Prescribing in Early Psychosis: Make Haste Slowly

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Yale University School of Medicine

“Who Said the Voices Aren’t Real?”
Northern Rivers Family of Services
September 22, 2017
Outline

• Natural history of psychosis
• Why prescribe?
• Barriers to recovery
• One solution: A team-based approach
• What if it doesn’t work?
• ? Future approaches to psychotic symptoms and med management
Course of the Primary Non-Affective Psychoses: The Schizophrenia(s)

Phase of illness

Premorbid  Prodrome  Acute  Plateau / Chronic

Onset of illness  First episode  Phase of illness

A (8-16%)

Most of the clinical and psychosocial deterioration occurs in first 5 years (Lieberman et al., 2001)

B

De-synchrony of symptoms and functioning: phases are different

C (8-9%)

Prognostically important period: Symptom duration in first 2 years is strongest predictor of outcome (Harrison et al, 2001); Highest Suicide risk; Onset of substance misuse; Longer DUP associated with poorer outcomes (Marshall, 2006)

Age (years)

5 10 15 20 25 30 35 40 45 50 55 60

Primary  Secondary  Tertiary Prevention

from Srihari et al. Psych Clin of N America, 2012
Why Prescribe?

• To promote recovery
• To achieve higher quality of life (QOL):
  – Two recent studies showed significantly greater improvement in QOL than those treated with placebo.
  – One of these found that long-acting risperidone (25 mg q 2 weeks) improved QOL to levels “not significantly different from normal.”
• Medication is a tool in a holistic treatment approach aimed at recovery:
  – Can allow for engagement with other specialties focused on minimizing decrements in QOL and overall potential

Barriers To Recovery

• Failure to engage
  – Difficulty accepting new diagnosis of a serious mental illness
  – Stigma associated with illness
  – Fear of loss of freedom

• Non-adherence
  – 25-50% of people with schizophrenia are believed to be non-adherent with maintenance therapy

Prescribing in First-Episode Psychosis: A Team-Based Approach
Prescribing in First-Episode Psychosis: A Part of Coordinated Specialty Care (CSC)

• A recovery-oriented treatment program for people with first episode psychosis (FEP), valuing:
  – Shared decision-making
  – Personalized treatment planning, targeting patient-identified goals
  – Utilization of a multidisciplinary team to offer comprehensive care for FEP
Prescribing in First-Episode Psychosis: A Part of Coordinated Specialty Care (CSC)

• Parts of CSC might include:
  – Medication management
  – Individual psychotherapy
  – Family psychoeducation
  – Case management
  – Supported employment/education services
Does CSC work?

- Hospitalized (over 6 mos prior to enrollment)
- Hospitalized (over 1 year after enrollment)
- Vocationally engaged (at enrollment)
- Vocationally engaged (1 year after enrollment)

**Graph:**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP</td>
<td>49/60</td>
</tr>
<tr>
<td>TAU</td>
<td>46/57</td>
</tr>
<tr>
<td>STEP</td>
<td>25/57</td>
</tr>
<tr>
<td>TAU</td>
<td>25/37</td>
</tr>
</tbody>
</table>

**References:**

Why does it work?

• Is this adherence therapy?
  – No
  – Adherence therapy widely discredited as ineffective

• Patient-centered, allows identification of patient goals, and enhanced engagement
What is a prescriber’s role in CSC?

- Patient, non-judgmental listening and development of a differential diagnosis
- Determination of patient’s goals
- Offering health-related services to aid with achieving those goals
  - Screening for secondary causes of psychosis (labs, imaging, referral to specialty services as indicated)
  - Pre-medication screening
  - Starting medications in a way that maximizes long-term adherence
  - Performing routine maintenance to troubleshoot, manage adverse effects
Diagnostic Assessment

Brain on Fire: Anti-NMDA, A Clinical and Case perspective

Susannah Cahalan, Writer and Journalist
Secondary Psychosis

• Consider life-threatening causes (delirium, including EtOH w/d)

• Consider easily diagnosed and treatable (e.g. syphilis, thyroid)

• Consider common (primary)

• Remain alert for uncommon presentations of illnesses requiring different Rx (e.g. epilepsy)

Sources: Coleman & Gillberg (1996), Coleman & Gillberg (1997), Goff et al. (2004), and Hyde & Lewis (2003).
Pragmatic Work-Up vs. the Quest for Certainty

1. Test for common disorders, co-morbidities
2. Revisit treatable secondary causes (but consider risks/costs of testing)
3. Test for rare but more easily treatable disorders
4. Establish baseline cardiovascular risk (and monitor!)

<table>
<thead>
<tr>
<th>TABLE 5. Medical work-up for first-episode psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam with emphasis on neurological exam</td>
</tr>
<tr>
<td>Vital signs</td>
</tr>
<tr>
<td>Weight and height (BMI), waist circumference</td>
</tr>
<tr>
<td>ECG (if cardiac risk)</td>
</tr>
<tr>
<td>Laboratory tests</td>
</tr>
<tr>
<td>Broad screening and medical baseline:</td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>Electrolytes including calcium</td>
</tr>
<tr>
<td>Renal function tests (BUN/creatinine)</td>
</tr>
<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>Fasting glucose</td>
</tr>
<tr>
<td>Lipid profile</td>
</tr>
<tr>
<td>Consider prolactin level</td>
</tr>
<tr>
<td>Consider hepatitis C (if risk factors)</td>
</tr>
<tr>
<td>Pregnancy test (in women of child-bearing age)</td>
</tr>
<tr>
<td>Urine drug screen</td>
</tr>
<tr>
<td>Exclude specific treatable disorders:</td>
</tr>
<tr>
<td>TSH</td>
</tr>
<tr>
<td>FTA-ABS (fluorescent treponemal antibody absorbed)</td>
</tr>
<tr>
<td>HIV test</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
</tr>
<tr>
<td>Vitamin B12</td>
</tr>
<tr>
<td>Neuroimaging</td>
</tr>
<tr>
<td>MRI (preferred over CT)</td>
</tr>
<tr>
<td>Ancillary tests</td>
</tr>
<tr>
<td>Expand aetiological search if indicated, taking into account epidemiology:</td>
</tr>
<tr>
<td>For example, CXR, EEG, lumbar puncture, karyotype, heavy metal testing</td>
</tr>
<tr>
<td>Expand medical monitoring if indicated:</td>
</tr>
<tr>
<td>For example, eye exam (if risk factors for cataracts)</td>
</tr>
</tbody>
</table>

Diagnostic Assessment
Summary/Principles

1. Take a Bayesian perspective
   • Knowledge of horses and zebras: educated prior probability
   • Critical interpretation of tests (labs, imaging, exams)
   • Tests perform differently at different base prevalence rates

2. Probabilistic, revisionist approach (vs. diagnostic certainty)

3. Longitudinal f/u + capacity to be surprised
Pre-Medication Screening

• Good PMH

• Consider:
  – CBC
  – Lipids
  – LFTs
  – TFTs
1. ‘Positive’ symptoms: ‘Psychosis’
   - Reality distortion (delusions, hallucinations)
   - Disorganization (thought, behavior, expression of feeling)

2. ‘Negative’ symptoms
   - lack of motivation (avolition)
   - reduction in spontaneous speech (alogia)
   - social withdrawal (apathy)

Loss of anticipatory but not consummatory pleasure
3. Cognitive deficits

- Memory (working and long term)
- Attention, processing speed
- Executive functioning
- Social cognition

4 & 5. Affective dysregulation

- Depressive symptoms
- Manic symptoms
Neurochemistry of Schizophrenia: Glutamate, GABA, Dopamine, ....
The Dopamine Model - Updated


Treating with Antipsychotic medications

• Which medication(s)?
  
  – FGA (high vs. low potency) vs. SGAs or better: ‘Dopamine receptor antagonists’ with variable side effect profiles

• How to dose?

• For how long?

• Common side effects?
Antipsychotic medications: which one?

from D. Cyril D’Souza
Antipsychotics: Dose matters

Large (30-80%) variability in dose-to-occupancy correlation: search for easy effective dose

D2 occupancy:
EPS & Antipsychotic effects

Farde et al., 1992

blunting of cognition/mood/motivation
Antipsychotic medications: what dose?

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED₅₀</th>
<th>Near-maximal Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>150 mg/d</td>
<td>400–450 mg/d</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5–2 mg/d</td>
<td>3.5–10 mg/d</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>25 mg/mo</td>
<td>100–200 mg/mo</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>—</td>
<td>10–15 mg/d</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>—</td>
<td>&lt;10 mg/d</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>—</td>
<td>&lt;6.9 mg/d</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>—</td>
<td>25 mg/2 wk</td>
</tr>
<tr>
<td><strong>SGAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>9 mg/d</td>
<td>&gt;16 mg/d</td>
</tr>
<tr>
<td>Olanzapine IM</td>
<td>&gt;6 mg/d</td>
<td>&gt;10 mg/injection</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2 mg/d</td>
<td>4 mg/d</td>
</tr>
<tr>
<td>Risperidone depot</td>
<td>15 mg/mo</td>
<td>50 mg/mo</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>50 mg/d</td>
<td>200 mg/d</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>&lt;1.5 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>80–215 mg/d</td>
<td>150–600 mg/d</td>
</tr>
<tr>
<td>Remoxipride</td>
<td>60 mg/d</td>
<td>120–240 mg/d</td>
</tr>
<tr>
<td>Sertindole</td>
<td>10 mg/d</td>
<td>12–20 mg/d</td>
</tr>
<tr>
<td>Clozapine</td>
<td>—</td>
<td>&gt;400 mg/d</td>
</tr>
<tr>
<td>Ziprasidone, acute</td>
<td>63 mg/d</td>
<td>120–160 mg/d</td>
</tr>
<tr>
<td>Ziprasidone, maintenance</td>
<td>40 mg/d</td>
<td>80–160 mg/d</td>
</tr>
</tbody>
</table>


Davis & Chen, J of Clin Psychopharm, 2004;
How Long?

Clinical response (not remission). Overall, 77% responded over median of 206 days.

Emsley Am J Psych 2006
Make Haste...Slowly

Why make haste?
– Because decreasing DUP is important for maximizing outcomes

Why slowly?
– Therapeutic alliance is still the best protection against non-adherence
– There may be some lack of insight into the presence of a mental illness and the relevance of drug treatment.
  • Despite this, there are likely points for common engagement:
    – Reducing stress
    – Improve sleep
    – Improve appetite
    – Addressing distressing symptoms: hallucinations, delusions, disorganization
– Adequate discussion of potential effects and adverse effects takes time, and tailoring adverse effect profile to patients takes discussion
– Starting at a low dose allows monitoring for early emergence of side effects like EPS and weight gain
Principles of Treatment:

1. Maximize tolerability & adherence in service of positive symptom remission & relapse prevention: finding the window of D2 blockade (60-70%)

   • Lethargy, sedation, sexual dysfunction: drop dose or switch

   • Parkinsonism, akathisia, dystonia (acute EPS): anticholinergics/benzodiazepines, dose, switch

   • Tardive Dyskinesia: ? dose related, no established Tx, Clozapine is lower risk (and maybe other SGAs)

   • Minimize adverse effects on cognition, mood, motivation: dose, but may be inevitable for some...

   Use the least effective dose and proactively address side effects
What do antipsychotic medications do to the subjective experience of psychosis?

1. **Behavioral Impact of the experience**
2. **Emotional involvement**
3. **Cognitive Preoccupation with the psychotic experience**
4. **Conviction in the psychotic experience**
5. **External Perspective about the experience**

*from Mizrahi et al. Schiz Research 2006*
Principles of Treatment:

2. Address Cardiovascular Risk in your treatment approach

- FGAs - slightly higher risk of EPS (except low-potency FGAs) and TD but better CV profile (except low potency FGAs)

  • *Abilify and Ziprasidone appear to have lower metabolic burden (but most studies are short-term)*

- Clozapine - reduces overall mortality (likely early suicide/accidental death advantage but increased late CV risk). Olanzapine should be reserved for those who respond to no other weight-sparing choice: AVOID AS FIRST-LINE

- Minimize polypharmacy (mood stabilizers, antidepressants, antipsychotics)

- Monitor, monitor, monitor and taper or discontinue unnecessary medications. Don’t be afraid to switch off Olanzapine or Seroquel or Risp to a weight sparing alternative: even if it has been effective

- Target lifestyle: smoking, exercise, diet

- Improve access to primary care, develop relationship with internist (e.g. Metformin for weight loss or IFG)
Principles of Treatment:

3. Integrate with rehabilitation & psychotherapy:

a) core cognitive, negative (deficit) symptom domains not currently improved by medications

b) D2 blockade can cause affective flattening, reduced motivation...(dose responsive)

- Supported Employment
- Supported Education
- Supported Housing
- CBT
- Family Education & Support
- Social Skills Training
- Cognitive Remediation
Phase of Illness: Medication targets

1. ACUTE
Safety: aggression/hostility
Symptoms: remission of ‘positive’ symptoms, mood/anxiety
Suicide, cognitive losses, stigma, substance use, -ve sx

2. STABILIZATION
Prevent relapse
Support rehabilitation
Work/school, relationships

3. RECOVERY
Prevent relapse
Maintain functioning
Cardiovascular risk
Stage 1: ‘First-episode’ Psychosis
   Trial of a single SGA (except Olanzapine) or high-potency FGA toward remission
   Consider Clozapine for recurrent suicidality/violence

Stage 2: Sub-optimal Response
   Second trial of SGA or FGA (toward remission)
   Consider Clozapine for recurrent suicidality/violence

Stage 3: Clozapine

Stage 4: Clozapine + high potency agent

Stage 5: ECT or enroll in clinical trial of new agent

Consider long acting (IM) medications at all stages for (a) non-adherence or (b) dose related side effects
Summary

• Treatment with antipsychotic medications promotes recovery and allows engagement with other important services within a coordinated specialty care (CSC) setting

• Prescribers are responsible for:
  – Patient, non-judgmental listening and development of a differential diagnosis
  – Determination of patient’s goals
  – Offering health-related services to aid with achieving those goals
    • Screening for secondary causes of psychosis (labs, imaging, referral to specialty services as indicated)
    • Pre-medication screening
    • Starting medications in a way that maximizes long-term adherence
    • Performing routine maintenance to troubleshoot, manage adverse effects

• Use guidelines and team members as resources for troubleshooting
Thank You
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The Yale Department of Psychiatry

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• Nadine Avellani
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• Gail Sicilia
• Geanine Peck
• Brian Spence
• Genevieve Muñoz
• Rebecca McKeon

Funding
• Detre Fellowship in Translational Neuroscience
• Brain & Behavior Research Foundation
• Society of Biological Psychiatry
• Department of Psychiatry
Future Directions:
Targeted Symptom-Based Treatment
Auditory Hallucinations

- Present in roughly 70% of individuals with psychosis
- 10-30% don’t respond to antipsychotics
- Unknown neural mechanism
- Understanding auditory perception may provide insights
Unconscious Inference

Belief

Top-Down  Bottom-Up

Input
Predictive Coding and Delusion Formation

Top-Down

Input

Belief

Bottom-Up (increased salience, driving aberrant learning)
Predictive Coding and Hallucinations

Test:
Are hallucinations produced when top-down influence is enhanced?
HALLUCINATIONS PRODUCED BY SENSORY CONDITIONING *

BY DOUGLAS G. ELLSON

Stanford University

INTRODUCTION

The literature of ‘psychic’ phenomena is replete with incidents in which perceptions are reported to have occurred in the absence of physical events appropriate to evoke them. In many cases the event
Voice-Hearing in the General Population

Psychotic experiences (28%?)

Psychotic symptoms (4%)

Psychotic disorder (3%)

van Os et al. (2009) Psych Med
Phenomenological Comparison:

Powers, Kelley, Corlett (2017) *SchizBull*
Trial Structure of Train/Test Sequence

Probability of Detection

Log Intensity (dB)

Powers, Mathys, Corlett (2017) Science
Likelihood of Conditioned Hallucinations by Group

Probability of Answering “Yes” During No-Tone Trials

H⁺  P⁺H⁻  P⁻H⁻

Powers, Mathys, Corlett (2017) Science
Likelihood of Detection
By Condition

Probability of Answering “Yes”

No Tone  25% Likelihood Detection  50% Likelihood Detection  75% Likelihood Detection

Powers, Mathys, Corlett (2017) Science
Confidence

$P^+H^+$  $P^-H^+$  $P^+H^-$  $P^-H^-$

No Tone

"Yes"  "No"  All

No Tone

25%

"Yes"  "No"  All

50%

"Yes"  "No"  All

75%

"Yes"  "No"  All

Powers, Mathys, Corlett (2017) Science
Proportion of Conditioned Hallucinations Correlates with Symptom Severity

Probability of Answering “Yes” on No-Tone Trials

Powers, Mathys, Corlett (2017) *Science*
Confidence In Reporting Conditioned Hallucinations Correlates with Symptom Severity

Powers, Mathys, Corlett (2017) Science
Imaging Results:
Tone-Responsive Region of Interest

Powers, Mathys, Corlett (2017) Science
Parameter Estimates
No-Tone Trials

-2  1  0  1  2

"Yes"

Responses

"No"

Responses

Powers, Mathys, Corlett (2017) Science
Whole-Brain Analysis: “Yes” vs “No” on No-Tone Trials

Powers, Mathys, Corlett (2017) Science
Regions Involved in Hallucinations: Symptom Capture

Jardri et al. (2011) AJP
Behavioral Measures of Perceptual Belief Differ Among Groups

Powers, Mathys, Corlett (2017) Science
Neural Correlates of Perceptual Belief Differ Among Groups

Powers, Mathys, Corlett (2017) Science
Conclusions

• Sensory conditioning is capable of producing hallucination-like phenomena.
• Participants who experience spontaneous hallucinations are more likely to report conditioned hallucinations.
• A network similar to that identified in symptom capture-based imaging studies of hallucinations is engaged during conditioned hallucinations and may be parsed based upon a computational model of perception
• On HGF analysis, parameters signifying perceptual belief weighting and belief volatility distinguished participants with hallucinations and psychosis, respectively.
• Dissection of the conditioned hallucinations network based upon belief trajectories identified regions subserving different computational functions that also differed across groups.
Future Directions

- Effective connectivity
- Pharmacological manipulations
- TMS
- Early diagnosis (pludrome)
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Phenomenological Comparison:
Formal Measures of Voice-Hearing

<table>
<thead>
<tr>
<th></th>
<th>P+H+ Mean ± SEM</th>
<th>P-H+ Mean ± SEM</th>
<th>p</th>
<th>p (corr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AHRS Score</td>
<td>25 ± 1.09</td>
<td>22.78 ± 0.91</td>
<td>0.1277</td>
<td>ns</td>
</tr>
<tr>
<td>AHRS Score Frequency Item</td>
<td>4.38 ± 0.81</td>
<td>1.65 ± 0.35</td>
<td>0.0036</td>
<td>0.0288</td>
</tr>
<tr>
<td>AHRS Score Reality of Voices</td>
<td>4.44 ± 0.18</td>
<td>4.56 ± 0.16</td>
<td>0.6070</td>
<td>ns</td>
</tr>
<tr>
<td>AHRS Score Loudness of Voices</td>
<td>2.81 ± 0.25</td>
<td>3.12 ± 0.26</td>
<td>0.3966</td>
<td>ns</td>
</tr>
<tr>
<td>AHRS Score Number of Voices</td>
<td>4 ± 0.5</td>
<td>4.85 ± 0.39</td>
<td>0.1866</td>
<td>ns</td>
</tr>
<tr>
<td>AHRS Score Extent of Utterance</td>
<td>3.44 ± 0.29</td>
<td>2.82 ± 0.29</td>
<td>0.1419</td>
<td>ns</td>
</tr>
<tr>
<td>AHRS Score Influence of Voices</td>
<td>3.31 ± 0.37</td>
<td>4.65 ± 0.37</td>
<td>0.0169</td>
<td>ns</td>
</tr>
<tr>
<td>AHRS Score Distress Due to Voices</td>
<td>2.63 ± 0.41</td>
<td>1 ± 0</td>
<td>0.0003</td>
<td>0.0024</td>
</tr>
<tr>
<td>BAVQR Malevolence Score</td>
<td>5.69 ± 1.29</td>
<td>0 ± 0</td>
<td>0.0001</td>
<td>0.0008</td>
</tr>
<tr>
<td>BAVQR Benevolence Score</td>
<td>4.06 ± 1.36</td>
<td>13.53 ± 0.69</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>BAVQR Omnipotence Score</td>
<td>7.6 ± 1.12</td>
<td>4.71 ± 0.68</td>
<td>0.0315</td>
<td>ns</td>
</tr>
<tr>
<td>BAVQR Resistance Emotion Score</td>
<td>6.14 ± 1.02</td>
<td>0.59 ± 0.41</td>
<td>0.0000</td>
<td>0.0001</td>
</tr>
<tr>
<td>BAVQR Resistance Behavior Score</td>
<td>8.93 ± 1.22</td>
<td>0.88 ± 0.4</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>BAVQR Engagement Emotion Score</td>
<td>1.67 ± 0.77</td>
<td>8.76 ± 0.54</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>BAVQR Engagement Behavior Score</td>
<td>2.53 ± 0.89</td>
<td>8.38 ± 0.69</td>
<td>0.0000</td>
<td>0.0002</td>
</tr>
<tr>
<td>Age at First Voice</td>
<td>22.93 ± 3.4</td>
<td>7.47 ± 1.35</td>
<td>0.0002</td>
<td>0.0016</td>
</tr>
</tbody>
</table>
Experiences Divulging Voice-Hearing for the First Time
Auditory-responsive regions respond to hallucinated tones as if they were present
Those who hallucinate may be more susceptible to sensory conditioning.
Computational Implementational

Hidden States Model

Visible States

Algorithmic

Occluding Object

Hypothesis - Top down prior – NMDA receptors

Data - Bottom up prediction error – AMPA receptors

Gain – Neuromodulators, Dopamine Acetylcholine

\[ P(H|D) = P(D|H) P(H) \]

\( P(D) \) is probability of observing Data, D

\( P(D|H) \) is likelihood – the probability of seeing D given H is true

\( P(H) \) is prior probability of H – the probability of H before seeing D

\( P(H|D) \) is the posterior probability – the probability of hypothesis given the data

Neuronal population e.g. cortical layer or region in hierarchy

Corlett & Fletcher, 2014
General Methods