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Italian patients with more recent onset of Major Depressive Disorder have a shorter duration of untreated illness

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Summary

Background: Previous investigation on the duration of untreated illness (DUI) in patients with Major Depressive Disorder (MDD) revealed a different latency to first antidepressant treatment, with adverse consequences in terms of outcome for individuals with a longer DUI. Recent reports, moreover, documented a reduced DUI, as observed with the passage of time, in patients with different psychiatric disorders. Hence, the present study was aimed to assess DUI and related variables in a sample of Italian patients with MDD as well as to investigate potential differences in subjects with onset before and after 2000.

Methods: An overall sample of 188 patients with MDD was assessed through a specific questionnaire investigating DUI and other variables related to the psychopathological onset and latency to first antidepressant treatment, after dividing them in two different subgroups on the basis of their epoch of onset.

Results: The whole sample showed a mean DUI of approximately 4.5 years, with patients with more recent onset showing a significantly shorter latency to treatment compared with the other group (27.1±42.6 vs 75.8±105.2 months, $P<.05$). Other significant differences emerged between the two subgroups, in terms of rates of onset-related stressful events and benzodiazepine prescription, respectively, higher and lower in patients with more recent onset.

Conclusions: Our findings indicate a significant DUI reduction in MDD patients whose onset occurred after vs before 2000, along with other relevant differences in terms of onset-related correlates and first pharmacotherapy. Further studies with larger samples are warranted to confirm the present findings in Italy and other countries.

1 | INTRODUCTION

Major Depressive Disorder (MDD) is one of the most prevalent mental illnesses, often characterised by a chronic-relapsing course and a relevant overall burden for patients and related caregivers.[1] It represents the second leading cause of disability worldwide in terms of years lived with disability,[2] with an annual prevalence of approximately 6.9% in Europe.[3] Despite the prevalence of MDD, only half of the affected patients are recognised and adequately treated, frequently after a significant delay.[4]

A clinical variable used to measure latency to treatment is the duration of untreated illness (DUI), defined as the time elapsing between the psychopathological onset of a specific disorder and the administration of the first pharmacological treatment, at standard dosages, and for an adequate period of time, in compliant subjects.[5–8]

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Previous investigation by our group focused on the assessment of clinical and epidemiological correlates of the DUI in patients with MDD. In particular, a prior study assessing patients on the basis of a DUI shorter vs longer than 1 year found that the latter subjects had a mixture of unfavourable illness characteristics including an earlier age at onset, a longer duration of illness, a higher number of recurrences and more frequently comorbid Axis I disorders with onset later than MDD.[5] A subsequent study conducted with the same methodology on a different sample found that patients with a DUI >1 year had an earlier age at onset, a longer duration of illness and a higher number of depressive episodes occurring before the first antidepressant treatment.[9] Of note, this study reported a mean DUI of approximately 4 years (47.8 months) for the overall sample. More recently, an epidemiologic study comparing DUI in patients with different psychiatric disorders found a mean value of 39.08 months for patients with MDD.[10] Furthermore, a recent meta-analysis [11] including two additional studies from other groups [12,13] reported that a longer DUI is a valid predictor of poorer response to antidepressant treatment, lower rate of remission, higher risk of chronicity and higher number of recurrences. Of note, a recent Japanese study reported a higher frequency of single status in MDD patients with a DUI exceeding 1 year.[14] Finally, from the neuroimaging perspective, a longer DUI has been associated with hippocampal volume reduction,[15] with antidepressant treatment apparently having a protective effect.[16]

Investigation on DUI and related variables may be relevant for clinical practice, considering that it is a modifiable parameter,[17–19] strongly influencing the overall course of illness.[20,21] Moreover, identifying reasons for delay in consulting a clinician, particularly a psychiatrist, and obtain a diagnosis, which may include secretiveness, social stigma and difficult access to psychiatric services, could provide a valuable contribution to ameliorate strategies for early diagnosis and treatment.[22,23]

Indeed, the DUI is a complex variable, influenced by different socio-demographic and clinical parameters.[6] For instance, along with its closely related variables (ie, age of onset and age of first treatment), other parameters related to the psychopathological onset (eg, nature of first symptoms, occurrence of stressful events before onset, presence of family members and caregiver) and first therapist/setting (eg, psychiatrist vs other clinician, outpatient/inpatient) have been investigated and found to differ in relation to DUI among patients with different psychiatric disorders.[24] In addition, recent studies have stressed that the epoch of onset, in turn, significantly influences the DUI of different psychiatric disorders,[25] including schizophrenia spectrum disorders,[26] with an overall reduction in its estimates throughout time.

Therefore, the aim of the present study was to analyse DUI and multiple related correlates across two different epochs of onset in patients with MDD, in order to investigate possible changes in the clinical recognition and management of the illness, which have occurred in the last decades in Italian patients. In particular, we hypothesised that acquisitions in diagnostic and treatment algorithms over time, the progressive implementation of psychiatric services with higher levels of expertise, better organisation and increased clinician availability as well as a different attitude towards mental illness from society might have determined a progressive reduction and change in DUI and related variables throughout time, as recently observed in patients with schizophrenia spectrum disorders.[26]

What's known

- Major Depressive Disorder (MDD) is characterised by high prevalence and burden of illness: it represents the second leading cause of disability worldwide and it frequently remains unrecognised and untreated.
- The duration on untreated illness (DUI) is a valid predictor of outcome in terms of treatment response, remission rates, risk of chronicity and recurrence, and it is a modifiable parameter.

What's new

- The present study analysed DUI and socio-demographic and clinical variables related to the psychopathological onset and first pharmacological treatment across two different epochs of onset in patients with MDD in order to evaluate potential changes occurred over time.
- Significant differences in terms of DUI between groups with onset in different epochs emerged, which may be of interest in order to assess progress and developments in the diagnostic and therapeutic pathways of MDD in clinical practice.

2 | METHODS

2.1 | Sample

Study sample included 188 outpatients, selected and recruited from January 2011 to December 2014 on the basis of their diagnosis, from an original sample of 562 consecutive patients, attending different Italian major outpatient psychiatric services through the National Health Service system, within a multicenter investigation on the latency to first psycho-pharmacological treatment and psychopathological onset in patients affected from different psychiatric disorders. For the present study, only participants who met diagnostic criteria for MDD, according to the DSM-IV-TR,[27] were included. Diagnoses were assessed through the Structured Clinical Interview for DSM-IV Axis I Disorders, patient edition,[28] administered by specifically trained psychiatrists. In case of comorbidity, the disorder assessed for the DUI and related variables had to be the one causing the greatest discomfort to the patient, the most significant impact on quality of life, and representing the main motivation for help seeking.

After providing their written informed consent for participating in the study and having their clinical records examined for research purposes, patients underwent the clinical interview, aimed to collect their socio-demographic and clinical data.

2.2 | Assessment

A brief, clinician-administered tool—the psychopathological onset and latency to treatment questionnaire (POLT-Q)[24]—was administered to collect patients' socio-demographic and clinical variables. More in detail, the questionnaire includes a preliminary part, collecting patient's socio-demographic features (ie, age, gender, occupational and marital status, family history for psychiatric disorders), and two sections, respectively, focused on psychopathological onset (section 1) and first psycho-pharmacological treatment (section 2). Section 1 explores age at onset and the presence of onset-related stressful events, while section 2 assesses help-seeking decision (autonomous or driven by others), first therapist referral and first therapy setting, first clinical contact delay, age at first diagnosis and at first pharmacological treatment, DUI, duration of first pharmacological therapy and reasons for its interruption, use of benzodiazepines as first treatment, and age at their first intake. In respect to stressful life events, we considered any condition disrupting personal life, exceeding the adaptive capacity of the individual (ie, trauma, abuse, mourning, physical illness, work and family stressors).[29]

The above-mentioned questionnaire was specifically designed to investigate and collect variables potentially influencing the psychopathological onset and the latency to first psycho-pharmacological treatment in psychiatric patients and it has been already used in recent studies in the field.[24–26] In particular, the DUI was considered as the time (measured in months) elapsing between the psychopathological onset and the administration—in compliant patients—of the first psycho-pharmacological treatment, at appropriate dosage and for an adequate period of time,[24] according to the most recently updated International treatment guidelines.[30]

The psychopathological onset was considered as the outbreak of first symptoms causing an impaired functioning in at least one major area of daily life (eg, work, familial, social), recognised by the patient or his/her caregiver as debilitating and, thus, a clinical condition suitable for proper diagnosis and pharmacological treatment. The first psycho-pharmacological treatment was considered regardless whether it was initiated within the psychopathological onset or later.

2.3 | Statistical analysis

Descriptive analyses were conducted in relation to the socio-demographic and clinical variables of the total sample. Furthermore, the study sample was divided into two subgroups, in relation to the psychopathological onset, to compare the same variables across different epochs of onset and investigate potential changes in latency to psycho-pharmacological treatment and related variables. As previously done in recent studies,[23,26] a temporal cut-off for psychopathological onset was arbitrarily established for the year 2000, which not only represents the first year of the new millennium but also the year of publication of the previous edition of the DSM (DSM-IV-TR). The study sample was divided accordingly in two subgroups: patients with onset before and after 2000.

Student's *t* test for continuous variables and chi-square test for dichotomous ones were then performed to compare variables between subgroups. The level of significance for all statistical analyses was set at .05. In light of the statistically significant difference in terms of age between the two subgroups, MANCOVA was performed for the continuous variables, setting age as covariate.

All the aforementioned statistical analyses were performed using SPSS for Windows software (version 22.0, SPSS Inc., Chicago, IL).

3 | RESULTS

The main socio-demographic and clinical variables of the total sample and the two subgroups are summarised in Table 1.

The study sample consisted of 188 patients, divided in two subgroups, according to the epochs of onset: 99 subjects (53%) with onset before the year 2000 and 89 (47%) with onset after 2000.

The subgroups did not significantly differ in terms of gender; as expected, they differed in terms of age (before 2000: 56.7±11.7, after 2000: 47.8±14.5; $P<.001$), which was selected as covariate for comparison analyses.

Considering clinical continuous variables, we found a later age at onset (31.5±11.4 vs 40.5±15.8; $P<.001$), age at first diagnosis (36.0±12.1 vs 43.3±14.0; $P<.001$) and age at first pharmacological treatment (37.8±11.5 vs 42.8±15.0; $P<.001$) in patients with onset after 2000, compared with those with previous onset.

The comparison between the two subgroups showed a statistically significant difference in terms of onset-related stressful events (Figure 1): in particular, patients with onset after 2000 more frequently reported the presence of a stressor occurring before the first episode of illness (65% vs 81%; $P=.02$).

With respect to benzodiazepine (BDZ) use, subjects with onset after 2000 were characterised by a less frequent prescription of BDZ as first therapy (47% vs 30%; $P=.02$; Figure 1) and an older age at first BDZ administration (34.4±10.0 vs 41.2±15.2; $P<.001$).

Focusing on the reasons for first pharmacological treatment interruption, a significant difference between the two subgroups emerged ($P<.001$): in particular, lower rates of remission (29% vs 16%) and lack of efficacy (29% vs 15%) were observed more frequently in patients with onset after 2000.

Finally, the analysis showed a statistically significant difference in terms of DUI between the two subgroups, with a shorter DUI in patients with onset after 2000 (75.8±105.2 vs 27.1±42.6 months; $P=.011$; Figure 2).

The remaining socio-demographic and clinical variables did not show any statistically significant difference in the comparison of the two subgroups.

4 | DISCUSSION

The present study sought to assess whether patients with MDD showed any difference in relation to the DUI and related parameters,

TABLE 1 Main socio-demographic and clinical variables of the total sample and related subgroups, divided according to the epoch of onset

Epochs of onset	Onset ≤2000 n=99 (53%)	Onset >2000 n=89 (47%)	Total sample n=188
Age (years)	**56.7±11.7****	**47.8±14.5****	52.5±13.8
Gender			
Males	42 (42%)	43 (48%)	85 (45%)
Females	57 (58%)	46 (52%)	103 (55%)
Occupational status			
Student/worker	37 (37%)	47 (53%)	84 (45%)
Housewife/unemployed	29 (29%)	24 (27%)	53 (28%)
Retired	33 (33%)	18 (20%)	51 (27%)
Marital status			
Married/partner	56 (57%)	51 (57%)	107 (57%)
Single/widowed	28 (28%)	27 (30%)	55 (29%)
Divorced	15 (15%)	11 (12%)	26 (14%)
Family history for psychiatric disorders			
Negative	48 (49%)	50 (57%)	98 (53%)
Positive	50 (51%)	38 (43%)	88 (47%)
Age at onset (years)	**31.5±11.4****	**40.5±15.8****	35.4±14.1
Onset-related stressful events			
Yes	**64 (65%)***	**71 (81%)***	135 (72%)
No	**35 (35%)***	**17 (19%)***	52 (28%)
Help seeking decision			
Autonomous	47 (48%)	33 (38%)	80 (43%)
Other	52 (52%)	54 (62%)	106 (57%)
First therapist			
Psychiatrist	35 (35%)	33 (37%)	68 (36%)
Psychologist	14 (14%)	15 (17%)	29 (15%)
Other clinician	50 (51%)	41 (46%)	91 (48%)
First therapy setting			
Outpatient	83 (84%)	78 (88%)	161 (86%)
Inpatient	16 (16%)	11 (12%)	27 (14%)
First contact delay (months)	**42.8±62.1***	**10.7±21.9***	28.8±51.1
Age at first diagnosis (years)	**36.0±12.1****	**43.3±14.0****	39.5±13.5
Age at first pharmacological treatment (years)	**37.8±11.5****	**42.8±15.0****	40±13.2
DUI (months)	**75.8±105.2***	**27.1±42.6***	54.6±86.8
Duration of first pharmacological treatment (months)	28±37.6	21.4±33.6	25.1±35.8
Reasons for first pharmacological treatment interruption			
Remission	**27 (29%)****	**14 (16%)****	41 (23%)
Side effects	10 (11%)	3 (4%)	13 (7%)
No efficacy	**27 (29%)****	**13 (15%)****	40 (22%)
Relapse	7 (8%)	11 (13%)	18 (10%)
Other	6 (7%)	6 (7%)	12 (7%)
Ongoing	**16 (17%)****	**39 (45%)****	55 (31%)
BZD at first treatment			
Yes	**47 (47%)***	**27 (30%)***	74 (39%)
No	**52 (53%)***	**62 (70%)***	114 (61%)
Age at first BDZ administration (years)	**35.4±10.0****	**41.2±15.2****	37.9±12.8

Values for categorical and continuous variables are expressed in percentages and mean±SD, respectively. In case of missing data, total cumulative rates may be lower than 100%. BDZ, benzodiazepines; DUI, duration of untreated illness. Bold values are statistically significant; *$P<.05$; **$P<.001$.

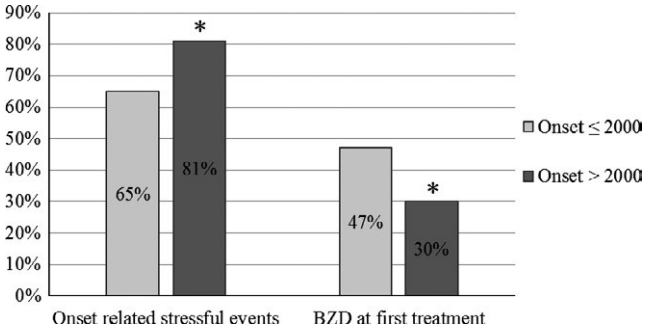

FIGURE 1 Differences in terms of onset-related stressful events and use of benzodiazepine (BZD) as first treatment between the two subgroups (onset before and after 2000). Statistics: *Onset-related stressful events: $P<.05$; Benzodiazepine (BZD) at first treatment $P<.05$

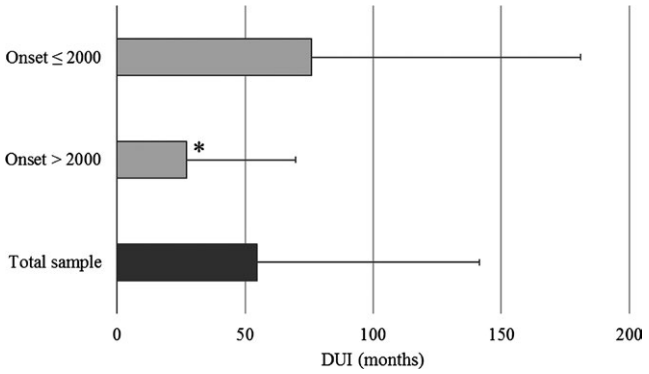

FIGURE 2 Comparison of duration of untreated illness (DUI) between the two subgroups of patients with MDD (onset before and after 2000). Statistics: *$P<.05$

on the basis of their epoch of onset. Significant differences were observed, with relevant implications from an epidemiologic and clinical point of view.

Considering the total sample, our findings on age and age at onset are consistent with prior data reported from our group.[9,10] In specific regard to the DUI, its mean value (approximately 4.5 years) appears to be slightly longer compared with our earlier reports on different samples (54 months in the present sample vs 48 and 39 months, respectively).[9,10] This result supports the notion that patients suffering from MDD may expect many years, on average, from the beginning of their illness before receiving an adequate treatment.

When focusing on patients with onset after vs before 2000, a significant reduction in the latency to treatment emerged between them (roughly <50%), identifying the lowest mean value (27 months), compared with the above-mentioned studies. This finding highlights the importance to relate the DUI to a specific onset epoch, to reduce its variability and get more insightful information about its epidemiology and clinical correlates, particularly in relation to long-term outcome and treatment response. In fact, considering previous and more recent estimates of DUI in MDD patients, a large variability may been observed, ranging from 8.2 years in an Australian report[31] to 4 months in a recent Japanese study.[14] Hence, such a variability is likely influenced by the epoch of onset of assessed patients as well as by other factors.

Consistently with the significant reduction in the DUI throughout time observed in the present study, another recent report from our group documented a decreasing latency to first pharmacological treatment across epochs (defined as: onset before 1978, between 1978–2000 and after 2000) in a large sample of patients with schizophrenia spectrum, mood and anxiety disorders,[25] as previously mentioned. In addition, Thompson and colleagues reported that older generations of patients more likely show a longer delay in treatment seeking than younger ones.[31] Taken as a whole, these results stress the importance of assessing not only the mean DUI in different psychiatric diagnoses but also its potential changes across different epochs of onset in subjects affected by the same disorder. For instance, it is worth stressing the influence of methodological differences amongst studies (eg, sample, setting and assessment measures), as well as the role of socio-cultural factors, such as stigma, health literacy[32] and accessibility to mental healthcare services, that may affect DUI, either throughout time and across countries. Furthermore, the DUI reduction across epochs, observed in the present study, may reflect some of the relevant changes occurred in Italian psychiatric services in the last decades, in terms of easier accessibility and higher quality of care as well as availability of more specific and accurate diagnostic tools, together with an overall reduced stigma towards mental illnesses and related treatment.[33,34] According to a recent study on changes in mental health system accessibility in the Italian Lombardy region in the period 1999–2009, in fact, an increased rate of treatment incidence and prevalence was observed. This was probably related to the introduction of an organisational model of intervention based on multi-disciplinary teams, after the approval of the first Regional Mental Health Plan of the 1980s.[35]

When comparing MDD patients according to their epoch of onset, we found that those with a more recent onset showed a later age at onset and, consequently, a later age at first diagnosis and first pharmacological treatment. Nonetheless, the interval between age at onset and first diagnosis as well as first pharmacological treatment (DUI) decreased significantly throughout time. These findings might also be considered in light of a different composition of the two subgroups. In fact, among subjects with onset before 2000, there might have been a higher prevalence of individuals with a more severe form of illness—that is, with early onset and longer DUI—as hypothesised in previous studies from our group reporting a correlation between a longer DUI and an earlier age at onset.[5,9] On the other hand, patients with more recent onset might have suffered from more reactive expressions of MDD, as confirmed by the higher frequency of onset-related stressful events, including trauma, abuse, mourning, physical illness, work and family stressors, observed in this subgroup. Consistently, Sweeting and coworkers reported an increase in psychological distress throughout time (from 1987 to 2006) in young population, potentially related to the influence of exposure and individual vulnerability (eg, economic, familial, educational and lifestyle factors) and likely resulting in a lower resilience and greater susceptibility to depressive disorders.[36]

In relation to pharmacological treatment, it is worth noting that benzodiazepine prescription was found to be decreased in patients with onset after 2000 and approximately half of them reached clinical observation while on antidepressant treatment. Such a scenario may reflect the lower use of symptomatic compounds (benzodiazepines) and a more appropriate and guideline-oriented prescription of antidepressant compounds. To the authors' knowledge, although trends in benzodiazepine prescriptions have been widely addressed in literature,[37] with a recent American study reporting an increased clinical use of such drugs in the USA between 1996 and 2013,[38] no report about the Italian reality has been made available up to date.

The reported family history for psychiatric disorders did not vary between epochs, suggesting no relevant changes in the genetic susceptibility for depression. Nonetheless, patients with onset >2000 reported a significant increase in onset-related stressful events, that might be indicative of a higher prevalence of reactive expression of MDD among these subjects.

As expected, no significant difference emerged in terms of help-seeking decision: patients who autonomously decided to look for treatment represented the majority in both subgroups, thus suggesting a high degree of insight and illness awareness. Similarly, we did not find any difference in the first therapy setting, confirming that most of MMD patients come to clinical attention in outpatient setting, regardless of their epoch of onset.

Unexpectedly, the choice of the first therapist did not significantly differ between the two subgroups, with—on average—only 36% of depressed subjects choosing a psychiatrist as first consultant, while 15% of them a psychologist and 48% another clinician. Among other clinicians, the most represented was the general practitioner (GP). This result highlights the importance of the GP in identifying and managing patients suffering from MDD, particularly with mild forms of illness.[39–41] Nevertheless, the GP's diagnostic accuracy for psychiatric conditions might need additional empowerment.[41] In fact, educational methods have shown to be effective in improving diagnostic competency of GPs for psychiatric disorders.[42]

The aforementioned results also point out the need of improving health literacy of depression and the access to psychiatric services, particularly for most severe cases, within the general population.[43]

The following methodological limitations should be considered when interpreting the aforementioned findings. Although the administration of POLT-Q, used to retrospectively collect socio-demographic and clinical variables, was aimed at standardising the source of information, the presence of recall bias cannot be excluded, particularly for patients with most remote onset and for elderly people, who have a higher risk of cognitive impairment, and, therefore of lower reliability. Nonetheless, as already specified, clinical information from the POLT-Q was cross-checked with available family members/caregivers and previous medical files, when possible. The recruitment of patients from different catchment areas might have played a role as well, reflecting local differences regarding the presence and efficiency of psychiatric services as well as different socio-cultural attitudes. Comorbidity was not a collected variable and the assessment with POLT-Q was focused on the disorder causing the greatest discomfort to the patient, the most significant impact on quality of life, and representing the main motivation for help seeking. Finally, it is worth noting that not all the patients recruited in the present study were at their first clinical presentation to a psychiatric service and that a long duration of illness, previous psychiatric services discontinuation and illness chronicity might have affected DUI as well.

In conclusion, the assessment of the DUI in patients suffering from MDD across two different epochs pointed out significant differences, documenting a reduction in its value throughout time along with other differences in related parameters, as well as in terms of benzodiazepine vs antidepressant prescription. Reported findings are of epidemiological and clinical relevance in order to evaluate progress and developments in the diagnostic and therapeutic pathways of MDD in Italy and other countries.

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AUTHOR CONTRIBUTIONS

B. D. conceived and designed the study and provided critical revision of the article; L. C., B. G., F.D., B. B., G. C., C. A., C. D., L.O. and M. P. contributed, to different degrees, in searching the literature and writing the article; M. V performed data collection; A. C. A. provided final revision of the article.

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