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Duration of untreated illness in major depressive disorder: a naturalistic study

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SUMMARY

Background: Most of the studies on the duration of untreated illness (DUI) as a possible predictor of the clinical outcome and the course have focused on the psychotic disorders. The present naturalistic study was aimed to evaluate the possible relationship between the DUI and some clinical characteristics of a sample of patients with major depressive disorder (MDD). Methods: Sixty-eight patients with MDD, according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revision (DSM-IV-TR) criteria, followed-up for 4 years, were selected, interviewed and their clinical charts reviewed. The DUI was defined as the interval between the onset of the first major depressive episode and the first adequate antidepressant treatment. The sample was divided in two groups according to a DUI ≤ 12 months (n = 45) and > 12 months (n = 23). The main demographic and clinical course variables were compared between the two groups using t-tests or chi-squared tests. Results: Patients with a DUI > 12 months were more frequently women (χ² = 4.005, p = 0.045), had an earlier onset (t = 2.515, p = 0.014), a longer duration of illness (t = 2.483, p = 0.016), a higher number of recurrences (t = 2.262, p = 0.027) and had more frequently comorbid Axis I disorders with onset later than MDD (χ² = 5.595, p = 0.05). Conclusions: These findings suggest that a longer DUI may negatively influence the clinical course of MDD. Further studies on larger samples are warranted to confirm these preliminary results.

What’s known
Little is known about the relationship between the DUI and major depressive disorder. The role of the DUI, in fact, has been traditionally investigated in psychotic disorders. Nonetheless, it may be of clinical interest to study whether and how a delayed effective treatment, i.e. a longer DUI, may influence the outcome and the course of mood disorders.

What’s new
The present study is specifically aimed to study the possible influences between a longer DUI and a worse outcome in a sample of patients with MDD recruited in two Italian centres.

Introduction

Over the last two decades, the duration of untreated illness (DUI), defined as the interval between the onset of the first psychiatric episode and the first adequate pharmacological treatment, has been increasingly investigated as a predictor of the clinical outcome and course across different psychiatric disorders. However, the majority of published studies on this issue have been focused on the possible role of the DUI on the clinical outcome and course of schizophrenia and psychotic disorders (1–6).

Recently, two studies have investigated the role of the DUI in anxiety disorders. Patients with panic disorder showed that a DUI > 12 months was associated to a worse clinical course, i.e. a more frequent comorbidity with major depression with onset later than panic disorder (7). Another study performed in patients with generalised anxiety disorder (8) showed that a shorter DUI might improve the response to pharmacological treatment with antidepressants but not with benzodiazepines.

What’s new
With respect to mood disorders, a previous study (9) reported that a delayed administration of mood stabiliser treatment in bipolar disorder was related to an increased risk of suicidal behaviour, poorer social adjustment and more frequent hospitalisations. In addition, a longer DUI has been associated with a higher frequency of comorbid substance abuse disorders with onset later than bipolar disorder (10).

In major depressive disorder (MDD), previous studies reported that a longer DUI predicted the persistence of depressive symptoms and chronicity (11,12). The present naturalistic study was aimed to evaluate the possible relationship between the DUI and some clinical characteristics of a sample of patients with MDD.

Methods

The sample studied included 68 patients diagnosed as affected by MDD, according to DSM-IV criteria (13) as confirmed by the administration of a...
structured clinical interview based on DSM-IV criteria (SCID-I), (14). All patients with a diagnosis of MDD seen and followed-up in two centres between 2002 and 2006 were selected: the Mood Disorders Unit of the ‘Luigi Sacco’ Hospital within the University Department of Psychiatry of Milan and the ‘Santa Chiara’ Hospital within the University Department of Psychiatry of Pisa. Patients with complete clinical charts for the 4-year follow-up period were included in the study. Diagnostic interviews and review of the clinical charts available were administered by trained psychiatrists and the diagnoses were made according to the best estimate procedure.

For the purpose of this study, patients were divided into two groups: with DUI ≤ 12 months (n = 45) and with DUI > 12 months (n = 23). The DUI was defined as the interval between the onset of the first major depressive episode and the first antidepressant treatment that patients had received at recommended doses and for at least 4 weeks according to the currently available guidelines (15). Patients who had undergone psychotherapeutic intervention of any kind aimed at treating depressive episodes were excluded from the study. All patients had given their informed consent for being interviewed and for having reviewed all the clinical information included in the clinical charts.

The main demographic and clinical variables of the sample were collected during clinical interviews with the patients and the available relatives, and also reviewing the diagnostic interview data (SCID-I) and all the clinical charts available. The variables collected were: gender, age, age at onset, age at the time of the first adequate antidepressant treatment, duration of illness, DUI, family history for mood disorders in first-degree relatives, comorbidity with onset before and after the onset of MDD. In addition, the number of recurrences, the number of hospitalisations and the number of suicide attempts during the observation period of 4 years were collected.

The main demographic and clinical variables were computed and compared between the two groups defined by the DUI. Student’s t-test was used for the continuous variables and chi-squared test was used for the dichotomous ones. For all statistical analyses, the alpha level of significance was set at 0.05, and was not adjusted. All statistical analyses were performed using the SPSS for Windows software (version 14.0; SPSS Inc., Chicago, IL, USA).

Results

With regard to demographic variables, the group with a DUI > 12 months had a higher prevalence of women (χ² = 4.005, p = 0.045). With respect to clinical variables, the significant differences were found between the two groups: patients with a DUI > 12 months presented an earlier onset (t = 2.515, p = 0.014), a longer duration of illness (t = 2.483, p = 0.016) and a higher number of recurrences (t = 2.262, p < 0.027) in the 4-year follow-up observation period. They also had more frequently comorbid axis I disorders with onset later than MDD (χ² = 5.595, p = 0.05).

In addition, the group with a longer DUI showed a higher number of hospitalisations and suicide attempts in the observation period, even though these differences did not reach statistical significance (Table 1).

Discussion

The fact that a delayed effective treatment may negatively influence the clinical course of a specific disorder is a common sense observation. Nonetheless, relatively little is known about the extent to which

| Table 1 Demographic and clinical variables in the total sample and in the two subgroups of patients |
|---------------------------------|---------------------|---------------------|
| Variables                       | DUI ≤ 12 months (n = 45) | DUI > 12 months (n = 23) |
|---------------------------------|---------------------|---------------------|
| Gender                          |                     |                     |
| Males                           | 21                  | 5                   |
| Females                         | 24                  | 18                  |
| Age (years)                     | 46.33 (±13.98)      | 41.30 (±16.12)      |
| Age at onset (years)            | 41.80 (±15.14)      | 32.13 (±14.72)*     |
| Duration of illness (months)    | 52.11 (±76.79)      | 105.30 (±95.76)**   |
| Number of recurrences†          | 1.24 (±1.60)        | 2.17 (±1.61)***     |
| Number of hospitalisations†     | 0.31 (±0.63)        | 0.65 (±1.23)        |
| Number of suicide attempts†     | 0.20 (±0.70)        | 0.39 (±0.89)        |
| Major depressive disorder       | 15                  | 8                   |
| Bipolar disorder                | 4                   | 1                   |
| Anxiety disorders               | 4                   | 2                   |
| Psychotic disorders             | 1                   | 0                   |
| Suicide                         | 1                   | 0                   |
| Substance abuse                 | 1                   | 2                   |

Standard deviations are shown in parentheses. *Student’s t-test: t = 2.52, p = 0.014. †Events occurring during the 4-year follow-up period. **Student’s t-test: t = 2.48, p = 0.016. ***Student’s t-test: t = 2.26, p = 0.027. DUI, duration of untreated illness.
delays until beginning appropriate treatment may influence the clinical course, morbidity and mortality of psychiatric disorders, particularly of MDD.

To our knowledge, this is the first study investigating the impact of the DUI on the long-term course of major depression. In fact, other studies have focused mainly on the effect of the DUI on the antidepressant response and/or on the course of the index episode (11,12).

Results from this study suggest a negative influence of a longer DUI on the clinical course of MDD. Patients with a longer DUI have a longer duration of illness, a higher number of recurrences and more frequent comorbid axis I disorders with onset later than MDD. With respect to this last association, several studies, but not all, have pointed out that comorbidity may worsen the clinical course of MDD both in the short- and medium-term (16–18). The reasons for this association are not clarified yet.

It may be hypothesised that in MDD, as well as in schizophrenia, a delayed treatment may have a negative effect on specific brain areas. Some studies performed on schizophrenia patients have suggested that there would be a neurodegenerative process active during the acute psychotic phase of the illness. Thus, that the longer is the untreated psychotic phase, the more severe is the damage to brain structures (19–21).

On the other hand, the occurrence of plastic modifications in specific brain areas during the course of the illness has been reported as a possible consequence of repeated episodes of MDD (22). In our sample, a longer DUI was significantly associated with a higher number of recurrences. Thus, it would be difficult to identify which variable is the one that actually affect the course of the illness and its biological correlates. In addition, the administration of antidepressants may reverse these modifications as suggested by experimental models (23). However, the hypothesis that a worse clinical course in MDD is related to a delayed treatment as a consequence of a longer negative effect of the illness on brain structures is still controversial.

In our sample, patients with a longer DUI presented an earlier onset of illness. Previous studies reported that an earlier age at onset was associated with a history of suicide attempts (24) and predicted delayed onset of remission (25) in patients with mood disorders. Given the observed relationship between a longer DUI and an earlier age at onset, it might be hypothesised that younger depressed individuals would underestimate their depressive symptoms and, therefore, they would receive antidepressant treatment later than older subjects who, on the contrary, because of a greater number of life events, would look for treatment earlier. However, to date, there are no studies published confirming this observation.

Some limitations of this study should be considered. The study design implies the need to trust the reliability of the patient in providing information about the first episode of illness. Nevertheless, there is possibility that some patients identified as the onset of the disease an episode that, if correctly evaluated by a physician, would not meet the criteria for a MDD. Furthermore, the decision of assuming 12 months as threshold value for the DUI is arbitrary, and it has been chosen on the basis of published research on psychotic disorders.

In conclusion, findings from this study suggest that a longer DUI may have a negative influence on the clinical course of MDD. Further investigations on larger samples and additional outcome variables conducted with prospective design would be helpful to better clarify this topic.

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