An “Evidence-Based” Approach to Treatment-Resistant Schizophrenia

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Treatment Resistance in Schizophrenia: One Definition*

- Little or no symptomatic response to multiple (at least two) antipsychotic trials...
- Adequate duration (at least 6 weeks)
- Adequate dose (therapeutic range)

*Source: APA Practice Guidelines for the Treatment of Schizophrenia, 2
d Edition, 2004
Terms used to describe what we are talking about

- Treatment resistance / refractory / failure
- Non/ Incomplete/ Partial/ Suboptimal Response / Responder
- Incomplete Recovery
Algorithms and Guidelines

- **Algorithms**—Specifies sequences (stages) with specific options and tactics. Step-by-step flow charts of best practices in medication use. Recommends key decision points.

- **Guidelines**—Options with levels of evidence and principles of treatment. Suggests tactics, yet user develops sequences.
<table>
<thead>
<tr>
<th>Sponsoring Group/Project</th>
<th>Abv.</th>
<th>Year</th>
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<tbody>
<tr>
<td>Patient Outcome Research Team</td>
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<td>‘94, ‘04</td>
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<td>Texas Medication Algorithm Project</td>
<td>TMAP</td>
<td>‘96, ‘99, ‘04</td>
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<td>Canadian Psychiatric Association</td>
<td>CPA</td>
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Timeline of FDA Approval of Antipsychotics in the US

- Chlorpromazine ‘54
- Fluphenazine ‘59
- Thioridazine ‘59
- Haloperidol ‘67
- Many others ‘56-’70
- Clozapine ‘90*
- Risperidone ‘94
- Olanzapine ‘96
- Quetiapine ‘97
- Ziprasidone ‘01
- Aripiprazole ‘02

*developed in ‘58

Era of “First Generation AP’s”
Terms used to dichotomize antipsychotics

- Typical vs. Atypical (T vs. A)
- Conventional vs. Novel
- Older vs. Newer
- First Generation vs. Second Generation (FGA vs. SGA)
Pharmacological Treatment Algorithm for Schizophrenia (TMAP ‘99)

1. **Atypical (Risperidone, Olanzapine or Quetiapine)**
   - 4 - 8 week trial

2. If inadequate response, switch to a different atypical for additional 4-8 weeks

3. If inadequate response, switch to long acting typical agent (e.g., haloperidol decanoate) Monitor blood level

4. If inadequate response, switch to Clozapine
   - Titrate up to plasma level > 450 ng/ml as tolerated over 4 weeks
# Schizophrenia Guideline/Algorithm

## Recommendations: 1st Wave

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<tr>
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<tr>
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<td>C</td>
<td>A</td>
<td>C</td>
<td>C</td>
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<td>C</td>
<td>–</td>
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<td>–</td>
</tr>
<tr>
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**Key:**  
A = Atypicals  
T = Typicals  
C = Clozapine
Consensus that clozapine remains the gold standard treatment of choice for treatment resistant Schizophrenia.
Time frame of an adequate clozapine trial

- Carpenter vs. Meltzer debate
- 3 months vs. one year
- Meltzer – late responders – further benefit up to 1 year
- In reality, what constitutes a reasonable trial?
- 6 – 12 weeks at adequate doses
What is an adequate dose of clozapine?

- Good evidence for greater efficacy if Clozapine blood level is > 350ng/mL
- 350 – 420ng/mL appears optimal
- Dose range 175 – 825mg/day to achieve these levels across patients
# Schizophrenia Guideline/Algorithm

## Recommendations: 2\textsuperscript{nd} Wave

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<td>A</td>
<td>A</td>
<td>A,T</td>
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**Key:**
- A = Atypicals
- T = Typicals
- C = Clozapine
- C+ = Clozapine Augmentation
- 2AP = Combination Antipsychotics
Antipsychotic Sequence and Stage in Treatment Resistant Schizophrenia

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<thead>
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<th>Stage</th>
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<tr>
<td>First episode</td>
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<tr>
<td>First failure</td>
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<tr>
<td>Number of failures before clozapine</td>
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<td>Clozapine failure</td>
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<td>Clozapine augmentation</td>
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<td>Combination antipsychotics</td>
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<tr>
<td>Stage</td>
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<td>------------------------------</td>
</tr>
<tr>
<td>First Episode</td>
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<tr>
<td>Failure of first antipsychotic</td>
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<tr>
<td>Failure of second antipsychotic</td>
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<td>Failure of third antipsychotic</td>
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<tr>
<td>Failure of clozapine</td>
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<tr>
<td>Failure of clozapine</td>
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<tr>
<td>augmentation</td>
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Clozapine Augmentation Strategies

- Antidepressants
- Mood Stabilizers / Anticonvulsants
- Glutamate Modulators
- Antipsychotics

Recently reviewed in: Remington et al, CNS Drugs, 2005; 19(10) 843-872
Augmentation of Clozapine with Antidepressants

- Controlled Studies N = 2
- Fluoxetine; N = 33; 8 weeks; no benefit (Buchanan et al, '96)
- Mirtazapine; n = 24; 8 weeks; lots of benefit (Zoccali et al, '04)
Augmentation of Clozapine with Mood Stabilizers

- Controlled Studies N = 2

- Lithium; N = 20; 4 weeks, crossover design; (Small et al, ’03)
  - Improvement among SA subgroup
  - No improvement in SZ subgroup

- Lamotrigine; n = 34; 14 weeks; (Tihonen et al, ‘03)
  - Improvement in positive and general sx
  - No improvement in negative sx
Augmentation of Clozapine with Glutamatergic Agents*

- Controlled Studies N = 7
- Consistently negative
  - 2 showed dose related worsening in negative symptoms
  - 1 showed advantage in negative symptoms when added to typicals, but disadvantage when added to clozapine
  - 1 showed advantage in some cognitive measures

*Agents that stimulate Glutamate NMDA receptor-mediated activity, e.g., glycine, D-serine, D-cycloserine; CX-516
Augmentation of Clozapine with other Antipsychotics

- Controlled Studies N = 4
- Sulpride; n = 28; 10 weeks; improvement in BPRS, SAPS, SANS (Shiloh et al, '97)
- 3 studies with Risperidone
<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Journal</th>
<th>N</th>
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<tr>
<td>Jagcioglu et al, 2005</td>
<td>J Clin Psychiatry</td>
<td>30</td>
<td>6</td>
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<td>Josiassen et al, 2005</td>
<td>Amer J Psychiatry</td>
<td>40</td>
<td>12</td>
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<tr>
<td>Horner et al, 2006</td>
<td>New Eng J Medicine</td>
<td>68</td>
<td>8 + extension</td>
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</table>
Primary Results: Josiassen et al

Total Symptoms (BPRS)

Positive Sxs (BPRS)

Negative Sxs (SANS)

Josiassen et al, AJP, 2005
Primary Results: Horner et al study

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Findings for Primary Outcome</th>
<th>Mean Dose Risp.</th>
<th>Sponsor</th>
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<tr>
<td>Jagcioglu et al, 2005</td>
<td>Benefit for Placebo</td>
<td>5.1</td>
<td>Industry</td>
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<tr>
<td>Josiassen et al, 2005</td>
<td>Benefit for Risperidone</td>
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<td>Industry</td>
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<tr>
<td>Horner et al, 2006</td>
<td>No Difference</td>
<td>2.8</td>
<td>Non-industry</td>
</tr>
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</table>
Common Finding Across all 3 Risperidone + Clozapine Studies

- All found overall treatment effect
- Benefit of treatment across all patients over time
- Be wary of open, uncontrolled studies
So, what is a clinician to do?

- Many patients whose response is sub-optimal
- “Science to service” gap goes both ways
- It takes a while for science to catch up to clinical practice for effectiveness studies for complex approaches, e.g., polypharmacy
Antipsychotic Polypharmacy

- Chlorpromazine ‘54
- Fluphenazine ‘59
- Haloperidol ‘67
- Many others ‘56-‘70
- Clozapine ‘90*
- Risperidone ‘94
- Olanzapine ‘96
- Quetiapine ‘97
- Ziprasidone ‘01
- Aripiprazole ‘02

Era of “First Generation AP’s”
The Evidence Pyramid

- Systematic Reviews and Meta-analyses
- Randomized Controlled Double Blind Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Editorials, Opinions
- Animal research
- In vitro ('test tube') research
Sustained Use of 2 or more Antipsychotics

Iowa Medicaid Data 18-64 yo

≥2 AP
Antipsychotic Polytherapy

Chronic AP-users
Daily Cost of Atypicals, FY 2000

*Mean ± SD
“Treatment resistance” is not inherently dichotomous

- ~ 20% of pts with schizophrenia have complete resolution of symptoms
- ~ 30% have a clinically inadequate response
- What about the other 50%?

Source: R. Freedman, NEJM, 2003
Clozapine is not a panacea

- Agranulocytosis
- Weight gain / Metabolic syndrome / DM
- Tachycardia
- Hypersalivation
- Seizures (dose related)
- Nocturnal enuresis
- Monitoring barriers
Clozapine and Agranulocytosis

- Definition: ANC < 500/mm$^3$
- Risk estimated to be 1.3% - highest in 1$^{st}$ 6 months
- Prior to 1989 in US:
  - 149 cases, 48 fatalities (32%)
- 1989-1997 – with active monitoring
  - Of >150,000 users in national registry
  - 585 cases; 9 fatalities
“Top-down” vs. “Bottom-up” Approaches to Evidence-Based Practice

- Top down:
  - Implementation of interventions that have been repeatedly shown in rigorous studies to yield good outcomes in specific target populations

- Bottom-up:
  - Practicing in an “evidence-based manner”
Is “Evidence-Based” a Newly Popularized Term?

Medline Search Results

EBP = “Evidence-Based Practice (s)”
EBT = “Evidence-Based Treatment (s)”
EBM = “Evidence-Based Medicine”

<table>
<thead>
<tr>
<th>Years</th>
<th>EBP or EBT</th>
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<tbody>
<tr>
<td>Prior to 1990</td>
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<td>0</td>
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<tr>
<td>1990 - 1994</td>
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<td>1995 - 1999</td>
<td>328</td>
<td>3,521</td>
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<tr>
<td>2000 - 2005*</td>
<td>1,331</td>
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*Last updated August (week 1), 2005
The Evidence Based Practice Cycle

1. Agree upon and stick to intervention
2. Quantify and review priority outcomes regularly
3. Optimize priority outcomes
4. Modify intervention systematically
5. Identify and assess priority outcomes
Bottom Up Evidence-Based Approach

- Clear agreement of priority outcomes (target signs / symptoms, and more)
- Clear *a priori* endpoint (time)
- Assess barriers
- Try to limit changes to one at a time
What are the priority outcomes?

- According to who?
- Symptoms?
- Functional Status?
- How related are those?
Pathways from signs and symptoms to functional outcome

Cognition

Negative Symptoms

Positive Symptoms

Functional Outcome

SAMHSA National Outcome Measures (NOMs)

- Employment / Education
- Housing stability
- Crime / Criminal justice
- Social connectedness
- Decreased symptoms
- Perception of Care
- Access / Capacity
- Decreased hospitalization
- Cost effectiveness
- Use of EBP’s
“Recovery – Oriented” Outcomes

“...a decent job, a place called home and a date on Saturday night...”

Charles G. Curie
Common reasons for suboptimal response to pharmacologic treatment of schizophrenia

- Non-compliance
- Concurrent substance abuse
- Demoralization - lack of hope, purpose, connectedness and meaning in life;
- Problems associated with poverty
Decision Tree with compliance as a priority

Patient is need of an antipsychotic

Realistic to expect that person can or will take the medication daily?

- YES → Oral SGA
- NO → Can identify and address barriers?
  - YES → Oral SGA
  - NO → Long Acting SGA or FGA
Other Evidence-Based Approaches

- A host of non-pharmacological interventions have been demonstrated to be effective in schizophrenia

- Role of psychiatrists in these interventions
Evidence-Based Practices for Schizophrenia

- Assertive Community Treatment
- Supported Employment
- Integrated Treatment for Co-Occurring Substance Abuse
- Family Psycho-education
- Illness Management and Recovery
  - Cognitive Behavioral Therapy
Changing Paradigms and Models of understanding and treating schizophrenia

1950’s Asylum Neurobiological / Psychodynamic

1960’s De-institutionalization

1970’s Comm. Mental Health Bio-psychosocial

1980’s Revolving Door

1990’s Managed Care Neurobiological

2000’s Recovery? Holistic?
The message to individuals with schizophrenia:
Prior to Deinstitutionalization

- Either pull yourself up by the bootstraps and get with it, or, if you can’t, and no one in your family can, we have a place you can spend your life.

- It’s your fault – it’s your family’s fault
The message – 70’s and 80’s

- You have a serious mental illness.
- These are medical illnesses that affect the brain, and have to be managed as such.
- There are effective treatments
- It is not your fault – it is not your family’s fault
The Message: 80’s and 90’s

- You have an incurable mental illness. It’s not your fault; it’s not your family’s fault. It’s a chemical imbalance.

- The only thing that will help that is the right chemicals.

- Whatever you do, don’t work. It’s way too stressful, and may interfere with your taking medications and making appointments. Your career from now on is to be a psychiatric patient.

- It is our responsibility to take care of you. Just do what we say, and we’ll make sure you have almost enough money to survive.
The Message Now?

- You’ve got a mental illness.
- Lots of us do – some more severe, others less
- Now, let’s move on – together.
- What will it take for you to thrive?
“Recovery”

- Recovery refers to the process in which people are able to live, work, learn, and participate fully in their communities.

- For some individuals, recovery is the ability to live a fulfilling and productive life despite a disability.

- For others, recovery implies the reduction or complete remission of symptoms.

- Science has shown that having hope plays an integral role in an individual's recovery.

Source: President's New Freedom Commission on Mental Health
Our review for this interim report leads us to the united belief that America’s mental health service delivery system is in shambles. We have found that the system needs dramatic reform because it is incapable of efficiently delivering and financing effective treatments—such as medications, psychotherapies, and other services—that have taken decades to develop. Responsibility for these services is scattered among agencies, programs, and levels of government. There are so many programs operating under such different rules that it is often impossible for families and consumers to find the care that they urgently need. The efforts of countless skilled and caring professionals are frustrated by the system’s fragmentation. As a result, too many Americans suffer needless disability, and millions of dollars are spent unproductively in a dysfunctional service system that cannot deliver the treatments that work so well.
Mental Health System

"Transformation"

Mental Health & Health (1)
Technology & Information (6)
Consumer / Family Driven (2)
Evidence-Based Practices Training / Research (5)
Eliminate Disparities (3)
Early Intervention (4)
Recovery & Resilience
Key Recovery Concepts

- Hope
- Personal Responsibility
- Self Advocacy
- Education
- Support
Recovery – Other Perspectives

“Recovery involves the development of new meaning and purpose in one’s life as one grows beyond the catastrophic effects of mental illness”

Anthony, WA: Recovery from mental illness: the guiding vision of the mental health service system in the 1990’s.

Psychosocial Rehabilitation Journal 16: 11-23, 1993
Recovery – Definition used in the “Illness Management and Recovery” Toolkit

- “Recovery occurs when people with mental illness discover, or rediscover, their strengths and abilities for pursuing personal goals and develop a sense of identity that allows them to grow beyond their mental illness”

Psychiatric Services 53: 1272-1284, 2002
"The introduction of recovery into our national mental health dialogue is nothing short of revolutionary."

A. Kathryn Power, M.Ed.
Director, Center for Mental Health Services, SAMHSA
Conclusions

- Schizophrenia, by definition, tends to be a chronic and persistent illness.
- Medications are a key part of the solution, but for most, they are not the only part of the solution.
- The effectiveness literature will always lag behind efficacy studies and can only guide us so far.
- An evidence-based approach should be pursued.
- There are many other highly effective interventions.
- Psychiatrists may need to rethink their role.
Q and A

- **Contact information:**
  - michael-flaum@uiowa.edu
  - 319-353-4340
  - www.icmentalhealth.org
Core Principles of 6 EBP’s
Supported Employment: Core principles

- Eligibility is based on consumer choice
- Supported employment is integrated with treatment
- Competitive employment is the goal
- Job search starts soon in the process
- Follow-along supports are continuous
- Consumer preferences are important
Assertive community treatment

core principles (1)

- Services are targeted to a specific group of individuals with severe mental illness
- Rather than brokering services, treatment, support and rehabilitation services are provided directly by the ACT team
- Team members share responsibility for the individuals served by the team
- The staff to consumer ratio is small (~ 1:10)
Assertive community treatment
core principles (2)

- The range of treatment and services is comprehensive and flexible
- Interventions are carried out in vivo rather than in hospital or clinic settings
- There is no arbitrary time limit on receiving services
- Treatment, support and rehabilitation services are individualized
- Services are available on a 24-hour basis
- The team is assertive in engaging individuals in treatment and monitoring their response
How well does ACT work?

Controlled ACT Research (Bond, 2001)

- Time in hospital: 17 studies (ACT improved)
- Housing stability: 6 studies (ACT improved)
- Quality of life: 8 studies (ACT improved)
- Client satisfaction: 7 studies (ACT improved)
- Symptoms: 7 studies (ACT improved)
- Social Functioning: 9 studies (ACT improved)
- Vocational: 10 studies (ACT improved)
- Jail/arrests: 3 studies (ACT improved)

ACT improved | No difference
--- | ---
6 | 3
8 | 3
7 | 5
7 | 1
7 | 3
9 | 3
10 | 5
3 | 2
7 | 7

Number of Studies
Integrated dual disorders treatment

- More than half of all adults with MI have co-occurring substance abuse problems
- Recovery from both is more likely when MH and SA treatments are combined
Integrated dual disorders treatment

- Integrated services
  - Clinicians provide MH and SA services concurrently

- Stage-wise treatment
  - Individualized treatment approach: different stages focused on at different phases of recovery

- Assessment

- Motivational treatment

- Substance abuse counseling
Family psychoeducation

- A method of working in partnership with families to help them develop increasingly sophisticated and beneficial coping skills for handling problems posed by mental illness in their family, and skills for supporting the recovery of their loved one.
Family Psychoeducation Involves:

- Joining with consumers and their families
- Education about the illness and useful coping skills
- Problem-solving strategies for difficulties caused by illness
- Creating an optimal environment for recovery from mental illness
- Creating social and support groups
Illness Management and Recovery

- Weekly sessions where practitioners help consumers* develop personalized strategies for managing mental illness and achieving personal goals

- Individual or group format

- 3 – 6 months

- Designed for people who have had symptoms of schizophrenia, bipolar disorder, major depression
Illness Management and Recovery: Session Content

- Recovery strategies
- Practical facts about the 3 disorders
- Stress-vulnerability model and treatment strategies
- Building social supports
- Using medications effectively
- Reducing relapses
- Coping with stress
- Coping with problems and symptoms
- Getting your needs met in the mental health system
Does CBT work?

- Randomized controlled trials conducted in UK, using Beck’s model of Cognitive Therapy
- Studies primarily address medication-refractory symptoms; not CBT as a stand-alone treatment
- General finding that symptom reductions of about 25-30% occur in 60% of pts.
- Effect sizes average .65; .93 at follow-up
- CBT now mandated by British Health Trust
“Snowball” Effect

Psychotic Exacerbation

Sleep Disturbance