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"*When is it late*"? Optimal threshold for duration of untreated illness (DUI) to predict SSRI-treatment resistance in individuals with obsessive-compulsive disorder (OCD)

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A B S T R A C T

Background: Obsessive-compulsive disorder (OCD) is a chronic psychiatric condition in which delays to appropriate treatment—known as duration of untreated illness (DUI)—are common and clinically consequential. Although prolonged DUI has been associated with poor response, the specific time point beyond which treatment resistance becomes likely remains unclear.

Methods: We analysed 220 adults with DSM-5 OCD consecutively recruited at the University of Turin OCD clinic (2015–2023). DUI was defined as the interval between onset of clinically significant symptoms and the initiation of an adequate selective serotonin reuptake inhibitor (SSRI) trial (moderate-to-high dose for ≥12 weeks). Response was defined as a ≥35 % reduction in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score and a Clinical Global Impression–Improvement (CGI-I) rating ≤2. Receiver-operating-characteristic (ROC) analysis identified the DUI cut-off predicting SSRI non-response.

Results: Mean age was equal to 34.5 ± 12.4 years; mean DUI was 107.2 ± 116.7 months. Half of the sample (50.4 %) responded to first-line SSRIs. ROC analysis yielded area under the curve = 0.634 ($p < 0.001$). The optimal cut-off was 42 months, corresponding to a sensitivity of 70.1 % and a specificity of 53.9 %.

Conclusions: A DUI exceeding about 3.5 years is associated with a substantially lower probability of SSRI response. These data suggest that a duration of untreated illness beyond forty-two months may predict reduced responsiveness to first-line SSRI therapy in OCD, though replication in larger, multicentric samples is warranted.

1. Introduction

Obsessive-compulsive disorder (OCD) is a disabling neuropsychiatric illness characterised by intrusive thoughts and repetitive behaviours that cause profound distress and functional impairment. Despite the availability of effective therapies—selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioural therapy (CBT) with exposure and response prevention (ERP)—treatment is often delayed.

The duration of untreated illness (DUI), defined as the time between symptom onset and the start of an adequate treatment, mirrors the concept of *duration of untreated psychosis* and has emerged as a crucial determinant of prognosis in OCD. Longer DUI has been linked with greater chronicity, worse quality of life, and poorer pharmacological response (Dell'Osso et al., 2010; Albert et al., 2019a). Yet, the precise temporal threshold that marks "late" treatment remains unknown.

Our recent meta-analysis (Pellegrini et al., 2025) found that individuals with OCD seek help, on average, six years after symptom onset—a remarkable delay even within high-income settings. This finding sits within a broader treatment gap, defined as the proportion of affected individuals who never receive adequate treatment, estimated at ~25 % in Europe and ~50 % globally (Kohn et al., 2004; Hirschtritt et al., 2017).

Several barriers contribute to this delay: under-recognition of OCD by non-specialist clinicians, symptom concealment by patients due to shame or misunderstanding, and diagnostic ambiguities. Intrusive thoughts are sometimes misattributed to personality traits or moral

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conflicts, leading to misdiagnosis (Glazier et al., 2013). The *ICD-11* has improved recognition by grouping OCD and related disorders within a dedicated chapter and by clarifying symptom boundaries—a refinement validated by Kogan et al. (2020). However, dedicated early-intervention services remain rare. The pilot *Early-OCD* programmes described by Brakoulias et al. (2021) confirmed feasibility but limited reach, underscoring the need to define concrete thresholds to guide earlier care.

SSRIs remain the pharmacological cornerstone of OCD treatment. Adequate trials require higher doses and longer durations than for depression, typically 60–80 mg fluoxetine-equivalent for ≥12 weeks (Fineberg et al., 2020). However, recent data (Cohen et al., 2025) have questioned the universality of this 12-week rule, suggesting substantial inter-individual variability. The timing of initiation may be as critical as the dose and duration: a late start may reduce neurobiological plasticity and entrench maladaptive behaviours.

Previous research established the direction of the relationship—longer DUI, poorer outcomes—but not its quantitative threshold. Studies by Dell'Osso et al. (2010) and Albert et al. (2019a) used a 24-month cut-off selected a priori. To our knowledge, no study has empirically derived the optimal point at which untreated illness predicts resistance.

The present study therefore sought to determine this threshold using a data-driven approach. Our objectives were to (i) identify, through ROC analysis, the DUI duration most predictive of SSRI non-response and (ii) describe the demographic and clinical correlates of short versus long DUI. We hypothesised that longer DUI would significantly reduce the probability of pharmacological response.

2. Methods

2.1. Design and participants

This longitudinal observational study was conducted at the Department of Neurosciences "Rita Levi Montalcini", University of Turin, between 2015 and 2023. The protocol was approved by the institutional ethics committee (Prot. 0007375); all participants provided written consent. The sample comprised consecutive outpatients (aged 18 years and older) having a primary diagnosis of OCD (DSM-5) and a score on the Yale-Brown Obsessive-Compulsive Scale of at least 16 (moderate OCD). Semi-structured interviews (SCID-5) were carried out by psychiatrists with experience in OCD. Subjects with a previous or present diagnosis of schizophrenia or psychotic disorders or organic brain syndrome were excluded from the study. Other comorbidities were included in the study, provided OCD was the principal diagnosis. Of 273 individuals screened, 53 were excluded (18 subthreshold OCD, 9 psychosis, 26 incomplete data), leaving 220 participants for analysis (Supplementary Fig. S1).

2.2. Variables and definitions

Age at onset was defined as the age when obsessions/compulsions first caused significant distress or functional interference for ≥1 h/day. Duration of untreated illness (DUI) was defined as the interval between onset of clinically significant symptoms and age at first adequate treatment. An adequate SSRI trial was considered as administration of a moderate-to-high dosage maintained for at least 12 weeks, consistent with international guidelines (Bandelow et al., 2012; Fineberg et al., 2020).

2.3. Treatment and psychotherapy

All patients received an SSRI at clinically indicated dosages. Twenty-seven percent (27 %) underwent concurrent CBT incorporating ERP during the first pharmacological trial. No participant received antipsychotic augmentation or neuromodulation during this period.

2.4. Outcome definition

Treatment response was defined as ≥ 35 % reduction in Y-BOCS score + Clinical Global Impression–Improvement (CGI-I) 1 ("very much improved") or 2 ("much improved") sustained ≥1 week (Mataix-Cols et al., 2022). Responders were coded as 1; non-responders were coded as 0.

2.5. Statistical analysis

ROC curves were used to assess the predictive ability of DUI for SSRI non-response. Sensitivity, specificity, positive and negative predictive values (PPV, NPV), and area under the curve (AUC) with 95 % confidence intervals were computed. The optimal cut-off was determined using the Youden index (J = sensitivity + specificity – 1). Analyses employed IBM SPSS v30. Based on an expected 50 % response rate and 5 % margin of error, a minimum of 192 participants was required for 80 % power; the achieved sample (N = 220) exceeded this threshold.

3. Results

3.1. Sociodemographic and clinical profile

The final sample comprised 220 adults with primary OCD (119 males, 101 females; mean age = 34.5 ± 12.4 years) (see Table 1). Average education was 12.6 ± 3.6 years; 60 % were single and 46.8 % employed. Family history of OCD was reported by 19.1 %. Baseline Y-

Table 1
Sociodemographic and clinical characteristics of the sample.

Variable		N	%
Gender	Males	119	54.1
	Females	101	45.9
Marital Status	Single	132	60.0
	Married	73	33.2
	Separated	11	5.0
	Widowed	4	1.8
Occupation	Employed	99	46.8
	Unemployed	59	26.8
	Student	46	20.9
	Retired	12	5.5
Family history of OCD	Yes	42	19.1
	No	178	80.9
Type of onset	Abrupt	57	25.9
	Insidious	163	74.1
Type of course	Chronic, stable	45	20.5
	Chronic, waxing and waning	133	60.5
	Chronic, worsening	15	6.8
	Episodic	27	12.3
Responded to first-line SSRI[a]	Yes	111	50.4
	No	109	49.6
Y-BOCS severity[b]			
mild (16–19)		5	2.3
moderate (20–27)		116	52.8
severe (28–35)		85	38.7
extreme (>35)		14	6.2

	Mean	SD
Age	34.5	12.4
Education (years)	12.6	3.6
Y-BOCS	24.4	6.6
Age at symptoms onset (years)	16.4	7.7
Age at disorder onset (years)	21.5	8.8
Age at first adequate treatment (years)	31.2	11.9
Duration of untreated illness (months)	107.2	116.7

[a] Response defined as a clinically meaningful reduction in symptoms (time, distress, and interference associated with obsessions, compulsions, and avoidance) relative to baseline severity – specifically, a ≥35 % reduction in Y-BOCS scores plus CGI-I rating of 1 ("very much improved") or 2 ("much improved"), lasting for at least one week (Mataix Cols et al., 2022).
[b] Using the severity benchmarks proposed by Cervin et al. (2024).

BOCS score averaged 24.4 ± 6.6. Using the severity benchmarks proposed by Cervin et al. (2024), 2.3 % were mild (16–19), 52.8 % moderate (20–27), 38.7 % severe (28–35), and 6.2 % extreme (>35). Mean age at symptom onset was 21.5 ± 8.8 years, and mean age at first adequate treatment was 31.2 ± 11.9 years. The mean DUI was 107.2 ± 116.7 months (median = 68, range 2–450; Supplementary Fig. S2). 50.4 % (n = 111) of participants responded to their first SSRI trial according to the pre-defined criteria.

3.2. Psychotherapy

Twenty-seven percent of the cohort received concurrent CBT-ERP during the first SSRI trial. This variable showed no significant relationship with treatment response ($\chi^2 = 0.98$, p = 0.32).

3.3. ROC analysis and optimal cut-off identification

ROC analysis demonstrated an area under the curve (AUC) of 0.634 (SE = 0.037, 95 % CI 0.562–0.706, p < 0.001), indicating moderate accuracy of DUI in predicting SSRI non-response (Fig. 1). The highest Youden index (J = 0.240) was observed at 42 months. At this threshold, sensitivity was 70.1 % and specificity 53.9 %, with PPV = 60.7 % and NPV = 70.1 %. The ROC curve parameters for all tested cut-offs are detailed in Supplementary Table S1.

3.4. Comparison of short vs long DUI groups

Patients with shorter DUI (≤42 months, n = 114) were significantly younger (31.7 ± 10.8 years) than those with longer DUI (>42 months, n = 106, 37.3 ± 13.2 years; p = 0.004). Response rate was higher in the short-DUI group (63.2 % vs 36.8 %, p < 0.001). Baseline Y-BOCS scores, family-history prevalence, and gender distribution did not differ significantly (all p > 0.05). These comparisons are summarised in Supplementary Table S2.

4. Discussion

This study identifies, for the first time, a data-driven threshold for duration of untreated illness predicting SSRI treatment resistance in OCD. Our ROC analysis showed that a DUI longer than approximately 42 months (3.5 years) is associated with a markedly lower probability of response to first-line SSRI therapy. These findings advance previous literature by quantifying a clinically meaningful cut-off rather than relying on arbitrary timepoints. They also situate OCD within a broader early-intervention paradigm, akin to the established "critical period" model in psychosis (Howes et al., 2021), where delayed treatment correlates with persistent neurobiological dysfunction. The average DUI of over nine years in our cohort highlights the magnitude of this problem: most patients began appropriate pharmacotherapy well beyond the window associated with maximal responsiveness.

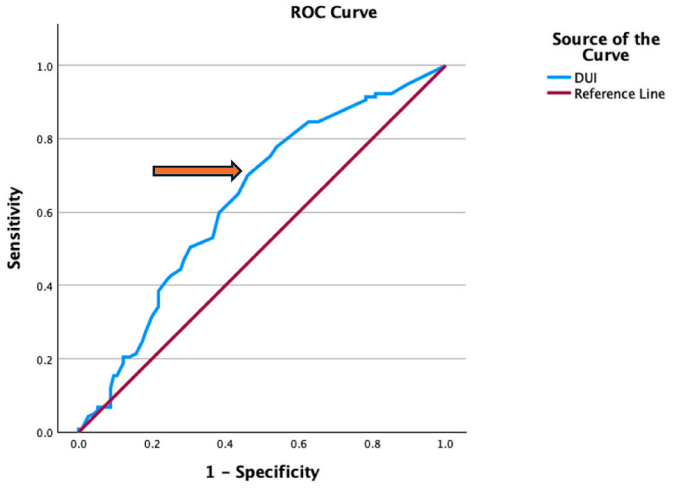

Fig. 1. Receiver Operating Characteristic (ROC) predicting treatment response. Blue line indicates AUC of the reference variable (response to first adequate SSRI treatment); red line indicates AUC where the null hypothesis (p < 0,05) is not rejected and the variable would have no predictive value; orange arrow indicates cut-off at which optimal sensitivity/specificity is reached.

Earlier work by Dell'Osso et al. (2010) and Albert et al. (2019a) demonstrated that prolonged DUI correlates with poorer SSRI outcomes, but both studies used pre-specified cut-offs (usually two years). Our analysis confirms the existence of a threshold effect and defines its location empirically. These results also complement meta-analytic evidence from Pellegrini et al. (2025), who demonstrated a significant negative correlation between DUI and treatment response across independent samples, and align with longitudinal findings that shorter latency to first pharmacological treatment improves prognosis in anxiety and mood disorders (Dell'Osso et al. (2010)).

The association between long DUI and treatment resistance likely reflects cumulative neurobiological, behavioural, and psychosocial changes. At the neurocircuitry level, prolonged symptom duration may reinforce maladaptive cortico-striato-thalamo-cortical (CSTC) loops, leading to habitual rather than goal-directed behaviour (Gillan et al., 2017).

Identifying an empirically derived threshold of 42 months has tangible clinical relevance.

First, clinicians should routinely record DUI during assessment, as it provides prognostic information independent of symptom severity. A DUI exceeding three years should alert the clinician to a higher likelihood of SSRI non-response, prompting earlier consideration of combined SSRI–CBT therapy or augmentation strategies. Second, our findings underscore the importance of early recognition and referral. Primary care physicians should be trained to distinguish OCD from overlapping anxiety or personality presentations (Glazier et al., 2013). Educational initiatives aimed at teachers and general practitioners may reduce diagnostic delay.

Third, from a public-health perspective, shortening DUI could substantially reduce the societal and economic burden of OCD. In the UK, the annual cost of OCD has been estimated at over £5 billion (Kochar et al., 2023). Earlier diagnosis and intervention may improve functional outcomes, reduce unemployment, and prevent chronic disability.

5. Limitations

The study's strengths—its well-characterised sample and empirical methodology—are tempered by several limitations. The single-centre design and Italian population limit external generalisability. Onset age was determined retrospectively, introducing potential recall bias. Psychotherapy was not standardised, and follow-up extended only through the first SSRI trial, preventing long-term outcome evaluation. Although the study was adequately powered, the sample remains modest relative to international multicentric cohorts. Finally, unmeasured variables such as comorbidities, insight and symptom dimension could modulate the DUI–response relationship.

Future research should replicate these findings in larger, multicentric samples with prospective designs. Neuroimaging studies could explore whether specific structural or functional markers mediate the association between DUI and resistance to first-line pharmacotherapy. Interventional trials should test whether reducing DUI through early-detection campaigns translates into improved outcomes. Furthermore, international consensus on operational definitions of "adequate treatment" and "treatment delay" is urgently needed to harmonise future studies.

6. Conclusions

A duration of untreated illness longer than approximately 42 months is associated with substantially lower probability of response to first-line SSRI therapy in OCD. This threshold provides a practical benchmark for clinicians and policymakers and reinforces the principle that *when* treatment begins may be as important as *what* treatment is given. Efforts to reduce DUI—through public education, professional training, and accessible early-intervention services—should be prioritised to prevent chronicity and improve quality of life for individuals with OCD.

CRediT authorship contribution statement

Luca Pellegrini: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Gabriele Di Salvo:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Nicola Rizzo Pesci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation. **Gianluca Rosso:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giuseppe Maina:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Umberto Albert:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors have no interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2026.01.056.

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