Understanding medication nonadherence in a sample of Egyptian patients with schizophrenia in relation to illness severity and insight

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Background

Nonadherence to medication remains a challenging problem in the management of patients suffering from schizophrenia. Studies on the association between the severity of schizophrenia symptoms and lack of insight into medication adherence have yielded conflicting results. Very few studies have been conducted on Egyptian patients with schizophrenia to determine the impact of these factors on medication adherence.

Aim of the study

The aim of this study was to identify the clinical features of schizophrenia that correlate with nonadherence to medication.

Patients and methods

This is a prospective study in which 109 patients were recruited from Ain Shams University, Institute of Psychiatry. Patients were interviewed initially using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), Axis I Diagnosis Clinical Version and the Positive and Negative Syndrome Scale (PANSS). Six months later, the patients were reassessed with PANSS, the Brief Adherence Rating scale, and the Scale to Assess Unawareness of Medical Disorder.

Results

Two-thirds (68.8%) of the studied patients were nonadherent and only one-third (31.2%) were adherent, according to the Brief Adherence Rating scale. It was found that the majority of adherent patients (61.8%) were insightful, whereas most of the nonadherent patients (94.7%) were insightless, with highly significant statistical difference. Severity of illness was found to be significantly higher at the beginning of the study compared with that at the time of reassessment. The comparison of PANSS scores in adherent versus nonadherent patients revealed a highly significant statistical difference, with lower mean scores in total and all subscales of PANSS in adherent patients. Finally, logistic regression analysis was performed to evaluate the predictive factors for nonadherence, which revealed that more severely ill patients were less compliant with medication and insightful patients were significantly more compliant.

Conclusion

Medication nonadherence is considered a highly prevalent problem among Egyptian patients with schizophrenia. The present study supported earlier findings in Western countries on the role of insight and illness severity in medication nonadherence among schizophrenic patients. Thus, it is mandatory to assess patients' insight and implement various interventions to improve it very early in the management plan.

Keywords:

insight, medications, nonadherence, schizophrenia

Introduction

Nearly 50% or more of patients with chronic psychiatric illnesses do not take their medications regularly as prescribed. Failure to receive medication could have a negative impact on short-term and long-term outcomes of psychiatric illnesses, especially schizophrenic disorders [1].

The term adherence has been frequently used nowadays instead of the term compliance in an effort to place the clinician-patient relationship in its best perspective. Adherence is defined as 'the extent to which the patient's behavior (in terms of taking medications, following diets, or executing other lifestyle changes) matches medical recommendations jointly agreed between patient and prescriber' [2–4].

Compliance is defined as 'the degree to which the patient's behavior matches the prescriber's recommendations'. The usage of such a term could imply disregard for the patient's autonomy because it refers to a process where the clinician decides on a suitable treatment, which the patient is expected to comply with unquestioningly; thus therapeutic relationship would be negatively affected [5–8].

Despite the progress made in the field of psychotropics, the adherence rate in patients with schizophrenia is still very low. It was found that the rate of adherence among patients with schizophrenia is 50–60% [9], and rate of discontinuation of treatment within 2 years of hospital discharge reaches 75% of all patients with schizophrenia [2]. Nonadherence to treatment is considered a challenging problem in the management of patients with schizophrenia; it has been associated with poorer clinical, social, and functional outcomes, increased use of emergency psychiatric services, and an increased number of hospital admissions [10,11] and relapses [12].

Medication adherence in schizophrenia has multiple determinants, like sociodemographic variables, illness-related variables, treatment-related variables, and patients' general values and attitudes toward illness and medications [13–19].

One of these variables that has been widely studied in Western culture and has been claimed to impact patients' adherence is the degree of patient insight, which is regarded as a multidimensional concept that includes the degree of psychic self-perception and awareness that patients have of their illness and symptoms, and the extent to which they are able to examine their different levels of motivation and accept new views that undermine their beliefs [20]. Insight also includes the attribution of symptoms to the illness and awareness of the social consequences of the disease and of the necessity of treatment [21].

Various studies on the association of medication adherence in schizophrenic patients with their insight have yielded conflicting results. Some studies [19,22] found that poor insight on illness increased the risk for noncompliance with medication, compared with good insight. Others failed to prove this relation, as seen in a recent meta-analysis that showed that increasing awareness and knowledge about the illness and treatment alone did not have any influence on medication adherence. In addition, researchers raised doubts about the predictive power of insight for medication adherence because the results of longitudinal studies were inconsistent [23].

Other studies focused on the impact of severity of illness psychopathology on the adherence rate. However, it revealed inconsistent results, as some attributed medication nonadherence mainly to the severity of negative symptoms – for example, apathy may reduce patients' motivation to adhere to a treatment regimen [24]. Other studies found that positive symptoms are the main causes of medication nonadherence as patients who feel persecuted or are afraid they will be poisoned will be reluctant to take medication [11].

All of the above-mentioned studies have been conducted in Western countries. To our knowledge, in Egypt, one study examined the role of insight on medication adherence among Egyptian patients with schizophrenia [25], and none has investigated the effect of illness severity on patients' adherence.

This prospective study is a part of a departmental project aiming to investigate the relation between nonadherence and various sociodemographic and clinical variables, including cognitive functions, memory, executive functions, motor side effects of antipsychotics, and weight gain in patients with schizophrenia [26,27].

Hypothesis
We hypothesize that specific illness-related variables (illness severity and poor level of insight) would negatively influence the adherence rate to medications among patients with schizophrenia.

Aim of the study
Specifically, we aimed to clarify the effect of illness severity and lack of insight on medication adherence among patients with schizophrenia and investigate whether these factors detailed in western literature would predict adherence in a developing country like Egypt.

Patients and methods
Site of the study
This is a prospective cohort study; the sample was recruited from patients who were admitted to the inpatient unit and then followed up in the outpatient clinics of the Institute of Psychiatry, Ain Shams University Hospitals.

Selection of patients
The sample consisted of 137 patients with the diagnosis of schizophrenia disorder according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), during the period from May 2011 to May 2012. Patients of both sexes, aged 18–50 years, with a duration of illness not less than 1 year and who agreed to sign the informed consent form were eligible for inclusion in this study. We excluded patients who had received electroconvulsive therapy before enrollment or during the follow-up period (as electroconvulsive therapy is associated with transient cognitive impairment and memory affection, which in turn can affect the insight level) [28,29], who had chronic medical, neurological diseases, comorbid psychiatric disorders, and substance abusers. A total of 109 patients completed the study, while 28 patients declined participation, yielding a 24% dropout rate (14 patients refused to complete the study, seven patients were followed up in another hospital, and contact was lost with seven patients).

Procedure
Assessment schedule
The patients were interviewed twice – at the time of initial assessment and 6 months later – in order to avoid

the recall bias. Data were verified through collateral information gathering from a reliable informant who was living with the patient after receiving the patient's permission.

Upon enrollment the participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I Diagnosis Clinical Version to confirm the diagnosis of schizophrenia and the Positive and Negative Syndrome Scale (PANSS) to determine the severity of illness. After 6 months the patients were reassessed for severity of symptoms, insight, and adherence to medications.

Tools
Structured Clinical Interview for DSM-IV Axis I Diagnosis Clinical Version [30]
This is a semistructured diagnostic interview based on an efficient but thorough clinical evaluation. Here we used the Arabic version of the Structured Clinical Interview for DSM-IV Axis I Disorders [31].

The Positive and Negative Syndrome Scale [32]
This scale is a semistructured clinical interview, which is well defined and standardized for typological and dimensional assessment of schizophrenia. It was developed by Kay *et al.* [32].

Data gathered from the semistructured interview are applied to the PANSS ratings. Each of the 30 PANSS items and the three supplemental items are accompanied by a specific definition as well as detailed anchoring criteria for all seven rating points.

Brief Adherence Rating Scale [33]
This is a pencil-and-paper clinician-administered instrument for assessing adherence to antipsychotic medications in patients with schizophrenia. The Brief Adherence Rating Scale (BARS) provides valid, reliable, sensitive, and specific estimates of antipsychotic medication adherence with schizophrenia and schizoaffective disorder. It is one of the measures that showed higher validity in comparison with other psychometric scales in evaluating adherence itself, unlike other measures that assess adherence-related attitudes and behaviors [34,35].

Adherence has been defined as follows.

The BARS rating is reported on a percent scale of adherence (0–100%), with lower than 70% indicating nonadherence. The BARS was rated by clinical psychiatrists who were blinded to the neuropsychological findings.

Scale to Assess Unawareness of Mental Disorder [36]
It is a semistructured open interview that evaluates global insight, insight into illness, and insight into symptoms. The Scale to Assess Unawareness of Mental Disorder has shown good reliability and validity and has demonstrated certain advantages over previous measures of insight, suggesting the usefulness of a multidimensional view of this complex concept.

Ethical consideration
Ethical approval of the protocol of research was obtained from the Ain Shams University Ethical and Research Committee. The researchers described the study to the patients, ensured the confidentiality of information, and obtained their informed consent for participation. It was stated that participation in the study was voluntary and they have the freedom to withdraw from the assessment at any time.

Statistical analysis
Data were recorded and analyzed using statistical package for social sciences, version-17 (SPSS Inc., Chicago, Illinois, USA). The paired *t*-test was used for comparison between means of the different groups of patients. The Student *t*-test was used to compare between two independent means. Pearson's χ^2 was used for comparison between qualitative variables. Logistic regression analysis was used to examine the extent to which a set of variables independently predict a dependent variable. *P* values were used to indicate the level of significance where *P*-value less than or equal to 0.05 was considered significant, *P*-value less than or equal to 0.01 was considered highly significant, and *P*-value less than or equal to 0.001 was considered very highly significant.

Results
Sociodemographics, clinical, and medication adherence characteristics of the study sample
A total of 109 patients completed the study.

Patients' adherence was assessed using the BARS 6 months after patients' recruitment, which revealed that about two-thirds (68.8%) of patients were nonadherent to medications (Fig. 1).

Comparison of adherent patients (group I) with nonadherent patients (group II) in terms of demographic variables revealed that the mean age of adherent patients was 32.26 ± 8.6 versus 32.28 ± 9.3 of nonadherent patients, with no significant statistical difference between them. Male sex was more prevalent in both groups (56% of the adherent patients vs. 77% of the nonadherent patients). In terms of marital status, the majority of adherent patients were single (75%), similar to nonadherent patients (68%). Unemployment was a common feature in both groups as 53% of adherent patients were unemployed in comparison with 59% of nonadherent patients. There was no significant statistical difference between the two groups in terms of social class, marital status, or occupation (*P* > 0.05).

In terms of the type of prescribed antipsychotic medication, our results pointed out that 70.6% (24 patients) of adherent patients were prescribed atypical antipsychotics, 20.6% (seven patients) were prescribed typical antipsychotics, and 8.8% (three patients) were prescribed both types of antipsychotics. On the other hand 62.7% (47 patients) of nonadherent patients were prescribed atypical antipsychotics, 30.7% (23 patients) were prescribed typical antipsychotics, and 6.7% (five

patients) were prescribed both types of antipsychotics. The mean dosage of prescribed antipsychotics in the former group was 290.31 and that in the latter group was 288.72 chlorpromazine equivalent. We did not find a statistically significant difference between adherent and nonadherent patients regarding the type of prescribed antipsychotic ($P = 0.567$).

Relation between patient adherence and severity of illness during admission and 6 months after admission

We compared the severity of illness using PANSS in adherent and nonadherent patients. The nonadherent patients showed significantly higher mean scores on PANSS (total, positive, and negative subscales) compared with adherent patients, but not on the general psychopathology subscale. This difference in mean scores between adherent and nonadherent patients was statistically significant ($P < 0.05$). Statistically significant difference was found between scores of adherent versus nonadherent patients with lower mean scores in total and all subscales of PANSS 6 months after discharge (Table 1).

Relation between patient adherence and insight

In general, the majority of studied patients (77.1%) lacked insight into their psychotic illness, symptoms, and need for treatment. It was found that most of the adherent patients (61.8%) were insightful, whereas most of the nonadherent patients (94.7%) were insightless (Fig. 2), with highly significant statistical difference between the two groups ($\chi^2 = 42.14$, $P = 0.000$) (Table 2).

Figure 1
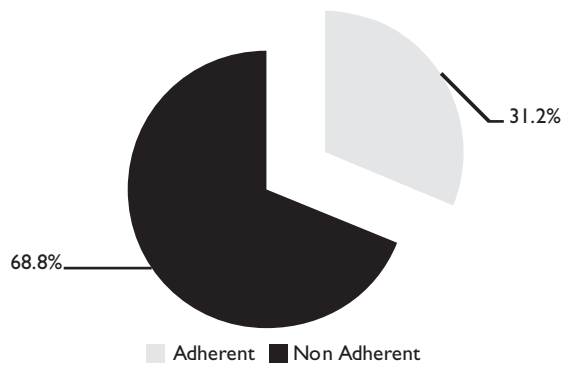
Patients' adherence 6 months after discharge.

Predictive factors of nonadherence to medications

We performed logistic regression analysis to identify the predictive factors for nonadherence to medications. We used patient adherence after 6 months as the dependent factor and used variables that showed statistical significance in the univariate analysis. Multiple regression analyses showed multi-colinearity between total PANSS score and the subscales and therefore we only used the total PANSS subscale scores for the logistic regression analysis.

It revealed that lack of insight was highly predictive of nonadherence ($P = 0.029$), followed by severity of illness on admission (as assessed by PANSS) ($P = 0.049$) (Table 3).

Discussion

Despite the introduction of new antipsychotics with broader efficacy and improved side effect profiles, nonadherence continues to be a frequent phenomenon that is associated with severe clinical consequences [37–40].

In the current study, the majority (68.8%) of patients did not adhere to their antipsychotic regimens. Few studies in developing countries have investigated the adherence rate in patients with schizophrenia. A recent study in Egypt [25] indicated that a total of 74% did not adhere to their antipsychotic regimen, and a Palestinian study [41] revealed that 66% of their sample had low or medium adherence rate. These results suggest that Egyptian patients in our study had higher rates of nonadherence, similar to previous studies on Arabs, which even used different tools for assessment of adherence. There were no significant differences between medication-adherent and medication-nonadherent respondents with regard to sociodemographic variables (age of onset, marital status, education, and level of socioeconomic status) and type of prescribed antipsychotic.

The current study was conducted to specifically investigate the influence of severity of illness and degree of insight on the rate of medication adherence in schizophrenic patients.

Relation between rate of adherence and severity of illness during admission

Severity of schizophrenia symptoms may decrease the patients' ability to engage in the treatment process.

Table 1 Comparison of schizophrenia severity between adherent and nonadherent patients using PANSS

	Adherent ($N = 34$)	Nonadherent ($N = 75$)	t-Test	P-value
Total PANSS (on admission)	77.9 ± 12	89.7 ± 7.6	5.26	0.00**
Positive PANSS subscales (on admission)	29.7 ± 7.2	34.16 ± 6.2	3.04	0.00**
Negative PANSS subscales (on admission)	21.1 ± 7.1	26.6 ± 5.9	4.2	0.00**
General psychopathology (on admission)	28.29 ± 7.5	28.54 ± 3.6	4.4	0.67
Total PANSS (after 6 months)	52.38 ± 13.3	74.8 ± 17.7	6.59	0.00**
Positive PANSS subscales (after 6 months)	14.55 ± 5.8	25.21 ± 10.3	6.83	0.00**
Negative PANSS subscales (after 6 months)	15.94 ± 6.7	23.06 ± 6.2	5.36	0.00**
General psychopathology (after 6 months)	21.73 ± 4.3	26.16 ± 4.7	4.619	0.00**

PANSS, Positive and Negative Syndrome Scale.
**Means very high statistical significance.

We found that nonadherent patients had significantly higher mean scores for the total PANSS and two subscales (PANSS) compared with the adherent group.

Our study confirmed the results of a previous 1-year follow-up study on 56 psychotic patients that used Cox survival analysis to reveal three predictors of noncompliance: diagnosis of schizophrenia versus other two diagnoses, positive symptoms during admission, and lack of insight at discharge [22]. Similarly, a prospective study conducted by Verdoux *et al.* [42] studied patients with psychotic disorders in their first hospitalization for 2 years after discharge; they concluded that higher baseline intensity of delusion and suspiciousness was associated with nonadherence during subsequent follow-up.

In contrast, our results showed that higher mean scores on the PANSS negative symptom subscale were found to be related to nonadherence. Our results are in accordance with previous studies such as the one by Fleischhacker *et al.* [11] who reported that negative symptoms were predictive of nonadherence. Severe negative symptoms were assumed to impair adherence through their impairing effects on the patient's basic self-care abilities [43] and may interfere with the ability to take medications [40]. On the contrary, Rosa *et al.* [44] concluded that illness severity is not necessarily a cause of noncompliance, but it may act in a bidirectional manner – that is, noncompliance causing worsening of symptoms and worsening leading to lower compliance.

Controversial results were found in the study by Yang *et al.* [45] who recruited 51 patients diagnosed with schizophrenia and monitored them over an 8-week period. They found that total PANSS score, positive subscale, and negative subscale were not significantly different between adherent and nonadherent patients, whereas excitement, impulse control, and preoccupation symptoms on PANSS were significantly higher in nonadherent patients than in adherent patients.

Our results concurred with previous study results [11,22,40,42–44] on the correlation between either positive or negative symptoms (separately or both of them) and medication nonadherence. However, it is difficult to establish a causal direction as nonadherence naturally leads to a worsening of symptoms, and vice-versa.

### Relation between rate of adherence and insight

Impaired insight is regarded as an important feature of schizophrenia that contributes to functional outcome, prognosis, and treatment adherence [46].

Our study revealed that 77.1% of studied patients lacked insight into their illness as measured by the Scale to Assess Unawareness of Mental Disorder. This finding is higher than that detected in previous studies such as that by Lincoln *et al.* [23], who found that the rate of incidence of impaired insight among patients with schizophrenia ranged between 30 and 50%, Lysakar *et al.* [47], who found that 53.8% were classified as insightful and 46.2% were insightless, and the earlier mentioned Egyptian study [25], which found that only 49.3% of the studied patients with schizophrenia lacked insight. Similar to our results are those by Dickerson *et al.* [48], who showed that only 24.1% of their study participants were insightful and 75.9% lacked insight into their illness, and the study by Amador and David [49], who found that the rate of impaired insight reached up to 80% among schizophrenic patients.

The difference in results may be attributed to different methodological factors between studies. For example, in the study by Lysakar *et al.* [47] all participants were receiving outpatient treatment and were in a more stable phase of their illness, as defined by no hospitalizations, or changes in medication or housing for 30 days.

Sendt *et al.* [50] stated that insight is associated with better adherence, which is consistent with the 'health belief model', which proposes that the patient must perceive themselves as vulnerable to a condition and anticipate benefits that outweigh risks associated with a treatment if they are to remain adherent to it. Moreover, insight into illness is considered to reflect one's awareness of the illness and is therefore anticipated to play a role in influencing adherence behavior.

Figure 2
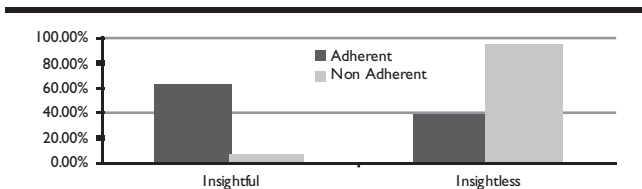
Comparison of insight level between adherent and nonadherent groups of patients using Scale to Assess Unawareness of Medical Disorder.

Table 2 Degree of insight in relation to adherent versus nonadherent patients

	Adherent (N = 34) [n (%)]	Nonadherent (N = 75) [n (%)]	χ^2	P-value
Insightful	21 (61.8)	4 (5.3)	42.149	0.00**
Insightless	13 (38.2)	71 (94.7)		

Table 3 Predictive factors of nonadherence

Factors	B	SE	Wald	Significance	Exp[B]
Insight (SUMD)	− 3.270	1.49	4.75	0.029*	26.31
Severity of illness on admission (total PANSS)	− 0.221	0.11	3.88	0.049*	0.802
Severity of illness 6 months after discharge (total PANSS)	− 0.011	0.05	0.03	0.851	0.98

PANSS, Positive and Negative Syndrome Scale; SUMD, Scale to Assess Unawareness of Medical Disorder.

It was obvious from the results of our study that there is a significant association between nonadherence and patients' lack of insight into their illness, as almost all of the nonadherent patients were insightless (94.7%) in comparison with only 38% of adherent patients who were found to be insightless.

Previous studies [23,40,51–55] found a similar directional relation in which lack of illness insight was associated with nonadherence and reported that individuals who used to ignore the stress of their illness or the magnitude of their symptoms were less adherent to their medication. These studies demonstrated that patients with severe impairment in insight present with worse treatment adherence and less overall improvement in both clinical and functional measures [23].

Similar results came from a cross-sectional study on 104 patients with schizophrenia. It found that patients with better insight into mental illness had better compliance, less severe psychopathologic conditions, and less negative subjective response to the side effects of antipsychotics [56].

However, some studies [25,56] could not identify a relation between adherence and lack of insight. They attributed it to sample contamination through the inclusion of more adherent patients, which may, in turn, influence the overall findings concerning patient adherence. Moreover, insight has been related to other factors like depression, hopelessness, lower self-esteem, and internalization of stigmatic beliefs.

Our study concludes that lack of insight is the highest predictive factor for nonadherence in schizophrenic patients, as it came first in order when logistic regression analysis was performed.

Similarly, a recent survey by Velligan *et al*. [40] rated poor illness insight as the most important factor contributing to nonadherence. Other researchers raised doubts about the predictive power of insight for medication adherence because results of longitudinal studies were inconsistent [23] or showed lower power of insight in the prediction of adherence [40].

We agreed with Velligan and colleagues, but there could be other mediating variables between insight and medication adherence that need to be further investigated in future studies (like concerns regarding the medications), which supports the idea of a meditational model by Beck *et al*. [57].

Conclusion
Medication nonadherence is a prevalent problem in schizophrenia. Adherence to medication is a multifactorial process. Our study examined only certain illnesses and medication-related factors that could have an influence on treatment adherence. We concluded that the major drivers and risk factors for nonadherence among schizophrenic patients are the severity of illness and lack of insight. Practicing clinicians should be aware of the importance of building a good therapeutic alliance with the patient as well as integrating insight-oriented psychotherapy programs early in the treatment plan.

Strength and limitations
Although nonadherence to medications in patients with schizophrenia is a commonly encountered problem in our daily clinical practice, scanty research has been conducted to find out the main causes of nonadherence.

Our study is one of the few to assess adherence among Egyptian patients with schizophrenia using validated tools with clinician-rated assessment for adherence that has higher validity among other scales and evaluate the adherence itself; however, our study has a few limitations. First, the small sample sizes may limit the generalizability of the study. Second, the relatively short length of follow-up may have limited the ability to ascertain the long-term follow-up of adherence to medications. Third, there is a lack of objective adherence measures – for example, plasma drug concentration. Finally, the present study may not generalize to the general patient population as it is based on a convenience sample rather than an epidemiological cohort.

Further research has to be conducted on a larger sample size and follow-up patients for longer duration and investigate more variables and study various insight-mediating factors and the negative consequences of nonadherence on the patient and healthcare system.

Clinical implications
On the basis of our results we can state that medication nonadherence depends on specific psychopathological aspects of the patients' illness. Lack of insight and illness severity are the strongest predictive factors for nonadherence in patients with schizophrenia. These findings highlight the importance of addressing the problem of insight in schizophrenic patients early in their course of treatment and implementing psychoeducational programs to improve insight, such as insight-oriented psychotherapy and behavioral family therapy. Moreover, these results indicate that partially insightful and insightless patients should be monitored carefully to avoid nonadherence.

Conflicts of interest
There are no conflicts of interest.

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