Variables influencing antidepressant medication adherence for treating outpatients with depressive disorders

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Article info

 Objective: Medication adherence is associated with the treatment outcomes. The reported consequences of non-adherence for patients with depressive disorders include chronication, poor psychosocial outcomes and increased suicide rates. The aim of this study is to determine whether insight is directly associated with the medication-taking adherence of patients with depressive disorders. In addition, we compared the various kinds of adherence measures for the depressive patients.

Method: Consecutively 76 patients with depressive disorders were recruited from the outpatient clinic of our center. All patients were on mono-antidepressant therapy during at least 4-weeks’ evaluation period, and evaluated with 17 item Hamilton Rating Scale for Depression (HRSD), Multidimensional Scale of Perceived Social Support (MSPSS) and Mood Disorders Insight Scale (MDIS). Medication adherence was assessed by using medication event monitoring system (MEMS), clinician rating scale of compliance, pill count and patient’s self-report. Agreement among the three continuous adherence measures was evaluated. The relationship between the adherence variables and the other clinical scale scores was assessed by using partial correlation correcting for age.

Results: The patients perceived poor social support from other people in relation to increasing severity of depression. The adherence rates for the MEMS, the pill count, the clinician rating scale of compliance and self-report were 51.9%, 71.4%, 79.2% and 75.3%, respectively. The HRSD scale score negatively correlated with the MDIS scores. No correlation was found between the adherence variables and the other clinical scale scores was assessed by using partial correlation correcting for age.

Conclusion: Patients with more severe depression tend to have greater insight. However, the increased insight of depressive patients was not associated with an increase in treatment adherence.

1. Introduction

Patient adherence can be defined as “the extent to which a patient’s behavior coincides with the medical advice the person has received.” (Perkins, 2002). When we confine the meaning to medication, non-adherence involves failure to fill a prescription, refusal to take medication, discontinuing medication prematurely and taking the wrong amount of medication at the wrong times (Perkins, 2002). Various methods are now used to measure adherence, and although some studies have used quantitative methods such as patient reports, clinical reports and objective measures, many issues have been raised about the accuracy of these methods. The medication event monitoring system (MEMS) is a medication bottle cap with a microprocessor that records the occurrence and time of each opening of the bottle. The MEMS has been used in a variety of populations with medical disorders and it
is currently recognized as the most accurate method to assess adherence (Claxton et al., 2001).

The reported consequences of non-adherence for patients with depressive disorders include chronification, poor psycho-social outcomes and increased suicide rates (Cramer and Rosenheck, 1998; Weiss and Gorman, 2005). Adherence with taking antidepressant medication is needed for successful treatment outcomes and to prevent relapse and recurrence (Keller et al., 2002). Accordingly, many factors influencing the adherence with taking medication have been investigated in the field of psychiatry (Cohen et al., 2004; Pampallona et al., 2002).

The relationship between adherence and insight has been reported in previous studies, and insight has been reported to be an important clinical issue (Goldberg et al., 2001). Insight has been widely studied for many mental disorders. Research over the past few decades has revealed that lack of insight may be related with poorer treatment adherence and poorer clinical outcomes for schizophrenic patients (Donohoe et al., 2001). Poor insight was reported to be the best predictor of non-adherence for first episode schizophrenic patients who do not misuse alcohol or other drugs (Kamali et al., 2006).

Yet until now, most insight studies have been conducted in the context of schizophrenia (Ghaemi and Pope, 1994), and there are limitations associated with the use of the current insight measures for patients with mood disorders. The assessment tools were validated for patients with psychosis and as a result, the items on these scales are not targeted for those patients with mood disorders and who have not shown psychotic symptoms. Although mood-disorder patients can experience psychotic symptoms, these features are course specifiers and they are not the core symptoms of the disorder based on the DSM-IV diagnostic criteria (Sturman and Sproule, 2003). It might be more reasonable to use insight measures that are devised for depressive disorders. Sturman and Sproule (2003) developed the Mood Disorders Insight Scale (MDIS). This scale measures three dimensions of insight (awareness of illness, attribution of symptoms and the participants' belief in the necessity of treatment). Further studies can now employ the MDIS for evaluating the insight of patients with depressive disorders.

The relationship between medication adherence and insight into illness outcome has been extensively studied in schizophrenic patients, whereas this issue has not been sufficiently evaluated in patients with depressive disorder. As far as we know, little work has been carried out on the relationship of adherence and insight with using the appropriate methods that are specifically designed for mood-disorder patients.

Social support was reported to be an important predictor for the outcomes of major depression (Rubenstein et al., 2007), and poorer subjective social support was related with higher 12-month depression scores (Bosworth et al., 2008). The association between social support and medication adherence also has been studied. Meta-analyses established significant correlation between adherence to medical treatment and social support (DiMatteo, 2004). It would be valuable to measure the relationship between social support and the medication adherence.

The aim of this study is to determine whether insight and other variables including social support are associated with the medication adherence in patients with depressive disorders. In addition, we tried to compare the various kinds of adherence measures that are used for patients who suffer with depression.

2. Methods

2.1. The study population and procedures

Patients who were diagnosed with depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition were recruited from outpatient psychiatric settings at Korea University Medical Center, Guro Hospital in Seoul, Korea. All of them had received a formal diagnosis of depression-related disorders from their doctors. Their past and present mood-disorder symptoms, their histories of hospitalization for depressive disorder and their psychotic features (including delusion and hallucination) were obtained from diagnostic interviews and reviews of their chart records. These patients were given antidepressant medication in a bottle with an electronic monitor cap, the MEMS. They were asked to return for a follow-up visit after 1 month. At the follow-up visit, an interview was performed and the data was downloaded from the MEMS cap. This study was approved by the Institutional Review Board of Guro Hospital, Korea University Medical Center.

2.2. Measurements

We used various measures to evaluate the variables that have been previously identified to influence insight. Adherence itself was also assessed through a number of approaches.

2.2.1. Insight

Mood Disorders Insight Scale (MDIS): The MDIS is an 8-item scale that measures 3 dimensions of insight, awareness of illness (2 items, original total scores range from 0 to 4), attribution of symptoms (3 items, original total scores range from 0 to 6) and the participants' belief in the necessity of treatment (3 items, original total scores range from 0 to 6). The MDIS items were presented as a series of statements that were read by research assistants, and the participants were asked if they agreed, disagreed or were unsure. Although the items of the MDIS were read aloud by an interviewer in our study, it is essentially a self-report instrument as the participant has a limited set of response options and there are no judgments required from the interviewer. The primary reason for having an interviewer is that some questions must be skipped depending on prior responses, which may be confusing for some individuals. Higher MDIS scores indicate greater insight (Sturman and Sproule, 2003). This scale has also been used in another study that explored the levels of insight in patients with depressive disorders (Yen et al., 2005).

2.2.2. Adherence

Adherence was assessed by four methods (MEMS, a pill count, a clinician rating scale of compliance and the patient's self-report). Each variable, except the clinician's rating, was also treated as a dichotomous variable with using a threshold of 80%. This threshold was thought be the necessary level of adherence to achieve a therapeutic response in another
similar study (Remington et al., 2007). For the clinician’s rating, a specific scale score was used to get a dichotomous result. A score of 5 or greater was used to designate adherence.

### 2.2.2.1. MEMS

As the MEMS is known to be the gold standard for the measurement of adherence, the primary outcome measure was the MEMS and the downloaded data was used to establish if the subjects opened their antidepressant bottle during the prescribed number of times daily. We measured the adherence with taking antidepressants as the proportion of the times the medication vial caps were opened in a given month relative to the prescribed doses for that month. The patients were made aware of MEMS cap’s function prior to the start of the study. The results were dichotomized into adherence and non-adherence with using a threshold of 80%.

### 2.2.2.2. Pill count

A pill count adherence index was derived from the ratio of the actual pill count as recorded by the investigator at the follow-up visit. The results were also dichotomized into adherence and non-adherence with using a threshold of 80%.

### 2.2.2.3. Clinician rating scale of compliance (Byerly et al., 2005)

The clinician’s assessment of compliance was conducted without the clinician being aware of the MEMS cap data. As asking for an absolute value from 0 to 100% was not realistic for the clinicians, we instead adopted an assessment scale (Byerly et al., 2005). Measuring the patient’s adherence by the researcher usually required approximately 10 min and this involved questions regarding the patients’ symptoms and sense of well-being, the patient’s functional status and attitude towards taking medication and the medication side effects, and there was a specific question regarding the number of days the patient was adherent to taking medication in the past month. During the assessments, no statements were made regarding the desirability of being compliant with taking medication. The clinician rating scale is an ordinal scale of 1–7, with the higher numbers meaning better adherence. In the previous studies that used this scale, a score of 5 or greater was used to designate adherence (Byerly et al., 2005; Kemp et al., 1996). Accordingly, we also employed a score of ≤4 as the threshold for clinically meaningful non-adherence.

### 2.2.2.4. Patient self-report

At the study’s endpoint, the participants were also asked to estimate their adherence with their antidepressant treatment between 0 and 100%. The results were dichotomized into adherence and non-adherence with using a threshold of 80%.

### 2.3. Clinical symptoms

Specific depressive symptoms were assessed using the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960).

### 2.4. Social support

The patients were administered and completed the Multidimensional Scale of Perceived Social Support (MSPSS). The MSPSS is a 12-item scale that evaluates perceptions of social support (Zimet et al., 1990). The items are rated on a 7-point scale (1 = very strong disagree; 7 = very strongly agree), with each of the 3 subscales (i.e., friends, family, significant other) assessed by four items. The items are written in the present tense and the patients were required to answer each question with reflecting how they usually feel. Higher scores show higher perceived social support. The psychometric properties of the MSPSS were previously investigated in a non-Western country (Eker and Arkar, 1995).

### 2.5. Statistical analysis

In order to summarize the demographic characteristics, we calculated means and standard deviations for the continuous variables and frequencies and percentages for the categorical variables. To analyze the insight measurements, we conducted correlation analyses among the 3 dimensions of insight on the MDIS. For the evaluation of agreement among the three continuous adherence measures, we used a concordance correlation analysis (Lin, 1989) that evaluates the degree to which pairs of observations fall on the 45° line through the origin. This correlation coefficient accounts for both a measure of precision (the usual correlation coefficient) and a measure of accuracy. We also calculated Kappa statistics to evaluate the agreement among the three dichotomized adherence measures. We performed partial correlation analyses to assess the relationship between the adherence measures and the other clinical scale scores.

### 3. Results

#### 3.1. Demographic characteristics

A total of 80 outpatients was enrolled in the study. Four patients were excluded because of consent withdrawal. All the remaining 76 outpatients (30 men and 46 women) completed the study. Their mean age was 49.11 ± 14.59 years, and their mean duration of illness was 45.51 ± 50.14 months. The oral medications that were taken during the study were as follows: venlafaxin (n = 24, 31.6%), escitalopram (n = 21, 27.6%), paroxetine (n = 10, 13.2%), sertraline (n = 9, 11.8%), mirtazapine (n = 6, 7.9%), milnacipran (n = 5, 6.6%) and bupropion (n = 1, 1.3%). The mean HRSD score was 14.04 ± 6.87. The details of the 76 participants included in the study are given in Table 1. As the severity of depression increased, the patients tended to perceive poorer social support from others on the correlation analysis. Each of the MSPSS subscale scores was also significantly correlated with each other (Table 2).

#### 3.2. Insight

The reliability coefficient of the MDIS (Cronbach’s alpha) is reported to be 0.636 in this study. The mean for each of the MDIS subscale scores (maximum = 4) was high: awareness of illness (2.30 ± 1.41), attribution (3.14 ± 1.29) and the need for treatment (3.14 ± 1.29). The correlations among the 3 dimensions of insight on the MDIS and the socio-demographic (age, educational years, duration of illness) and clinical characteristics (the level of depression by the HRSD and social support by the MSPSS) were analyzed. Only the level of depression by the HRSD was positively correlated with the MDIS scores (awareness of illness: r = 0.244, p = 0.037;
3.3. Adherence

We evaluated adherence in two ways. First, we treated adherence as a continuous variable. The mean values for the various measures of adherence were as follows (mean ± standard deviation): MEMS 68.49 ± 30.84%, pill count 84.96 ± 21.08% and self-report 87.13 ± 16.22%. The mean scale score of the clinician rating scale of compliance for the cases was 5.55 ± 1.00. We converted the continuous results of this adherence into dichotomous variables (compliant/non-compliant). Employing this approach, the adherence rates for the MEMS, the pill count, the clinician rating scale of compliance and self-report were 52.6%, 72.4%, 80.3% and 76.3% respectively. The concordance correlations among those adherence variables are presented in Table 3. We were also interested in how those adherence measures agreed with the MEMS when those variables were dichotomized. The Kappa coefficients were 0.380 (pill count vs. MEMS), 0.320 (clinician rating scale score vs. MEMS) and 0.495 (self-report vs. MEMS).

![Fig. 1. Correlations between HRSD and each MDIS scale score. The lines are the best-fit straight lines describing the correlations between HRSD and the MDIS scores (awareness of illness: \( r = 0.244, p = 0.037 \); attribution of symptoms: \( r = 0.184, p = 0.118 \); the necessity of treatment: \( r = 0.277, p = 0.023 \); total MDIS score: \( r = 0.336, p = 0.006 \)). HRSD: Hamilton Rating Scale for Depression. MDIS: Mood Disorders Insight Scale.](image-url)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Basic demographic characteristic, baseline scores on measures, and comparison between compliant and non-compliant groups.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 76)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>30/46</td>
</tr>
<tr>
<td>Age (age)</td>
<td>49.11 ± 14.59</td>
</tr>
<tr>
<td>Educational years (years)</td>
<td>10.47 ± 3.68</td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td>45.51 ± 50.14</td>
</tr>
<tr>
<td>Marital status</td>
<td>N.S.</td>
</tr>
<tr>
<td>Single</td>
<td>14 (18.4%)</td>
</tr>
<tr>
<td>Married/living together</td>
<td>50 (65.8%)</td>
</tr>
<tr>
<td>Divorced</td>
<td>5 (6.6%)</td>
</tr>
<tr>
<td>Separated</td>
<td>7 (9.2%)</td>
</tr>
<tr>
<td>Job</td>
<td>Unemployed</td>
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<tr>
<td>Housework</td>
<td>28 (38.8%)</td>
</tr>
<tr>
<td>Employed</td>
<td>33 (43.5%)</td>
</tr>
<tr>
<td>DSM-IV diagnosis</td>
<td>Major depressive disorder, single episode</td>
</tr>
<tr>
<td>Major depressive disorder, recurrent</td>
<td>8 (10.5%)</td>
</tr>
<tr>
<td>Dystolic disorder</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Depressive disorder Not otherwise specified</td>
<td>17 (22.4%)</td>
</tr>
<tr>
<td>Mood Disorders Insight Scale</td>
<td>Awareness of illness subscale (0–4)</td>
</tr>
<tr>
<td>Attribution subscale (0–6)</td>
<td>2.53 ± 1.47</td>
</tr>
<tr>
<td>Need for treatment subscale (0–6)</td>
<td>3.14 ± 1.29</td>
</tr>
<tr>
<td>Total score (0–16)</td>
<td>7.99 ± 3.17</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Depression score</td>
<td>14.04 ± 6.87</td>
</tr>
<tr>
<td>Multidimensional Scale of Perceived Social Support score</td>
<td>Friends</td>
</tr>
<tr>
<td>Family</td>
<td>20.84 ± 7.39</td>
</tr>
<tr>
<td>Significant others</td>
<td>14.43 ± 8.22</td>
</tr>
<tr>
<td>Total scores</td>
<td>50.42 ± 19.12</td>
</tr>
</tbody>
</table>

N.S.: Not significant, p values are calculated using t- and chi-square tests.

![Table 2](image-url)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Correlations between the depressive symptoms' scores and the level of social support.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRSD score</td>
</tr>
<tr>
<td>HRSD score</td>
<td>–0.333**</td>
</tr>
<tr>
<td>MSPSS — other</td>
<td>0.399**</td>
</tr>
<tr>
<td>MSPSS — family</td>
<td>0.380**</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, HRSD: Hamilton Rating Scale for Depression, MSPSS: Multidimensional Scale of Perceived Social Support.
We performed further analysis of the relationships between these adherence variables and the other demographic variables (age and the total number years of education). Age was significantly correlated with some of adherence measures (the clinician rating scale score of compliance: \( r = 0.387, p = 0.001 \); pill count: \( r = 0.286, p = 0.013 \); self-report: \( r = 0.365, p = 0.002 \)), but age did not show significant correlation with the MEMS (\( p = 0.198 \)). Partial correlation analyses that were corrected for age were done to assess the relationship between the adherence variables and the other clinical scale scores (insight by the MDIS, the level of depression by the HRSD and social support by the MSPSS). However, we did not find any statistical significance for these partial correlations.

4. Discussion

Comprehensive studies have shown that between 50% and 80% of all patients with schizophrenia do not believe that they have a disorder (Amador and Gorman, 1998). Thus, lack of insight is a very common phenomenon in schizophrenia. As the symptoms get severer, schizophrenics tend to show more impaired insight. For schizophrenia patients, damaged reality testing is directly related with a lack of insight, a high risk of non-adherence and poorer clinical outcomes (Kamali et al., 2006).

Although there are limited studies on the insight of the patients with depressive disorder, the reported results from these previous studies are rather different from those results of the previous studies on schizophrenia. We can easily infer that the participants in this study were in a relatively stable state because they showed relatively low mean HRSD scores and they didn’t need to have their medication changed for at least 1 month prior to the study. Depressed patients showed greater insight into awareness of their illness and the attribution dimensions in a previous report that used the same MDIS (Yen et al., 2005) that was used in our study. The level of depression was also significantly correlated with the 2 dimensions of MDIS (awareness of illness and the necessity of treatment) and with the total MDIS scores in our study. These results are consistent with the “depressive realism” hypothesis, i.e., in the depressed state, patients may be more aware of external reality or of psychological symptoms or cognitive states than when they are in the euthymic mood state (Ghaemi et al., 1997; Sackeim and Wegner, 1986). Dysphoric individuals seem to have accurate perceptions, even-handed judgment and unbiased self-awareness.

MEMS monitoring detected clinically meaningful antidepressant non-adherence in nearly 50% of the participants of our study when using the dichotomous variable. All the adherence measures were significantly correlated with each other. As the clinician rating scale score showed a relatively lower kappa coefficient than did the other two adherence measures (the pill count and even self-report), this finding suggests the possibility of the clinician’s limited capacity to detect antidepressant non-adherence in actual clinical practice. Although age was significantly correlated with some of the adherence measures, it failed to show meaningful correlations with adherence as measured by the gold standard, that is, the MEMS. We think that age might affect the results of other adherence measures. As other adherence measures were performed using self-report or interview, many other possible age-associated intervening factors (Lotrich and Pollock, 2005) could also potentially influence medication adherence.

Of particular note, the adherence variables did not show any significant relationship with the level of insight in this study. For schizophrenia patients, poor insight is already known to be related to non-adherence. But for the non-psychotic patients who do not have severely impaired reality testing, insight was not related with any measure of adherence. This means that more insight is not directly related with the change of treatment behavior, as represented by adherence, for patients with depressive disorders. Simply improving insight into depression is not enough for better treatment adherence and outcome in depressive disorder patients. A previous study reported on the complexity of the factors that influence whether a person adheres to his medication regimen (Donohoe et al., 2001). Furthermore, they reported that these factors may vary within the same person over time. Taken together, for predicting the treatment adherence of patients with depressive disorder, we should consider various factors that influence treatment adherence, in addition to insight.

We observed significant negative correlations between social support and adherence. This result is in line with those of the previous reports. For the cases of subjects with perceived psychiatric/psychological problems, they were reported to feel less social support when compared with the other normal, nonclinical samples (Eker and Arkar, 1995).

In the previous other study, both the poorer subjective social support and greater medication non-adherence were related with higher 12-month adherence depression scores (Bosworth et al., 2008). When we examined the direct relationship between medication adherence and social support, the correlation was not apparent. Although both social support and adherence are important prognostic factors for management of depression, a simple direct relationship between social support and adherence is not clear in stable patients with depressive disorders.

Although these are clinically interesting findings, these results need to be interpreted in light of several study limitations: (1) Utilizing the clinical ratings of a research member rather than those of the doctor who actually prescribed the medicine may have interfered with the exact evaluation of adherence due to the lack of clinical rapport. (2) Other unmeasured variables may influence insight in patients with depressive disorders and the influence of these variables on adherence was not explored. (3) Although the patients were not informed about the exact results of the

### Table 3
Concordant correlations (95% confidence interval) among the adherence rates with employing different measures for the stabilized outpatients with depressive disorder.

<table>
<thead>
<tr>
<th></th>
<th>MEMS</th>
<th>Pill count</th>
<th>Self-report</th>
</tr>
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<tbody>
<tr>
<td>MEMS</td>
<td>0.419 (0.254, 0.561)</td>
<td>0.386 (0.247, 0.510)</td>
<td>0.365 (0.224, 0.500)</td>
</tr>
<tr>
<td>Pill count</td>
<td>0.365 (0.224, 0.500)</td>
<td>0.669 (0.523, 0.773)</td>
<td>0.419 (0.254, 0.561)</td>
</tr>
<tr>
<td>Self-report</td>
<td>0.365 (0.224, 0.500)</td>
<td>0.669 (0.523, 0.773)</td>
<td>0.386 (0.247, 0.510)</td>
</tr>
</tbody>
</table>

MEMS: Medication Event Monitoring System.
MEMS measurements, they were made aware that this study’s intent was to better understand adherence. This might have encouraged adherence during the study’s relatively short duration and so the adherence rates might have been inflated by this. (4) The relatively small numbers of participants and use of various antidepressants can also influence the study results.

The relationship between insight and adherence for depressive disorder seems to be rather different from that for psychotic disorders, including schizophrenia. The relationship between adherence and the treatment response is well established (Keller et al., 2002). For better adherence and eventually a more favorable clinical outcome, more variables for depressive patients should be considered, including insight, for predicting the treatment adherence of these patients.

Role of the funding source
The investigators designed and conducted the survey, collected, analyzed and interpreted data, and prepared the final manuscript. This study was self-funded.

Conflict of interest
No conflict declared.

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