First Episode Psychosis

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Overview

1. Why we need new treatment models and methods for first episode psychosis
2. The new model
3. RAISE
4. Beyond RAISE
Rationale for A Focus on FEP

- A critically important time for the future of the course of the condition.
- The hope is that proper management during this critical period can maximize the chance of a positive short- and long-term trajectory of illness and outcome.
- We now know that long-term deterioration is not an inevitable feature of psychotic disorders.
What Are Outcomes *Typically* Like After a First Psychotic Episode?
Results—The rate of full symptom remission maintained for 6 months was 36%, while the rate of recovery for 6 months was 10%. When the same criteria were applied for a continuous period of one year, 22% of patients were found to achieve symptom remission but only 1% of patients met recovery criteria.
OPUS: 1-5 Year Follow-up
(Bertelsen et al., 2009, Schizophrenia Research)
“…much of the poor outcome in psychosis is an artifact of late detection, crude and reactive pharmacotherapy, sparse psychosocial care, and social neglect” (McGorry et al., 2014, *JAMA Psychiatry*)
MEDICATION:
It’s More Complicated Than You Think
CAFÉ Study - Results

• Secondary efficacy – change to mild or fewer symptoms – at any time
  – Olanzapine 64%
  – Quetiapine 58%
  – Risperidone 65%

• All-cause treatment discontinuation
  – Olanzapine 68%
  – Quetiapine 71%
  – Risperidone 71%
Relapse rate of individuals with schizophrenia 9.7 months after initial treatment

- Relapse rate in percentage:
  - Continued to take medications: 16%
  - Stopped taking medications: 53%

These data are taken from 66 different studies, involving a total of 4,365 people (Gilbert et al., 1995, Archives of General Psychiatry)
Medication Prescription Practices for the Treatment of First Episode Schizophrenia-Spectrum Disorders: Data from the National RAISE-ETP Study

Delbert G. Robinson, M.D. 1,2,3, Nina R. Schooler, Ph.D. 4, Majnu John, Ph.D. 1,3, Christoph U. Correll, M.D. 1,2,3,5, Patricia Marcy, BSN 3, Jean Addington, Ph.D 6, Mary F. Brunette, M.D. 7,8, Sue E. Estroff, Ph.D. 9,11, Kim T. Mueser, Ph.D. 10, David Penn, Ph.D. 11, James Robinson, M.Ed. 12,13, Robert A. Rosenheck, M.D. 14, Joanne Severe, M.S. 15, Amy Goldstein, Ph.D. 15, Susan Azrin, Ph.D. 15, Robert Heinssen, Ph.D. 15, and John M. Kane, M.D. 1,2,3,5
Findings from Robinson et al. (2015) Study

- 39.4% of the sample (N=159) could benefit from changes in their psychotropic prescriptions.
- Of the 159 subjects
  - 8.8% were prescribed recommended antipsychotic medications at higher than recommended doses
  - 32.1% were prescribed olanzapine (often at high doses)
  - 23.3% were prescribed more than one antipsychotic drug
  - 36.5% were taking an antipsychotic drug but also an antidepressant without a clear indication
  - 10.1% were taking psychotropic medications without an antipsychotic drug
  - 1.2% were prescribed stimulants
Early Use of Clozapine

Clozapine

Agid et al., JClinPsychopharm 2007
Reasons for Caution with Medication for FEP

• More severe side effects
• Faster onset of side effects
• Greater distress and discomfort from side effects
• Side effects (including weight gain) are often reasons for discontinuation
Looking More Closely At Medication, and Outcomes
Do All Patients Need Medication?

- Placebo response can approach 40%.
- Many 1st episode patients do well on no medication (on placebo; Rapoport, 1978), and have better post-hospital functioning (e.g., fewer relapses after 3 years) (NIMH 9 hospital trial; Carpenter et al, 1977).
- Soteria projects in CA and Bern
- Finnish “need-based care” studies (Lehtinen et al, 2000)
- Long-term studies (Harrow, Harding, WHO, etc.)
- Sensitization hypothesis
### TABLE 9.1
**Schizophrenia Outcomes:**
**Developing vs. Developed Countries**

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<tr>
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<th>Developing Countries</th>
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<tbody>
<tr>
<td><strong>Drug Use</strong></td>
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<tr>
<td>On antipsychotic medication 76% to 100% of follow-up period</td>
<td>15.9%</td>
<td>61%</td>
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<tr>
<td><strong>Best Possible Outcomes</strong></td>
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<tr>
<td>Remitting course with full remission</td>
<td>62.7%</td>
<td>36.9%</td>
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<tr>
<td>In complete remission 76% to 100% of follow-up period</td>
<td>38.3%</td>
<td>23.3%</td>
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<tr>
<td>Unimpaired</td>
<td>42.9%</td>
<td>31.6%</td>
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<tr>
<td><strong>Worst Possible Outcomes</strong></td>
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<tr>
<td>Continuous episodes without complete remission</td>
<td>21.6%</td>
<td>38.3%</td>
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<tr>
<td>In psychotic episodes for 76% to 100% of follow-up period</td>
<td>15.1%</td>
<td>20.2%</td>
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<tr>
<td>Impaired social functioning throughout follow-up period</td>
<td>15.7%</td>
<td>41.6%</td>
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Two-year outcome in first-episode psychosis treated according to an integrated model. Is immediate neuroleptisation always needed?


- N=106; Experimental group stressed minimal use of drugs, control group was TAU.
- In the experimental group 42.9% of the patients did not receive neuroleptics at all during the whole two-year period, while the corresponding proportion in the control group was 5.9%.
- The outcome of the experimental group was equal or even somewhat better than that of the control group.
- An integrated approach, stressing intensive psychosocial measures, is recommended in the treatment of acute first-episode psychosis.
The first study to identify major advantages of a dose-reduction (DR) strategy over maintenance therapy (MT) in patients with at least 6 months remission of FEP.

After 3 years, there were more relapses in DR group.

But, after 7 years, recovery and functional remission rates in the DR group were more than twice those of patients who were assigned to MT (40.4% vs 17.6% and 46.2% vs 19.6%, respectively).

Discontinuation or dose reduction = to a mean daily dose of less than 1 mg of equivalents of haloperidol during the last 2 years of follow-up.
Antipsychotic Medication During the Critical Period Following Remission From First-Episode Psychosis
Less Is More

Patrick McGorry, MD, PhD, FRCP, FRANZCP; Mario Alvarez-Jimenez, PhD; Eoin Killackey, DPynch

*If you come to a fork in the road, take it.*
Yogi Berra
Perspectives from McGorry et al. 2013

• It now seems probable for patients who achieve clinical remission from FEP that as many as 40% can achieve a good long term recovery with use of no or low-dose antipsychotic medication.

• It is important to identify these patients at an early stage.

• Combining DR strategies with proactive psychosocial recovery interventions maximizing early functional recovery, delivered in specialized, optimistic systems of early psychosis care, is likely to further increase the percentage of full functional recovery.

• Physical health would also be expected to improve through reduction of antipsychotic load and greater levels of social inclusion and employment.
“Modest exacerbations of symptoms, which are more common in the 3 to 5 years after diagnosis, may be a price worth paying for better longer-term functional recovery. A trade-off may be available” (McGorry et al., 2013, JAMA Psychiatry).
Recent Treatment Models
Interventions Shown to Reduce Symptoms and Improve Functioning in People with FEP

- Low doses of antipsychotic medication
- CBT
- Family education and support
- Educational and vocational rehabilitation
- Cognitive remediation

*Integrated treatment should be provided for up to 5 years*
2 Critical Points

• All care should be recovery-oriented and focused on client goals

• It is critical to maintain the therapeutic alliance at all times regardless of adherence status.
Coordinated Specialty Care (CSC)

• Team-based
  – Typically delivered by 4-6 clinicians
  – Persons with lived experience of psychosis can effectively deliver interventions

• Multiple interventions
  – Assertive case management
  – Individual and/or group therapy
  – Supported employment or education services
  – Family education and support
  – Low dose medication
  – 24 hour coverage

• Recovery oriented, and includes shared decision making focused on client goals

• Successfully implemented in Australia, UK, Canada and Scandinavia
# Key CSC Roles and Clinical Services

<table>
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<tr>
<th>CSC Role</th>
<th>Description</th>
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<tr>
<td>Team Leader</td>
<td>Trains team on principles of early psychosis intervention; leads weekly team meetings; creates referral pathways with community schools and agencies.</td>
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<tr>
<td>Case Manager</td>
<td>Frequent in-person contact, with sessions occurring in the clinic, community, and home; focus is on addressing practical problems and coordinating services.</td>
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<tr>
<td>Supported Employment and Education (SEE) Specialist</td>
<td>Emphasizes rapid placement and support; liaison with outside educators and employers.</td>
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<tr>
<td>Individual/Group Therapist</td>
<td>Emphasis is on CBT methods, focusing on resiliency, illness and wellness management, and coping skills.</td>
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<tr>
<td>Family Education and Support Clinician</td>
<td>Teaches family about FEP; engages family in decision making; helps them participate in the recovery process</td>
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<tr>
<td>Psychiatrist</td>
<td>Evidence-based pharmacotherapy for FEP; Special emphasis on health issues such as smoking, diabetes, lipid levels, substance abuse; coordinates with primary care providers.</td>
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Skills Required of ALL Team Members

• Shared decision-making
• Strengths and resiliency focus
• Motivational enhancement
• Psychoeducational skills
• Collaboration with natural supports
Conclusions: “Specialized early psychosis programs can deliver a higher recovery rate at one-third the cost of standard public mental health services.”
CSC Outcomes After 8 Years

• CSC group had fewer inpatient admissions, and less use of mental health services
• CSC group had a lower level of positive symptoms
• CSC group more likely to be in remission
• CSC group had a more favorable course of illness
• 56% of the CSC group were in paid employment over the last 2 years, compared with 33% of controls
• The cost of treatment of CSC patients was 1/3 that of the cost of treatment as usual
RAISE: Recovery After an Initial Schizophrenia Episode

• Based on 2 large NIMH-funded studies of CSC
• Inspired by international demonstrations
• Programs currently operating in 20 states
• At least 5 additional states are setting up programs
• Preliminary data indicate positive outcomes for symptoms and functioning compared to treatment as usual.
2 Variants of RAISE Model in USA

• NAVIGATE

• OnTrackNY
  – OnTrackUSA
OnTrackNY is an innovative treatment program for adolescents and young adults who recently have had unusual thoughts and behaviors or who have started hearing or seeing things that others don’t. OnTrackNY helps people achieve their goals for school, work, and relationships.
Have you or someone you know:

- started withdrawing from family and friends?
- recently had thoughts that seem strange to you or others?
- become fearful or suspicious of others?
- begun hearing or seeing things that others don’t?

If left untreated, these thoughts, feelings, and behaviors can become worse over time.

The good news: You can feel better. Care and treatment can help.

OnTrack NY
RAISE: Resources

• Manuals:
  – Outreach and Recruitment
  – Implementation
  – Performance, Quality, and Fidelity indicators
  – Team Members Guide
  – Team Leader Manual
  – Individual psychotherapy (resiliency training)
  – Supported education and employment
  – Pharmacotherapy

• Voices of Recovery video series
Outcomes of NAVIGATE
(Kane et al., 2015, American Journal of Psychiatry)

• 223 received NAVIGATE (ETP); 181 received typical community care (CC)

• Clients assigned to NAVIGATE:
  – Received more treatment (23 vs. 17 months)
  – Were more likely to have received mental health outpatient services each month
  – Showed greater improvements in reported QoL
  – Were more likely to return to work or school
  – Demonstrated greater symptom reduction (PANSS, CDSS)
But……

- Clinical Global Impression (CGI):
  - no group difference
- PANSS: 4.3 point mean difference between groups at 2 years (baseline of ~76)
  - The only symptom dimension that changed significantly was depression
- Quality of Life: 6 point difference (baseline of ~52)
- No difference in re-hospitalization rate
  - 34% vs. 37% in the CC group were re-hospitalized
RAISE (OnTrackNY): Secondary Outcomes and Intervening Variables
(Marino et al., 2015, J Nervous and Mental Disease)

• Sixty-five individuals across two sites were enrolled and received services for up to 2 years.
• Results demonstrate that the program was effective in improving quality of life and recovery over time.
• Treatment fidelity, engagement, and family involvement were identified as mediators of improvement in social and occupational functioning.
• Issue: Not a controlled study….
What Else Is Needed?

• Cognitive enhancement
• Physical exercise
• Focus on inflammation
COGNITION
Means (and SEs) for factor scores on PCA-derived domains of general and social cognition in first episode schizophrenia (FES) (N=56). FES scores were standardized to control (n=112) norms. Results confirmed in new sample of N=59
(from Williams, Whitford, Flynn, Wong, Liddell, Silverstein, Galletly, Harris, & Gordon Schizophr Res. 2008)
General and Social-emotional cognitive measures predict functional status, explaining up to 79% variance in

- Social and Occupational Functioning (SOFAS)
- Quality of Life (WHOQOL)
Neurodevelopmental context:
Progressive Grey Matter Loss in Superior Temporal and Inferior Frontal Regions after 2.5 years from first onset of schizophrenia

Fig. 1. Regions of reduced grey matter volume at baseline in 41 FES patients compared to 47 matched healthy controls. The regions of reduction are displayed as a rendered, three-dimensional statistical parametric map (SPM); height threshold: $P < 0.05$ corrected for family-wise error; extent threshold = 100 voxels.

Fig. 3. Regions where 25 FES patients lost more grey matter volume over the 2- to 3-year follow-up interval compared to 26 matched healthy controls. These regions are displayed as a rendered, three-dimensional statistical parametric map (SPM); height threshold: $P < 0.05$ corrected for family-wise error; extent threshold = 100 voxels. There were no regions in
Cognition and Brain Structure in First Episode Schizophrenia

• Gray matter volume is reduced in people at ultra-high risk for schizophrenia, and at first episode, especially in frontal, temporal, and hippocampal regions (Witthaus et al., 2009, Psychiatry Research).

• Cognitive deficits are directly related to brain volume abnormalities in frontal and temporal-parietal cortices at first episode (Minatogawa-Chang et al., 2009, Schizophrenia Research).

• There is evidence that degree of gray matter loss is related to anticholinergic load of prescribed antipsychotic medication, and use of medication in general (Ho et al., 2011; Wojtalik et al. 2010, SRP)
“If cognitive function is not restored during the remission period after the first acute phase of illness, the patient’s social functioning may be insufficient, with a poor outcome as a consequence” (Flyckt et al., 2006, *Journal of Clinical Psychiatry*, p. 922)
“Currently, no drugs exist that effectively treat cognition in people with schizophrenia” (Tamminga, Journal of Clinical Psychiatry, 2007).
Cognitive Rehabilitation for People Who Had Their First Psychotic Episode in the Past 5 Years
(Eack et al., 2010, Archives of General Psychiatry)

- Cognitive rehabilitation vs. Illness management and psycheducation
- N=53
- The CR group had a significantly greater preservation of gray matter in several brain regions known to be impaired in schizophrenia (e.g., hippocampus, fusiform gyrus).
- Reduced gray matter loss was related to better improved cognitive functioning during treatment.
UCLA Pilot Program to Enhance Neuroplasticity in FEP

• Weekly treatment for 6 months:
  – 4 hours a week of cognitive training
  – 3 hours of aerobic exercise (using a monitor to ensure that HR was within 60-80% of max.)
  – 1 hour bridging group for generalizability

• Serum-based BDNF increased
• Increased brain activity in regions related to memory
• Scores on neuropsychological measures of memory and learning, and global cognition increased.
Metabolic syndrome and aerobic fitness in patients with first-episode schizophrenia, including a 1-year follow-up

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b Horsens Regional Hospital, Department of Medicine, Denmark
c SEARCH — Research Group for Synthesis of Evidence and Research, Research Unit for Musculoskeletal Function and Physiotherapy (FoF), Department of Sports Sciences and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark
d Center for Evidence-based Practice, Bergen University College, Bergen, Norway

Results: Compared with healthy controls patients with FES had a higher baseline prevalence of MetS (p = .07), and metabolic abnormalities: WC (p < .01), TG (p < .01), HDL (p = .017), and fasting glucose (p = .04). Patients with FES had significantly increased prevalence of MetS (p = .03), WC (p = .04), and TG (p = .01) during the study period. Antipsychotics and low physical activity were significantly correlated with the increase in metabolic abnormalities. In multivariate analyses low aerobic fitness was the most consistent and significant predictor of metabolic abnormalities and MetS.

Conclusion: MetS and metabolic abnormalities are highly prevalent in patients with FES, and both increase significantly during 1 year of treatment. Apart from confirming the metabolic adverse effects of antipsychotics, our study highlights that low aerobic fitness is a significant risk factor for MetS. Promoting a healthier lifestyle should be part of psychiatric treatment and rehabilitation.
Inflammation
Elevated Microglia Levels
(Bloomfield et al., 2015, *Am J Psychiatry*)

Brain scans discovered higher activity levels in part of the brain's immune system in schizophrenia patients than in healthy volunteers.
Association of Serum Interleukin 6 and C-Reactive Protein in Childhood With Depression and Psychosis in Young Adult Life: A Population-Based Longitudinal Study

Golam M. Khandaker, PhD, Rebecca M. Pearson, PhD, Stanley Zammit, PhD, Glyn Lewis, PhD, and Peter B. Jones, PhD
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Abstract

IMPORTANCE—Longitudinal studies have linked the systemic inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP) with the risk of developing heart disease and diabetes mellitus, which are common comorbidities for depression and psychosis. Recent meta-analyses of cross-sectional studies have reported increased serum levels of these inflammatory markers in depression, first-episode psychosis, and acute psychotic relapse; however, the direction of the association has been unclear.

OBJECTIVE—To test the hypothesis that higher serum levels of IL-6 and CRP in childhood would increase future risks for depression and psychosis.
Adjunct Treatments for Schizophrenia and Bipolar Disorder: What to Try When You Are Out of Ideas

E. Fuller Torrey¹, John M. Davis²

Abstract

The pharmacologic treatment of schizophrenia and bipolar disorder leaves much to be desired. Repurposed drugs, which are approved for other medical conditions, represent an underutilized therapeutic resource for patients who have not responded to other drugs. Using experience gained from a decade of repurposed drug studies by the Stanley Medical Research Institute and search of the literature, we have identified nine such drugs for which there is some evidence of efficacy for schizophrenia and/or bipolar disorder. These include: aspirin; celecoxib; estrogen/raloxifene; folate; minocycline; mirtazapine; omega-3 fatty acids; pramipexole; and, pregnenolone. The evidence of efficacy is reviewed for each drug. Because there is little or no financial incentive for pharmaceutical companies to promote such drugs, there is a paucity of definitive trials, and these drugs are less widely known than they deserve to be. Biomarker studies should also be carried out to identify subgroups of patients who do respond to these drugs.

Key Words: Aspirin, Celecoxib, Estrogen, Folate, Minocycline, Mirtazapine, Omega-3 Fatty Acids, Pramipexole, Pregnenolone
Summary

• Optimal outcomes in FEP can be achieved with rapid entry into treatment, adherence to treatment, learning and using illness-management skills, family involvement, and avoidance of drugs and alcohol.

• New FEP models show great promise.

• But, they are relatively unavailable and most families do not know about effective interventions.

• Improving access to evidence-based care is paramount.

• Nonadherence is to be expected.

• It is critical to maintain the therapeutic alliance at all times regardless of adherence status.
Resources

• Materials on RAISE website
  – http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml (also go to Resources page…)

• OnTrack USA website

• NAVIGATE Manuals
  – https://raiseetp.org/studymanuals/

• Schizophrenia.com (incl. list of programs)

• Family information
  – knowledgex.camh.net/amhspecialists/resources_families/Documents/PromotingRecovery_FirstEpisodePsychENG.pdf (Canada)
  – http://www2.nami.org/firstepisode/firstepisodesurvey.pdf (NAMI)
Voices of Recovery Videos Series

• A series of 24 vignettes of consumer and family members, the videos share inspirational and informative recovery stories focusing on a variety of topics.

• A manual is available to help integrate the videos into treatment and training.

• Available for free at: http://practiceinnovations.org/ConsumersandFamilies/ViewAllContent/tabid/232/Default.aspx