Improvement in Patient-Rated Influences on Medication Adherence and Association With Psychopathology in Non-Compliant Patients With Schizophrenia Treated With Orally Disintegrating Olanzapine Tablets

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ABSTRACT

Objective: To determine acute changes in patient attitude toward medication, and relationship between patient attitude and psychopathology in previously non-compliant patients treated with orally disintegrating olanzapine tablets (ODOT).

Methods: Eighty-five acutely ill, non-compliant patients with schizophrenia or schizoaffective disorder received open-label ODOT (10-20 mg/day) for up to 6 weeks. Post-hoc analyses included mean change from baseline to 1 week in Rating of Medication Influences (ROMI) items, principal component analysis to determine ROMI factors, and correlation between ROMI items or factors with clinical psychopathology measured by Positive and Negative Syndrome Scale factors.

Results: Patients experienced significant increases in endorsement of compliance items involving Perceived Benefits of Medication, Fear of Relapse off Medication, and Side-Effect Relief; and significant decreases in endorsement of non-compliance items involving No Daily Benefit, Never Was Ill, Interferes With Life Goals, Distressed by Side Effects, Medication Currently Unnecessary, and Outside Opposition to Taking Medication. Perceived Benefit and No Benefit had the largest standardized score of change, 0.55 and -0.68, respectively. Four of 7 factors derived from ROMI showed significant improvement from baseline to Week 1: Perceived Medication Benefit, Denial of Illness, Outside Opposition, and Negative Aspects of Medication. Improvement in Perceived Medication Benefit factor was significantly correlated with improvement in 2 of the 5 psychopathology factors - positive and disorganized thoughts.

Conclusion: Patient attitude toward medication adherence significantly improved, driven primarily by perceived medication benefit. Rapid improvement in psychopathology may be the most relevant step in early changes in patient attitude favoring medication adherence.
INTRODUCTION

- Non-adherence with prescribed antipsychotic medication is prevalent among patients with schizophrenia and is associated with exacerbation of symptoms.
- A better understanding of patient attitudes toward medication compliance from the patient perspective and of whether specific compliance attitudes change with initiation of an effective treatment may help to provide useful insight on strategies to improve compliance.
- This post-hoc analysis sought to utilize the Rating of Medication Influences (ROMI)\(^1\) to examine the change in patient-reported reasons for compliance and non-compliance with medication following treatment with orally disintegrating olanzapine tablets (ODOT) and the relationship between patient attitude toward compliance and psychopathology measured by the Positive and Negative Syndrome Scale (PANSS).

STUDY DESIGN

- 6-week, open-label study
- Enrolled 85 acutely ill, noncompliant patients (age 18-55) with schizophrenia or schizoaffective disorder
  - BPRS \(_{1-7}\) score (extracted from the PANSS) \(\geq 42\)
  - CGI-Severity score \(\geq 4\)
- Patients participated in a supervised medication program during the first week of treatment.
- Initial treatment was 10 mg/day orally disintegrating olanzapine tablets (range 10-20 mg/day)
- Patients could be switched to standard olanzapine tablets following the end of the supervised medication portion of the study (end of Week 1)

ANTIPSYCHOTIC MEDICATION NONCOMPLIANCE CRITERIA

Defined as belonging to one of the following 4 groups:

I. Inpatients or outpatients demonstrating 2 or more episodes of any of the following within the past 72 hours:
   A. Refusal of prescribed antipsychotic medication.
      Refusal may be:
      1. Active - Verbal refusal of medication, or
      2. Passive - A significant level of effort is required by the nurse in order to coax patient to take medication
   B. Direct evidence or suspicion of cheating or spitting prescribed antipsychotic medication
   C. Display of significant ambivalence toward taking prescribed antipsychotic medication

II. Newly admitted inpatients with a recent history of outpatient noncompliance as evidenced by at least 7 days of antipsychotic medication noncompliance within the past month.

III. Outpatients with a recent history of noncompliance such that the clinical decision has been made to place the patient on supervised medication within the past month.

IV. Inpatients who claim that they cannot swallow antipsychotic drug tablets or capsules despite the absence of any obvious physical condition that would impede swallowing of medications.

RATE OF MEDICATION INFLUENCE (ROMI)\(^1\)

- Reasons for Compliance - 9 items assessing subjective reasons for medication compliance; score indicates degree of influence on compliance (1=none, 2=mild, 3=strong)
  1. Perceived daily benefit
  2. Fear of relapse
  3. Side effect relief
  4. Fulfillment of life goals
  5. Deference to authority
  6. Positive relation with clinical staff
  7. Outside positive opinion about taking medications
  8. Outside opinion that current medication is better
  9. Outside pressure/force

- Reasons for Noncompliance - 10 items assessing subjective reasons for medication noncompliance; score indicates degree of influence on noncompliance (1=none, 2=mild, 3=strong)
  10. No daily benefit
  11. Medications currently unnecessary
  12. Never was ill
  13. Interferes with life goals
  14. Distressed by side effects
  15. Embarrassment or stigma over medications/illness
  16. Change in appearance
  17. Outside opposition to taking medications
  18. Treatment access problems
  19. Substance abuse

PANSS FACTORS\(^2\)

- PANSS Positive Symptoms (PANSSPOS)
  - Conceptual disorganization
  - Grandiosity
  - Suspiciousness/persecution
  - Hallucinatory behavior
  - Unusual thought content
  - Delusions
  - Stereotyped thinking
  - Lack of judgment and insight
  - Preoccupation

- PANSS Negative Symptoms (PANSSNEG)
  - Emotional withdrawal
  - Motor retardation
  - Blunted affect
  - Poor rapport
  - Passive/apathetic social withdrawal
  - Lack of spontaneity and flow of conversation
  - Active social avoidance

- PANSS Disorganized thoughts (PANSSDIS)
  - Tension
  - Mannerisms and posturing
  - Disorientation
  - Difficulty in abstract thinking
  - Poor attention
  - Disturbance of volition

- PANSS Impulsivity/hostility (PANSSHOS)
  - Hostility
  - Uncooperativeness
  - Excitement
  - Poor impulse control

- PANSS Anxiety/depression (PANSSDEP)
  - Somatic concern
  - Anxiety
  - Guilt feelings
  - Depression
The proportion of patients with a score of 1 (none), 2 (mild) and 3 (strong) were given at all measured time points (baseline, 1, 2, 4, and 6 weeks) for each of the 19 items of ROMI.

Principal Component Analysis (PCA) was conducted to investigate the underlying dimensions of the 19-item ROMI scale.

- The number of factors extracted was determined based on the criteria of an eigenvalue of 1 or greater.
- The VARIMAX rotational method was applied to obtain orthogonal rotation of the factors.
- Cronbach's coefficient alpha was used to measure internal consistency of the factors.
- Items that lowered the Cronbach’s alpha levels were excluded (noncompliance Items 10-No Daily Benefit and 15-Embarrassment or Stigma over Medications/Illness).

To assess the significance of change in influence on medication compliance since baseline, mean changes in each of the ROMI items and ROMI factors were analyzed using Wilcoxon signed-rank test.

The correlation between ROMI items and previously derived PANSS factors and between ROMI factors and PANSS factors were given by Pearson’s correlation coefficients.

**PATIENT BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Gender (male/female %)</th>
<th>69.4 / 30.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean +/- SD)</td>
<td>40.35 ± 9.55</td>
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<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>55.3</td>
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<tr>
<td>African Descent</td>
<td>35.3</td>
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<tr>
<td>Other</td>
<td>9.4</td>
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<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>74.1 / 15.58</td>
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<tr>
<td>Schizoaffective</td>
<td>25.9 / 16.70</td>
</tr>
</tbody>
</table>

**COMPLETION RATE AND DOSE**

- Numbers of patients available at Weeks 1, 2, 4, and 6 were 74, 73, 68 and 66;*2
- One (1.2%) patient who had prior abnormal ECG and hypertension at study entry discontinued due to adverse event of atrial flutter;
- The mean daily dose of olanzapine during the study was 11.94±1.84 mg/day.

*2 patients were discontinued at time of Week 6 due to noncompliance.

**STATISTICAL METHODS**

Very rapid response in ROMI items:

Mean change from baseline to Week 1

Significant changes in ROMI items for compliance (ROMI-C): 1. perceived benefit, 2. fear of relapse, and 3. side effect relief; and for non-compliance (ROMI-NC): 10. no benefit, 11. unnecessary, 12. never was ill, 13. interferes with life goals, 14. distressed by side effects, and 17. outside opposition to taking medication.

**CHANGES IN ROMI ITEMS WERE MAINTAINED:**

Mean change from baseline to Week 6

Except for Item 2, changes that were significant at Week 1 were significant at Week 6.

**MEAN CHANGE FROM BASELINE TO Each VISIT FOR ROMI FACTORS**

*Factors 1 (mean change±SD = 0.32±0.64; standardized score=0.51; p<.001) and Factor 3 (mean change±SD = -0.38±0.79; standardized score=-0.49; p<.001) were significantly improved from baseline to 1 week.
### RESULTS

- Statistically significant mean changes from baseline in ROMI items for compliance (ROMI-C): 1 (perceived benefit), 2 (fear of relapse) and 3 (side effect relief), and for non-compliance (ROMI-NC): 10 (no benefit), 11 (unnecessary), 12 (never was ill), 13 (interferes with life goals), 14 (distressed by side effects), and 17 (outside opposition to taking medication) occurred by Week 1; and, except for Item 2, these changes were significant at Week 6
  - Perceived Benefit and No Benefit had the largest standardized score of change, 0.55 and -0.68, respectively.
- The factor analysis yielded 7 factors for the 19 ROMI items:
  - Factors 1-Perceived Medication Benefit (mean change±SD=0.32±0.64; standardized score=0.51; p<.001 )
  - and 3-Denial of Illness (mean change±SD= -0.38±0.79; standardized score= -0.49; p<.001 ) rapidly improved within 1 week of treatment. Factors 5-Negative Aspects of Medication and 6-Substance abuse improved more gradually over the six weeks.
- Significant correlation coefficients between ROMI items and PANSS factors at baseline (p<.05) involved primarily ROMI-C Items 1, 2, and 3 and PANSS factors for positive, negative, disorganized and hostile symptoms with negative correlations and ROMI-NC Items 11 and 14 and PANSS factors for hostility and depression with positive correlations, respectively.
- Change in ROMI factor 1-Perceived Medication Benefit was significantly associated with symptom improvement for PANSS positive symptom and disorganized thought domains. No other ROMI factors showed a similar pattern, but improvement in the ROMI negative aspects of medication factor was associated with improvement in negative symptoms.

### CONCLUSIONS

- Patient attitude toward medication adherence significantly improved, driven primarily by perceived medication benefit and improved insight.
- Rapid improvement in clinical psychopathology, in particular positive symptoms and disorganization may, in part, be the basis for early changes in patient attitude favoring medication adherence.
- The results demonstrated that patient attitude towards treatment compliance can be influenced by treatment response, suggesting that noncompliant patients may become compliant with proper and effective treatment.
- Further studies are needed to confirm and to better understand the findings.

### REFERENCES