckingham, UK
- OPUS, Denmark
- PIER, Maine
- EDIPPP, USA
- GRN
- PACE I, II, Australia
- EDIE I, II, III, UK
- Addington, Canada
- PRIME, North America
- Omega-3 FAs, Austria

Family psychoeducation
Cognitive therapy
Biological treatment
**Early intervention is prevention**

One year rates for conversion to psychosis

- **Risk reduction = 66%**

- Controls
- Experimental

**Meta-analyses of RCTs**

Conversion to psychosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (risk reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusar-poli, et al, 2013</td>
<td>0.34 (-66%; n=554)</td>
</tr>
<tr>
<td>van der Gaag, et al, 2013</td>
<td>0.46 (-54%)</td>
</tr>
<tr>
<td>Stafford, et al, 2013</td>
<td>0.54 (-46%; n=1246)</td>
</tr>
<tr>
<td>Integrated treatment</td>
<td>0.19 (-81%)</td>
</tr>
<tr>
<td>(Nordentoft, 2006, Bechdolf, 2012, McFarlane, 2014)</td>
<td></td>
</tr>
</tbody>
</table>
Portland Identification and Early Referral (PIER)

Reducing the incidence of major psychotic disorders in a defined population, by early detection and treatment:
Indicated prevention
Professional and Public Education

- Reducing stigma
- Information about modern concepts of psychotic disorders
- Increasing understanding of early stages of mental illness and prodromal symptoms
- How to get consultation, specialized assessments and treatment quickly
- Ongoing inter-professional collaboration
Assessing Risk for Psychosis

Psychosis Occurs on a Spectrum

**Grandiosity**
- Youth enjoys basketball and expects to attend college on a full scholarship.
- Youth is heading to New York City because he believes he is talented enough to join the Knicks.

**Suspiciousness**
- Young woman goes to the mall and feels like people are looking at her.
- She refuses to go to the mall because she is certain that a specific person is out to harm her.

**Auditory Hallucinations**
- Hearing indistinct buzzing or whispering
- Hearing a voice clearly outside your head saying, “You’re a loser” or “You’re a failure.”
Signs of prodromal psychosis
Schedule of Prodromal Syndrome (SOPS), McGlashan, et al

A clustering of the following:
Changes in behavior, thoughts and emotions, with preservation of insight, such as:

- Heightened perceptual sensitivity
  - To light, noise, touch, interpersonal distance

- Magical thinking
  - Derealization, depersonalization, grandiose ideas, child-like logic

- Unusual perceptual experiences
  - “Presence”, imaginary friends, fleeting apparitions, odd sounds

- Unusual fears
  - Avoidance of bodily harm, fear of assault (cf. social phobia)

- Disorganized or digressive speech
  - Receptive and expressive aphasia

- Uncharacteristic, peculiar behavior
  - Assumption preoccupation, unphilosophical, bizarre appearance

- Reduced emotional or social responsiveness
  - “Depression”, aloxia, anergia, mild dementia

Unusual perceptual experiences

- “Presence”, shadows, visual trails, ghosts
- Imaginary friends
- Fleeting apparitions
- Odd sounds
- Somatic illusions or hallucinations
- Heightened or dulled perceptions
- Vivid sensory experiences
- Sensations and thoughts located outside the body
- Frequent distortions or illusions
- Brief but frank hallucinations, minimal effect on behavior or thinking
Signs of prodromal psychosis

Changes in behavior, thoughts and emotions, with preservation of insight, such as:

- Unusual fears
  - Marked guardedness, distrustful
  - Fear of assault (not social phobia)
  - Avoidance of bodily harm
  - Somatic delusions
  - Severe nihilism
  - Persistent persecutory self-referential thoughts
  - Paranoia
  - Extreme guilt, fear of harming others
  - Bizarre obsessional preoccupations
  - Fears of mind-reading
  - Frank delusions, without full conviction

• 2. Significant deterioration in functioning
  - Unexplained decrease in work or school performance
  - Decrease in personal hygiene
  - Decrease in the ability to cope with life events and stressors

• 3. Social withdrawal
  - Loss of interest in friends, extracurricular sports/hobbies
  - Increasing sense of disconnection, alienation
  - Family alienation, resentment, increasing hostility, paranoia
**Intervening to Prevent Onset**

Family-aided Assertive Community Treatment (FACT): Clinical and functional intervention

- Rapid, crisis-oriented initiation of treatment
- Psychoeducational multifamily groups
- Case management using key Assertive Community Treatment methods
  - Integrated, multidisciplinary team; outreach PRN; rapid response; continuous case review
- Supported employment and education
  - Collaboration with schools, colleges and employers
Family-aided Assertive Community Treatment (FACT):
Clinical and functional intervention

- Cognitive assessments used in school or job
- Low-dose atypical antipsychotic medication
  - aripiprazole 2-20 mg, quetiapine 300-600 mg, risperidone 0.25-3 mg
- Mood stabilizers, as indicated by symptoms:
  - Mood stabilizing drugs: lamotrigine 50-150 mg, valproate 500-1500 mg, lithium by blood level
- SSRIs, with caution, especially with aripiprazole and/or a family history of manic episodes

Team Staff

- Psychiatrist
- Nurse
- Social Worker or Family Clinician (LMFT)
- Supported Employment/Education Specialist
- Occupational Therapist
- Peer Counselor
Key clinical strategies in family intervention specific to prodromal psychosis

• Strengthening relationships and creating an optimal, protective home environment:
  – Reducing intensity, anxiety and over-involvement
  – Preventing onset of negativity and criticism
  – Adjusting expectations and performance demands
• Minimizing internal family stressors
  • Marital stress
  • Sibling hostility
  • Confusion and disagreement
• Buffering external stressors
  • Academic and employment stress
  • Social rejection at school or work
  • Cultural taboos
  • Entertainment stress
  • Romantic and sexual complications

Relapse Outcomes in Clinical Trials with Schizophrenia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No medication</th>
<th>Individual therapy &amp; medication</th>
<th>FPE &amp; medication</th>
<th>PEMFG &amp; medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>65</td>
<td>41</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>
**Components of first episode psychosis services:**
Evidence level A *and* rated as essential by international experts

<table>
<thead>
<tr>
<th>Domain names and Components with level of supporting evidence (A-D)</th>
<th>Semi-Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection of Antipsychotic Medication (Level of evidence: A)</td>
<td>.5</td>
</tr>
<tr>
<td>Clozapine for Treatment-Resistance (Level of evidence: A)</td>
<td>.5</td>
</tr>
<tr>
<td>Use of Single Antipsychotics (Level of evidence: A)</td>
<td>.5</td>
</tr>
<tr>
<td>Psychoeducational Multifamily Group Psychoeducation (MFG) (Level of evidence: A)</td>
<td>.5</td>
</tr>
<tr>
<td>Supported Employment (Level of evidence: A)</td>
<td>.37</td>
</tr>
</tbody>
</table>


**Outcomes**
### Efficiency of identification:
Diagnosis for those eligible by geography and age

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred for another disorder</td>
<td>314</td>
<td>40.2%</td>
</tr>
<tr>
<td>Prodromal</td>
<td>148</td>
<td>19.0%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>79</td>
<td>10.1%</td>
</tr>
<tr>
<td>Any psychiatric illness</td>
<td>589</td>
<td>69.4%</td>
</tr>
</tbody>
</table>

### Referral sources

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>185</td>
<td>23.7%</td>
</tr>
<tr>
<td>Educational professionals</td>
<td>158</td>
<td>20.3%</td>
</tr>
<tr>
<td>Mental health agencies</td>
<td>204</td>
<td>26.2%</td>
</tr>
<tr>
<td>Tertiary hospitals, ERs</td>
<td>168</td>
<td>21.5%</td>
</tr>
<tr>
<td>Community physicians, therapists</td>
<td>38</td>
<td>4.9%</td>
</tr>
<tr>
<td>Self and other</td>
<td>10</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
Treated cases converting to psychosis within 24 months (n = 148)

- Cases not converted: 121, 81.8%
- Cases converted, 1-30 days: 14, 9.4%
- SOPS psychosis conversions: 13, 8.8%

Role functioning in FACT:
% working or in school, baseline vs. 24 months

Baseline: 83%
24 months: 90%
First hospitalizations for psychosis
Maine Urban controls areas vs. Greater Portland

- Urban Control Areas: +8%
- Portland Area: -24%

Net difference = 32%*

* p<0.0001

Cost savings for first admissions to a hospital for psychosis
Greater Portland vs. Rest of Maine

- Difference in incidence 1994-2000 vs 2001-2007: 11.7 per 100,000 population
- Portland population average 2001-2007: 340,476
- Cases prevented: 39
- Mean LOS days: 13
- Bed Day Rate: $900

Annual savings, Greater Portland: $456,300
Total savings, Greater Portland: $2,737,800
Annual per capita savings, 2001-2006: $1.34

Incidence:
- Average 1994-2000: 18.2
- Average 2001-2007: 11.7

Mean LOS:
- Average 1994-2000: 15.8 days
- Average 2001-2007: 13 days

Bed Day Rate:
- Average 1994-2000: $900
- Average 2001-2007: $900
PIER long-term outcome
4-12 years after identification of risk

During 2-year treatment, 2001-2009

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received any treatment</td>
<td>139</td>
<td>100%</td>
</tr>
<tr>
<td>Severe episode</td>
<td>14</td>
<td>10%</td>
</tr>
</tbody>
</table>

Post-2-year treatment, 2-10 years

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Followed-up</td>
<td>72</td>
<td>52%</td>
</tr>
<tr>
<td>Severe psychosis or hospitalization</td>
<td>9</td>
<td>13%</td>
</tr>
<tr>
<td>In school or working</td>
<td>55</td>
<td>76%</td>
</tr>
</tbody>
</table>

Early Detection and Intervention for the Prevention of Psychosis (EDIPPPP)

A national multisite effectiveness trial of indicated prevention

Reducing the incidence of major psychotic disorders in a defined population, by early detection and treatment:

Indicated prevention
Early Detection and Intervention for the Prevention of Psychosis

- Effectiveness Trial at six sites:
  - Portland, Maine / Maine Medical Center
  - Glen Oaks, New York / Albert Einstein College of Medicine
  - Ann Arbor, Michigan / University of Michigan
  - Salem, Oregon / Oregon Health Sciences University
  - Sacramento, California / University of California at Davis
  - Albuquerque, New Mexico / University of New Mexico
- Sponsored by RWJF
- Risk-based allocation and incidence reduction
- Regression discontinuity and time series analyses
- Large and diverse nationally representative sample
- PIER community outreach and identification systems
- For further information: www.ChangeMyMind.org

Outreach activities and referrals over two years

- California
- One dot = one event Year 2 (3/09-3/10)
- Catchment Areas Outreach Activities Referrals
Entry and assignment criteria

- Ages 12-25
- Living in the experimental catchment area
- Positive symptom score by SIPS criteria:
  - Clinical Low Risk (CLR) Control
    - Sum <7; OR
  - Clinical High-Risk (CHR) Treatment
    - Sum = 7 or more; OR
  - Early First Episode Psychosis (EFEP) Treatment
    - Any 6 for < 1 month
- IQ 70 or higher
- No previous psychosis
- Not toxic or medical psychosis

Outcomes
Early identification across sites

<table>
<thead>
<tr>
<th>SITE</th>
<th>Population</th>
<th>Age-corrected rate**, at 25/100,000*</th>
<th>Years of community outreach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maine</td>
<td>323,105</td>
<td>63%</td>
<td>8</td>
</tr>
<tr>
<td>Michigan</td>
<td>344,791</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Oregon</td>
<td>631,853</td>
<td>29%</td>
<td>2.5</td>
</tr>
<tr>
<td>California</td>
<td>466,488</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>New York</td>
<td>557,725</td>
<td>17%</td>
<td>1.5</td>
</tr>
<tr>
<td>New Mexico</td>
<td>662,564</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,986,526</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

**Proportion (69.2%) of ages 12-35 population represented by ages 12-25 population.

*Rate for Nottingham, U.K., in Kirkbride, et al., Arch Gen Psychiatry. 2006;63:250-258

Demographic and Psychosocial Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 337)</th>
<th>Clinical Low Risk (n = 87)</th>
<th>Treatment High-Risk (n = 250)</th>
<th>Early 1st Episode (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>16.6</td>
<td>16.2</td>
<td>16.4</td>
<td>17.9</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>134 (40%)</td>
<td>26 (30%)</td>
<td>89 (43%)</td>
<td>19 (42%)</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>62%</td>
<td>71%</td>
<td>61%</td>
<td>47%</td>
</tr>
<tr>
<td>African-American, (%)</td>
<td>9%</td>
<td>6%</td>
<td>8%</td>
<td>22%</td>
</tr>
<tr>
<td>Asian-American, n (%)</td>
<td>13 (4%)</td>
<td>4 (5%)</td>
<td>9 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15%</td>
<td>8 (8%)</td>
<td>33 (17%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>In School/Working, %</td>
<td>83%</td>
<td>84%</td>
<td>84%</td>
<td>80%</td>
</tr>
<tr>
<td>Income (dollars)</td>
<td>40K – 50K</td>
<td>50K – 60K</td>
<td>40K – 50K</td>
<td>30K – 40K</td>
</tr>
</tbody>
</table>
## Clinical Characteristics

<table>
<thead>
<tr>
<th>Current SCID-IV Axis-I Diagnoses</th>
<th>Total (n = 337)</th>
<th>Clinical Low-Risk (CLR) (n = 87)</th>
<th>Treatment (High-Risk) (n = 250)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clinical High Risk (CHR) (n = 205)</td>
<td>Early First Episode (EFEP) (n = 45)</td>
<td></td>
</tr>
<tr>
<td>No Diagnosis</td>
<td>14%</td>
<td>22%</td>
<td>14%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>42%</td>
<td>37%</td>
<td>49%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>(1) Bipolar</td>
<td>16 (5%)</td>
<td>2 (2%)</td>
<td>12 (6%)</td>
<td>.38</td>
</tr>
<tr>
<td>(2) Major Depression</td>
<td>114 (34%)</td>
<td>27 (31%)</td>
<td>83 (41%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>28 (8%)</td>
<td>8 (9%)</td>
<td>7%</td>
<td>.66</td>
</tr>
</tbody>
</table>

### Rates of Conversion or Relapse

#### Over 24 months

<table>
<thead>
<tr>
<th></th>
<th>CLR</th>
<th>CHR</th>
<th>EFEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>87</td>
<td>205</td>
<td>45</td>
</tr>
<tr>
<td>Severe Psychosis</td>
<td>2.3%</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Events*</td>
<td>22%</td>
<td>25%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Hospitalizations, incarcerations, suicide attempts, assaults, rape
Psychotic Symptoms

Baseline 6 Months 12 months 24 months

Controls APS EFEP

CHR vs. CLR = 0.0034
EFEP vs. CLR <0.0001

Negative Symptoms

Baseline 6 Months 12 months 24 months

Controls APS EFEP

CHR vs. CLR = 0.099
EFEP vs. CLR <0.012
Social Functioning

In school or working:
Baseline and 24 months
Increases in participation in school, work or work and school from baseline to 24 months*

* Odds Ratio: CHR+EFEP vs. CLR; = 3.44, 95% C.I. 1.16, 11.0, p=0.025

Effect for FACT Components:
Reduction of psychotic symptoms

<table>
<thead>
<tr>
<th>Intervention</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual therapy</td>
<td>+1.84</td>
<td>0.07</td>
</tr>
<tr>
<td>Single family</td>
<td>+0.23</td>
<td>0.82</td>
</tr>
<tr>
<td>Multifamily group</td>
<td>-3.10</td>
<td>0.002</td>
</tr>
<tr>
<td>Supported education/employment</td>
<td>-0.40</td>
<td>0.69</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>-0.95</td>
<td>0.34</td>
</tr>
<tr>
<td>Antidepressant drugs</td>
<td>+0.81</td>
<td>0.42</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>-1.93</td>
<td>0.054</td>
</tr>
</tbody>
</table>
First Episode Psychosis hospital admissions
Intervention areas / control areas: CA, ME, MI, NY, OR

Outcomes in four California county PIER prevention programs
San Diego, Santa Clara, Ventura

N=125
Baseline 12 Month
Working 15% 49%
In school 57% 56%
Average GAF score 44 62
Psychosis 21% 3%
Suicides & attempts: 0% 2%
Conclusions

- Community-wide education is feasible in 10 US cities.
- Referrals were 30% up to 60% of the at-risk population.
- Global outcome in FACT was better than regular treatment.
- The 2-year conversion rate for CHR is 1/5 of expected.
- The 2-year relapse rate for FEP is 1/4 of expected.
- Average functioning was in the normal range by 24 months.
- >80% were in school or working at 2 years.
- ¾ were in school or working up to 10 years later.
- Five cities show a declining incidence.
- Four county-wide California programs are replicating.

Conclusions

Most mental health services in most communities in the United States can now begin to prevent onset of the initial psychosis in youth and young adults. We have the tools. The health, social and economic benefits are very substantial.

Yes, we can.
For further information:

www.piertraining.com

PTI@maine.rr.com