The Pharmacologic Treatment of Schizophrenia: Progress and Challenges

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John M. Kane Disclosures 2016

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A systematic review and meta-analysis of recovery in schizophrenia

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Conclusions:
Based on the best available data, approximately, 1 in 7 individuals with schizophrenia met our criteria for recovery. Despite major changes in treatment options in recent decades, the proportion of recovered cases has not increased.
Clinical Characteristics of First-episode Psychosis

- Typically adolescent or young adult
- Have lived with severe untreated psychotic symptoms
  - On average, for at least a year
- Compared to peers
  - Cognitively impaired
  - Poorer psychosocial functioning
  - More likely to smoke
  - More likely to abuse substances
- Families are typically actively engaged
- Goals are to return to mainstream functioning

Reported Mean Duration of Untreated Psychosis

Presented by Diana O. Perkins, MD, MPH. University of North Carolina at Chapel Hill, 26th Sept 2003

(available at: www.medscape.org/viewarticle/460974)
**Duration of Untreated Psychosis**

**RAISE ETP**

n=404

- Median DUP=74 weeks (mean=193.5±262.2 weeks)
- 68% of participants had DUP >6 months
- Correlates of longer DUP included:
  - earlier age of first psychotic symptoms
  - substance use
  - positive and general symptom severity
  - poorer functioning
  - referral from outpatient treatment settings


**Implications of Delayed Treatment**

- Greater decrease in functioning
- Loss of educational opportunities
- Impaired psychosocial and vocational development
- Personal suffering/family burdens
- Potential poorer response once treatment is provided
- Greater costs
Strategies to Reduce the Duration of Untreated Psychosis

Anonymous E-surveys of high school and college students, linkages to psycho-ed website and referral to specialty program

Interviews of early phase patients (and families) to understand pathways to care and internet social media utilization and how it was effected by incipient psychosis

Asking for access to social media communications for further examination using word count/linguistic analysis

Working with teenagers to develop social media strategies to educate and respond

Treatment Goals

- Resistance
- Exacerbation
- Response
- Resolution
- Relapse
- Remission
- Recovery

Illness Severity

Psychiatric Comorbidities
- Cognitive Dysfunction
- Physical Comorbidities

Non-Adherence
- Comorbidities
- Residual SXS

Acute
- Stabilization
- Maintenance
- Relapse Prevention
- Treatment Phase

Recovery
Treat Comorbid Conditions

- Psychiatric comorbid conditions
  - Depression: 81% lifetime risk vs 7% to 25% in general population
  - Obsessive compulsive disorder: 7.8% to 46% vs 1.2% to 2.4% in general population
  - Suicide: 50% attempt suicide
  - Substance abuse: 47% vs 16% in general population
- 50% increased risk of death and from medical causes in schizophrenia, and 20% shorter lifespan
- Higher mortality from medical causes than the general population
  - SMR in Men
    - Respiratory disease x 3.2
    - Infectious diseases x 3.4
    - Diabetes x 2.7
    - Cardiovascular disease x 2.3
- HIV infection among psychiatric patients: 3.1% to 23.9%
- Health habits: poor nutrition, smoking, lower socioeconomic level

SMR=standard mortality ratio; observed deaths among schizophrenics/expected deaths among general population.


RAISE: smoking, lipid abnormalities, hypertension diabetes + metabolic syndrome with related drug treatment

After 47 days average lifetime antipsychotic treatment, olanzapine and quetiapine were related to higher metabolic values; dyslipidemia: TC ≥200 mg/dL or TG ≥150 mg/dL, or low HDL;
TC=total cholesterol; TG=triglyceride; HDL=high-density lipoprotein; LDL=low-density lipoprotein
Correll et al. JAMA Psychiatry 2015
Key concepts for optimal first-episode medication treatment

- Response rates for positive symptoms are very high
  - No antipsychotic has demonstrated superior efficacy for the treatment of the initial psychotic episode. Tolerability is key
- Effective antipsychotic doses are usually lower than those needed for multi-episode patients
- Despite low antipsychotic doses, rates of side effects are high
- Relapse is frequent and the most important factor driving relapse is medication non-adherence
- There is often an overwhelming drive by patients and their families to stop treatment

The Risk For Psychotic Relapse is High

<table>
<thead>
<tr>
<th>Year*</th>
<th>Relapse rate (%)</th>
<th>95% CI</th>
<th>Patients still at risk at end of year, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>1</td>
<td>16.2</td>
<td>8.9</td>
<td>23.4</td>
</tr>
<tr>
<td>2</td>
<td>53.7</td>
<td>43.4</td>
<td>64.0</td>
</tr>
<tr>
<td>3</td>
<td>63.1</td>
<td>52.7</td>
<td>73.4</td>
</tr>
<tr>
<td>4</td>
<td>74.7</td>
<td>64.2</td>
<td>85.2</td>
</tr>
<tr>
<td>5</td>
<td>81.9</td>
<td>70.6</td>
<td>93.2</td>
</tr>
</tbody>
</table>

n=104 first-episode schizophrenia patients; *year(s) after recovery from the previous episode; CI=confidence interval

Robinson et al. Arch Gen Psychiatry 1999;56:241–247
Stopping medication is the most powerful predictor of relapse

- Survival analysis: risk of a first or second relapse when not taking medication is ~5 times greater than when taking it

![Hazard ratio for the first and second relapse](image)

n=104


NAVIGATE:
A comprehensive and integrated treatment for FEP

- Overall goal is recovery – not management or maintenance
- Team-based care including psychiatry, nursing, psychology, social work, and supported employment & case management specialists
- Training and on-going consultation to insure treatment fidelity
- Shared decision-making model insures client and family involvement in treatment planning and execution
- Services paid for through current reimbursement mechanisms
Navigate

- Team based
  - Shared decision-making
  - Strength & resiliency focus
  - Psychoeducational teaching skills
  - Motivational enhancement teaching skills
  - Collaboration with natural supports

- Four components
  - Psychopharmacology – COMPASS Decision Support System
  - Individual Resiliency Training (IRT)
  - Family psychoeducation
  - Supported employment/education

NAVIGATE Components

- Medication therapy
  - Computerized Decision Support System (CDSS)
  - Provides patient-centric, measurement-based treatment

- Family treatment
  - Psychoeducation about FEP and recovery process
  - Module-based focus on communication and problem solving

- Individual Resiliency Training
  - Psychoeducation on FEP and recovery
  - Module-based focus on symptomatic recovery and growth

- Supported employment/education
  - Return to full community participation – not rehabilitation!
Randomized Controlled Trial (RCT)

**Experimental Intervention**

“NAVIGATE”
17 Sites,
223 FEP participants

**Control Intervention**

“Community Care”
17 Sites,
181 FEP participants

2 year Outcomes:
- Engagement in treatment
- Quality of Life
- Return to school or work
- Symptom severity

Subject Inclusion Criteria

- Age 15 – 40
- SCID confirmed diagnosis
  - Schizophrenia
  - Schizophreniform disorder
  - Schizo-affective disorder
  - Psychosis NOS
  - Brief Psychotic Disorder
- No more than six months of anti-psychotic medication
  - Actually taken
- First episode of psychosis
### Demographics

**Adjusted for Cluster Design**

<table>
<thead>
<tr>
<th></th>
<th>NAVIGATE</th>
<th>Community Care</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age and Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>23.5</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>77.6</td>
<td>66.2</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>65.9</td>
<td>49.9</td>
<td></td>
</tr>
<tr>
<td>African American (%)</td>
<td>25.4</td>
<td>44.1</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>8.7</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td><strong>Role Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In school (%)</td>
<td>14.9</td>
<td>25.5</td>
<td>.03</td>
</tr>
<tr>
<td>Working (%)</td>
<td>12.6</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td><strong>Prior Hospitalization (%)</strong></td>
<td>76.2</td>
<td>81.6</td>
<td>.05</td>
</tr>
</tbody>
</table>

### NAVIGATE Participants Stayed in Treatment Longer

**Time to Last Mental Health Visit**

(Difference between treatments, p=0.009)
Group Differences in Overall Quality of Life
(Group by time interaction, p<=0.02)

Total Symptom Score (p<0.02)
% With Any Work or School Days per Month
(Group by time interaction: p=0.05)

Quality of Life Scale: Effects of Shorter vs Longer Duration of Untreated Psychosis (DUP; p< 0.03)
Time to First Psychiatric Hospitalization
(Difference between treatments, p=0.75)

Do the right things, at the right time.
Conclusions

- Recipients of NAVIGATE were significantly more likely to remain in treatment and experienced significantly greater improvement in the primary outcome measure (i.e., quality of life).
- They were more likely to be working or going to school.
- NAVIGATE participants showed a significantly greater degree of improvement on overall symptoms, including depression.
- Recipients of NAVIGATE showed the greatest degree of improvement when treatment was offered within the first 18 months of illness.
- These results show that a coordinated specialty care model can be implemented in a diverse range of community clinics and that the quality of life of first episode patients can be improved.

Conclusions cont.

- Early and effective intervention is key for achieving the best outcomes in schizophrenia
- Recovery rates remain disappointingly low
- Different symptom domains require attention
- A combination of pharmacotherapy and psychosocial treatments are critical to facilitate recovery
- Prevention and management of comorbid medical conditions is key.
What is my risk of relapse if I miss my medications?

- Survival analysis: risk of a first or second relapse when not taking medication is ~5 times greater than when taking it.

Stopping Medication is the Most Powerful Predictor of Relapse

- Survival analysis: risk of a first or second relapse when not taking medication is ~5 times greater than when taking it.
Relapse Fuels the Progression of Illness

- With each relapse:
  - Recovery can be slower and less complete
  - More frequent admissions to hospital
  - Illness can become more resistant to treatment
  - Increased risk of self-harm and homelessness
  - Regaining previous level of functioning is harder
  - Patient has a loss of self-esteem and social and vocational disruption
  - Greater use of healthcare resources

- Increased burden on families and caregivers


Consequences of a First and Second Relapse in Early Phase Illness

- After a first episode a young person might go back to school or work

- What happens if they relapse, will they be able to return a second time, or a third time?

- How do close friends or lovers react to a psychotic episode, and then a relapse?

- Many of life’s opportunities, and a person’s potential, can be eroded by a small number of relapses early in the illness
**UCLA Recovery Criteria**

- Recovery criteria must be met in each of 4 domains
- Improvement in each domain must be sustained concurrently for ≥2 years
- Level of recovery in these 4 domains is measured by symptom remission, appropriate role function, ability to perform day-to-day living tasks without supervision, and social interactions


**Cumulative Recovery Rates by Year in Study**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cumulative recovery rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
</tr>
<tr>
<td>3</td>
<td>9.7</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>12.3</td>
<td>5.4</td>
</tr>
<tr>
<td>5</td>
<td>13.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

CI=confidence interval

What is the role of long-acting injectable formulations of antipsychotics?

- Maintenance treatment / relapse prevention are critical treatment goals
- Non-adherence is a major barrier to maximizing the acute and long-term effectiveness of pharmacotherapy
- The % of time spent experiencing psychotic symptoms in the first 2 years is the strongest predictor of long-term symptoms and disability
- With subsequent exacerbations, treatment response tends to decrease
- Neuropathological brain changes may progress with each new episode
- LAIs remove the uncertainty about possible non-adherence, and may therefore have the potential to achieve better outcomes by improving adherence

LAI, long-acting injectable antipsychotic


Characteristics of FGA-LAIs and SGA-LAIs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Fluphenazine decanoate (LAI)</th>
<th>Haloperidol decanoate (LAI)</th>
<th>Risperidone (LAI)</th>
<th>Paliperidone palmitate (LAI)</th>
<th>Olanzapine (LAI)</th>
<th>Aripiprazole (LAI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active moiety</td>
<td>Fluphenazine</td>
<td>Haloperidol</td>
<td>Risperidone</td>
<td>Paliperidone palmitate</td>
<td>Olanzapine</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Approved indications</td>
<td>Management of patients requiring prolonged parenteral neuroleptic therapy (e.g., chronic schizophrenia)</td>
<td>Schizophrenic patients who require prolonged parenteral antipsychotic therapy</td>
<td>Schizophrenia, bipolar disorder maintenance treatment (monotherapy or adjunctive to lithium or valproate)</td>
<td>Schizophrenia</td>
<td>Schizophrenia</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Dosage forms/amounts</td>
<td>25 mg/ml, 5-ml multiple dose vials</td>
<td>50 and 100 mg/ml, 1- and 5-ml ampoules/vials</td>
<td>Im, site not specified</td>
<td>Im, site not specified</td>
<td>Delirial or gluteal muscle</td>
<td>Delirial or gluteal muscle</td>
</tr>
<tr>
<td>Approved injection sites</td>
<td>Im, sc, site not specified</td>
<td>Im, site not specified</td>
<td>Delirial or gluteal muscle</td>
<td>Delirial or gluteal muscle</td>
<td>Gluteal muscle</td>
<td>Gluteal muscle</td>
</tr>
<tr>
<td>Needle gauge (G)</td>
<td>21</td>
<td>21</td>
<td>20 or 21</td>
<td>20 or 23</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Injection volume</td>
<td>25 mg/ml</td>
<td>50 or 100 mg/ml, not to exceed 3 ml</td>
<td>Approximately 2 ml</td>
<td>156 mg/ml, range 0.25–1.5 ml</td>
<td>150 mg/ml, range 1.0–2.7 ml</td>
<td>200 mg/ml, range 0.8 ml (160 mg) to 2 ml (400 mg)</td>
</tr>
<tr>
<td>Injection interval (weeks)</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2 or 4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td>12.5–25 mg (0.5–1 ml)</td>
<td>Varies (see text, 100 mg/day, 1 balance 3–7 days later)</td>
<td>25 mg</td>
<td>234 mg/day 1 and 196 mg/day 2 (delirial)</td>
<td>Varies (see text, range up to 300 mg/2 weeks)</td>
<td>40 mg (adjust for CYP2D6 or CYP3A4 issues)</td>
</tr>
<tr>
<td>Maintenance dose Individualized, maximum 100 mg/2 weeks</td>
<td>Varies (see text, maximum 450 mg/4 weeks)</td>
<td>25 mg, maximum 50 mg/2 weeks</td>
<td>177 mg, range 39–234 mg/weeks</td>
<td>Varies (see text, range up to 350 mg/3 weeks)</td>
<td>310 or 400 mg/4 weeks (adjust for CYP2D6 or CYP3A4 issues)</td>
<td></td>
</tr>
</tbody>
</table>

Most common adverse effects with SGA-LAIs

- **RLAI**: The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increase (5% in monotherapy trial), and tremor and parkinsonism (≥10% in adjunctive therapy trial).

- **PLAI**: The most common adverse reactions (incidence ≥5% and occurring at least twice as often as placebo) were injection-site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

- **OLAI**: The most common adverse reactions (≥5% in at least one of the treatment groups and greater than placebo) associated with OLAI treatment included: headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite and vomiting.

- **ALAI**: The most commonly observed adverse reaction with oral aripiprazole (incidence ≥5% and at least twice that for placebo) was akathisia.

Prevention of Relapse with Selected LAIs vs Placebo

(vs 45 mg/4 weeks olanzapine pamoate for OLA-LAI)

<table>
<thead>
<tr>
<th>Treatment and dosage</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone palmitate LAI</td>
<td>5</td>
</tr>
<tr>
<td>flexibly dosed 39-156 mg/4 weeks</td>
<td></td>
</tr>
<tr>
<td>Olanzapine pamoate LAI 150 mg/2 weeks</td>
<td>7</td>
</tr>
<tr>
<td>Olanzapine pamoate LAI 300 mg/2 weeks</td>
<td>4</td>
</tr>
<tr>
<td>Olanzapine pamoate LAI 400 mg/4 weeks</td>
<td>5</td>
</tr>
<tr>
<td>Aripiprazole-OM 400 mg/4 weeks</td>
<td>4</td>
</tr>
</tbody>
</table>

OLA=olanzapine; OM=once-monthly

Paliperidone LAI 3 Monthly vs Placebo

In Mirror-image Studies, LAIs Reduce Risk of Hospitalization Compared with Oral Antipsychotics

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girardi et al. 2010</td>
<td>0.024</td>
<td>0.009</td>
</tr>
<tr>
<td>Beuauxier et al. 2005</td>
<td>0.092</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arató &amp; Erdös 1979</td>
<td>0.204</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DeVito et al. 1978</td>
<td>0.333</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Denham &amp; Adamson 1971</td>
<td>0.343</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morriss 1974</td>
<td>0.369</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lam et al. 2009</td>
<td>0.391</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lindholm 1975</td>
<td>0.412</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peng et al. 2011</td>
<td>0.529</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gottfrois &amp; Green 1974</td>
<td>0.529</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rosa et al. 2012</td>
<td>0.557</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chang et al. 2012</td>
<td>0.570</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Johnson &amp; Freeman 1972</td>
<td>0.597</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crivera et al. 2011</td>
<td>0.661</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ren et al. 2011</td>
<td>1.286</td>
<td>0.569</td>
</tr>
<tr>
<td>Swetka et al. 1984</td>
<td>1.286</td>
<td>0.569</td>
</tr>
</tbody>
</table>

Total (16 studies) (n=4,066) 0.430 <0.001

25 studies, N=5,940

APs=antipsychotics; CI=confidence interval; RR=relative risk.

The published results of the Finnish cohort cannot be extrapolated to other markets’ antipsychotic clinical study results; do not utilize this guidance when making therapeutic decisions.


Factors Which Discourage Doctors from Starting LAIs –Top 10 Reasons

<table>
<thead>
<tr>
<th>Reason</th>
<th>Not at all</th>
<th>Moderately</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient cannot afford</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-feasible combination Tx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible patient refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fewer choices of SGA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More EPS than oral medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impossible to discontinue/reduce</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low reimbursement for hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatively short injection interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult linkage to the next care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassle of the injection procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Expressed mean with 95%CI  N=170

Kishimoto and Kane. In preparation
WHY ME?

• Not just you → we recommend this with everyone
• We think that this is an optimal way to treat your illness
• Need to work with your provider to stay well
• We have had a lot of experience with people just like you
• It’s best if we can get the illness under control early and keep it under control

WHY EARLY PHASE?

• Most people have trouble taking meds regardless of the illness
• Avoid relapse
• Avoid hospitalization
• Avoid missing school/work
• Avoid missing friends
Impact of Initiating LAI Atypical Antipsychotics Early in the Disease Course

- Patients initiated on an atypical LAI within 5 years of onset of illness (24.2%) were compared with those on an atypical LAI >5 years after the onset of illness (75.8%):
  - Longer time to discontinuation ($P=0.003$)
  - Greater improvement in PANSS™ scores ($P<0.01$)
  - Longer time to relapse ($P=0.018$)
  - Higher remission rates ($P<0.001$)
  - Greater improvements in BPRS scores ($P<0.01$)

N=1879
BPRS=Brief Psychiatric Rating Scale; LAI=long-acting injectable;
PANSS=Positive and Negative Syndrome Scale.

Detke HC et al. Poster presented at the 52nd Annual New Clinical Drug Evaluation Unit (NCDEU) meeting; May 29-June 1, 2012; Phoenix, AZ.

Relapse Risk Despite RIS-LAI Adherence

- Stepwise Cox proportional predictors: Canada vs US: $HR=2.8$; Illness Duration >10 y > 05 years: $HR=2.3$; previous AP >4 vs ≤4 mg/day: $HR=1.8$

N=323; 1-year relapse prevention study of RIS-LAI 25 mg vs 50 mg / 2 weeks: 18.3% relapsed
Nasrallah H et al. Poster presented at the 52nd Annual New Clinical Drug Evaluation Unit (NCDEU) meeting; May 29-June 1, 2012; Phoenix, AZ.
35% vs 5% Relapse in 86 FE Schizophrenia Patients Randomized to Oral RIS vs RIS LAI

Summary

- LAIs are a valuable, yet underutilized treatment option
- Design and patient population characteristics influence the outcome and interpretation of available studies
- Attitudinal, service, setting and system barriers to the appropriate use of LAIs need to be addressed.
- To prevent relapse and relapse-related consequences, clinicians, patients and families require mental health care and treatment experiences that positively influence attitudes.
- Greater and earlier LAI use can help preserve psychosocial functioning, prevent deterioration, stigma and self stigma.
- The risk:benefit balance of available medications requires consideration when choosing treatment options

LAI, long-acting injectable antipsychotic
Meta-Analysis of 19 RCTs of Antipsychotic Combinations: Inefficacy As Defined By Study

<table>
<thead>
<tr>
<th>Study or Sub-Cat.</th>
<th>AP</th>
<th>AP</th>
<th>N</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artikov 2005</td>
<td>14/14</td>
<td>10/14</td>
<td>0.76</td>
<td>95% CI: 0.63-0.90</td>
<td>0.002</td>
<td>NNT: 7, CI: 4-17, p=0.0008</td>
<td></td>
</tr>
<tr>
<td>Perlman 2007</td>
<td>5/10</td>
<td>5/10</td>
<td>1.05</td>
<td>95% CI: 1.00-1.10</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Bentall 2007</td>
<td>9/12</td>
<td>9/12</td>
<td>1.25</td>
<td>95% CI: 1.10-1.40</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Chen 2012</td>
<td>8/13</td>
<td>8/13</td>
<td>1.00</td>
<td>95% CI: 0.85-1.15</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Liu 2008</td>
<td>20/20</td>
<td>20/20</td>
<td>1.00</td>
<td>95% CI: 0.85-1.15</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Liu 2007</td>
<td>10/10</td>
<td>10/10</td>
<td>1.25</td>
<td>95% CI: 1.10-1.40</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Peng 2007</td>
<td>10/10</td>
<td>10/10</td>
<td>1.00</td>
<td>95% CI: 0.85-1.15</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Takeda 1994</td>
<td>0/20</td>
<td>0/20</td>
<td>0.00</td>
<td>95% CI: not assessable</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Wang 1994</td>
<td>0/20</td>
<td>0/20</td>
<td>0.00</td>
<td>95% CI: not assessable</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
<tr>
<td>Yang 2007</td>
<td>0/20</td>
<td>0/20</td>
<td>0.00</td>
<td>95% CI: not assessable</td>
<td>0.002</td>
<td>NNT: 10, CI: 6-14, p=0.002</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 320 (AP = 40%, 280 (AP)

For test of heterogeneity: CH² = 59.07, df = 18 (p = 0.0001), I² = 70.9%.

For overall effect: Z = 3.05 (p = 0.002).

Clozapine for the Treatment-Resistant Schizophrenic

A Double-blind Comparison With Chlorpromazine

John Kane, MD; Gilbert Heinzfeld, PhD; Jack Bigger, MD; Herbert Meltzer, MD; and the Clozaril Collaborative Study Group

The treatment of schizophrenic patients who fail to respond to adequate trials of neuroleptics is a major challenge. Clozapine, an atypical antipsychotic drug, has long been of scientific interest, but its clinical development has been delayed because of an associated risk of agranulocytosis. This report describes a multicenter clinical trial to assess clozapine’s efficacy in the treatment of patients who are refractory to neuroleptics. 619 clozapine patients who had failed to respond to at least three different neuroleptics underwent a prospective, single-blind trial of triclopron (mean dosage, 81 ± 14 mg/day) for six weeks. Patients whose condition remained unchanged were then randomly assigned, in a double-blind manner, to clozapine (up to 900 mg/day) or chlorpromazine (up to 1200 mg/day) for six weeks. The two hundred sixty-eight patients were divided into the double-blind comparison. When a priori criteria were used, 33% of the clozapine-treated patients were categorized as responders compared with 4% of chlorpromazine-treated patients. Cloza- pine produced significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impression Scale, and Nurses’ Observation Scale for Inpatient Evaluation; this improvement included “negative” as well as positive symptom areas. Although no cases of agranulocytosis occurred during this relatively brief study, in our view, the apparently increased comparative risk requires that the use of clozapine be limited to selected treatment-resistant patients.

(Arch Gen Psychiatry 1988;45:785-790)
Guidelines Regarding Clozapine

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Basic Use</th>
<th>Specific Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Psychiatry Association (APA)</td>
<td>• Persistent psychotic Sx after 2 AP trials&lt;br&gt;– &quot;should be given strong consideration&quot;</td>
<td>• Persistent hostility, aggressive behavior&lt;br&gt;• Persistent SI&lt;br&gt;• TD</td>
</tr>
</tbody>
</table>
| Schizophrenia Patient Outcomes Research Team (PORT) | • Persistent and clinically significant positive Sx after ≥2 AP trials (including ≥1 SGA)<br>– "should be used" | • Persistent hostility/ violent behaviors<br>– "should be used"
• Marked and persistent SI/ behaviors<br>– "should be offered"
• NMS, persistent dystonia/severe or very distressing TD – "should be offered"
| Texas Medication Algorithm Project (TMAP) | • No-response or partial response to 2 AP trials (including ≥1 SGA) | • History of recurrent suicidality, violence or comorbid substance abuse – "consider earlier trial"
• Persistent positive Sx ≥2 years – "warrants"
• Persistent positive Sx >5 years – "requires" clozapine trial independent of # of AP trials |
| Canadian Psychiatric Association | • No-response to AP trials from 2 classes | • Persistent SI/ behaviors – "should be considered"
• Persistent aggressivity – "may be helped by"
| National Institute for Health and Clinical Excellence (NICE) | • Sequential use of ≥2 APs (including ≥1 SGA) | |

AP=antipsychotic, NMS=neuroleptic malignant syndrome, SI=suicidal ideation, Sx=symptoms, TD=tardive dyskinesia

SGAs Prescription Change in USA (Including All SGA Prescriptions)

Source: IMS’ National Prescription Audit (NPA)
Clozapine Prescription Change in USA

Note: 2011 is full year projection based on the data from Jan to Apr data 2011

Source: IMS’ National Prescription Audit (NPA)

Clozapine Prescription Obstacles
-why psychiatrists do not even try-

<table>
<thead>
<tr>
<th>Risk of Side Effects</th>
<th>agranulocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>body weight gain</td>
</tr>
<tr>
<td></td>
<td>other metabolic side effects</td>
</tr>
<tr>
<td></td>
<td>seizures</td>
</tr>
<tr>
<td></td>
<td>myocarditis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible Patients’ Refusal</th>
<th>blood work</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>frequent visit</td>
</tr>
</tbody>
</table>

| Possible Patients’ non-adherence | |
|----------------------------------| |

<table>
<thead>
<tr>
<th>Structure</th>
<th>Lack of clozapine clinic (blood draw, blood monitoring, registered-pharmacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lack of close connection to hematologist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lack of time/ Hassle/ Complexity</th>
<th>Blood draw/monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Documentation</td>
</tr>
<tr>
<td></td>
<td>Initial dosing</td>
</tr>
</tbody>
</table>

| Cost | |

Kishimoto et al. in preparation
What Psychiatrists Find Most Problematic About Clozapine and What They Think Patients Find

What psychiatrists find most problematic
What psychiatrists think patients find most problematic

Nielsen et al. 2010 J Psychopharmacol

Original Article

Clozapine and Haloperidol in Moderately Refractory Schizophrenia
A 6-Month Randomized and Double-Blind Comparison

John M. Kane, M.D. Stephen R. Marder, M.D. N. H. Scholer, M.D. William C. Whitmey, M.D.
Daniel Weinberger, M.D., Robert W. Baker, M.D., Thomas A. Wistrich, M.D., Allen Saffern, M.D.
Ashwin Gangoli, M.D., Marjory Maccormak, Ph.D., Michael J. Rosenberg, Ph.D.

Background: Despite the demonstrated efficacy of clozapine, modestly refractory schizophrenic patients, questions remain regarding its efficacy for primary negative symptoms, comparison with a moderate dose of a first-generation antipsychotic, and adverse effects during a long-term trial. This unaddressed efficacy in partially responsive, community-based patients compared clozapine with a moderate dose of haloperidol, and extended treatment to 6 months.

Methods: Randomized, double-blind, 24-week trial comparing clozapine (45 mg) with haloperidol (4 mg). Subjects with schizophrenia who were being treated in community settings at 5 collaborating clinical facilities were enrolled.

Results: Subjects treated with haloperidol were significantly more likely to discontinue treatment for lack of efficacy (17% in haloperidol vs. 4% in clozapine). A higher proportion of clozapine-treated subjects met an a priori criterion of improvement (37%) compared with clozapine-treated subjects (23%). Significantly greater improvement was seen in symptoms of psychomotor retardation, anxiety-depression, thought disturbance, and total score measured on the Brief Psychiatric Rating Scale. No differences were detected in negative symptoms using the Brief Psychiatric Rating Scale or the SANS for Assessment of Negative Symptoms. Subjects treated with clozapine experienced more extrapyramidal side effects, dizziness, and sweating and less dry mouth and decreased appetite than those treated with haloperidol.

Conclusions: Compared with a first-generation antipsychotic given at a moderate dose, clozapine offers substantial clinical benefits to treatment-refractory subjects who can be treated in the community. Advantages are seen in a broad range of symptoms but do not extend to negative symptoms.

Arch Gen Psychiatry, 2002;59:945–952
SGAs vs. FGAs: Overall Symptoms (Chronological Order: N= 150 DB RCTS, n= 21,533)

Data are Hedges’g (95% CI). Note that the results are significant at p<0.05 if the 95% CIs do not overlap the x axis. SGA=second-generation antipsychotic drug.

Adapted from: Leucht S. et al. Lancet 2009;373(9657):31-41

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**Relevant Facts**

- 90% of the world’s data was created in the last 2 years
- 80% of data is unstructured
- Medical data doubles every 5 years
- Medical evidence doubles every 4 years
- 34% of 2.3 trillion dollar health spend (18% of GDP) is wasted
- Costs vary by as much as 10x
- MDs prescribe evidenced based medicine less than 50% of the time
- 81% of MDs spend less than 5 hours per month reading journals
Perspectives

- The management of chronic diseases in the U.S. accounts for more than 75% of health care expenditures—$2 trillion.
- 44,000–98,000 people die in hospitals each year as a result of medical errors that could have been prevented. IOM 1999
- “Multiple studies have shown that it has taken about 17 years for a medical discovery or new validated clinical knowledge to become a fixture of daily clinical practice.” Topol, 2012

E-Health: Potential to Address Problem Areas of In-Person Services

1. Severe mental illness: treatment is insufficient
   - >50% do not receive specialty mental health services (Mojtabai et al, 09)
   - 4%-15% receive minimally adequate treatment (far short of standards for care) (Wang et al, 02)
2. 15-25 years for EBPs to reach routine care [IOM, 01]
   - Lack of expertise in community treatment settings
   - High cost of setting up & maintaining an EBP
   - Too few clients for economy of scale in clinics, or geographic areas
3. Once reach routine care EBPs often lack fidelity [Drake et al, 01]
4. Travel adds burden
5. Families/supporters left out of treatment
6. Healthcare is poorly understood—regardless of education level
7. Chronic illness management occurs at home
Home Healthcare

1. In home self assessment
2. Physiologic monitoring
3. Telemedicine evaluations
4. Early detection of exacerbation/relapse
5. Cost-saving
6. Decrease patient burden, increase patient satisfaction

Health Technology Program

• Focuses upon the 6 months following hospital discharge
• Engages patient with a treatment team
• Uses innovative tech tools to provide treatment
• Outcome assessment and monitoring is integrated in treatment
• Treatment is tailored to patient needs and preferences
  – Shared decision making
The Health Technology Program Components

- **Relapse Prevention Plan**
  - In-person guidance to create “My Relapse Prevention Plan”
- **Daily Support Website**
  - Web-based support for patients and families
- **FOCUS**
  - Smart phone app to cope with adherence, mood, sleep, social dysfunction and voices
- **Coping with Voices and Paranoia**
  - Web-based computer CBT programs
- **Prescriber Decision Assistant**
  - Web-based Medication Decision Support System

Multi-Modal Sensing
**CrossCheck: Detecting Risk for Relapse**

![Graph showing standardized score over days](image)


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**ORIGINAL RESEARCH**

First Experience With a Wireless System Incorporating Physiologic Assessments and Direct Confirmation of Digital Tablet Ingestions in Ambulatory Patients With Schizophrenia or Bipolar Disorder

John M. Kane, MD; Ray H. Perlis, MD, MSc; Lorenzo A. DiCarlo, MD; Kiydee Au-Yeung, PhD; Jessie Duong, BA; and Georgios Petrides, MD

**ABSTRACT**

**Objective:** To characterize the feasibility and safety of a wireless networked system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder.

**Method:** In this 4-week observational study conducted between May 2010 and May 2011 at 2 US academic clinical study sites, 12 adults with bipolar disorder and 16 adults with schizophrenia (all diagnosed according to DSM-IV criteria) utilized a digital health feedback system (DHF). All subjects were on a stable regimen of oral medication. The DHF utilized a digital tablet, consisting of an ingestion sensor that was embedded in a tablet containing nonpharmacologic excipients, which subjects ingested with their regularly prescribed medication. The formulation of this digital tablet allowed ingestion sensor separation and activation by stomach fluids after ingestion, followed by communication of a unique identifying signal from the ingestion sensor to an adhesive sensor worn on the torso which automatically logged the date and time of each digital tablet ingestion.

Numerous studies across all areas of medicine identify the actual taking of medication as prescribed as one of the major challenges in promoting public health. Although medication adherence in the setting of acute illness is often higher, the management of many chronic diseases suffers from problems in continued medication adherence, which in turn contributes to an enormous proportion of avoidable emergency department visits and hospital days, as well as poor overall outcomes. Osterberg and Blaschke, in their comprehensive review of the topic, suggested that, of all medication-related hospital admissions in the United States, 33%-69% are due to poor medication adherence, with a resulting cost of approximately $100 billion per year.

Component 1: Tiny Event Marker Placed In Medication

Ingestible Event Marker (IEM) shown on pills

- Tiny: < 1mm square
- Accurate: >99% detection in human clinical trials
- Safe: made from ingredients in food
- Inexpensive: fractions of a penny
- Private: EKG-like signal conducted only in body; not RFID

Identifies and communicates when a pill has been ingested

RAISIN SYSTEM: Theory of Operation

1. Upon ingestion, an Ingestible Event Marker (IEM) is activated by gastric fluid and begins communicating with the Raisin Data Recorder (RDR).

2. RDR gathers information from the IEM. It also collects heart rate, activity, and sleep data via its internal accelerometer.

3. Data from RDR are transmitted to the mobile phone for server upload. Other subjective input can be manually entered using the phone.
Rich, Integrated Data Set from Emitter 3.0 CV-HF

Table showing data from Day/Night 1, Day/Night 2, and Day/Night 3 for Pill detects (8/8), Activity/Sleep, Step Count, Position, and Heart Rate.

Figure 3. Physiologic Metrics, Medication-Taking Adherence, and Scheduling Adherence as a Function of Study Day

Graph showing adherence and target, sleep duration, activity, and sleep score over the study days.

Conclusions

Healthcare in the future will be heavily influenced by:

- Genomics
- Biomics
- Neuroimaging
- Technology
- Stratification strategies
- Consumerism
- Cost containment