Gaining insight into lack of insight

An evidence-based examination of lack of insight and its implications for the treatment of psychotic disorders

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Dr. Eric Teboul declares that he has received honoraria for presentations and/or advisory board consultations from:

- Astra Zeneca
- BMS
- Janssen
- Lilly
- Lundbeck
- Novartis
- Otsuka
- Pfizer
- Sunovion

If you voted for me, it means you liked my message, It does not mean I liked yours.
- Ronald Reagan
Objectives

➢ Review the complex phenomenon of impaired insight in psychotic illness

➢ Appreciate the related challenge of antipsychotic nonadherence/partial adherence

➢ Consider the ways we can help psychotic persons despite the fact that they may not consider themselves sick and so may see no need for treatment
Definitions of Insight

General definition:
the capacity to gain an accurate and deep intuitive understanding of a person or thing; e.g. *the signals would give marine biologists new insights into the behavior of whales.*

ORIGIN Middle English (in the sense [inner sight, mental vision, wisdom])

In Psychodynamic theory:
A general self-awareness, particularly of one’s unconscious drives and motivations.

In Gestalt Psychology:
The sudden appreciation of how parts relate to an organised whole

In Psychiatry:
- the ability to recognize one's own mental illness

Anosognosia

A deficit of self-awareness, a condition in which a person who suffers a certain disability seems unaware of the existence of his or her disability.

From Greek:
- \(a\) = negative prefix
- \(nosos\) = "disease"
- \(gnosis\) = "knowledge"
Anosognosia

Anosognosia

“The patient behaves as though he knew nothing about his hemiplegia, as though it had not existed, as though his paralyzed limbs were normal, and insists that he can move them and walk as well as he did before.”

When such a patient is shown the affected limb he or she will be indifferent to it...or will reveal delusional ideas (insisting, e.g., that the limb is someone else’s)

- Josef Gerstmann 1942

Gerstmann J. Archives of Neurology and Psychiatry 1942;48:890-913
Anosognosia in Neurology

- can appear with virtually any neurological impairment
- can manifest with various specific deficits:
  - motor (hemiplegia)
  - sensory (hemianesthesia, hemianopia)
  - spatial (unilateral neglect)
  - memory (dementia)
- not related to:
  - global mental confusion
  - cognitive flexibility
  - other major intellectual disturbance
  - sensory/perceptual deficits.
- can be selective: an affected person with multiple impairments may be unaware of only one handicap, while being fully aware of others.

Insight in Psychiatry

➢ Described since 1896 when Kraepelin noticed that pts with Dementia Praecox “were completely unaware of the gravity of their illness”

➢ A multi-dimensional concept that includes:
  - awareness of having a mental disorder
  - understanding the social consequences of the disorder
  - awareness of specific signs and symptoms of the disorder
  - attribution of symptoms to the disorder

Overlapping dimensions of Insight

**Treatment compliance**
- Complies but does not acknowledge being ill, no insight into delusions or hallucinations (seen esp. in chronic schiz.)

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**Awareness of illness**
- Pt attributes feeling ill to psychotic experiences which are not questioned, and so does not accept the role of psychiatric treatment
- Takes meds but talks of being depressed due to voices or frightening beliefs (ex: says he is ill due to being poisoned)
- Aware of illness and that strange beliefs and voices are part of it, yet attributes both to normal phenomenon (ex: stress or hypnosis) so does not see relevance of meds

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**Complete insight**
- Complete insight into illness and psychotic symptoms with full and informed consent to treatment
- Relabels psychotic experiences correctly (ex: “I know the voices aren’t real”, “I know that it is impossible”) but attributes them to “being drugged”, “lack of sleep”, etc – this is equivalent to normal person’s attitude to a vivid nightmare
- Accepts help and takes meds to “damp down” voices (ex: pt knows voices are not real but attributes them to some outside force, so does not see himself as ill)

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Poor Insight is the most prevalent feature of schizophrenia.

### Table 2. Number, percentage, and rank order of occurrence of the flexible system criteria in the CCHS and IPSS populations

<table>
<thead>
<tr>
<th>Criteria</th>
<th>CCHS</th>
<th>IPSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Restricted affect</td>
<td>584</td>
<td>76.0</td>
</tr>
<tr>
<td>Poor insight</td>
<td>686</td>
<td>89.3</td>
</tr>
<tr>
<td>Thoughts aloud</td>
<td>154</td>
<td>20.1</td>
</tr>
<tr>
<td>Waking early</td>
<td>258</td>
<td>33.6</td>
</tr>
<tr>
<td>Poor rapport</td>
<td>537</td>
<td>69.9</td>
</tr>
<tr>
<td>Depressed facies</td>
<td>229</td>
<td>29.8</td>
</tr>
<tr>
<td>Elation</td>
<td>99</td>
<td>12.9</td>
</tr>
<tr>
<td>Widespread delusions</td>
<td>342</td>
<td>44.5</td>
</tr>
<tr>
<td>Incoherent speech</td>
<td>354</td>
<td>46.1</td>
</tr>
<tr>
<td>Unreliable information</td>
<td>255</td>
<td>33.2</td>
</tr>
<tr>
<td>Bizarre delusions</td>
<td>352</td>
<td>45.8</td>
</tr>
<tr>
<td>Nihilistic delusions</td>
<td>36</td>
<td>4.7</td>
</tr>
<tr>
<td>Total n</td>
<td>768</td>
<td></td>
</tr>
</tbody>
</table>

*Note.*—CCHS = Classification of Chronic Hospitalized Schizophrenics; IPSS = International Pilot Study on Schizophrenia.

*Reprinted, with permission, from Wilson et al. 1986, p. 260.*

Schedule for Assessing the 3 Components of Insight

1. Treatment Compliance

- Does pt accept treatment?
  - Often (2 points)
  - Sometimes (1 point)
  - Never (0 point)

- Does pt ask for treatment?
  - Often (2 points)
  - Sometimes (1 point)
  - Never (0 point)

Subtotal for Treatment Compliance: _ /4

Adapted from: David AS. Insight and Psychosis. Br J Psychiatry 1990;156:798-808
Schedule for Assessing the 3 Components of Insight

2. Awareness of Illness

- “Do you think you have an illness?” or “Do you think there is something wrong with you?”
  - Often (2 points)
  - Sometimes (1 point)
  - Never (0 point)

- “Do you think you have a mental illness?”
  - Often (2 points)
  - Sometimes (1 point)
  - Never (0 point)

- “How do you explain your illness”?
  - Reasonable account given based on possible mechanisms ex: excess stress, chemical unbalance, family history etc. (2 points)
  - Confused account; repetition of overhead explanation without adequate understanding; “I don’t know” (1 point)
  - Delusional explanation (0 point)

Subtotal for Awareness of Illness = __/6

Adapted from: David AS. Insight and Psychosis. Br J Psychiatry 1990;156:798-808
Schedule for Assessing the 3 Components of Insight

3. Relabels Psychotic Experiences Correctly

Ask pt: “Do you think that (insert specific delusion or hallucination) is not really true/happening?”

- Often i.e.: most of day, most days (2 points)
- Sometimes i.e.: occasionally, min once/day (1 point)
- Never (0 point)

Ask pt.: “How do you explain these phenomena (the belief that ..., hearing that voice/seeing that image, etc.)?”

- “Part of my illness” (2 points)
- Reaction to outside events (i.e.: tiredness, stress etc.) (1 point)
- Attributed to outside forces (may be delusional) (0 point)

Subtotal for Relabels Psychotic Experiences Correctly” = __/4

Adapted from: David AS. Insight and Psychosis. Br J Psychiatry 1990;156:798-808
### Schedule for Assessing the 3 Components of Insight

#### Scale for Assessment of Insight

Adapted from: David AS. Insight and Psychosis. Br J Psychiatry 1990;156:798-808

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment compliance</td>
<td>_/4</td>
</tr>
<tr>
<td>Awareness of Illness</td>
<td>_/6</td>
</tr>
<tr>
<td>Relabels psychotic experience correctly</td>
<td>_/4</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td>_/14</td>
</tr>
</tbody>
</table>

### Supplementary Question: Hypothetical Contradiction

“How do you feel when people don’t believe you (delusion or hallucination experiences)?

- “That’s when I know I am sick” (4 points)
- “I wonder whether something is wrong with me” (3 points)
- “I’m confused and don’t know what to think” (2 points)
- “I’m still sure despite what others say” (1 point)
- “They are lying” (0 point)
### Standardized Scales for Insight Assessment

<table>
<thead>
<tr>
<th>Type of insight scale</th>
<th>Measure of insight</th>
<th>No. Items</th>
<th>Features of scale</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-structured interview</td>
<td>Scale for Assessment of Unawareness of Mental Disorder (SUMD)</td>
<td>37</td>
<td>Evaluates present and past insight into mental disorder, social consequences, need for treatment, and attribution of symptom to disorder</td>
<td>Amador &amp; Strauss (^{78})</td>
</tr>
<tr>
<td></td>
<td>Scale for Assessment of Insight, Extended (SAI-E)</td>
<td>12</td>
<td>Assesses recognition of illness, compliance with treatment and ability to label mental events as pathological</td>
<td>David (^{25})</td>
</tr>
<tr>
<td></td>
<td>Insight and Treatment Attitudes Questionnaire (ITAQ)</td>
<td>11</td>
<td>Evaluates perception of treatment and acceptance of illness label</td>
<td>McEvoy et al. (^{75})</td>
</tr>
<tr>
<td></td>
<td>Measure of Insight into Cognition – Clinician Rated (MIC-CR)</td>
<td>12</td>
<td>Assesses both awareness and attribution of relative cognitive status in the areas of attention, executive functioning, and memory.</td>
<td>Medalia &amp; Thysen (^{72})</td>
</tr>
<tr>
<td>Self-report</td>
<td>Birchwood Insight Scale (BIS)</td>
<td>8</td>
<td>Measures awareness of illness, ability to re-label psychotic symptoms, and recognition of the need for treatment.</td>
<td>Birchwood et al. (^{79})</td>
</tr>
<tr>
<td></td>
<td>Insight Scale (IS)</td>
<td>32</td>
<td>Measures individuals’ degree of self-knowledge.</td>
<td>Markova &amp; Berrios (^{76})</td>
</tr>
<tr>
<td></td>
<td>Awareness of Being a Patient Scale (ABPS)</td>
<td>25</td>
<td>Assesses the recognition of the need for treatment and acceptance of the treatment situation.</td>
<td>Hayashi et al. (^{80})</td>
</tr>
<tr>
<td></td>
<td>Subjective Experience of Negative Symptoms (SENS)</td>
<td>24</td>
<td>Measures awareness, causal attribution, and disruption or distress.</td>
<td>Selten et al. (^{81})</td>
</tr>
<tr>
<td></td>
<td>Beck Cognitive Insight Scale (BCIS)</td>
<td>15</td>
<td>Measures reflectiveness, objectivity, openness to feedback and self-certainty</td>
<td>Beck et al. (^{77})</td>
</tr>
<tr>
<td></td>
<td>Self-Appraisal of Illness Questionnaire (SAIQ)</td>
<td>17</td>
<td>Assesses beliefs about the outcome of illness, acknowledgment of a need for psychiatric treatment, and extent of worry about illness and illness-related issues.</td>
<td>Marks et al. (^{74})</td>
</tr>
</tbody>
</table>

The paradox of impaired insight

Several studies used case vignettes to assess the capacity of psychotic patients to identify psychopathology in others:

- these studies found that patients had the ability to recognize the symptoms of mental illness in others and correctly label psychotic phenomena as abnormal although they had impaired awareness of illness in themselves, even when their symptoms were similar to the symptoms presented in the vignettes.

“The lack of awareness of mental illness is not caused by lack of knowledge but by the difficulty in applying it to oneself.”

Startup M. Schizophr Res 1997;26:203-211
David AS. Br J Psychiatry 1999;174:210-6
What causes lack of insight?

• an inherent aspect of psychosis?
  [related to positive symptoms ("a delusion of health") or
  negative symptoms ("mental withdrawal")]

• a psychological defense mechanism?
  [against low self-esteem and other painful feelings]

• a cognitive dysfunction?

• a neuropsychological deficit?
i.e. a form of anosognosia caused by
  neurological (esp. frontal lobe) dysfunction

• a combination of the above?

Osatuke K et al. Insight in schizophrenia: a review of etiological models and supporting research. *Compr Psychiatry* 2008;49:70-77
The Functional Neuroanatomy of Insight

➢ Cognitive test data have related lack of insight in schizophrenia to deficits in frontal cortical systems

➢ Structural neuroimaging studies have reported an association between poor insight and:
  • reduced total brain volume
  • ventricular enlargement
  • frontal lobe atrophy
  • reduced frontal lobe volume
  • gray matter deficits in the cingulate gyrus, temporal lobe, parietal lobe, precuneus, right posterior insula

Does improvement in psychosis lead to improvement in insight?

➢ Cuesta et al. studied the evolution of 75 psychotic patients (with schizophrenia, schizoaffective disorder or affective disorder with psychotic symptoms) at 2 time points: • after remission of an acute episode • 6-24 months later (in a phase of clinical stability).

• Results:
  • certain dimensions of insight improved over time, regardless of diagnosis
  • Pts with fair to poor insight of having a mental disorder:
    - At baseline assessment: 49-66%
    - At follow-up: 29-49%
  • Psychopathological dimensions (delusions, hallucinations) were independent of insight.
  • the remitting course of insight dimensions differed from that of positive and affective symptoms but there were semi-independent relationships between negative and disorganisation dimensions and the “attitude to treatment” dimension of insight.

• Conclusion:
  • Insight and psychopathology seem to be semi-independent domains

Does improvement of insight with $R_X$ lead to more favorable attitudes regarding medication treatment?

“Overall, the pts showed significant improvement in symptoms (BPRS), severity of illness (CGI), functional level (GAF), insight (SUMD), but attitudes toward $R_X$ (DAI) did not change significantly”

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>All patients</th>
<th>Atypical group</th>
<th>Conventional group</th>
<th>Mixed group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS(^a)</td>
<td>45.8±10.1</td>
<td>43.4±9.8</td>
<td>47.5±10.2</td>
<td>51.6±9.1</td>
</tr>
<tr>
<td>Admission</td>
<td>31.1±5.9***</td>
<td>32.4±5.7***</td>
<td>26.6±3.4***</td>
<td>31.6±8.0**</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI(^b)</td>
<td>4.3±1.1</td>
<td>4.0±1.0</td>
<td>4.3±1.1</td>
<td>5.4±9.9</td>
</tr>
<tr>
<td>Admission</td>
<td>3.4±1.2***</td>
<td>3.2±1.0***</td>
<td>3.1±1.1*</td>
<td>4.6±1.3</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAF(^c)</td>
<td>30.6±8.7</td>
<td>31.2±9.0</td>
<td>29.8±9.7</td>
<td>30.2±7.1</td>
</tr>
<tr>
<td>Admission</td>
<td>49.2±10.6***</td>
<td>49.2±10.3***</td>
<td>52.5±10.4**</td>
<td>44.0±11.9</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUMD(^d)</td>
<td>15.7±5.6</td>
<td>14.2±6.6</td>
<td>17.4±5.1</td>
<td>18.2±2.9</td>
</tr>
<tr>
<td>Admission</td>
<td>10.8±5.2***</td>
<td>10.3±5.7*</td>
<td>10.4±4.3*</td>
<td>13.3±4.1</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAI(^e)</td>
<td>6.4±2.4</td>
<td>6.7±2.4</td>
<td>5.5±2.5</td>
<td>7.2±2.3</td>
</tr>
<tr>
<td>Admission</td>
<td>7.4±1.9</td>
<td>7.1±2.3</td>
<td>8.6±8*</td>
<td>6.6±9</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>12.7±7.6</td>
<td>12.0±8.6</td>
<td>12.6±6.4</td>
<td>22.2±12.6</td>
</tr>
</tbody>
</table>

Mean ± SD scores on measures of symptoms, severity of illness, functional level, insight into illness, and attitudes toward medications in a sample of 36 state hospital patients at admission and discharge.

Sajatovic M et al. Insight into illness and attitudes toward medications among inpatients with schizophrenia. *Psychiatric Services* 2002;53:1319-1321
Implications of poor insight

➢ The evidence is inconsistent/contradictory/complicated regarding the association of lack of insight and:

• age of onset
• gender
• educational level
• severity of positive, negative symptoms
• depressive symptoms
• anxiety
• neurocognitive functions: executive functioning, memory, attention

Implications of poor insight

➢ Poor insight has a strong impact on:
  • clinical outcome
  • # of hospitalizations
  • social and interpersonal functioning
  • vocational rehabilitation
  • treatment compliance (adherence)*


ORAL ANTIPSYCHOTIC MEDICATION

DO PATIENTS REALLY TAKE THEM?

“Drugs don’t work in patients who don’t take them”
- C. Everett Koop, MD
former US Surgeon General
The problem of medication nonadherence in patients with Schizophrenia

➢ In a comprehensive literature review, Lacro et al found that the prevalence of “nonadherence”* was:

49.5 %

➢ Risk factors for nonadherence:

Patient-related:
• poor insight
• negative attitude toward meds
• negative subjective response to meds
• previous nonadherence
• shorter duration of illness
• current or past history of substance abuse

Medication-related:
• higher AP dose

Environmental:
• poor alliance
• less outpatient contact
• inadequate d/c planning
• poor aftercare environment

➢➢ More insight significantly predicts higher pt ratings of the alliance


* “nonadherence” defined as < 75% adherence to treatment
Reasons for non-adherence according to patients and their family

Figure 3  Les raisons de non-observance du traitement.

Obstacles to adherence with oral antipsychotic medication

1. Pt sees no need for medication (poor insight)
2. Pt is still mildly paranoid even after stabilization
3. Pt is opposed to medication in general
4. Poor therapeutic alliance
5. Pt has mild cognitive impairment
6. Pt lacks a daily routine
7. Pt simply forgets sometimes
8. Pt feels stigmatized by having to take a pill (influenced by negative attitudes of family/friends regarding meds)
9. When pt takes the pill, his self-esteem takes a hit


- Eric Teboul MD
Obstacles to adherence with oral antipsychotic medication

10. Pt abuses alcohol or drugs sometimes and thinks he should skip his medication on these days.

11. Pt attributes normal variations in sleep, energy, weight, etc to the medication.

12. When pt misses a few days for whatever reason and does not relapse, he thinks this proves he no longer needs medication (pt may even feel better temporarily before next relapse).

13. Pt may have been discharged from hospital without having achieved remission (whether MD realizes it or not) which puts them at increased risk for nonadherence.

Dolder CR et al. Antipsychotic Medication Adherence: Is There a Difference Between Typical and Atypical Agents?

*Am J Psychiatry* 2002; 159:103–108

At 12 months, compliant fill rates for antipsychotics were:
- “typicals”: 50.1%
- “atypicals”: 54.9%

![Figure 1. Medication Adherence Rates at 12-Month Follow-Up for Outpatients Filling Prescriptions for Typical and Atypical Antipsychotic Medications in a Veterans Affairs (VA) Health Care System](image)

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\(^{a}\) Percentage of total medication fills that occurred at time-appropriate intervals. No significant difference between patients prescribed typical and atypical antipsychotics (F=0.84, df=4, 283, p=0.50).

\(^{b}\) Percentage of total study days during which medication was unavailable because of a delayed refill. Significant difference between patients prescribed typical and atypical antipsychotics (F=3.61, df=4, 283, p=0.007). No significant differences between individual antipsychotics (p=0.12–1.00, Scheffé).
ORAL ANTIPSYCHOTIC DISCONTINUATION RATES IN LARGE RANDOMISED CONTROLLED TRIALS
CATIE Study – Time to Discontinuation For Any Reason

<table>
<thead>
<tr>
<th>Legend</th>
<th>n</th>
<th>% Drop-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>330</td>
<td>64%</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>257</td>
<td>75%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>329</td>
<td>82%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>333</td>
<td>74%</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>183</td>
<td>79%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1432</td>
<td>74%</td>
</tr>
</tbody>
</table>


p < 0.001 OLA vs. QUET
p = 0.002 OLA vs. RIS
CAFÉ All-Cause Treatment Discontinuation

PARTIAL ADHERENCE TO ORAL ANTIPSYCHOTICS IN NATURALISTIC STUDIES
The majority of patients are only \textit{partially} adherent

Docherty and colleagues found that 90\% of patients with schizophrenia had some degree of partial compliance.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure1.png}
\caption{Spectrum of Adherence\textsuperscript{a}}
\end{figure}

\textsuperscript{a}Data from Valenstein et al.\textsuperscript{1}


Valenstein M, Copeland LA, Blow FC, et al. Pharmacy data identify poorly adherent pts with schizophrenia at increased risk for admission. \textit{Med Care} 2002;40:630–639

Adherence Rates* Employing Different Measures Among Outpatients** with Schizophrenia

*% of patients at least 80% adherent in the 4 week study period

** Competent, stabilized outpatients on one antipsychotic who agreed to participate in a clinical trial

How well do schizophrenia pts adhere to oral antipsychotics after discharge from hospital?

Velligan et al recruited 68 schizophrenia patients willing to participate in a study post d/c from hospital on oral atypical antipsychotic Rx. This involved a “baseline” period of 10-14 days post d/c and a subsequent assessment 3 months post d/c with blood levels.

10-14 day Baseline period observations:

- of the first 14 pts d/c’ed to group homes, 10 missed multiple doses, only 60% of all med doses were administered
- Observations during the 1st home visit suggested d/c instructions were routinely misunderstood:
  - several pts were planning to take both the recently Rx’ed AP and the previous AP taken before the hospitalization
  - bottles of the same Rx from inpt and outpt pharmacies were found; pts were planning to take both
  - pts had combined different strengths of the same Rx in one pot
  - Different types of Rx (e.g. AP & MS) were mixed together; pts were unable to identify accurately the different pills in these containers

Velligan DI et al. Perspectives on medication adherence and atypical antipsychotic medications. Psychiatric Services 2003;54:665-667
How well do schizophrenia pts adhere to oral antipsychotics after discharge from hospital? (cont’d)

➢ Living environment:

- the places where pts kept their meds (e.g. cars, homes of relatives) made it unlikely they would be able to take all prescribed doses

- pts were often asleep at dosing times; if home visit staff had not awoken them they probably would have missed >50% of doses

- Pts lives were often chaotic and unstructured:
  - several slept at the home of a different relative every night
  - many did not eat regular meals or follow a regular hygiene routine that could be linked with taking medication.

- Even pts in group homes missed doses. If they were not present at medication distribution times or failed to appear at the distribution desk, staff rarely followed up to give Rx later

How well do schizophrenia pts adhere to oral antipsychotics after discharge from hospital? (cont’d)

3 month follow-up:

- 25% (17/68) were readmitted to hospital
- 12% (8/68) went to jail or became homeless
- of the 55 pts seen at baseline and after 3 mo.:
  - Perfect adherence: 
    - self-report: 55 %
    - pill count: 9 %
  - Adequate* adherence: 
    - pill count: 40 %
    - blood level analysis: 23 %

N.B.
- During the baseline period, they made certain that all pts had all Rx
- the least adherent pts had already been eliminated from the sample.


* ≥ 80 % adherence
Impact of nonadherence and partial adherence on risk of rehospitalization
Degree of Adherence and increase in 1-year Hospitalization Rates (n = 4325)

- 6.4% (n = 327)
- 12% (≈ 2X) (n = 1710)
- 16% (2.5 X) (n = 1166)
- 21.6% (≈ 3.5 X) (n = 1122)

All pairwise comparisons were significant at p < .005

Are treatment gaps of $\geq 30$ days a frequent occurrence?

“\textit{The finding of pervasive patient-initiated treatment gaps indicates that nonadherence was widespread in this group of patients. Most gaps occurred during the first few months after discharge, which points to the transition from inpatient to outpatient care as a period of high risk of discontinuation of treatment.}”

Mojtabai R et al. \textit{Psychiatric Services} 2002;53:337–339,
Other negative outcomes associated with antipsychotic non-adherence

➢ Patients who interrupted treatment for ≥ 30 days had a 4-fold increased risk for attempting suicide\(^1\)

➢ Patients with < 85% AP medication adherence had\(^2\):
  • greater risk of psychiatric hospitalizations
  • more use of emergency psychiatric services
  • more arrests
  • more incidents of violence
  • more incidents of being the victim of a crime
  • poorer mental functioning
  • poorer life satisfaction
  • greater substance use
  • more alcohol-related problems

\(^1\) Herings RM, Erkens JA. *Pharmacoepidemiol Drug Saf* 2003;12(5):423-4
Increasing Time to Remission with Successive Psychotic Episodes

ORAL versus LONG ACTING INJECTABLE (LAI) ANTIPSYCHOTIC MEDICATION
Clinical advantages of LAI antipsychotic medication

1. Non-adherence is known immediately, allowing for clinical intervention as required

2. The exact dose actually received is precisely known, so dose adjustments can be made without doubt regarding partial adherence (efficacy failure can be reliably differentiated from adherence failure)

3. Regular contact with nurse who may detect early signs of relapse and who may become an important supportive relationship in the patient’s life

4. Third parties are reassured (family, friends, mental health review board, probation officer)

Keith SJ, Kane JM. J Clin Psychiatry 2003; 64: 1308–1315
McEvoy JP. J Clin Psychiatry 2006;67[suppl 5]:15–18
Are patients less likely to stop taking LAIs compared to oral antipsychotic medication?

Average discontinuation rates in large RCTs:

- **Oral antipsychotics**: 70 - 74 %\(^1,2\)
- **LAI antipsychotics**: 29 - 35 %\(^3,4,5\)

Are randomized controlled trials or non-randomized observational studies more relevant to general clinical practice?

![Figure 2. Meta-Analysis of Adjusted Risk Ratios, by Study Design](image)

**Study** | Favors Depot | Favors Oral | RR  | 95% CI | Weight |
---|---|---|---|---|---|
RCTs |  |  |  |  |  |
Gaebel et al, 2010 |  |  | 0.58 | 0.39–0.86 | 15.13 |
Gaebel et al, 2010 |  |  | 0.50 | 0.38–0.67 | 17.14 |
Kane et al, 2010 |  |  | 2.03 | 1.31–3.16 | 14.38 |
Keks et al, 2007 |  |  | 0.92 | 0.72–1.18 | 17.77 |
Macfadden et al, 2010 |  |  | 1.07 | 0.84–1.37 | 17.76 |
Rosenheck et al, 2011 |  |  | 0.89 | 0.70–1.13 | 17.82 |
Pooled RCTs |  |  | 0.89 | 0.64–1.22 |  |
Prospective studies |  |  |  |  |  |
Ciudad et al, 2008 |  |  | 0.80 | 0.60–1.06 | 24.18 |
Kim et al, 2008 |  |  | 0.30 | 0.14–0.67 | 8.15 |
Olivares et al, 2009 |  |  | 0.52 | 0.43–0.64 | 28.07 |
Olivares et al, 2009 |  |  | 0.89 | 0.57–1.39 | 17.07 |
Zhu et al, 2009 |  |  | 0.59 | 0.43–0.81 | 22.53 |
Pooled prospective studies |  |  | 0.62 | 0.48–0.81 |  |
Retrospective studies |  |  |  |  |  |
Emsley et al, 2008 |  |  | 0.25 | 0.09–0.70 | 5.02 |
Emsley et al, 2008 |  |  | 0.38 | 0.22–0.64 | 15.06 |
Tavcar et al, 2000 |  |  | 0.71 | 0.49–1.01 | 26.45 |
Tiihonen et al, 2006 |  |  | 0.61 | 0.38–0.99 | 17.91 |
Tiihonen et al, 2011 |  |  | 0.16 | 0.02–1.05 | 1.53 |
Tiihonen et al, 2011 |  |  | 0.69 | 0.35–1.35 | 10.48 |
Tiihonen et al, 2011 |  |  | 0.46 | 0.16–1.34 | 4.66 |
Tiihonen et al, 2011 |  |  | 0.64 | 0.41–1.02 | 18.89 |
Pooled retrospective studies |  |  | 0.56 | 0.44–0.71 |  |

Adjusted Relative Risk (log scale) |

Abbreviations: RCT = randomized controlled trial, RR = risk ratio.

Mirror-image studies

“...RCTs might enroll a disproportionate number of patients with better treatment adherence and lower illness severity. Mirror-image studies, which compare periods of oral vs LAI treatment in the same patients, might better reflect the real-world impact of LAIs”

When a patient is switched from an oral to an injectable antipsychotic, does this add or save costs in the health care system?

Vincent P et al. Analyse rétrospective de la durée d’hospitalisation chez les patients souffrant de schizophrénie avant et après l’introduction du palmitate de palipéridone – étude RABAIS. Presented at the 48th congrès de l’AMPQ, June 4-7 2014:

✧ The system saves $9,000 to 12,500 / patient / year*

Stip E. Impact of switching to LAI-AP on health services use in the treatment of schizophrenia. Presented at the 48th congrès de l’AMPQ, June 4-7 2014:

✧ The system saves $11,000 / patient / year**

*switched to paliperidone palmitate
** switched to various 1st and 2nd generation LAIs
Among patients having tried both orals or LAIs, which formulation do they prefer?

“The evidence reviewed showed clear patient preference for depot antipsychotic medication over oral antipsychotic medication...
One possible explanation is convenience. Wistedt (1995) found that 67% of their sample thought it easier to have an injection than taking tablets once or twice daily. Hoencamp et al (1995) also found convenience to be an important factor, because 42% of those who preferred depots cited this as a reason why.” *

bar chart from: Waddell L, Taylor M. BJP 2009;195:S43-S50
What do the families think about LAIs?

Figure 7  Opinion des proches vis-à-vis du traitement injectable.

Is it reasonable to prescribe LAIs for a patient in a first psychotic episode?

1. Do they really need antipsychotic meds to prevent relapse?

*For this study, nonadherence was defined as patients with <50% adherence of the prescribed medication dose for at least 2 weeks.

Missing as little as 25% of the prescribed dosage over a period of ≥2 weeks significantly raised the risk of returning psychotic symptoms.
Is it reasonable to prescribe LAIs for a patient in a first psychotic episode?

2. Why not just trust them to take oral meds?

➢ Tiihonen et al examined the risk of rehospitalization and drug d/c 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.

• “The results showed that in Finland, a high-income country where the cost of antipsychotic medication is fully reimbursed, more than half of patients either did not collect an antipsychotic prescription within 30 days after discharge from their first hospitalization or discontinued their initial antipsychotic medication within 30 days.”

• “Depot injections were associated with about a 50%–65% lower risk of rehospitalization than oral formulations of the same compounds...”

• “patients who are adherent and cooperative enough to participate in a RCT would not likely receive much additional benefit from a formulation designed to enhance adherence. Since nonadherent patients cannot be forced to participate in RCTs, observational studies are the only way to investigate this issue.”

Do the experts think it is reasonable to use LAIs in first episode psychosis?

Emmanuel Stip, MD, MSc, CSPQ (Université de Montréal)
Amal Abdel-Baki, MD, FRCPC, MSc (Université de Montréal)
David Bloom, MD, FRCPC (McGill University)
Sylvain Grignon, MD, PhD (Université Sherbrooke)
Marc-André Roy, MD, FRCP, MSc (Université Laval)

Long-acting injectable antipsychotics: an expert opinion from the Association des médecins psychiatres du Québec
Treatment Algorithm* for Psychotic Illness: AMPQ

**Psychotic episode**
- Propose nonpharmacological treatment (e.g., individual and family social therapy, cognitive-behavioural therapy, motivational therapy etc.)
- Propose atypical LAIs as a first-line pharmacotherapy option

**Established first-episode psychosis**
- **Adherent:** If patient accepts, atypical LAI
  - If not oral antipsychotic
- **Nonadherent, or high-risk profile**
  - (e.g., suspiciousness, hostility, homelessness, substance abuse, lack of social support and insight, etc.)
  - Support program for increasing compliance
    - (e.g., psychotherapy, pill dispenser, electronic aid, liquid antipsychotic under supervision, etc.)
  - Refusal of treatment:
    - Outpatient commitment (LAI for 2-3 years)

**Established treatment-resistant psychosis**
- **Voluntary treatment with an atypical LAI**
- **Support program for increasing compliance**
  - (e.g., psychotherapy, pill dispenser, electronic aid, liquid antipsychotic under supervision, etc.)
- **Therapeutic drug monitoring** (if possible)

**Stabilized:**
- Oral antipsychotic
  - Stabilized: Oral antipsychotic
  - Nonresponse or unstable:
    - Adequate plasma level: Establish nonresponse with at least two different LAIs before considering clozapine
  - Stabilized:
  - Nonresponse or unstable:
    - Low or no plasma level:
      - Outpatient commitment (LAI for 2-3 years)

What do the experts from PEPPs* across Canada recommend?


“It is recommended that LAIs should be considered as a treatment option for psychotic disorders across all phases, including the first 2 to 5 critical years”

*Prevention and Early Intervention for Psychoses Programs (Douglas Mental Health University institute, Montreal; IUSM, Québec City Dalhousie U, Halifax; U of Alberta; Western U, London; UBC)
This just in!

First direct comparison of LAI and PO versions of the same 2nd generation antipsychotic after a recent 1st episode of schizophrenia

➢ 12 month trial of 83 pts from the UCLA AfterCare Research Program randomized to LAI or PO risperidone

➢ Rate of relapse and/or psychotic exacerbation:
  - PO: 33%
  - LAI: 5%  \( P < .001 \)

➢ The LAI formulation provided better control of hallucinations and delusions throughout follow-up (\( P = .01 \))

➢ Adherence:
  - was better for the LAI (despite best efforts to engage PO pts)
  - was associated with prevention of exacerbation/relapse

➢ Conclusion: “The key clinical advantages are apparently owing to the more consistent administration of the LAI. Such formulations should be offered earlier in the course of illness.”

Subotnik KL et al. Long-Acting Injectable Risperidone for Relapse Prevention and Control of Breakthrough Symptoms After a Recent First Episode of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry.* Published online June 24, 2015. doi:10.1001/jamapsychiatry.2015.0270
Other data from the UCLA AfterCare Research Program which compared LAI vs PO risperidone in first episode pts found that use of the LAI led to:

➢ Better maintenance of intracortical myelination\(^1\)

George Bartzokis and colleagues propose that:
- dysregulation of the normal myelination trajectory may contribute to the etiology of schizophrenia
- deficient myelination may lead to the functional deterioration and “treatment resistance” observed in chronic schizophrenia
- antipsychotic medications may promote white matter development and specifically intracortical myelin as one of their mechanisms of action

➢ Improved cognitive functioning\(^2\)


Which patients are appropriate candidates for **oral** antipsychotics?

➢ Patients who:

   1) refuse injectable antipsychotics **despite adequate explanations of the advantages**
   AND 2) do not have a clear history of nonadherence
   AND 3) have not been a serious danger to self or others when in an acute psychotic episode

➢ Patients living in supervised settings where medication is administered reliably and compliance is verified

➢ Patients unresponsive or intolerant to both a second generation and a first generation LAI antipsychotic

➢ Patients treated with Clozapine

Eric Teboul MD
Educating patients and their families about the illness should lead to improved adherence with treatment.

TRUE
OR
FALSE?
A systematic literature review examined psychosocial interventions for improving medication adherence

• “Our review suggests that psychoeducation for patients with schizophrenia and their families is largely ineffective in improving adherence with antipsychotic medications.”

• “For some patients, increasing knowledge about their illness and about medication and its side effects may actually be disturbing”*

• “Family therapy programs were generally ineffective in improving adherence.”


The LEAP method for promoting adherence despite poor insight

1. **Listen**

   - *really* listen to what the person feels, wants, believes without commenting, disagreeing, or arguing

   *When people talk, listen completely. Most people never listen.* - Ernest Hemingway

   - if you can reflect back an accurate understanding of his experiences, hopes, and expectations, he may be more open to talking with you and, more importantly, he may be more open in hearing what you have to say

   "The most basic of all human needs is the need to understand and be understood. The best way to understand people is to listen to them." - Ralph Nichols

Amador X. *I AM NOT SICK. I don’t need help! How to help someone with mental illness accept treatment.* Vida Press, 2012
The LEAP method
for promoting adherence despite poor insight

2. **Empathize**

- empathize with all the reasons he has for not wanting to accept treatment, especially with any feelings related to delusions (such as fear, anger, or even elation if the delusion is grandiose)

- empathizing with how a delusion makes one feel is not the same as agreeing that the belief is true

“It's got to do with putting yourself in other people's shoes and seeing how far you can come to truly understand them.” - Christian Bale
3. Agree

- look for common ground and for whatever motivation the person has to change (e.g. staying out of hospital, getting an apartment, getting a job) or to accept medication (e.g. sleep better, feel less scared, more calm, get mother off his case, etc)

- Rather than stating to him what happened, ask questions like:
  "So what happened after you stopped your meds?"
  "Did the voices quiet down after you stopped?"
  "How long was it before you went to hospital?"
The LEAP method
for promoting adherence despite poor insight

4. Partner

• once you know the areas where you can agree, form a partnership to achieve *shared* goals
  *(e.g. staying out of hospital, getting an apartment, a job, etc.)*

• You may call the goal “recovery from illness” while the person calls it “getting a job”, but the names are irrelevant to arriving at a shared plan of action that will usually involve accepting treatment and services
“I tried to talk to him. But you can’t. He wouldn’t let you”

- Randy Loughner, father of Jared Lee Loughner

“Almost everyone who crossed paths with Jared Loughner in the year before he shot former U.S. congresswoman Gabrielle Giffords described a man who was becoming more unhinged and delusional by the day.”

An compulsory community treatment order should be obtained when:

1. The person clearly requires treatment but categorically and consistently refuses it.

Taking oral treatment in an erratic manner (non-adherence, partial adherence) has been established by the courts as being equivalent to a categorical refusal.

**AND**

2. Due to lack of insight into their condition, the person is **not competent to refuse** treatment.
Which criteria are relevant in determining whether a person has the capacity to refuse treatment?

1) Does the person understand the condition for which the specific treatment is proposed?

2) Does the person understand the nature and purpose of the specific treatment?

3) Does the person understand the risks and benefits involved in undergoing the specific treatment?

4) Does the person understand the risks and benefits involved in not undergoing the specific treatment?

5) Is the person’s capacity to understand impaired by the illness?
Treatment Algorithm* for Psychotic Illness: AMPQ

Psychotic episode
- Propose nonpharmacological treatment (e.g., individual and family social therapy, cognitive-behavioural therapy, motivational therapy etc.)
- Propose atypical LAIs as a first-line pharmacotherapy option

Established first-episode psychosis
- Adherent: If patient accepts, atypical LAI
  If not-oral antipsychotic
- Nonadherent, or high-risk profile (e.g., suspiciousness, hostility, homelessness, substance abuse, lack of social support and insight, etc.)
  - Voluntary acceptance: 1-2 years of LAI before reevaluation
  - Support program for increasing compliance (e.g., psychotherapy, pill dispenser, electronic aid, liquid antipsychotic under supervision, etc.)
  - Refusal of treatment: Outpatient commitment (LAI for 2-3 years)
  - Stabilized: LAI or oral antipsychotic, if patient wishes to continue
  - Stabilized: Continue oral antipsychotic
  - Nonresponse or unstable: Outpatient commitment (LAI for 2-3 years)

Established treatment-resistant psychosis
- Voluntary treatment with an atypical LAI
  - Support program for increasing compliance (e.g., psychotherapy, pill dispenser, electronic aid, liquid antipsychotic under supervision, etc.)
  - Therapeutic drug monitoring (if possible)
  - Stabilized: Oral antipsychotic
  - Nonresponse or unstable: Establish nonresponse with at least two different LAIs before considering clozapine
  - Stabilized: Oral antipsychotic
  - Nonresponse or unstable
  - Adequate plasma level: Establish nonresponse with at least two different LAIs before considering clozapine
  - Low or no plasma level: Outpatient commitment (LAI for 2-3 years)

Are CTOs effective?

➢ 4 Canadian studies of CTO effectiveness: all support a positive effect including reduction in the number of hospital admissions.

➢ The most recent study found:
  • a significant reduction in the rate of readmission
  • while under CTO, the number of readmissions =
    0 (none): 58 %
    1 : 28 %
    ≥ 2 : 14 %
  • Patients stayed out of hospital 4 times longer
  • the effect is sustained even after the CTO has expired

Take-home messages

• Lack of insight/unawareness of illness/anosognosia:
  - is one of the most prevalent features of psychotic illness
  - leads understandably to treatment non-adherence

• Long-acting injectable antipsychotics have considerable advantages over oral medication including improved adherence and better relapse prevention.

• Patients may be helped to accept treatment using the LEAP method, but when lack of insight proves to be an insurmountable barrier to treatment, a Community Treatment Order (i.e. an Outpatient Commitment Order) should be obtained.