Predicting What the Treatment of Schizophrenia Will Look Like in a Decade

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Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
A Systematic Review and Meta-Analysis of Recovery in Schizophrenia

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.
Mean Duration of Untreated Psychosis

Meta-analyses:
Menezes et al (2006) = 73.6 weeks

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

Specified Aims of RAISE

- Develop a comprehensive and integrated intervention to
  - Promote symptomatic recovery
  - Minimize disability
  - Maximize social, academic, and vocational functioning
  - Be capable of being delivered in real world settings utilizing current funding mechanisms

- Assess the overall clinical impact and cost-effectiveness of the intervention as compared to currently prevailing treatment approaches
  - Conduct the comparison in nonacademic, real world community treatment settings in the United States

RAISE = Recovery After an Initial Schizophrenia Episode.
RAISE Trial Design: Participants

• Sample size: 404
• Age 15–40
• The following diagnoses are included in the differential
  – Schizophreniform disorder
  – Schizophrenia
  – Schizoaffective disorder
  – Psychotic disorder NOS
  – Brief psychotic disorder
• < 6 months of treatment with antipsychotic medications

Randomized Controlled Trial

- Randomized controlled trial to compare
  - NAVIGATE – experimental intervention
  - Community Care – treatment as offered in local clinics in the United States
- Cluster/site randomization of 34 sites in 21 states
- 2-year treatment period
- Assessment model includes
  - On-site recruitment, engagement, and retention
  - Remote assessors of primary and secondary clinical outcome

Conduct the Comparison in Nonacademic, US Community Treatment Settings: *ETP Sites are in 21 Contiguous States*

ETP = Early Treatment Program.
RAISE–ETP Study Design with Cluster/Site Randomization

RAISE–ETP  
n=404

NAVIGATE  
17 sites  
n=223

Community Care  
17 sites  
n=181

RAISE Trial: Outcomes

• Primary outcome measure: Quality of Life Scale
  – Primary hypothesis
    • RAISE intervention compared to community care will improve Quality of Life
• Other measured outcomes
  – Service utilization
  – Cost
  – Consumer perception
  – Prevention of relapse
  – Enhanced recovery

NAVIGATE

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

• 4 components
  – Psychopharmacology – COMPASS
  – Individual Resiliency Training (IRT)
  – Family psychoeducation
  – Supported employment/education

Duration of Untreated Psychosis in Community Treatment Settings in the United States

Jean Addington, Ph.D., Robert K. Heinssen, Ph.D., Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Patricia Marcy, B.S.N., Mary F. Brunette, M.D., Christoph U. Correll, M.D., Sue Estroff, Ph.D., Kim T. Mueser, Ph.D., David Penn, Ph.D., James A. Robinson, M.Ed., Robert A. Rosenheck, M.D., Susan T. Azrin, Ph.D., Amy B. Goldstein, Ph.D., Joanne Severe, M.S., John M. Kane, M.D.

**Objective:** This study is the first to examine duration of untreated psychosis (DUP) among persons receiving care in community mental health centers in the United States.

**Methods:** Participants were 404 individuals (ages 15–40) who presented for treatment for first-episode psychosis at 34 nonacademic clinics in 21 states. DUP and individual- and site-level variables were measured.

**Results:** Median DUP was 74 weeks (mean=193.5±262.2 weeks; 68% of participants had DUP of greater than six months). Correlates of longer DUP included earlier age at first psychotic symptoms, substance use disorder, positive and general symptom severity, poorer functioning, and referral from outpatient treatment settings.

**Conclusions:** This study reported longer DUP than studies conducted in academic settings but found similar correlates of DUP. Reducing DUP in the United States will require examination of factors in treatment delay in local service settings and targeted strategies for closing gaps in pathways to specialty FEP care.

*Psychiatric Services 2015; 66:753–756; doi: 10.1176/appi.ps.201400124*
Psychopharmacological Treatment in the RAISE-ETP Study: Outcomes of a Manual and Computer Decision Support System Based Intervention

Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Christoph U. Correll, M.D., Majnu John, Ph.D., Benji T. Kurlan, M.D., M.P.H., Patricia Marcy, B.S.N., Alexander L. Miller, M.D., Ronny Pipes, M.A., L.P.C.-S., Madhukar H. Trivedi, M.D., John M. Kane, M.D.

Objective: The Recovery After an Initial Schizophrenia Episode—Early Treatment Program compared NAVIGATE, a comprehensive program for first-episode psychosis, to clinician-choice community care over 2 years. Quality of life and psychotic and depressive symptom outcomes were found to be better with NAVIGATE. Compared with previous comprehensive first-episode psychosis interventions, NAVIGATE medication treatment included unique elements of detailed first-episode-specific psychotropic medication guidelines and a computerized decision support system to facilitate shared decision making regarding prescriptions. In the present study, the authors compared NAVIGATE and community care on the psychotropic medications prescribed, side effects experienced, metabolic outcomes, and scores on the Adherence Estimator scale, which assesses beliefs related to nonadherence.

Method: Prescription data were obtained monthly. At baseline and at 3, 6, 12, 16, and 24 months, participants reported whether they were experiencing any of 21 common antipsychotic side effects, vital signs were obtained, fasting blood samples were collected, and the Adherence Estimator scale was completed.

Results: Over the 2-year study period, compared with the 181 community care participants, the 223 NAVIGATE participants had more medication visits, were more likely to receive a prescription for an antipsychotic and more likely to receive one conforming to NAVIGATE prescribing principles, and were less likely to receive a prescription for an antidepressant. NAVIGATE participants experienced fewer side effects and gained less weight; other vital signs and cardiometabolic laboratory findings did not differ between groups. Adherence Estimator scores improved in the NAVIGATE group but not in the community care group.

Conclusions: As part of comprehensive care services, medication prescription can be optimized for first-episode psychosis, contributing to better outcomes with a lower side effect burden than standard care.

Duration of Untreated Psychosis and QLS and PANSS Outcomes

FIGURE 3. Heinrichs-Carpenter Quality of Life (QLS) Total Score and PANSS Total Score: Effects of Shorter or Longer Duration of Untreated Psychosis (DUP) Based on a Model With Square Root Transformation of Months

QLS = Heinrichs-Carpenter Quality of Life Scale; PANSS = Positive and Negative Syndrome Scale.

In the model, DUP and DUP by square root of time by treatment terms were included as covariates in addition to the covariates listed in Table 2. The DUP by square root of time term was found not to be significant for either outcome. PANSS=Positive and Negative Syndrome Scale; CC=Community Care; NAV=NAVIGATE.

DUP by treatment by square root of time interaction, p=0.003.

DUP by treatment by square root of time interaction, p=0.043.

Coordinated Specialty Care Programs in 2008
Before RAISE: 12 Community Clinics
Coordinated Specialty Care Programs in 2018
$100M in FY16–FY17: 187 Community Clinics
Time to First Psychiatric Hospitalization
(Difference between Treatments, $P=.75$)

Product-Limit Survival Estimates

Robinson DG, et al. Submitted for publication.
Antipsychotic Drugs vs Placebo for Relapse Prevention in Schizophrenia: A Systematic Review and Meta-Analysis


<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of studies</th>
<th>Drug group (%)</th>
<th>Control group (%)</th>
<th>Mean study duration' (months)</th>
<th>Risk ratio (95% CI)</th>
<th>Absolute difference (95% CI)</th>
<th>NNT/HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse 7-12 months</td>
<td>24</td>
<td>32/37 (46%)</td>
<td>77/32 (64%)</td>
<td>11</td>
<td>0.40 (0.23 to 0.66)</td>
<td>-0.19 (-0.46 to 0.17)</td>
<td>3 (1 to 3)</td>
</tr>
<tr>
<td>Relapse independent of duration</td>
<td>62</td>
<td>74/75 (99%)</td>
<td>77/76 (99%)</td>
<td>9</td>
<td>0.35 (0.29 to 0.41)</td>
<td>0.03 (0.01 to 0.08)</td>
<td>3 (2 to 3)</td>
</tr>
<tr>
<td>Participants readmitted to hospital</td>
<td>16</td>
<td>112/113 (99%)</td>
<td>77/32 (64%)</td>
<td>13</td>
<td>0.38 (0.27 to 0.51)</td>
<td>-0.03 (-0.20 to -0.11)</td>
<td>5 (4 to 9)</td>
</tr>
<tr>
<td>Dropout when readmitted to hospital</td>
<td>15</td>
<td>243/598 (16%)</td>
<td>77/32 (64%)</td>
<td>9</td>
<td>0.31 (0.26 to 0.34)</td>
<td>-0.04 (-0.24 to -0.18)</td>
<td>1 (1 to 7)</td>
</tr>
<tr>
<td>Dropout because of tolerability</td>
<td>2</td>
<td>127 (59%)</td>
<td>65/64 (53%)</td>
<td>5</td>
<td>0.27 (0.31 to 0.81)</td>
<td>0.02 (-0.01 to 0.05)</td>
<td>=</td>
</tr>
<tr>
<td>Participants unavailable or worse</td>
<td>1</td>
<td>9/10 (90%)</td>
<td>7/7 (100%)</td>
<td>7</td>
<td>0.06 (0.75 to 1.52)</td>
<td>-0.06 (-0.17 to 0.05)</td>
<td>11 (6 to 100)</td>
</tr>
<tr>
<td>Violent/aggressive behavior</td>
<td>5</td>
<td>9/103 (8%)</td>
<td>77/32 (64%)</td>
<td>8</td>
<td>0.71 (0.45 to 1.12)</td>
<td>0.01 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>Participants employed</td>
<td>2</td>
<td>3 (13%)</td>
<td>65/64 (53%)</td>
<td>11</td>
<td>0.21 (0.39 to 1.29)</td>
<td>-0.15 (-0.47 to 0.17)</td>
<td>=</td>
</tr>
<tr>
<td>Death (any)</td>
<td>14</td>
<td>5/124 (41%)</td>
<td>7/116 (6%)</td>
<td>7</td>
<td>0.25 (0.13 to 0.47)</td>
<td>0.01 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>Suicide (any)</td>
<td>8</td>
<td>0/1021</td>
<td>2/361 (13%)</td>
<td>6</td>
<td>0.34 (0.13 to 0.80)</td>
<td>0.01 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>Death from natural causes</td>
<td>14</td>
<td>5/1277 (1%)</td>
<td>7/116 (6%)</td>
<td>7</td>
<td>1.71 (0.27 to 1.29)</td>
<td>0.01 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>Dropout because of AE</td>
<td>4</td>
<td>129/342 (37%)</td>
<td>78/189 (41%)</td>
<td>4</td>
<td>1.51 (0.70 to 3.21)</td>
<td>0.01 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>At least one AE</td>
<td>10</td>
<td>5/5 (100%)</td>
<td>7/116 (6%)</td>
<td>7</td>
<td>1.01 (0.81 to 1.27)</td>
<td>0.00 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>At least one MD</td>
<td>27</td>
<td>30/199 (15%)</td>
<td>77/32 (64%)</td>
<td>7</td>
<td>1.15 (0.75 to 1.29)</td>
<td>0.00 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>13</td>
<td>18/105 (17%)</td>
<td>77/32 (64%)</td>
<td>9</td>
<td>0.52 (0.28 to 0.97)</td>
<td>0.01 (-0.02 to 0.01)</td>
<td>100 (95 to 1000)</td>
</tr>
<tr>
<td>Use of antipsychotic medication</td>
<td>7</td>
<td>18/248 (72%)</td>
<td>9/35 (26%)</td>
<td>11</td>
<td>1.00 (1.03 to 1.89)</td>
<td>0.00 (-0.02 to 0.01)</td>
<td>11 (6 to 50)</td>
</tr>
<tr>
<td>Satiety</td>
<td>10</td>
<td>11/112 (10%)</td>
<td>7/7 (100%)</td>
<td>6</td>
<td>1.01 (0.52 to 1.94)</td>
<td>0.01 (-0.01 to 0.01)</td>
<td>=</td>
</tr>
<tr>
<td>Weight gain</td>
<td>10</td>
<td>128/1232 (10%)</td>
<td>6/30 (20%)</td>
<td>7</td>
<td>0.95 (0.90 to 1.00)</td>
<td>0.00 (-0.03 to 0.03)</td>
<td>20 (6 to 110)</td>
</tr>
</tbody>
</table>

Note: Data are n/N (%) unless otherwise stated. The random-effects model by DerSimonian and Laird was used throughout, with weights calculated by the Mantel-Haenszel method. NNT/HR = number needed to treat to benefit or harm. B = benefit. AE = adverse event. MD = movement disorder. *Weighted by sample size of individual trials. *Because of space limitations, we did not use the display suggested by Altman."
Stopping Medication is the Most Powerful Predictor of Relapse

- Survival analysis: Risk of a first or second relapse when not taking medication is \( \sim 5 \times \) greater than when taking it

N=104.
LAI shows strong superiority over oral APs in preventing hospitalization.

LAIs Reduce Risk of Hospitalization Compared with Oral Antipsychotics

AP = antipsychotic; LAI = long-acting injectable antipsychotic.

A Nationwide Cohort Study of Oral and Depot Antipsychotics after First Hospitalization for Schizophrenia

Objective: Data on the effectiveness of antipsychotics in the early phase of schizophrenia are limited. The authors examined the risk of rehospitalization and drug discontinuation in a nationwide cohort of 2,588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland.

Method: The authors linked national databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for the effects of sociodemographic and clinical variables, the temporal sequence of the antipsychotics used, and the choice of the initial antipsychotic for each patient.

Results: Of 2,588 patients, 1,507 (58.2%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and 1,182 (45.7%), 95% confidence interval [CI]: 43.7–47.6) continued their initial treatment for 30 days or longer. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI: 0.17–0.75). Compared with oral risperidone, clozapine (adjusted hazard ratio=0.48, 95% CI: 0.31–0.76) and olanzapine (adjusted hazard ratio=0.54, 95% CI: 0.40–0.79) were each associated with a significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio=0.45, 95% CI: 0.31–0.67).

Conclusions: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.

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Jari Haukka, Ph.D.
Mark Taylor, F.R.C.Psych.
Peter M. Haddad, M.D., F.R.C.Psych.
Maxine X. Patel, M.D., M.R.C.Psych.
Pasi Korhonen, Ph.D.

Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29,823 Patients With Schizophrenia

Jari Tiihonen, MD, PhD; Ellenor Mittendorfer-Rutz, PhD; Malla Majak, MSc; Juha Mahtälä, PhD; Fabian Hoti, PhD; Erik Jedenius, PhD; Dana Eriksson, MSc; Amy Leval, PhD; Jan Sermon, PhD; Antti Tanskanen, PhLic; Heidi Taipale, PhD

**IMPORTANCE** It has remained unclear whether there are clinically meaningful differences between antipsychotic treatments with regard to preventing relapse of schizophrenia, owing to the impossibility of including large unselected patient populations in randomized clinical trials, as well as residual confounding from selection biases in observational studies.

**OBJECTIVE** To study the comparative real-world effectiveness of antipsychotic treatments for patients with schizophrenia.

**DESIGN, SETTING, AND PARTICIPANTS** Prospectively gathered nationwide databases were linked to study the risk of rehospitalization and treatment failure from July 1, 2006, to December 31, 2013, among all patients in Sweden with a schizophrenia diagnosis who were 16 to 64 years of age in 2006 (29,823 patients in the total prevalent cohort; 4,603 in the incident cohort of newly diagnosed patients). Within-individual analyses were used for primary analyses, in which each individual was used as his or her own control to eliminate selection bias. Traditional Cox proportional hazards multivariate regression was used for secondary analyses.

**MAIN OUTCOMES AND MEASURES** Risk of rehospitalization and treatment failure (defined as psychiatric rehospitalization, suicide attempt, discontinuation or switch to other medication, or death).
33% vs 5% Relapse in 86 First-Episode Schizophrenia Patients Randomized to Oral Risperidone vs Risperidone LAI

Patients With Early Phase Schizophrenia Will Accept Treatment With Sustained Release Medication (LALs): Results from the Recruitment Phase of the PRELAPSE Trial

Kane, JM1, Schooler, NR1,2, Robinson DG1, Achteys, ED1, Marcy, P.4

1 The Zucker Hillside Hospital, Northwell Health, 2 SUNY Downstate Medical Center, 3 Cherry Health, 4 Vanguard Research Group

OBJECTIVE

To document the acceptability to early phase schizophrenia patients of treatment with long-acting injectable (LAI) antipsychotic medication as demonstrated by enrollment in a cluster-randomized LAI clinical trial.

RESULTS

At the 19 U.S. outpatient clinics randomized to provide LAI treatment, 676 potential participants were identified who met inclusion/exclusion criteria based upon a screening interview.

Of these, 83 (14.4%) declined participation because they would not consider LAI treatment and 165 (28.5%) declined for other reasons, resulting in 328 providing written study consent.

The first post-consent visit included detailed evaluations to confirm inclusion/exclusion criteria. Thirty-nine consented participants did not complete this evaluation and 55 were found to not meet criteria, resulting in a final sample of 234 participants.

Two hundred thirteen (91.0%) accepted at least one LAI injection during their first 3 months of study participation.

METHODS

The PRELAPSE study is a cluster-randomized, large simple trial being conducted in the US.

STUDY DESIGN

• Cluster-randomized trial
• 39 sites in 19 US states randomized to offer antipsychotic treatment
• 19 sites randomized to LAI Aripiprazole Once Monthly (AOM)
• 20 sites randomized to Clinician’s Choice (CC) of antipsychotic
• Two-year treatment/observation duration for subjects

CONCLUSIONS

Kane JM, et al. Presented at: Biennial Schizophrenia International Research Society Conference; April 7, 2018; Florence, Italy.
Staff Training Included

• Training in shared decision-making and communication

• Role-playing to develop skills

Kane JM, et al. Submitted for publication.
Diverse data sources can be used to measure established clinical symptoms, side effects, behaviors.

- Passively-recorded activity, location
- “Real” sensors, wearables, IoT
- Self-report, active tasks
- Digital Traces: Purchases, media
Number of health and wellness Apps have soared over the past few years…more being developed every day.

- **>165k** mHealth Apps on Google Play and Apple Store
- **~125k** Focus on fitness, lifestyle, diet, and other categories
- **~40k** Focus on medical Apps
- **~220** FDA Cleared Mobile Medical Apps


Enlight: A Comprehensive Quality and Therapeutic Potential Evaluation Tool for Mobile and Web-Based eHealth Interventions

Monitoring Editor: Gunther Eysenbach

Reviewed by Obinna Anya and John Torous

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Evaluating eHealth/mHealth Interventions

MindTools’ scientific approach rests on the rigorous and continuous development of Enlight – a comprehensive suite of criteria-based measurements. Enlight currently covers 11 different quality constructs and checklists that are produced by trained raters. Based on a rigorous systematic review assessing different aspects of both eHealth and mHealth interventions, Enlight is the first suite of measures to incorporate behavior change, persuasive design, and therapeutic alliance concepts – concepts that have been found to affect a program’s therapeutic potential. Enlight was developed to enable the examination of eHealth interventions, regardless of delivery medium (website/mobile/suite of products/text messaging/etc.) or clinical aim (mental health, chronic conditions, health-related behaviors, etc.).

Wearable Tech: Bringing Passive Monitoring and Big DATA into the Community

Where We are Headed:

• Wearable tech brings us in to the home, providing troves of objective data on sleep, movement, geolocation, and more

• Training algorithms to make sense of data to inform clinical decision-making

• Commercially available sensors built into devices (eg, Apple Watch and Fitbit) enable cost-effective monitoring
Wearables Industry is Expected to Double by 2021

Announcements over past few months

Garmin Vivoactive 3 announced – Is this a Fitbit Ionic smartwatch Killer

Apple just announced a new Apple Watch that doesn’t need an iPhone to work

Speedo and Samsung Make Waves with Partnership to Bring Industry-Leading Swim Tracking Capabilities to Gear Fit2 Pro and Gear Sport

The Fitbit Ionic: One Wearable To Rule Them All?

Amazon’s Coming Alexa-Powered Smart Glasses

Google and Levi’s ‘connected’ jacket that lets you answer calls, use maps and more is going on sale
Overarching Theme: *What are the unmet needs that can be addressed by technology and AI?*

How can technology be utilized to monitor, inform, and improve treatment and treatment outcome (in routine practice and in clinical trials)?

A. Real time passive and active/interactional monitoring, including “digital medicine”

B. Guidance to clinicians, patients, and family members based on technological monitoring and AI analysis

C. Earlier identification of exacerbation/relapse/improvement to provide actionable information to all stakeholders

AI = artificial intelligence.
Machine Learning

1. Make few *a priori* assumptions
2. Allow the data to “speak for themselves”
3. Mine knowledge from big data
Digital Data and Youth

- Over 90% of adolescents use social media
- 45% describe themselves as online “constantly”
- Disclose more about themselves online than offline
- Longitudinal data
Machine Learning

Machine learning uses quantitative models to induce general principles underlying a series of observations without explicit instructions. Such algorithmic methods are characterized by 1) making few a priori assumptions, 2) allowing the data to “speak for themselves”, and 3) the ability to mine structured knowledge from extensive data. Its members include supervised methods, such as support vector machines and neural-network algorithms, specialized for best-possible outcome prediction as well as unsupervised methods, such as algorithms for data clustering and dimensionality reduction, effective at discovering novel statistical configurations in data.

Harvesting Online/Social Media Activity

- Major advancements in computational techniques
- Established source for capturing personalized and population data from explicit commentary, patterns of use, intricacies of language
- Used to gather information including spread of influenza, seasonal allergies, HIV infection, cancer, smoking, and obesity
- Predict personality traits, intelligence, mood, substance use, religious, and political views

Pathways to Care: Sample Questions

• When did you first notice any concerning changes in your thoughts, feelings, or behaviors?
• What did you think was causing these changes?
• Where did you go to get answers?
• Did your social media habits change? In what ways?
• Did you ever discuss your concerns on social media?
• Did you ever receive any advice on social media?
• How would you feel if we at the ETP used the Internet or social media to reach out to you directly?
Social Media and Psychosis

- 344 participants (112 PSY, 38 APS, 40 mood, 79 control, 75 parents)
- 59% male; mean age: 21.8 years
- 94.5% currently use social media regularly
- Checked social media sites 11×/day
- Spent 2 hours/day online
- Used social media for the past 6.8 years
- Facebook most used followed by Instagram, YouTube

Birnbaum ML, et al. Submitted for publication.
Social Media and Psychosis (cont’d)

- 50.7% parents connected with their child via social media
- 26.7% participants (19.8% PSY, 31.6% APS, 40.6% mood) talked about their symptoms online
- 59.0% would be OK with proactive outreach
- 76.1% interested in getting help via social media/Internet
- 76.7% parents interested in getting help online
- 80.7% participants, 89.7% controls agreed to sharing social media data with the research team
Facebook Results

- Psychosis group (n=62), mood disorders (n=39), and healthy controls (n=24)
- Linguistic differences in use of negations (not, never), prepositions (under, above), concepts and themes (truth and faith), as well as in complexity of language
- **Psychosis vs Control**: 80% accuracy. High precision/PPV (.82) and high recall/sensitivity (.93)
- **Psychosis vs Depression**: 70% accuracy. High precision/PPV (.80) and recall/sensitivity (.67)

PPV = positive predictive value.
Birnbaum ML, et al. Submitted for publication.
Facebook Results (cont’d)

• Significant differences ($P<.005$) in profile pictures of relapse ($n=20$) vs non-relapse ($n=10$). Larger face, more blurry, less likely to include others

• Significant differences ($P<.005$) in length of messages. Longer messages interspersed with shorter messages

• Significant linguistic shifts within individuals who relapse

• Increases in swearing ($P<.05$), first-person pronouns ($P<.05$), and negations ($P<.05$)

Future Directions

• Understand how youth are using the Internet as means of obtaining information, communicating distress, seeking help, expressing psychotic thought content

• Determine the impact of early and appropriate online educational material on help seeking behaviors in youth

• Determine the impact of altering the social media experience of youth

• Understand optimal strategies of using the Internet and social media to connect with youth
Improving Outcomes/Reducing Costs

- 3 Daily prompts
- “On-demand” resources
- Native App
- 5 Targets: Voices, social, medications, sleep, mood
- Online clinician dashboard
- Tailored: Target selection, prompting schedule

Web-based therapy for patients and families

Ingestible Event Marker

Computerized Decision Support System

CrossCheck
A new Paradigm for Illness Monitoring and Relapse Prevention

Multi-Modal Sensing

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

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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 (DHFS). All subjects were on a stable regimen of oral medication. The DHFS 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,1 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.
Aripiprazole Tablets with Sensor

- The system records medication ingestion and communicates it to the patient and health care provider.
- In addition, it can collect data on activity level, as well as self-reported rest and mood which, with patient consent, can be shared with the health care provider and selected members of the family and care team. The system provides an objective summary of drug ingestion over time, to help facilitate a more informed dialogue with healthcare providers who treat patients with certain serious mental illnesses.

IMA, intelligent medical assistant, visually interacts with a patient as if a nurse was there in person.

- Confirms who the patient is and protects their identity through facial recognition.
- Ensures that the patient gets the right medication by verifying the shape and color.
- Guides the patient through administration and confirms that they have taken the medication properly.

"Unlike a video recording or photograph, IMA is an interactive visual recognition platform that takes a few seconds to use."

https://aicure.com/.
Antipsychotic Treatment and Striatal Functional Connectivity

DC = dorsal caudate.
Antipsychotic Treatment and Striatal Functional Connectivity (cont’d)

VSI = ventral caudate/nucleus accumbens.
Baseline Striatal Functional Connectivity as a Predictor of Response to Antipsychotic Drug Treatment

Objective: Clinical response to antipsychotic drug treatment is highly variable, yet prognostic biomarkers are lacking. The authors recently demonstrated that successful antipsychotic drug treatment alters resting-state functional connectivity of the striatum. The goal of the present study was to test whether intrinsic striatal connectivity patterns provide prognostic information and can serve as a potential biomarker of treatment response to antipsychotic drugs.

Method: The authors used resting-state functional MRI (fMRI) to develop a prognostic index in a discovery cohort of 42 first-episode schizophrenia patients, then tested this index in an independent cohort of 40 newly hospitalized chronic patients with acute psychosis. In the discovery cohort, patients underwent resting-state fMRI scanning at the initiation of randomized controlled treatment with a second-generation antipsychotic. Whole-brain functional connectivity maps were generated for each subject from striatal seed regions. A stringent measure of clinical response was calculated that required sustained improvement over two consecutive study visits. Clinical response was entered into a survival analysis, and Cox regression was applied to the functional connectivity data. A striatal connectivity index was created, comprising functional connections of the striatum that predicted treatment response. This striatal connectivity index was tested on a generalizability cohort of patients with psychotic disorders who were hospitalized for an acute psychotic episode.

Results: A total of 91 regions functionally connected with the striatum provided significant prognostic information. Connectivity in these regions was used to create a baseline striatal connectivity index that predicted response to antipsychotic treatment with high sensitivity and specificity in both the discovery and generalizability cohorts.

Conclusions: These results provide evidence that individual differences in striatal functional connectivity predict response to antipsychotic drug treatment in acutely psychotic patients. With further development, this has the potential to serve as a prognostic biomarker with clinical utility and to reduce the overall burden associated with psychotic illnesses.

Genetics: Definitions

• **Single Nucleotide Polymorphism (SNP)**
  – DNA sequence variation due to change in a single nucleotide

• **Allele**
  – One of several alternate forms of an SNP at a given locus

• **Copy Number Variation (CNV)**
  – DNA structural variation: change in # of nucleotides (< 2 or > 2)
No “gene for schizophrenia”
No APOE/BRCA1
Current Understanding of Schizophrenia

- Schizophrenia is a complex mental disorder that contributes the fifth leading cause of disability in the United States.
- Strong genetic component with heritability estimates of ~80%.
- To date, only 1% to 2% of heritability accounted for by common SNPs.
- Additional 1% to 2% accounted for by rare, penetrant CNVs.

GWAS = genome-wide association.

Goals of Genetic Investigations

• **Diagnosis / Prediction**
  – Refining diagnostic boundaries

• **Understanding Pathophysiology**
  – Targeting new treatments

• **Pharmacogenetics**
  – Personalized medicine
SNP Overlap

Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries

Hywel J. Williams, Nicholas Craddock, Giancarlo Russo, Marian L. Hamshere, Valentina Moskvina, Sarah Dwyer, Rhodri L. Smith, Elaine Green, Detelina Grozeva, Peter Holmans, Michael J. Owen and Michael C. O’Donovan*

The Druggable Genome

Figure 2 | **Number of drug targets.** The effective number of exploitable drug targets can be determined by the intersection of the number of genes linked to disease and the 'druggable' subset of the human genome.

The Druggable Genome: Evaluation of Drug Targets in Clinical Trials Suggests Major Shifts in Molecular Class and Indication

- 555 genes targets of approved pharmaceuticals (“established targets”)
- 475 genes targeted by compounds in clinical trials (“novel targets”)
- 1030 druggable genes (5.06% of all genes)

Cardiometabolic Risk of Second-Generation Antipsychotic Medications during First-Time Use in Children and Adolescents

Conclusions

- Computer science, engineering, and other disciplines should be brought to bear on challenges in public mental health
- Identification and engagement of individuals experiencing mental illnesses are key
- Sustained engagement is not necessarily the only goal. We need to understand what type and degree of engagement is most effective for that individual
- The potential of digital tools for garnering/generating ecologically valid, real-time objective data and providing personalized potential interventions has been well established
- The pharmaceutical industry should consider new experimental designs to make the best use of these potentially valuable data streams
- Health economic analyses must identify and assess the complex costs and benefits of digital interventions
Conclusions (cont’d)

• Although appropriately designed machine learning/AI-based models can perform well, they still have important limitations. Strategies to ensure data quality, accuracy, and the meeting of ethical standards remain key

• Genetics plays a key role in illness risk and treatment response, both therapeutic and adverse

• The process of treatment development based on genetics is complex and so far has had limited impact on mental illnesses

• Ultimately, genetic research holds great promise for refining diagnostic boundaries, targeting new treatments and personalizing medicine