# Duration of no treatment: impact on clinical picture and short-term outcome

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**Received** 6 January 2012
**Accepted** 20 March 2012

**Egyptian Journal of Psychiatry**
2013, 34:104–114

**Background**
The duration of untreated illness (DUI) represents a modifiable parameter, the reduction of which may positively influence the outcome and long-term course of related mental conditions. It has been suggested that a long duration of untreated psychosis (DUP) has a neurotoxic effect with expected consequent cognitive dysfunction.

**Aim**
The aim is to examine the clinical and cognitive effects of DUP and DUI on the 2-year clinical outcome of drug-naive patients having their first-episode psychosis.

**Patients and methods**
This prospective study was carried out at the Psychological Medicine Hospital, State of Kuwait, and consisted of two parts: (a) baseline assessment, in which all patients with first-contact psychosis were clinically and psychometrically assessed by DSM-I and SCID-I, Positive and Negative Syndrome Scale, Hamilton Depression Rating Scale, Young Mania Rating Scale, Subtests of Wechsler Memory Scale (3rd ed.), and Wechsler Adult Intelligence Scale (WAIS; 3rd ed.) and (b) end of a 2-year follow-up, in which patients who continued 2 years of follow-up were reassessed by all the clinical and psychometric studies used at baseline.

**Results**
Ninety patients were followed up, of whom 54.5% were nonaffective patients, 23.33% had bipolar psychosis, and 22.22% had depressive psychosis. In the schizophrenia spectrum, although improvement in neuropsychological and cognitive status was observed after treatment, persistent cognitive deficits and negative symptoms were still observed in clinically stable individuals. DUP was found to be related to current age, number of rehospitalizations, negative symptoms, and trail make A, and inversely related to memory subtest scores. In bipolar and depressive psychosis, DUI was significantly related to current age, rehospitalization, age at onset, and total positive symptoms. DUI also had a highly significant inverse relation to performance test and total WAIS ($P=0.000$ and 0.000) and a significant direct relation to speed and processing (trail make A) and with reasoning (trail make B) ($P=0.006$ and 0.006). After 2 years, DUI was significantly inversely related to the performance test of WAIS ($P=0.026$).

**Conclusion**
Long DUP is associated with lower levels of symptomatic and cognitive recovery. Therefore, early detection programs are required to decrease the period between illness onset, diagnosis, and treatment in first-episode psychotic patients, which could lead to improved therapeutic strategies and public health initiatives.

**Keywords:**
drug naive, duration of untreated illness, duration of untreated psychosis, first-episode psychosis

Egypt J Psychiatr 34:104–114

1110-1105

## Introduction

The duration of untreated illness (DUI) is defined as the interval between the onset of a psychiatric disorder and the administration of the first pharmacological treatment (Dell'Osso and Altamura, 2010). Many reasons pose a great deal of importance on the investigation of causes and consequences of the DUI, mainly because it represents a modifiable parameter, the reduction of which may positively influence the outcome and long-term course of related mental conditions (Altamura *et al.*, 2007).

Some authors explain this putative effect by presuming a negative effect of psychosis on a patient's brain or on

his/her psychological environment (Bottlender and Moller, 2003). However, estimation of the duration of untreated psychosis (DUP) is challenging because of the potential difficulties in dating the onset of psychosis, initiating effective treatment, and the episodic nature of active psychosis, but in most studies, DUP reflects the time from the initial onset of positive psychotic symptoms to the initiation of effective treatment (Norman and Malla, 2001).

However, it is unclear whether long DUI and/or DUP is a cause or a marker of poor outcome (Mc Glashan, 1999).

Several studies have reported longer DUP to be associated with higher levels of at least some aspects of negative or deficit symptoms at presentation for treatment (Black *et al.*, 2001; Malla *et al.*, 2002); others have found a relationship between longer DUP and higher positive symptoms (Drake *et al.*, 2000) and some investigators have found no relation between DUP and initial positive symptoms (Malla *et al.*, 2002a).

In multiple regression equations that included prodrome duration, premorbid adjustment, diagnosis, severity of drug use, and age at onset, DUI and DUP remained significant predictors of 1-year outcome scores on quality of life scale, and negative and positive symptoms (Drake *et al.*, 2000; Harrigan *et al.*, 2003), besides representing one of the first steps in planning early interventions (Dell'Osso and Altamura, 2010).

It has been suggested that a long DUP has a neurotoxic effect (Wyatt and Heuter, 2001). If such an effect exists, one can expect cognitive dysfunction (Norman *et al.*, 2001), where longer DUP was found to be related to cognitive deterioration (Amminger *et al.*, 2002), whereas shorter DUP was found to be related to performance on tasks requiring shifting attention (Joyce *et al.*, 2002). All the above data indicate a neurotoxic effect of untreated psychosis (Pantelis *et al.*, 2003).

Although several studies have examined the relationship between DUP and the general treatment response, individual symptoms have not been studied. Further, there is limited information on the time course of resolution of specific psychotic symptoms with antipsychotic treatment (Breier and Berg, 1999).

The main aim of this study is to examine the effect of DUP and DUI on the 2-year clinical outcome in drug-naive patients having their first-episode psychosis, in addition to studying their cognitive function at first contact.

## Patients and methods

This prospective study was carried out at the Psychological Medicine Hospital, State of Kuwait, which is a government hospital and is the only one providing psychiatric services at a tertiary level. Written consent was obtained from each participant and/or his family after approval of the research from the ethics review board.

The study has two parts:

(1) Baseline assessment:
   (a) All patients with first-contact psychosis and admitted during the duration between January 2008 and December 2009 were assessed by clinical interviews and psychometric scales.
(2) End of a 2-year follow-up:
   (a) Patients who continued 2 years of follow-up were reassessed by all the clinical and psychometric scales used at baseline. The study was complete by the end of the year 2011.

### Inclusion criteria

The researchers screened drug-naive patients of both sexes between 18 and 65 years of age with first-episode psychosis, who had not visited any psychiatric facility before being admitted to the psychiatric hospital. Those who were treated by traditional healers were included. In order to avoid the impact of cultural differences and to facilitate reach for follow-up, only Kuwaiti patients were included.

### Exclusion criteria

Patients were excluded if they had any neurological disorders, mental subnormality, current major medical illness, or a history of head trauma with loss of consciousness for more than 10 min. Patients treated with electroconvulsive therapy or those with a history of/or current substance abuse or dependence were also excluded.

### Procedure

At the end of the recruitment period, we had 176 patients with first-episode psychosis, of whom only 139 were Kuwaiti. However, 18 of them did not fulfill the inclusion criteria and 11 refused to participate in the study. Thus, 110 patients completed the baseline study, although only 90 patients were available on follow-up and continued throughout the entire study.

Consensus diagnoses were determined by members from the clinical and research team using the Structured Clinical Interview of DSM-IV (First *et al.*, 1995), and all available collateral information was obtained either from families and/or from previous caregivers, medical records, or information provided by the clinical and research team. This information generally included not only initial symptoms but also information over the course of 6–8 weeks of initial treatment. Also, repeated assessments were performed on clinical bases every 6 months or at times of rehospitalization.

#### *DUP*

DUP was defined as the number of weeks between the first expression of psychosis and study recruitment.

#### *DUI*

DUI was defined as the number of weeks between the start of any behavioral change and/or pathological change and the start of study recruitment.

### Tools

To maximize cooperation, patients were asked to complete the following neurocognitive tests when psychotic symptoms showed remission. This was recorded as the duration of treatment stability.

(1) The Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1986): The PANSS is used for rating the symptoms of patients. It includes 30 items on three subscales: seven items covering positive symptoms, seven covering negative symptoms, and 16 covering general psychopathology. Each item is scored on a seven-point item-specific scale ranging from 1 to 7; thus, the positive and negative subscales each range from 7 to 49, and the general psychopathology scale ranges from 16 to 112. It is a standard tool for assessing clinical outcome in treatment studies of psychotic disorders and is useful for tracking severity in clinical practice.
(2) Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960): The HDRS measures the severity of depressive symptoms in patients with primary depressive symptoms. It is a checklist of 17 items that are ranked on a scale of 0–4 or 0–2. Scoring: very severe, that is, greater than 23, severe 19–22, moderate 14–18, mild 8–13, and normal, that is, less than 7.
(3) Young Mania Rating Scale (YMRS) (Young *et al.*, 1978): The YMRS consists of 11 items on the basis of the patient's subjective report over the last 48 h, as well as clinical observations. Given a rating of severity, four of the items are graded on a 0–8 scale and seven on a 0–4 scale. Typical YMRS baseline scores are variable depending on the patients' clinical features such as mania (YMRS = 12), depression (YMRS = 3), or euthymia (YMRS = 2). The scale is generally administered by a clinician or other trained rater and takes 15–30 min to complete.

#### *Cognitive assessment*

Cognitive assessment was performed using a standardized cognitive battery, which was completed by all participants. It was carried out and scored by a trained member of the research team who was not involved in the patients' treatment both at baseline assessment and at the end of the 2-year follow-up. Neurocognitive tests were divided into six cognitive domains as suggested by the National Institute of Mental Health – Measurement and Treatment Research to Improve Cognition in Schizophrenia group (Measurement and Treatment Research to Improve Cognition in Schizophrenia, 2003; Nuechterlein *et al.*, 2004).

The following domains were separated:

(1) *Working memory*: using the spatial span backward subtests of the Wechsler Memory Scale (3rd ed.) (Wechsler, 1997) and the digit span backward subtests of Wechsler Adult Intelligence Scale (WAIS) (3rd ed.) (Wechsler, 1997).
(2) *Verbal learning and memory*: from the logical memory (LM) subtest of WMS-III, including immediate (LMI), delayed (LMD), and recognition (LMR).
(3) *Visual learning and memory*: from the visual reproduction (VR) subtests of WMS-III, including immediate (VRI), delayed (VRD), and recognition (VRR).
(4) *Speed and processing*: from the trail-making test A (completion time) (Reitan, 1992) and the digit symbol subtest of WAIS-III.
(5) *Reasoning and problem solving*: from the trail-making test B and block design subtest of WAIS-III.
(6) *Attention*: from the spatial span and digit span forward subtest of WAIS-III.
(7) *Intellectual ability*: using the two-subtest version of WAIS-III (verbal and performance subtests). It was measured both at baseline and at the follow-up end stage, which is after 2 years (Wechsler, 1997).

### Statistical analysis

Data were collected, coded, and then entered into an IBM compatible computer using the SPSS version 17 (IBM Company, Armonk, New York, USA) for Windows. The data entered were checked for accuracy and then for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests, and found to be normally distributed. Qualitative variables were expressed as number and percentage, whereas quantitative variables were expressed as median, mean ($\overline{X}$), and SD.

The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, whereas the SD was used as a measure of dispersion.

The arithmetic mean and the median were used as measures of central tendency, whereas the SD was used as a measure of dispersion.

The percent change was computed to express the change in the repeated variables as a percentage.

The following statistical tests were used:

(1) An independent-samples *t*-test was used as a parametric test of significance for comparison between two sample means, after carrying out Levene's test for equality of variances.
(2) Independent-samples Mann–Whitney's *U*-test (or *Z*-test) was used as a nonparametric test of significance for comparison between two sample medians.
(3) The $\chi^2$-test (or likelihood ratio) was used as a nonparametric test of significance for comparison between the distribution of two qualitative variables.
(4) Fisher's exact test was used as a nonparametric test of significance for comparison between the distribution of two qualitative variables whenever the $\chi^2$-test was not appropriate. It yields a *P*-value directly.
(5) A paired-samples *t*-test was used as a parametric test of significance for comparison between before and after values of a quantitative variable.
(6) The Wilcoxon signed-rank test (*Z*-value) was used as a nonparametric test of significance for comparison between before and after values of a qualitative or an ordinal variable when the paired *t*-test was not appropriate.

(7) The McNemar's $\chi^2$-test was used for a paired comparison of dichotomous variables.
(8) The Mann–Whitney *U*-test (*Z*-test) was used as a nonparametric test of significance for comparison between two sample means when the independent *t*-test was not appropriate.
(9) The one-way analysis of variance (*F*-test) was used as a parametric test of significance for comparison between more than two sample means using either Scheffe's or Tamhane's post-hoc tests for paired comparison according to the results of homogeneity testing.
(10) The Kruskal–Wallis test ($\chi^2$-value) was used as a nonparametric test of significance for one-way comparison between more than two sample means when the one-way analysis of variance test was not appropriate.
(11) The Pearson's correlation coefficient (*r*) was used as a parametric measure of the mutual relationship between two normally distributed quantitative variables.
(12) The Spearman's rank correlation coefficient (*r*) was used as a nonparametric measure of the mutual relationship between two non-normally distributed quantitative or ordinal variables.

## Results

### Sociodemographic and clinical characteristics

As shown in Table 1 and Figs 1–4, statistical analysis of the 90 patients included in our study showed that 49 patients (54.5%) had a diagnosis of the schizophrenia spectrum, which includes schizophrenia and schizoaffective disorders (the nonaffective group = group A), 21 patients (23.33%) had bipolar psychosis (manic and mixed states) (group B), and the other 20 patients (22.22%) had depressive psychosis (group C), of whom the majority of schizophrenia and bipolar mood disorders were in men (79.59 and 57.14%, respectively).

In terms of marital status, most of the patients with schizophrenia and bipolar psychosis were single (79.59 and 47.62%, respectively), compared with only 30% of the patients with depressive psychosis.

In terms of the level of education, surprisingly, 48.98% of patients in the nonaffective group had university education compared with only 33.33 and 35% of bipolar psychosis and depressive psychosis patients, respectively. However, 33.33% of the bipolar psychosis patients were not working compared with 8.16 and 30% of the nonaffective and depressive psychosis patients, respectively.

Interestingly, most of our sample had a negative family history to the psychiatric illness, as shown in Table 1.

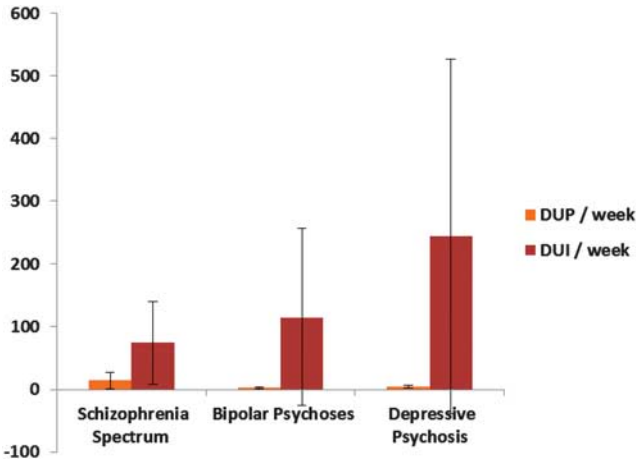
In terms of their antipsychotic treatment, Table 1 shows that 55 and 45% of patients with depressive psychosis received quetiapine and olanzapine, respectively, whereas patients with schizophrenia and those with bipolar psychosis received multiple different antipsychotics.

**Table 1 Sociodemographics of the patients included in the study**

| | Diagnosis [*N* (%)] | | |
|---|---|---|---|
| Items | Schizophrenia | BMD | MDD |
| Total number | 49 (54.5) | 21 (23.33) | 20 (22.22) |
| Sex | | | |
| Male | 39 (79.59) | 12 (57.14) | 10 (50) |
| Female | 10 (21.41) | 9 (43.16) | 10 (50) |
| Marital status | | | |
| Married | 7 (14.29) | 5 (23.81) | 8 (40) |
| Single | 39 (79.59) | 10 (47.62) | 6 (30) |
| Divorced | 3 (6.125) | 6 (28.57) | 8 (40) |
| Education | | | |
| Primary school | 6 (12.24) | 5 (23.81) | 2 (10) |
| Secondary school | 16 (32.65) | 8 (38.10) | 10 (50) |
| University/undergraduate | 24 (48.98) | 7 (33.33) | 7 (35) |
| Postgraduate | 3 (6.12) | 1 (4.76) | 1 (5) |
| Occupation | | | |
| Student | 30 (61.22) | 4 (19.05) | 3 (15) |
| Nonmanual work | 4 (8.16) | 4 (19.05) | 6 (30) |
| Manual work/housewife/ military | 11 (22.45) | 6 (28.57) | 5 (25) |
| Not working | 4 (8.16) | 7 (33.33) | 6 (30) |
| Family history | | | |
| Negative | 35 (71.43) | 16 (76.19) | 15 (75) |
| Positive | 14 (28.57) | 5 (23.81) | 5 (25) |
| Type of antipsychotic | | | |
| Risperidone | 13 (26.53) | 3 (14.29) | 0 (0) |
| Olanzapine | 16 (32.65) | 8 (38.10) | 9 (45) |
| Quetiapine | 13 (26.53) | 7 (33.33) | 11 (55) |
| Haloperidol | 6 (12.24) | 2 (9.52) | 0 (0) |
| Sulpiride | 1 (2.04) | 1 (4.76) | 0 (0) |

BMD, bipolar mood disorder; MDD, major depressive disorder.

**Figure 1**

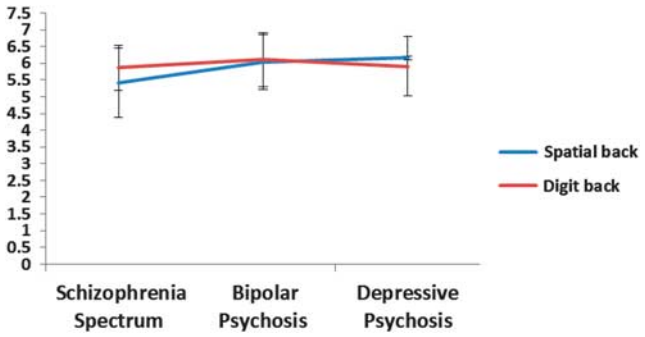



Comparison of duration of untreated psychosis (DUP) and duration of untreated illness (DUI) of different diagnostic groups.

As shown in Table 2, DUI was significantly longer in depressed and bipolar patients compared with schizophrenia spectrum patients ($P = 0.000$), but DUP was longer in schizophrenia patients, indicating that families can tolerate or may not detect affective symptoms as early as psychosis.

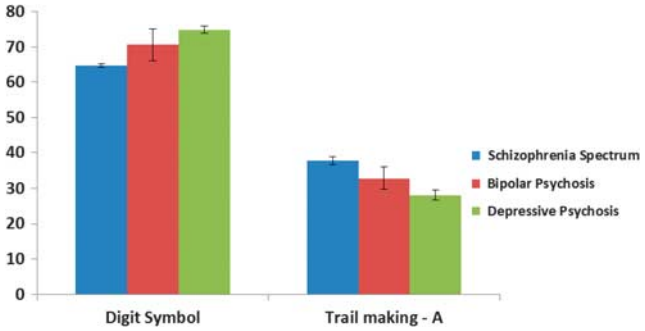
Drug-naive patients with first-episode psychosis showed a mixture of psychotic as well as affective symptoms at first contact, although they all showed improvement

**Figure 2**



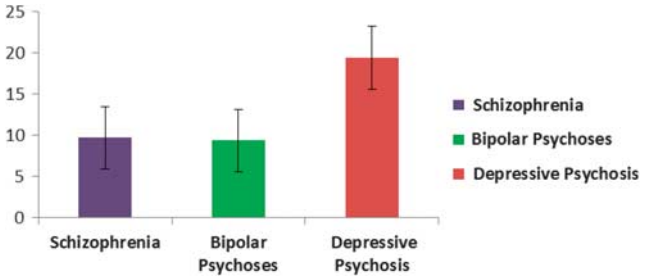

Comparison of working memory for different diagnostic patient groups of first-episode psychosis at baseline assessment.

**Figure 3**




Comparison of speed and processing for different diagnostic patient groups of first-episode psychosis at baseline assessment.

**Figure 4**




Hamilton Depression Rating Scale in different diagnoses of first-episode psychosis at baseline assessment.

after treatment; yet, some persistent negative as well as affective symptoms still remained on follow-up (Table 3).

As evident in Table 4, study of the relation between each of the age of onset of illness, current age, number of rehospitalizations, doses of antipsychotic received equivalent to chlorpromazine, and duration of illness to each of the DUP and DUI in all patients included in the study showed that in patients in group A, their current age was significantly related to the DUP ($P = 0.014$) and highly significant in relation to the DUI ($P = 0.000$). Also, rehospitalization was highly significant with DUP ($P = 0.000$) and significant with DUI ($P = 0.031$), whereas the duration of illness was only significantly related to the DUP ($P = 0.060$).

In patients with bipolar psychosis (group B), the DUI was highly significant with each of their current age and rehospitalization, and significantly related to their age at onset ($P = 0.000$, 0.000, and 0.002, respectively), as shown in Table 4.

Similarly, patients with depressive psychosis (group C) showed a highly significant relation with DUI in terms of their current age and rehospitalization, and a highly significant relation in terms of their age at onset ($P = 0.000$, 0.000, and 0.010, respectively), as in Table 4.

### Clinical features and schizophrenia

Younger age, early age at onset, and longer DUP were clear in schizophrenia spectrum patients than bipolar or depressive psychosis (Table 2).

In terms of the correlation between both DUP and DUI, and the clinical features of patients with schizophrenia, no significant statistical relation was found between the total scores of the HDRS, YMRS, or PANSS scale, and DUI/DUP, except for the scores of the negative subtest of PANSS at baseline, which was significantly positively related to the DUP ($P = 0.002$). In addition, there were inverse relations between both the YMRS score and the positive PANSS score (PP-T) at baseline and DUP. Another inverse relation was observed between the scores of HDRS, YMRS, PP-T, and G psych-T scores at baseline and the DUI; however, none had a statistical significance.

The percent change in all clinical scores was not related to either DUP or DUI, except for the negative subtest scores of PANSS, which was found to be related to DUP ($P = 0.012$), as shown in Table 5.

**Table 2 Characteristics of first-episode psychosis patients with different diagnostic outcomes**

| | Schizophrenia spectrum ($n=49$) | | Bipolar psychoses ($n=21$) | | Depressive psychosis ($n=20$) | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | *P* |
| Current age (years) | 21.84 | 2.88 | 25.38 | 4.41 | 30.60 | 8.56 | 0.000 |
| Age at onset (years) | 20.55 | 2.19 | 23.38 | 2.09 | 25.95 | 4.20 | 0.000 |
| Number of rehospitalizations (2 years) | 1.47 | 1.24 | 1.19 | 1.63 | 4.45 | 5.02 | 0.000 |
| Duration of untreated illness (week) | 74.33 | 65.89 | 115.10 | 140.49 | 243.60 | 282.87 | 0.000 |
| Duration of untreated psychosis (week) | 14.45 | 13.31 | 2.33 | 0.91 | 4.40 | 2.33 | 0.000 |
| Duration of treatment stability (day) | 12.00 | 3.70 | 8.81 | 2.34 | 7.85 | 1.84 | 0.000 |
| Chlorpromazine equivalent dose (mg) | 251.84 | 175.16 | 276.67 | 73.37 | 288.50 | 46.34 | 0.000 |

**Table 3 Scores of HDRS, YMRS, and PANSS among the three different diagnoses at baseline and follow-up**

| | Schizophrenia spectrum ($n=49$) | | | Bipolar psychosis ($n=21$) | | | Depressive psychosis ($n=20$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline (mean ± SD) | End of 2 years (mean ± SD) | *P* | Baseline (mean ± SD) | End of 2 years (mean ± SD) | *P* | Baseline (mean ± SD) | End of 2 years (mean ± SD) | *P* |
| Total HDRS scores | 9.67 ± 3.51 | 4.33 ± 1.64 | 0.00 | 9.38 ± 2.46 | 3.57 ± 1.63 | 0.00 | 19.40 ± 3.79 | 10.25 ± 3.37 | 0.00 |
| Total scores of YMRS | 19.63 ± 8.07 | 6.27 ± 2.7 | 0.00 | 46.38 ± 5.72 | 10.62 ± 2.9 | 0.00 | 6.50 ± 3.10 | 3.40 ± 1.73 | 0.00 |
| Total PANSS scores | 108.80 ± 13.12 | 52.35 ± 11.95 | 0.00 | 106.52 ± 13.47 | 39.57 ± 4.04 | 0.00 | 58.70 ± 8.55 | 36.60 ± 6.24 | 0.00 |
| Positive | 27.22 ± 7.46 | 10.04 ± 3.61 | 0.00 | 35.29 ± 4.11 | 10.33 ± 2.96 | 0.00 | 8.76 ± 0.88 | 7.55 ± 0.51 | 0.00 |
| Negative | 26.98 ± 6.79 | 17.41 ± 9.36 | 0.00 | 17.71 ± 5.12 | 7.71 ± 0.90 | 0.00 | 17.40 ± 1.82 | 9.85 ± 1.63 | 0.00 |
| General psychopathology | 54.63 ± 8.75 | 24.73 ± 5.00 | 0.00 | 53.52 ± 5.74 | 21.43 ± 1.75 | 0.00 | 40.40 ± 6.13 | 26.00 ± 4.44 | 0.00 |

HDRS, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

### Cognitive functions and schizophrenia patients

Our findings indicated that the baseline mean scores for most of the cognitive tests were significantly lower in schizophrenia patients than the other two groups of patients.

A correlation study between cognitive functions (at baseline) and DUP showed that memory scores in general were found to be inversely related to DUP; this was reflected by the scores of the spatial back, digit back, LMI, LMR, and verbal tests ($P = 0.004$, 0.005, 0.005, 0.025, and 0.008, respectively). Meanwhile, only the trail-making test – part A showed a significant direct relation to the DUP ($P = 0.024$), reflecting worse speed of information processing in schizophrenia patients with longer DUP.

Only the verbal and LMD tests were significantly inversely related to the DUI ($P = 0.019$ and 0.045, respectively) (Table 6).

On follow-up, the cognitive functions of schizophrenia patients were considerably improved compared with bipolar patients.

In terms of the 2-year percent change of the cognitive functions, there was a statistically nonsignificant inverse relation between the DUP and the scores of cognitive tests, (Table 6). The inverse relation was significant only for the block design test ($P = 0.025$). Similarly, there was an inverse relation between DUI and most of the cognitive function scores, but none of them reached a significant level (Table 6).

### Clinical features of patients with bipolar psychosis

At initial assessment, patients with bipolar psychosis had significantly higher scores on the YMRS and positive subscale of PANSS compared with the other two groups of patients ($P = 0.00$ and 0.001, respectively).

The correlation between the clinical features of the bipolar disorder patients in relation to the DUP and DUI at baseline and percent change showed no statistical significance, except for the PP-T, whose percent change had a direct relation with both DUP and DUI ($P = 0.004$ and 0.04, respectively), as shown in Table 7.

### Cognitive functions of patients with bipolar psychosis

At baseline, a significant inverse relationship was observed between VVR and DUP ($P = 0.01$) (Table 8). After 2 years of studying the percent change, an inverse significant relation between DUP and visual memory (VRD and VRR), speed of processing (digit symbol), as well as total WAIS scores was found (Table 8).

However, none of the cognitive function tests showed a statistically significant relation with the DUI, either at baseline or a significant percent change, except the spatial S-F test, which was significantly inversely changed ($P = 0.053$).

### Clinical features of patients with depressive psychosis

DUI had a significant direct relation with all clinical test scores at baseline, indicating worsening of all symptoms

**Table 4 Correlation between current age, onset age, rehospitalization, duration of illness, and dose of antipsychotic**

| | Schizophrenia | BMD | MDD |
|---|---|---|---|
| Current age | | | |
| DUP | | | |
| *r* | 0.347 | 0.203 | 0.087 |
| *P* | 0.014 (sig) | 0.378 | 0.721 |
| DUI | | | |
| *r* | 0.626 | 0.934 | 0.913 |
| *P* | 0.000 (sig) | 0.000 (sig) | 0.000 (sig.) |
| Age at onset | | | |
| DUP | | | |
| *r* | −0.002 | 0.166 | 0.072 |
| *P* | 0.988 | 0.471 | 0.762 |
| DUI | | | |
| *r* | 0.172 | 0.635 | −0.560 |
| *P* | 0.237 | 0.002 (sig) | 0.010 (sig) |
| Rehospitalization | | | |
| DUP | | | |
| *r* | 0.494 | 0.392 | 0.020 |
| *P* | 0.000 (sig) | 0.079 | 0.934 |
| DUI | | | |
| *r* | 0.309 | 0.870 | 0.919 |
| *P* | 0.031 (sig) | 0.000 (sig) | 0.000 (sig) |
| Dose chlorpromazine equivalent | | | |
| DUP | | | |
| *r* | 0.050 | −0.095 | −0.307 |
| *P* | 0.735 | 0.683 | 0.189 |
| DUI | | | |
| *r* | 0.018 | −0.166 | 0.350 |
| *P* | 0.901 | 0.473 | 0.130 |
| Duration of illness | | | |
| DUP | | | |
| *r* | 0.271 | 0.195 | 0.408 |
| *P* | 0.060 (sig) | 0.396 | 0.074 |
| DUI | | | |
| *r* | 0.067 | 0.118 | −0.176 |
| *P* | 0.647 | 0.610 | 0.457 |

BMD, bipolar mood disorder; DUI, duration of untreated illness; DUP, duration of untreated psychosis.MDD, major depressive disorder; *r*, Pearson's correlation coefficient; sig, significant.

**Table 5 Correlation between clinical features and both DUP and DUI in patients with schizophrenia disorder ($n=49$)**

| | DUP | | DUI | |
|---|---|---|---|---|
| Clinical features | Baseline | Percentage change | Baseline | Percentage change |
| HDRS-T | | | | |
| *r* | 0.140 | −0.086 | −0.048 | 0.118 |
| *P* | 0.339 | 0.559 | 0.743 | 0.418 |
| YMRS-T | | | | |
| *r* | −0.197 | 0.052 | −0.152 | 0.094 |
| *P* | 0.175 | 0.724 | 0.297 | 0.522 |
| PP-T | | | | |
| *r* | −0.219 | −0.024 | −0.154 | 0.141 |
| *P* | 0.130 | 0.872 | 0.290 | 0.333 |
| NP-T | | | | |
| *r* | 0.429 | 0.358 | 0.233 | 0.043 |
| *P* | 0.002 (sig) | 0.012 (sig) | 0.107 | 0.767 |
| G psych-T | | | | |
| *r* | 0.224 | −0.056 | −0.011 | 0.106 |
| *P* | 0.122 | 0.704 | 0.942 | 0.468 |
| PANSS-T | | | | |
| *r* | 0.255 | 0.163 | 0.049 | 0.121 |
| *P* | 0.077 | 0.262 | 0.737 | 0.406 |

DUI, duration of untreated illness, DUP, duration of untreated psychosis; G psych total, total score of general psychopathology of PANSS; HDRS-T, total score of Hamilton Depression Rating Scale; NP-T, total score of negative PANSS; PANSS-T, total score of Positive and Negative Syndrome Scale, PP-T, total score of positive PANSS; *r*, Pearson's correlation coefficient; sig, significant; YMRS-T, total score of Young Mania Rating scale.

with longer durations of DUI. For the HDRS, it had an inverse relation with DUI at baseline ($P=0.03$) (Table 9).

No significant relation was found between any of the clinical features and the DUP, either at baseline or in the percent change.

### Cognitive functions of patients with depressive psychosis

No relation was observed between cognitive functions of patients with depressive psychosis and DUP at either baseline or after 2 years, except for the performance test of WAIS, which showed a significant inverse percent change ($P=0.005$).

In terms of the DUI after 2 years (the recent change), the spatial back test, the performance subtest, and the total score of WAIS tests had a significant inverse relation with DUI ($P=0.014$, 0.000, and 0.000, respectively), whereas the trail make A and trail make B tests showed a direct significant relation ($P=0.008$ and 0.006, respectively), indicating worsening of these cognitive domains with longer DUI, as shown in Table 10.

**Table 6 Correlation between cognitive functions of patients with schizophrenia in relation to DUP and DUI**

| | DUP | | DUI | |
|---|---|---|---|---|
| Cognitive tests | Baseline | Percent change | Baseline | Percent change |
| Working memory | | | | |
| Spatial back | | | | |
| *r* | −0.406 | −0.146 | −0.251 | −0.20 |
| *P* | 0.004 (sig) | 0.318 | 0.082 | 0.893 |
| Digital back | | | | |
| *r* | −0.395 | −0.006 | −0.081 | 0.059 |
| *P* | 0.005 (sig) | 0.966 | 0.578 | 0.686 |
| Verbal learning and memory | | | | |
| LMI | | | | |
| *r* | −0.397 | −0.065 | −0.256 | −0.015 |
| *P* | 0.005 (sig) | 0.659 | 0.262 | 0.916 |
| LMD | | | | |
| *r* | −0.365 | −0.201 | −0.180 | −0.130 |
| *P* | 0.010 (sig) | 0.166 | 0.2217 | 0.372 |
| LMR | | | | |
| *r* | −0.320 | −0.151 | −0.287 | −0.065 |
| *P* | 0.025 (sig) | 0.301 | 0.045 (sig) | 0.656 |
| Visual learning and memory | | | | |
| VRI | | | | |
| *r* | 0.041 | −0.079 | 0.098 | −0.113 |
| *P* | 0.781 | 0.598 | 0.504 | 0.441 |
| VRD | | | | |
| *r* | −0.067 | −0.150 | −0.075 | −0.143 |
| *P* | 0.648 | 0.304 | 0.616 | 0.327 |
| VRR | | | | |
| *r* | −0.057 | −0.186 | 0.038 | 0.010 |
| *P* | 0.697 | 0.201 | 0.796 | 0.946 |
| Attention | | | | |
| Spatial span forward | | | | |
| *r* | −0.216 | −0.017 | −0.170 | 0.059 |
| *P* | 0.697 | 0.907 | 0.242 | 0.686 |
| Digital span forward | | | | |
| *r* | −0.027 | −0.167 | 0.034 | −0.113 |
| *P* | 0.853 | 0.251 | 0.815 | 0.438 |
| Reasoning and problem solving | | | | |
| Block design | | | | |
| *r* | 0.040 | −0.321 | −0.105 | −0.125 |
| *P* | 0.786 | 0.025 (sig) | 0.472 | 0.392 |
| Trail make B | | | | |
| *r* | 0.279 | −0.127 | −0.036 | 0.068 |
| *P* | 0.052 | 0.385 | 0.805 | 0.643 |
| Intellectual ability WAIS | | | | |
| Verbal | | | | |
| *r* | −0.377 | −0.020 | −0.344 | 0.064 |
| *P* | 0.008 (sig) | 0.892 | 0.019 (sig) | 0.662 |
| Performance | | | | |
| *r* | −0.112 | −0.157 | −0.094 | −0.025 |
| *P* | 0.446 | 0.283 | 0.519 | 0.864 |
| WAIS total | | | | |
| *r* | −0.153 | −0.197 | −0.082 | −0.176 |
| *P* | 0.295 | 0.175 | 0.575 | 0.228 |
| Speed and processing | | | | |
| Trail make A | | | | |
| *r* | 0.323 | 0.110 | 0.005 | 0.172 |
| *P* | 0.024 (sig) | 0.453 | 0.973 | 0.238 |
| Digit symbol | | | | |
| *r* | −0.100 | −0.254 | −0.182 | −0.111 |
| *P* | 0.493 | NS | 0.211 | 0.447 |

DUI, duration of untreated illness; DUP, duration of untreated psychosis; LMD, logical memory delayed; LMI, logical memory immediate; LMR, logical memory recall; *r*, Pearson's correlation coefficient; sig, significant; VRD, visual reproduction delayed recall; VRI, visual reproduction immediate recall; VRR, visual reproduction recognition; WAIS, Wechsler Adult Intelligence Scale.

## Discussion

### Descriptive data of the sample

Of the 90 patients enrolled in the study, 49 had schizophrenia/schizoaffective disorder, group A, 21 had bipolar psychotic disorder, group B, and 20 had depressive psychosis, group C. Majority of the patients in group A had a university education, whereas most of the patients in groups B and C had only a secondary education. A possible explanation for this finding is that affective patients had a long mean duration of untreated or even undiagnosed illness extending for 4–5 years before seeking treatment at our facility. Affective illnesses especially depression may demotivate patients from

**Table 7 Correlation between the clinical features of patients with BMD and both DUP and DUI**

| | DUP | | DUI | |
|---|---|---|---|---|
| Clinical features | Baseline | Percent change | Baseline | Percent change |
| HDRS-T | | | | |
| *r* | 0.097 | −0.194 | 0.135 | −0.248 |
| *P* | o.677 | 0.399 | 0.559 | 0.279 |
| YMRS-T | | | | |
| *r* | −0.236 | −0.004 | 0.043 | 0.120 |
| *P* | 0.303 | 0.985 | 0.853 | 0.605 |
| PP-T | | | | |
| *r* | −0.160 | 0.604 | −0.029 | 0.452 |
| *P* | 0.489 | 0.004 (sig) | 0.899 | 0.040 (sig) |
| NP-T | | | | |
| *r* | 0.193 | −0.089 | 0.110 | −0.164 |
| *P* | 0.403 | 0.702 | 0.635 | 0.476 |
| G psych-T | | | | |
| *r* | −0.178 | 0.260 | 0.068 | 0.157 |
| *P* | 0.440 | 0.239 | 0.770 | 0.489 |
| PANSS-T | | | | |
| *r* | −0.052 | 0.396 | 0.062 | 0.252 |
| *P* | 0.824 | 0.075 | 0.790 | 0.271 |

BMD, bipolar mood disorder; DUI, duration of untreated illness; DUP, duration of untreated psychosis; G psych-T, total score of general psychopathology of PANSS; HDRS-T, total score of Hamilton Depression Rating Scale; NP-T, total score of negative PANSS; PANSS-T, total score of Positive and Negative Syndrome Scale; PP-T, total score of positive PANSS; *r*, Pearson's correlation coefficient; sig, significant; YMRS-T, total score of Young Mania Rating Scale.

continuing their education. Similarly, 61.22% of the patients in group A were students, whereas 33.33% of the patients in group B were not working, and 30% of the patients in group C were either not working or had nonmanual jobs.

### Age of onset and rehospitalization in relation to DUI and DUP

It is well known that timely interventions with early-onset cases might help reduce the severity persistence of primary disorders, prevent or delay the onset of secondary disorders, or reduce severity persistence of secondary disorders (Amminger *et al.*, 2006). Determining the age of onset was therefore very important in our study, and it was found to be in accordance with other studies showing a positive correlation between long DUI and DUP and early onset of symptoms in the affective psychotic groups (Altamura *et al.*, 2007; Dell'Osso and Altamura, 2010).

When mentioned as a potentially modifiable prognostic factor (Perkins *et al.*, 2005), DUI was considered not only to influence response to treatment but also as reflecting a potentially malleable progressive pathological process, which is relevant to our findings in the current study, where a significance relation was found between longer DUI and DUP and higher rates of rehospitalization within 2 years of treatment, indicating more frequent relapses and severe forms of illnesses in all groups of patients in the study, as a result of their delay in the first treatment contact.

### Clinical features and their relation to DUI and DUP

Although improvements in neuropsychological and cognitive status were observed after treatment, persistent cognitive deficits and negative symptoms were still observed in clinically stable, treated individuals. The presence of cognitive deficits at first contact and their persistence after treatment may raise the possibility of neurodevelopmental origin.

**Table 8 Correlation between the cognitive features of patients with BMD and both DUP and DUI**

| | DUP | | DUI | |
|---|---|---|---|---|
| Cognitive features | Baseline | Percent change | Baseline | Percent change |
| Working memory | | | | |
| Spatial back | | | | |
| *r* | −0.236 | −0.029 | −0.269 | 0.116 |
| *P* | 0.304 | 0.902 | 0.464 | 0.615 |
| Digital back | | | | |
| *r* | −0.256 | −0.074 | −0.181 | 0.052 |
| *P* | 0.262 | 0.750 | 0.431 | 0.822 |
| Verbal learning and memory | | | | |
| LMI | | | | |
| *r* | −0.329 | −0.274 | −0.299 | −0.028 |
| *P* | 0.145 | 0.229 | 0.187 | 0.905 |
| LMD | | | | |
| *r* | 0.313 | 0.031 | −0.205 | 0.247 |
| *P* | 0.167 | 0.894 | 0.372 | 0.280 |
| LMR | | | | |
| *r* | −0.059 | −0.044 | −0.072 | 0.038 |
| *P* | 0.800 | 0.848 | 0.758 | 0.870 |
| Visual learning and memory | | | | |
| VRI | | | | |
| *r* | −0.290 | −0.264 | −0.204 | −0.134 |
| *P* | 0.202 | 0.248 | 0.374 | 0.563 |
| VRD | | | | |
| *r* | −0.360 | −0.509 | −0.361 | −0.163 |
| *P* | 0.109 | 0.019 (sig) | 0.108 | 0.479 |
| VRR | | | | |
| *r* | −0.662 | −0.541 | 0.408 | −0.163 |
| *P* | 0.001 (sig) | 0.011 (sig) | 0.066 | 0.479 |
| Attention | | | | |
| Spatial span forward | | | | |
| *r* | −0.185 | −0.160 | 0.070 | −0.427 |
| *P* | 0.421 | 0.488 | 0.762 | 0.053 (sig) |
| Digital span forward | | | | |
| *r* | −0.199 | −0.061 | 0.156 | −0.300 |
| *P* | 0.387 | 0.792 | 0.499 | 0.187 |
| Reasoning and problem solving | | | | |
| Block design | | | | |
| *r* | −0.222 | −0.278 | −0.340 | −0.096 |
| *P* | 0.333 | 0.222 | 0.131 | 0.678 |
| Trail make B | | | | |
| *r* | −0.0433 | 0.250 | −0.090 | 0.026 |
| *P* | 0.050 (sig) | 0.275 | 0.697 | 0.909 |
| Intellectual ability | | | | |
| Verbal | | | | |
| *r* | 0.016 | −0.279 | 0.029 | −0.077 |
| *P* | 0.945 | 0.220 | 0.900 | 0.740 |
| Performance | | | | |
| *r* | −0.213 | −0.402 | 0.132 | −0.276 |
| *P* | 0.355 | 0.071 | 0.570 | 0.225 |
| WAIS-T | | | | |
| *r* | −0.125 | −0.432 | 0.097 | −0.294 |
| *P* | 0.591 | 0.051 (sig) | 0.675 | 0.196 |
| Speed and processing | | | | |
| Trail make A | | | | |
| *r* | −0.278 | 0.183 | 0.022 | −0.113 |
| *P* | 0.222 | 0.426 | 0.924 | 0.626 |
| Digital symbol | | | | |
| *r* | 0.220 | −0.477 | 0.233 | 0.087 |
| *P* | 0.337 | 0.029 (sig) | 0.309 | 0.706 |

BMD, bipolar mood disorder; DUI, duration of untreated illness; DUP, duration of untreated psychosis; LMD, logical memory delayed; LMI, logical memory immediate; LMR, logical memory recall; *r*, Pearson's correlation coefficient; sig, significant; VRD, visual reproduction delayed recall; VRI, visual reproduction immediate recall; VRR, visual reproduction recognition; WAIS, Wechsler Adult Intelligence Scale.

**Table 9 Correlation between the clinical features of patients with MDD and both DUP and DUI**

| | DUP | | DUI | |
|---|---|---|---|---|
| Clinical features | Baseline | Percent change | Baseline | Percent change |
| H-T | | | | |
| *r* | −0.174 | −0.149 | −0.622 | 0.244 |
| *P* | 0.462 | 0.530 | 0.003 (sig) | 0.299 |
| Y-T | | | | |
| *r* | 0.000 | 0.007 | 0.766 | −0.041 |
| *P* | 1.000 | 0.977 | 0.000 (sig) | 0.865 |
| PP-T | | | | |
| *r* | 0.089 | −0.054 | 0.766 | −0.482 |
| *P* | 0.709 | 0.822 | 0.000 (sig) | 0.031 (sig) |
| NP-T | | | | |
| *r* | 0.022 | 0.039 | 0.804 | −0.075 |
| *P* | 0.925 | 0.872 | 0.000 (sig) | 0.754 |
| G psych-T | | | | |
| *r* | 0.084 | 0.014 | 0.819 | 0.094 |
| *P* | 0.724 | 0.954 | 0.000 (sig) | 0.694 |
| PANSS-T | | | | |
| *r* | 0.078 | 0.035 | 0.785 | 0.061 |
| *P* | 0.745 | 0.885 | 0.000 (sig) | 0.797 |

DUI, duration of untreated illness; DUP: duration of untreated psychosis; G psych-T, total score of the general psychopathology of PANSS; H-T, total score of Hamilton Depression Rating Scale; MDD, major depressive disorder; NP-T, total score of negative PANSS; PANSS-T, total score of Positive and Negative Syndrome Scale; PP-T, total score of positive PANSS; *r*, Pearson's correlation coefficient; sig, significant; Y-T, total score of Young Mania Rating Scale.

**Table 10 Correlation between the cognitive features of patients with MDD and both DUP and DUI**

| | DUP | | DUI | |
|---|---|---|---|---|
| Cognitive features | Baseline | Percent change | Baseline | Percent change |
| Working memory | | | | |
| Spatial back | | | | |
| *r* | −0.130 | 0.065 | −0.542 | −0.362 |
| *P* | 0.584 | 0.785 | 0.014 (sig) | 0.116 |
| Digit back | | | | |
| *r* | 0.120 | −0.128 | 0.127 | −0.174 |
| *P* | 0.613 | 0.592 | 0.592 | 0.464 |
| Verbal learning and memory | | | | |
| LMI | | | | |
| *r* | −0.289 | 0.063 | 0.105 | 0.091 |
| *P* | 0.217 | 0.792 | 0.661 | 0.703 |
| LMD | | | | |
| *r* | 0.089 | 0.339 | −0.392 | 0.093 |
| *P* | 0.708 | 0.144 | 0.087 | 0.697 |
| LMR | | | | |
| *r* | 0.140 | 0.302 | −0.198 | −0.312 |
| *P* | 0.557 | 0.195 | 0.404 | 0.181 |
| Visual learning and memory | | | | |
| VRI | | | | |
| *r* | 0.116 | −0.004 | −0.195 | 0.167 |
| *P* | 0.626 | 0.988 | 0.411 | 0.481 |
| VRD | | | | |
| *r* | −0.198 | 0.131 | −0.063 | −0.095 |
| *P* | 0.404 | 0.581 | 0.793 | 0.691 |
| VRR | | | | |
| *r* | −0.059 | 0.002 | −0.091 | 0.043 |
| *P* | 0.805 | 0.994 | 0.703 | 0.856 |
| Attention | | | | |
| Spatial span forward | | | | |
| *r* | 0.315 | −0.190 | −0.219 | −0.403 |
| *P* | 0.177 | 0.423 | 0.353 | 0.078 |
| Digit span forward | | | | |
| *r* | −0.068 | −0.034 | −0.166 | 0.398 |
| *P* | 0.776 | 0.887 | 0.485 | 0.082 |
| Reasoning and problem solving | | | | |
| Block design | | | | |
| *r* | −0.102 | −0.221 | −0.247 | 0.251 |
| *P* | 0.669 | 0.350 | 0.293 | 0.286 |
| Trail make B | | | | |
| *r* | 0.211 | 0.107 | 0.594 | 0.019 |
| *P* | 0.372 | 0.653 | 0.006 (sig) | 0.9366 (sig) |
| Intellectual ability | | | | |
| Verbal | | | | |
| *r* | −0.123 | 0.141 | −0.420 | 0.264 |
| *P* | 0.605 | 0.552 | 0.065 | 0.261 |
| Performance | | | | |
| *r* | 0.000 | −0.602 | −0.078 | −0.255 |
| *P* | 1.000 | 0.005 (sig) | 0.000 (sig) | 0.277 |
| WAIS-T | | | | |
| *r* | −0.077 | −0.279 | −0.827 | 0.043 |
| *P* | 0.747 | 0.234 | 0.000 (sig) | 0.858 |
| Speed and processing | | | | |
| Trail make A | | | | |
| *r* | 0.064 | 0.096 | 0.576 | −0.106 |
| *P* | 0.789 | 0.688 | 0.008 (sig) | 0.657 |
| Digital symbol | | | | |
| *r* | −0.098 | 0.019 | −0.116 | −0495 |
| *P* | 0.681 | 0.937 | 0.626 | 0.026 |

DUI, duration of untreated illness; DUP, duration of untreated psychosis; LMD, logical memory delayed; LMI, logical memory immediate; LMR, logical memory recall; MDD, major depressive disorder; *r*, Pearson's correlation coefficient; sig, significant; VRD, visual reproduction delayed recall; VRI, visual reproduction immediate recall; VRR, visual reproduction recognition; WAIS, Wechsler Adult Intelligence Scale.

An important aspect of this study was to show the relation between the various clinical features and the DUI at the first presentation, and follow this track after 2 years of treatment in order to explore how much the prognostic outcome was influenced. Accordingly, we found that in nonaffective psychotic patients (group A), negative symptoms were the only feature that was directly related to a long duration of no treatment, both at the first presentation and at the second checkpoint after 2 years, which is in agreement with previous studies reporting that the duration of initially untreated psychosis is associated with the severity of negative symptoms but not with the severity of positive symptoms or general psychopathology at the time of the initial clinical evaluation. (Craig *et al.*, 2000; Addington *et al.*, 2004; Perkins *et al.*, 2005). It seems quiet logical to find these symptoms prominent in patients with delayed onset of psychiatric treatment, unlike the positive symptoms, because this presentation can make it difficult for the patients themselves or their families to understand the nature of the patient's problems and move forward when seeking treatment (Thomas and Nandhra, 2009).

In contrast, in group B, there was no significant relation between long DUI and symptoms; however, in patients with depression (group C), the longer the DUI, the more the positive symptoms (delusions and hallucinations) as well as negative symptoms (isolation, withdrawal, decreased socializations, retardedness etc.). There was also an evident correlation between severity of illness in general and long DUI, which is a common attitude in Arab culture to come late with progressive presentation may be because of the greater social acceptance of physical complaints than of psychological complaints, which are either not taken seriously or are believed to be cured by rest or extrapraying (Okasha, 2004).

### Cognitive features in relation to the DUI and DUP

In terms of assessment of the cognitive functions at first presentation, as well documented previously, in the patients with nonaffective psychosis (group A), at their first presentation, there was a direct relation between long duration of no treatment and some cognitive impairments in working memory, verbal memory, intellectual abilities (verbal IQ), and speed and processing of information, which has long been known to be enduring and persistent features in schizophrenia and can be neurocognitive or related to social cognition (Heydebrand *et al.*, 2004).

In the current study, assessment of cognitive functions in affective patients yielded results similar to those of earlier reports of executive and memory affection of bipolar patients (Austin *et al.*, 2001; Martinez-Aran *et al.*, 2007). Our patients with bipolar psychosis had a direct relation between long DUI and impairment in their visual learning and memory, as well as problem solving and processing, whereas those with depression showed significant impairment in their working memory, reasoning, and problem solving, and some deterioration in their intellectual ability performance tests, and speed and processing. These cognitive deficits are related to the anatomy and physiology of brain function; these neuropsychological impairments reflect disruption in the anatomy and function of putative frontosubcortical neuronal pathways (Austin *et al.*, 2001), which is likely to occur after a long duration of disorder onset, especially if the pathological process was not stopped early by different curative interventions.

### Prognostic outcome

Duration of no treatment has long been reported to negatively influence the outcome of first-episode psychosis and schizophrenia in different ways, and increasing data point toward a similar conclusion in affective disorders (Dell'Osso and Altamura, 2010). Accordingly, in the current study, it was necessary to reassess our patients after a certain duration of treatment and follow-up in order to assess their outcome.

In the nonaffective psychotic group (group A), there was an evident persistence of severity of negative symptoms in those who had long DUI after 2 years of follow-up and treatment, which was mentioned earlier by Perkins *et al.* (2005) and Apiquian-Guitart *et al.* (2006). Meanwhile, those with short DUI showed improvement only in some aspects of their executive functioning (reasoning and problem solving, speed and processing, working memory, and some aspects of verbal learning and memory). However, they retained low scores in the verbal and performance parts of WAIS. In fact, there is no clear demarcating line between these recorded cognitive deficits and the existing negative symptoms. Hence, it is acknowledged that the neurobiological processes that give rise to symptomatology and cognitive dysfunction in schizophrenia are partially overlapping (Heydebrand *et al.*, 2004); thus, we cannot actually state that DUI is the only prognostic factor to which the clinical outcome of patients is directly related.

However, in terms of the clinical outcome of patients with affective psychosis (group B), who had a long DUI, the current study showed a poor outcome in their positive symptoms, on the PANSS score, after 2 years of follow-up and treatment. Similarly, they still had impairments in their attention, speed, and processing, as well as some decrease in their intellectual abilities, as evident from the low scores in the WAIS, which is in agreement with most of the data collected from the literature (Keshavan *et al.*, 2003; Harris *et al.*, 2005; Dell'Osso and Altamura, 2010; De Diego-Adeliño *et al.*, 2010).

Among the patients with depression in group C, there was a direct relation between having long DUI and persistence of cognitive impairments, where their second assessment after 2 years indicated deficits in executive functions (reasoning and problem solving, and speed and processing), besides persistence in the decreased intellectual abilities (performance IQ and total WAIS). These findings are in agreement with those of Altamural *et al.* (2007), Altamura *et al.* (2010) and De Diego-Adeliño *et al.* (2010), who reported that long DUI negatively influences the course and prognosis of depression, a fact that reflects the pre-existing anatomical changes after a long DUI (Austin *et al.*, 2001).

## Conclusion

Long DUP is associated with lower levels of symptomatic and cognitive recovery from the first psychotic episode. Being a potentially modifiable factor, understanding its relation with outcome could lead to improved therapeutic strategies and public health initiatives. Although the importance of an early pharmacological intervention in relation to a pathological onset may be variable according to the specific disorder, it is generally believed that the earlier the administration of an effective treatment, the better the outcome. Psychiatric patients often wait for many years before initiating a proper pharmacological treatment or even consulting a clinician because of the social stigma that is linked to mental disorders, as well as the lack of insight that is characteristic in major psychoses. Therefore, early detection programs are required to decrease the period between illness onset, diagnosis, and treatment in first-episode psychotic patients.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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