Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder

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ABSTRACT

Background: The duration of untreated illness (DUI) is a potentially modifiable parameter associated with worst prognosis in several psychiatric disorders, but poorly investigated in Obsessive-Compulsive Disorder (OCD). Our aims were to estimate the mean DUI in a large sample of individuals with OCD and its impact on response to the first ever adequate SRI treatment.
Methods: We retrospectively examined records of 251 patients with OCD (SCID-I, DSM-IV) who referred to our Department and were prospectively and naturalistically treated according to International Guidelines. The DUI was defined as the interval between age at onset and age at which patients received their first adequate pharmacological treatment. Response rates were compared in subjects with brief ($\leq$24 months) versus long DUI. Logistic regression models predicting response and 12-week Y-BOCS score were run with DUI (among others) as independent variable.
Results: The mean DUI was 106.19 ± 118.14 months, with a mean interval between onset of the disorder and when patients sought professional help of 82.27 ± 112.30 months. Response rates were significantly reduced in subjects with a long DUI, using both the cut-off of 24 months and the median value of 60 months. Regression analyses confirmed that a long (>24 months) DUI predicts poorer response and higher Y-BOCS scores at 12 weeks.
Conclusions: Our results, although preliminary, seem to suggest that a longer duration of untreated illness in OCD is associated with poorer outcome in terms of response to SRI treatments. It is imperative to do all the possible to shorten the DUI, both by improving access to mental health services, improving the ability of primary care physicians and mental health professionals to recognize OCD, and disseminate best-practice prescription guidelines.

1. Introduction

The treatment gap (difference between individuals with OCD needing treatment and those actually receiving it) for Obsessive-Compulsive Disorder (OCD) is estimated in Europe of 25% in 2004 (50% approximately in the world), despite effective treatments, namely Cognitive-Behavioural Therapy (CBT) and serotonergic compounds (SSRIs and clomipramine), are available for this disorder [1–3]. The situation has not changed in recent years; the proportion of subjects not being treated worldwide in more recent epidemiological studies is estimated to vary between 22 and 92%, with 38-to-90% of individuals not even seeking treatment or advice for their OCD [4]. The phenomenon is then relevant. Even when subjects with OCD do seek help, the mean delay in help-seeking behaviours is significant: it is estimated that individuals with OCD take up to 11 years to seek professional help [4].

Even when patients do receive treatment, often this is inadequate. Moderate-to-high doses for at least 12 weeks are required in order to elicit a response, with maintenance treatment indicated for at least 1 year after response [1,2]. It is not uncommon for subjects with OCD to receive inadequate treatments, in terms of choice of the proper compound (antidepressants other than SSRIs or clomipramine) or psychological treatment (e.g. psychodynamic therapy), in terms of doses (sub-therapeutic doses) and/or time

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(clinicians may switch to other treatments after only 4-to-6 weeks as in the case of resistant Major Depressive Disorder, ignoring that it takes 12 weeks for an anti-obsessional treatment to be effective).

As a consequence, the duration of untreated illness (DUI) may be considerable. Originally proposed, as a concept, for psychosis (duration of untreated psychosis - DUP), the DUI is measured as the interval between onset of the disorder and when the patient receives the first *adequate* treatment for that psychiatric disorder (right medication, at minimally effective dosages, for an adequate period of time depending on the specific psychiatric disorder) [5–8]. The DUP/DUI may be relevant for clinicians as it has been suggested that response to treatments is poor and suicidality risk higher when the DUI is long [9,6,10], indicating a possible neurotoxic effect of the DUI [11]. Moreover, being modifiable, the DUI could be a key to early intervention in severe mental disorders [12].

The DUI has been poorly investigated in OCD. A first group of researchers published several studies in individuals with OCD (it is unclear whether the sample of subsequent studies included patients enrolled in the previous ones), showing that the mean DUI (defined as the interval between onset of the disorder and when the patient received the first adequate treatment according to the World Federation of the Societies for Biological Psychiatry guidelines [13,14]) was comprised between 87.5 and 94.5 months [15,16,8, 17–19]. In one of their studies [8], moreover, subjects with a long DUI (>24 months, cut-off chosen on the basis of previous studies performed in non-OCD samples) had lower response rates than those with a brief DUI. A logistic regression analysis, however, did not find a significant correlation neither between response nor remission rates and the DUI expressed as a continuous variable in months. The other study which investigated the relationship between DUI and treatment outcome [20] found that the DUI was not predictive of remission in terms of symptomatology. The sample included was relatively small (N = 96), the mean DUI was 7.05 ± 8.52 years, and the cut-off used in defining the groups with short and long DUI was 4 years (median value in that sample). A possible confounding factor in both studies is that response was evaluated to SRI treatment, without differentiating between current versus the first ever adequate treatment. It is possible that discrepancies found could be attributed to differences in the number of previous treatments received in the two samples, and that the difference between individuals with brief versus long DUI is more evident when examining response to the first ever adequate treatment.

Given the relatively poor investigation on DUI and OCD (as compared to other mental disorders) and being the DUI a potentially modifiable factor, we wanted to: 1. estimate the mean duration of untreated illness in a large sample of individuals with OCD; and 2. to investigate its impact on response to the first ever adequate pharmacological treatment.

2. Methods

2.1. Sample

The sample of the study was comprised of adult patients (≥18 years of age) with a principal (SCID-I, DSM-IV) OCD diagnosis and Y-BOCS total score ≥16 who referred to our Department in the years 1998-2017.

All subjects who present at our inpatient and outpatient service do sign a written informed consent (reviewed by our Ethical Committee) to have their clinical data potentially used for teaching and research purposes (provided that these data are anonymously treated). For the purposes of the present study, a specific request was made to our Ethical Committee (Comitato Etico Interaziendale A.O.U. San Luigi Gonzaga di Orbassano, Italy) in order to have access to clinical records of all OCD patients who agreed and signed the abovementioned written informed consent; the protocol was reviewed and approved by the Ethical Committee.

2.2. Assessments and procedures

All patients with a principal diagnosis of OCD were evaluated through the administration of a semi-structured interview developed and used routinely at our centre. All diagnoses (principal and Axis I comorbid disorders) were confirmed by means of the Structured Clinical Interview for DSM Axis I Disorders (SCID-I). Personality disorders were ascertained with the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). At study entry, general socio-demographic information and clinical data were collected for each subject through the administration of a semi-structured interview that we developed and used in previous studies [21], covering the following areas: a) socio-demographic data: age, gender, occupational and marital status, b) OCD clinical characteristics: age at onset (symptoms and disorder onset), modality of onset (abrupt, insidious), course (episodic and chronic); c) Obsessive–Compulsive symptoms: OCD symptoms were measured with the Y-BOCS Check List. In addition, the following rating scales were included in the assessment: Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Anxiety Rating Scale (HAM-A), and 17-item Hamilton Depression Rating Scale (HAM-D).

Age at symptoms onset was defined as the age at which subjects first presented OCD symptoms. Age at disorder onset (age at onset - AAO) was defined as the first reliably diagnosed OCD episode according to DSM-IV diagnostic criteria, using all the available medical records. Illness duration was calculated subtracting AAO from age. External corroboration for AAO was obtained, whenever possible, by directly interviewing, with patient's consent, a first-degree family member or other significant individuals. An attempt was made to date the onset of symptoms and of OCD in a 4-week period; if there was uncertainty between patient's and family members' estimates, a range was plotted and its mid-point was used for the analysis. Age at first help seeking (for OCD) and age at first adequate pharmacological treatment received were recorded for each subject.

The duration of untreated illness (DUI) was calculated subtracting AAO from age at first *adequate* treatment received.

2.3. DUI and response to treatments

We retrospectively examined all records of patients with a principal (SCID-I, DSM-IV) OCD diagnosis who referred to our Department, were prospectively and naturalistically treated according to International Guidelines (clomipramine and/or SSRIs, for at least 12 weeks, at adequate doses) [13,14] and had at least two Y-BOCS administered (baseline and 12-week). No patient was excluded due to comorbid disorders as long as his/her principal diagnosis was OCD. Response was defined as a ≥25% decrease in Y-BOCS total score with respect to baseline. We focused our attention on the first ever received adequate pharmacological treatment.

Which is the minimum effective dose required for a drug to elicit a response in OCD is still a matter of debate; Bloch and colleagues [22], in their meta-analysis, suggested that moderate-to-high doses are required, and some International Guidelines for the treatment of OCD (namely the APA guidelines and the NICE, for example) do indicate that minimum effective doses are at least moderate, while others (namely the WFSBP) seem to suggest that even low doses are indicated. Previous studies on DUI and response to adequate treatment used different methodologies: Dell'Osso and coworkers [8] referred to the WFSBP guidelines [13,14] in defining an *adequate* treatment for OCD, while no mention was made by Poyraz and colleagues [20] on the minimum effective dose they considered *adequate*. We then chose to define an

adequate treatment, in terms of minimum prescribed doses, according to the WFSBP guidelines: 75 mg for clomipramine, 10 mg for escitalopram, 20 mg for citalopram, 40 mg for both fluoxetine and paroxetine, 50 mg for sertraline and 100 mg for fluvoxamine.

2.4. Statistical analysis

In order to investigate whether response to treatments is dependent on the DUI, the sample was divided according to the duration of untreated illness (brief versus long), using two different cut-offs: 1. The median value in our sample (below median versus above median value), 2. The previously used [8] cut-off of 24 months (brief versus long DUI). Percentages of responders in each group were compared using the $\chi 2$ test. The mean DUI in responders versus non-responders were compared with the independent Student t-test.

Regression models were also performed with response (yes, no) and 12-week Y-BOCS scores as dependent variables, and DUI (both as a binary and a continuous variable), baseline Y-BOCS scores, age, gender and age at disorder onset as independent variables.

3. Results

3.1. Patients' characteristics

Two-hundred fifty-one patients were enrolled in the study; for them it was possible to determine DUI and the interval between disorder onset and when they first sought professional help. Socio-demographic and clinical characteristics of patients included are reported in Table 1.

3.2. Duration of untreated illness

Considering the initial sample of 251 individuals with OCD, a mean DUI of 106.19 ± 118.14 months was calculated. Table 2 and Fig. 1 present data regarding help-seeking latency and DUI.

The median DUI in our sample was 60 months; we calculated then percentages of patients having a brief DUI according to the previously used cut-off (arbitrarily chosen by Dell'Osso and colleagues, [8]) of 24 months (brief DUI: ≤24 months) and to our median value (below median value DUI: ≤60 months). Using both cut-offs, a significant percentage of our patients reported a long DUI (that is received a first adequate pharmacological treatment years after the onset of the full-blown impairing disorder – OCD onset).

3.3. Response rates according to duration of untreated illness

Two-hundred and forty individuals received a first ever adequate treatment for at least 12 weeks and had a baseline and a 12-week Y-BOCS in order to determine response rates; 134 of them received only one lifetime pharmacological treatment, while for the remaining 106 individuals (who received more than one lifetime pharmacological treatments) we considered only the first

Table 1
Socio-demographic and clinical characteristics of patients included (N = 251).

Characteristics	Value	DUI	
		Brief (≤24 months)	*Long (>24 months)*
Females, n (%)	116 (46.2)	40 (46.0)	76 (46.3)
Age (years), mean ± *SD*	37.36±13.62	31.61±11.32	40.41±13.78*
Education (years), mean ± *SD*	12.79±4.35	12.32±3.51	13.04±4.72
Currently working (yes), n (%)	119 (47.4)	35 (40.2)	84 (51.2)
Marital status, Single, n (%)	148 (59.0)	62 (71.3)	86 (52.4)#
Age of symptoms onset (years), mean ± *SD*	16.51±7.79	17.92±8.04	15.76±7.57*
Age of disorder onset (years), mean ± *SD*	22.21±9.19	24.22±8.83	21.14±9.23*
Duration of illness (months), mean ± *SD*	183.98±136.77	94.52±73.32	231.44±138.99#
Onset, abrupt, n (%)	64 (25.5)	31 (35.6)	33 (20.1)*
Course, chronic, n (%)	222 (88.4)	73 (83.9)	149 (90.9)
Life events (≥1) prior to onset, n (%)	130 (51.8)	40 (46.0)	90 (54.9)
Y-BOCS, mean ± *SD*			
Total score	24.15±6.42	23.82±5.71	25.01±5.38
Obsession score	12.31±3.43	11.75±3.83	12.61±3.17
Compulsion score	11.84±3.60	11.20±3.91	12.18±3.39
Y-BOCS Check-List Obsessions			
Aggressive	163 (64.9)	51 (58.6)	112 (68.3)
Contamination	135 (53.8)	39 (44.8)	96 (58.5)*
Sexual	51 (20.3)	18 (20.7)	33 (20.1)
Hoarding/Saving	43 (17.1)	15 (17.2)	28 (17.1)
Religious	56 (22.3)	18 (20.7)	38 (23.2)
Need for symmetry or exactness	123 (49.0)	41 (47.1)	82 (50.0)
Somatic	68 (27.1)	22 (25.3)	46 (28.0)
Y-BOCS Check-List Compulsions			
Cleaning/Washing	139 (55.4)	42 (48.3)	97 (59.1)
Checking	178 (70.9)	61 (70.1)	117 (71.3)
Repeating Rituals	126 (50.2)	48 (55.2)	78 (47.6)
Counting	52 (20.7)	20 (23.0)	32 (19.5)
Ordering/Arranging	70 (27.9)	24 (27.6)	46 (28.0)
Hoarding/Collecting	39 (15.5)	11 (12.6)	28 (17.1)
HAM-D, mean ± *SD*	10.66±6.51	9.59±6.14	11.23±6.64
HAM-A, mean ± *SD*	11.43±6.84	11.34±7.49	11.47±6.49
Lifetime Axis I Comorbid Disorders, n (%)	185 (73.7)	60 (69.0)	125 (76.2)
Anxiety Disorders	64 (25.5)	21 (24.1)	43 (26.2)
Mood Disorders	128 (51.0)	43 (49.4)	85 (51.8)
Eating Disorders	10 (4.0)	2 (2.3)	8 (4.9)
Substance Use Disorders	20 (8.0)	2 (2.3)	18 (11.0)*

Y-BOCS: Yale-Brown Obsessive Compulsive Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; SD: Standard Deviation.
* $p < .001$ # $p < .05$.

Table 2
DUI and latency in help-seeking in 251 individuals with OCD.

	Value
Age of symptoms onset (years), mean ± *SD*	16.51 ± 7.79
Age of disorder onset (years), mean ± *SD*	22.21 ± 9.19
Age at help seeking (years), mean ± *SD*	29.03 ± 12.05
Age at first adequate pharmacological treatment (years), mean ± *SD*	31.04 ± 12.24
Interval between disorder onset and help-seeking (months), mean ± *SD*	82.27 ± 112.30
Interval between help-seeking and first ever adequate pharmacological treatment (months), mean ± *SD*	23.89 ± 56.80
DUI (months), mean ± *SD*	106.19 ± 118.14
Type of DUI, median value, n (%)	
Below median (≤60 months)	120 (47.8)
Above median (>60 months)	131 (52.2)
Type of DUI, previously used cut-off[a], n (%)	
Brief (≤24 months)	87 (34.7)
Long (>24 months)	164 (65.3)

DUI: Duration of Untreated Illness; OCD: Obsessive-Compulsive Disorder; SD: Standard Deviation.
[a] Dell'Osso et al., 2010.

Table 3
Mean DUI and response rates to first ever adequate SRI treatment (N = 240).

	Value
Y-BOCS total score at baseline, mean ± *SD*	24.58 ± 5.58
Y-BOCS total score at 12 weeks, mean ± *SD*	16.32 ± 8.17
Percentage change in Y-BOCS score, mean ± *SD*	34.64 ± 29.27
Responders, N (%)	122/240 (50.8)
First adequate treatment received, N (%):	
Clomipramine (mean dose: 185.3±59.8 mg/day)	22 (9.2)
Citalopram (mean dose: 49.4±19.8 mg/day)	17 (7.1)
Escitalopram (mean dose: 20.0±5.6 mg/day)	25 (10.4)
Fluoxetine (mean dose: 47.1±12.7 mg/day)	14 (5.8)
Fluvoxamine (mean dose: 240.7±57.8 mg/day)	105 (43.8)
Paroxetine (mean dose: 43.9±7.9 mg/day)	28 (11.7)
Sertraline (mean dose: 146.2±45.9 mg/day)	29 (12.1)
DUI (months), mean ± *SD*	103.76 ± 116.39
responders (N=122)	82.83 ± 110.05*
non-responders (N=118)	125.40 ± 119.24*
Type of DUI, median value, n (%)	
Below median (≤60 months)	127 (52.9)
Above median (>60 months)	113 (47.1)
Type of DUI, previously used cut-off[a], n (%)	
Brief (≤24 months)	84 (35.0)
Long (>24 months)	156 (65.0)

Y-BOCS: Yale-Brown Obsessive Compulsive Scale; DUI: Duration of Untreated Illness; SD: Standard Deviation.
* t = 2.875, p = .004.

ever pharmacological treatment received. Table 3 reports mean DUI (in months) in responders versus non-responders to the first ever adequate pharmacological treatment (together with treatments received, mean baseline and 12-week Y-BOCS scores and percentage change in Y-BOCS score); a significantly longer mean DUI is associated with non-response to the first ever treatment. Table 3 presents also data on the specific SRI treatment received. Twenty-one patients out of the 240 (8.8%) had prior CBT (or were maintained on a preexisting CBT while starting the new pharmacological treatment). No patient started concomitantly CBT and the SRI treatment.

Table 4 presents responder rates (reduction ≥25% in the Y-BOCS total score) and final Y-BOCS scores according to the type of DUI (brief versus long; below versus above median value); response rates were significantly reduced in subjects with long and above median DUI, Y-BOCS scores at 12 weeks were significantly higher, and percentage changes lower.

A logistic regression was performed to ascertain the effects of DUI (brief versus long), baseline Y-BOCS scores, age, gender, age at disorder onset on the likelihood of response to the first ever adequate SRI treatment. The logistic regression model was statistically significant, χ^2 (5) = 22.614, p = .001. The model explained 12.0% (Nagelkerke R^2) of the variance in response and correctly classified 61.7% of cases. Individuals with a brief DUI (≤24 months) were 9.6 times more likely to respond than those with a long DUI (see Table 5).

Multiple linear regression models were run to predict 12-weeks YBOCS scores from baseline YBOCS, age, gender, age at disorder onset, and DUI; in the first model, DUI was considered as a binary variable (brief versus long), in the second as a continuous variable (in months) (Table 6). In the first model, these variables statistically significantly predicted 12-weeks YBOCS scores, F(5, 234) = 31.146, p < .001, R^2 = .400. Only baseline Y-BOCS scores and DUI brief versus long added statistically significantly to the prediction, p < .05. In the second model, the variables statistically significantly predicted 12-weeks YBOCS scores, F(5, 234) = 28.800, p < .001, R^2 = .381, but only baseline Y-BOCS scores added statistically significantly to the prediction, p < .05.

4. Discussion

The aim of the present study was to estimate the mean duration of untreated illness in a large sample of individuals with OCD and to investigate whether response to treatments is dependent on the DUI. More specifically, we aimed at expanding literature data suggesting that a DUI longer than 2 years is associated with lower response rates [8], examining response rates to the first ever adequate SRI treatment received.

We found that the mean interval elapsing from onset of the disorder and when patients received an *adequate* pharmacological treatment is approximately 9 years. This mean interval is comparable to previous results in other samples (87.5 to 94.5 months in the sample of Dell'Osso and coworkers [8,17–19,15,16] and 7 years in the Poyraz sample [20]). This impressive long duration of untreated illness is mainly to be attributed to the delay of patients in seeking help (the mean interval between onset of the disorder and when patients sought professional help for the first time is 82 months – approximately 7 years).

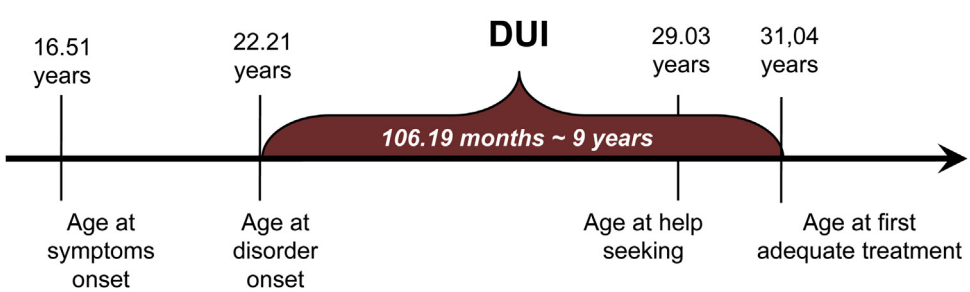

Fig. 1. Duration of untreated illness in a sample of 251 individuals with OCD.
DUI: Duration of Untreated Illness; OCD: Obsessive-Compulsive Disorder.

Table 4
Responder rate to first ever adequate SRI treatment according to the DUI (N = 240).

	DUI		t/χ^2	p
	Brief (≤24 months) N = 84	*Long (>24 months) N = 156*		
Responders: N (%)	58 (69.0)	64 (41.0)	17.154	<.001
Y-BOCS score at 12 weeks, mean ± *SD*	13.37 ± 7.37	17.90 ± 8.16	−4.245	<.001
Mean % change in Y-BOCS score, mean ± *SD*	44.34 ± 27.86	29.41 ± 28.76	3.879	<.001
	DUI		t/χ^2	p
	Below median (≤60 months) N = 127	*Above median (>60 months) N = 113*		
Responders: N (%)	77 (60.6)	45 (39.9)	10.358	.001
Y-BOCS score at 12 weeks, mean ± *SD*	14.69 ± 7.94	18.15 ± 8.07	3.350	.003
Mean % change in Y-BOCS score, mean ± *SD*	39.95 ± 29.23	28.67 ± 28.26	−3.030	.001

DUI: Duration of Untreated Illness; SD: Standard Deviation; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

Table 5
Binomial logistic regression model predicting response (yes, no) to first ever adequate SRI treatment (N = 240).

Dependent variable: response (yes, no) to first ever adequate SRI treatment				
	B	*SE*	*Wald*	*p*
baseline Y-BOCS score	−.037	.025	2.257	.133
Gender	.307	.277	1.222	.269
Age	−.006	.014	.194	.660
Age at disorder onset	.021	.019	1.155	.282
DUI, brief versus long	−1.023	.330	9.618	.002
Constant	1.249	.747	2.797	.094

χ^2 (5) = 22.614, p = .001.
Nagelkerke R^2 = .120.

Table 6
Multiple linear regression models predicting 12-week Y-BOCS score (N = 240).

Dependent variable: 12-week Y-BOCS score with DUI as a dichotomous variable[a]				
	B	*SE*	*t*	*p*
baseline Y-BOCS score	.832	.075	11.102	<.001
Gender	−1.144	.844	−1.355	.177
Age	.010	.043	.017	.808
Age at disorder onset	−.044	.059	−.755	.451
DUI,[b]rief versus long	3.142	1.003	3.132	.002
Constant	−5.018	2.259	−2.222	.027
Dependent variable: 12-week Y-BOCS score with DUI as a continuous variable[b]				
	B	*SE*	*t*	*p*
baseline Y-BOCS score	.839	.076	11.012	<.001
Gender	−1.215	.857	−1.418	.158
Age	−.016	.068	−.228	.820
Age at disorder onset	−.025	.081	−.309	.757
DUI, months	.010	.007	1.572	.117
Constant	−3.658	2.284	−1.602	.111

[a] F (5, 234) = 31.146, p < .001; R^2 = .400.
[b] F (5, 234) = 28.800, p < .001; R^2 = .381.

Several factors have been found to be associated with non-treatment or delayed treatment seeking in OCD, such as shame about the symptoms (or specific symptom dimensions e.g. sexual or religious obsessions) or other "internal/cognitive" factors (e.g. reluctance to admit that there may be a problem), fear of criminalization and/or other stigma related factors, or just not knowing where to find help [4,23]. Educational campaigns presenting OCD as an illness that can be cured and resources to improve access to mental health services could in the near future shorten the delay in seeking treatments.

However, it is surprising that it took additional 2 years for our patients to receive an *adequate* pharmacological treatment since when they first sought professional help. This means that there is some difficulty for physicians and/or mental health professionals in recognizing and appropriately diagnosing OCD (indeed high rates of OCD symptom misidentification by mental health professionals were found [24]), or in prescribing/offering an *adequate* treatment. It may be that some professionals misdiagnose OCD but also that antidepressants other than clomipramine/SSRIs are prescribed, or for less than the required 12 weeks, or at sub-therapeutic doses. Dissemination of best-practice prescription guidelines for OCD, then, still remains a major educational goal for the future even in high-income countries like Italy.

The importance of shortening the DUI becomes evident when examining response rates according to this modifiable parameter. The literature on the topic is scant and results are contradictory; a

first study [8] found that a DUI longer than 24 months is associated with a significantly reduced response rate in OCD, although, in the same sample, DUI as a continuous variable was not predictive of treatment response nor remission. A second study [20] found that DUI was not predictive of remission when considered continuously, although the p-value revealed a trend toward significance ($p = .074$) and no other analyses were preformed using a dichotomous DUI. It is also possible that negative results depend on the analysis of response to the current treatment instead of to the first ever adequate SRI treatment received; we then decided to focus our analyses on the first ever adequate SRI treatment received and considered the DUI both as a dichotomous (brief versus long, below versus above median value) and a continuous variable.

We showed that response rates are significantly reduced when DUI is longer than 24 months (41% versus 69%) or is above the median value (>60 months) (40% versus 61%) and that the mean DUI is significantly longer in subjects not responding to the first ever adequate SRI treatment. Y-BOCS scores at 12 weeks were also higher and percentage changes in Y-BOCS scores lower in individuals with long/above median DUI. Our regression analyses showed that DUI longer than 24 months predicted response and 12-week Y-BOCS scores, but not DUI as a continuous variable (exactly replicating results of the previous researchers). This means that how one defines DUI (as a continuous or dichotomous variable, using different cut-offs) matters to the results and raises the question of exactly how long would be a long DUI impacting on the probability of response. It may be that future investigations could benefit from using a data-driven approach to find out what duration of untreated illness might really make a difference. Overall, however, we think that we found evidence supporting a possible negative impact of long DUI on treatment response in OCD and that the window of opportunity for an early and effective treatment for OCD is less than 24 months.

Several possible explanations of the association found between long DUI and poor treatment response have been suggested; first of all, it may be that more benign cases of OCD are more likely to come to the clinic and seek help or treatment compared to more severe or resistant cases, resulting in a brief DUI and a better response rate (selection bias). A second possibility is that the biology of the illness may progress with time, as suggested by brain-imaging studies, which provided evidence that neuro-circuitry abnormalities associated with OCD evolve with age, from childhood to adulthood, as a biological correlate to the increasing clinical complexity of OCD [42,43]. Two recent studies from an international collaborative group (ICOCS) [40,41], moreover, have also identified duration of illness as a mediating factor of outcomes and have separated this out from early age at onset; it is not so much an early onset of the disorder, then, that may impact on treatment outcome, but rather the duration of untreated illness. Studies finding reduced hippocampal and amygdalar volumes associated with longer DUI [25] and reduced N-acetyl aspartate among others neurochemical measures (using magnetic resonance spectroscopy) in several cerebral areas in OCD [26] provide additional evidence of a possible biological damage associated with the duration of severe symptoms. In favor of a possible "toxic" nature of episodes of untreated illness are results of a study [27] where relapses after discontinuation of drug in OCD are associated with increased resistance to treatments. Neurocognitive studies, moreover, suggested that a potential explanatory model for how OCD becomes more resistant to conventional strategies with time could be an exaggerated bias toward habitual responding [44,45]. An imbalance between the habit-learning system and the goal-directed system that exerts control over habits is postulated to be central in explaining compulsivity; it is plausible that, with time, as long as compulsions are repeatedly performed by untreated individuals with OCD, a further progressive shift from goal-directed control over habits to overreliance on habits could explain the increased rate of treatment resistance. Another possible contributing factor is a greater family accommodation (family responses specifically related to obsessive-compulsive symptoms) [28], found to be associated both with lower quality of life and greater burden [29,30], and with resistance to treatments [31–36]. It could be that family members do accommodate OCD symptoms to a progressively greater degree as long as the duration of untreated illness progresses, finally loosing insight themselves into the pathological nature of some behaviours and leading to treatment resistance. It is also possible that the longer the duration of untreated illness the lower could be the degree of insight of patients, thus impairing adherence of patients to treatments. The exact relationship between poor insight and a long DUI, however, is not clear, as both subjects with poor insight may take longer to seek help and receive appropriate treatment, but also one may hypothesize that the longer the duration of untreated, active illness, the higher the probability of losing insight into the pathological nature of obsessive-compulsive symptoms. Another potential negative consequence of a long duration of untreated OCD could be the development of a greater burden in terms of associated general medical conditions; in another study from our research group we found that OCD subjects with general medical conditions have longer DUI [38].

Independently from speculative inferences about mechanisms associated with treatment resistance, however, it is imperative to do all the possible to shorten the DUI, both by improving access to mental health services worldwide, improving the ability of primary care physicians and mental health professionals to recognize OCD, and disseminate best-practice prescription guidelines. Our opinion is also that standards of care programmes for tertiary-care OCD centres should be implemented and disseminated [39]. Our work, moreover, makes a strong argument for developing specialized early intervention services for OCD (as we have for psychosis) to ensure patients get early intervention with effective treatments.

Among possible limitations of our study is the retrospective investigation of AAO, which is subject to recall bias. However, following the same methodology used in previous researches [21], we tried to limit this bias by investigating the patient carefully, having in all possible cases another informant (generally a family member) confirming the AAO, and by examining medical records of patients. A second limitation is that we defined duration of untreated illness as the interval between the onset of the disorder (that means when symptoms were of sufficient severity to impair patients' functioning or when they occupied at least one hour per day) and the first adequate pharmacological treatment. Other investigators, on the contrary, calculated the interval between symptoms onset and when patients received the first adequate treatment. We think that age at onset, as opposed to age at symptoms' onset, is retrospectively identifiable with greater ease, and thus we decided to use age at disorder onset. However, if we assume that the DUI is associated with a biological damage, it may be that even subthreshold symptoms could potentially interfere with treatment response. Another limitation could be the choice of how adequate dose was defined; we referred to the WFSBP guidelines [13,14], that indicated rather low minimal effective doses (e.g. 75 mg of clomipramine and 100 mg of fluvoxamine). Inspection of doses actually received by our patients, however, demonstrated that mean doses conformed to those in the moderate-to-high interval (see Table 3; e.g. 240 mg of fluvoxamine). Moreover, no differences in mean doses received by individuals in the brief versus long DUI subgroups were found (data not shown, available upon request). It is not plausible, then, that differences in response rates are to be attributed to differences in mean doses received. Finally, the use of a response rate defined

as ≥25% reduction in the Y-BOCS could be a limitation; we then performed a sensitivity analysis and confirmed that our results held using a greater response (≥35% reduction in Y-BOCS) [responders in brief versus long DUI: 57(67.9%) versus 61(39.1%), $\chi^2 = 18.063$, $p < .001$; responders in below median versus above median DUI: 73(57.5%) versus 45(39.8%), $\chi^2 = 7.459$, $p = .006$]. The logistic regression model with response (≥35% reduction in Y-BOCS) as dependent variable and DUI as independent one confirmed that individuals with long DUI have a lesser chance of responding.

5. Conclusions

Despite limitations, we confirmed in a larger sample and using the first ever treatment, that a long DUI is associated with lower response rates to pharmacological treatments in OCD. It is both possible that the duration of untreated symptoms could determine a biological damage responsible for increased resistance to treatments, or that untreated illness could determine greater family accommodation, which in turn could make the disorder more resistant to treatments. It is also possible that the longer the duration of untreated illness the lower could be the degree of insight, thus impairing adherence of patients to treatments.

Being the duration of untreated illness a modifiable parameter, and considering that the mean DUI in OCD is even longer than that of other psychiatric disorders, our study points to the need of continuing education of the general population, primary care physicians and psychiatrists concerning the existence of OCD, its phenomenological expression, how to correctly diagnose it and how to early intervene with appropriate treatments. Moreover, the study of factors delaying help-seeking behaviours among OCD sufferers is strongly needed, in order to decrease the treatment gap in OCD.

Disclosure of interest

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