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. It has been poorly investigated in Obsessive-Compulsive Disorder (OCD). Our aims were to estimate the mean DUI in a huge sample of individuals with OCD and to investigate its impact on treatment response.

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 (≥25% reduction in Y-BOCS total score) to the current treatment and to the first ever adequate pharmacological treatment were compared in subjects with brief versus longer DUI.

Results. The mean DUI was 106.19±118.14 months. This impressive long DUI is mainly to be attributed to the delay of patients in seeking help (the mean interval between the onset of the disorder and when patients sought professional help was 82 months). Response rates were significantly reduced in subjects with longer DUI, using both the cut-off of 24 months and the median value of 60 months, to the current and to the first ever adequate pharmacological treatment.

Conclusions. 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.

Introduction

Despite having effective treatments for Obsessive-Compulsive Disorder (OCD), namely Cognitive-Behavioural Therapy (CBT) and serotonergic compounds (SSRIs and clomipramine) (Skapinakis et al., 2016; Hirschtritt et al., 2017), there is a treatment gap (difference between those individuals with OCD needing treatment and those actually receiving it) estimated to be in Europe of 25% in 2004 (50% approximately in the world) (Kohn et al. 2004). The situation has not changed in more 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 (Garcia-Soriano et al., 2014). The phenomenon is then relevant. Even when subjects with OCD do seek help, the mean delay in help-seeking behaviours is substantial: it is estimated that individuals with OCD take up to 11 years to seek professional help (Garcia-Soriano et al., 2014).

A second barrier in the pathway to optimal care for OCD lies in the specificity of the pharmacological treatment for this disorder. Moderate-to-high doses for at least 12 weeks are required in order to elicit a response, and patients need to be on treatment for at least 1 year in order to maintain the response and achieve remission, and often it is not easy for them to fully adhere to psychiatrists' prescriptions. 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. psychodynamically-oriented therapy), in terms of doses (subtherapeutic doses) and/or time (clinicians may switch to other treatments when the first is not effective after only 4-to-6 weeks as in the case of Major Depressive Disorder, not knowing that the time required for OCD is at least 12 weeks, preventing pharmacological treatments to be effective).

As a consequence, the duration of untreated illness (DUI) may be long. Originally studied in relation to psychosis (duration of untreated psychosis - DUP), the DUI has been defined as the interval between the onset of the disorder and the time when the patient receives the first *adequate* treatment for that psychiatric disorder (correct medication, at standard dosages, for an adequate period of time depending on the specific psychiatric disorder) (McGlashan, 1999; Perkins et al., 2005; Compton et al., 2007; Dell'Osso et al., 2010). 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 longer (Marshall et al., 2005; Perkins et al., 2005; Clarke et al., 2006), indicating a possible neurotoxic effect of the DUI (Anderson et al., 2014). Moreover, being modifiable, the DUI could be a key to early intervention in severe mental disorders (Murru and Carpiniello, 2018).

The DUI has been poorly investigated in OCD; only two researcher groups estimated in clinical samples the DUI. A first group published several studies investigating the mean DUI in individuals with OCD (not specifying whether each subsequent study included the sample enrolled in the previous ones), showing that the mean DUI (defined as the interval between the onset of the disorder and when the patient received the first adequate treatment defined according to guidelines published by the World Federation of the Societies for Biological Psychiatry – Bandelow et al., 2008-2012) was comprised between 87.5 and 94.5 months (the

samples comprised 51 to 124 patients with OCD)(Altamura et al., 2010; Benatti et al., 2016; Dell'Osso et al., 2010, 2013, 2015, 2017). Preliminary data indicated that even in OCD a longer DUI (more than 2 years) is associated with lower response rates (Dell'Osso et al., 2010); in that study, the mean DUI was 93.1±110.9 months, and subjects with a DUI>24 months (this cut-off was chosen on the basis of previous studies performed in non-OCD samples) had lower response rates than those with a briefer DUI. Response was defined as a ≥25% reduction in Y-BOCS total scores after 12 weeks and was prospectively evaluated. However, this was not necessarily the first ever pharmacological treatment. Moreover, a logistic regression analysis did not find a significant correlation neither between response nor remission rates and the DUI expressed in months. The only other study which investigated the possible relationship between the DUI and treatment outcome (Poyraz et al., 2015) 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).

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 huge sample of individuals with OCD; and 2. to investigate whether response to treatments is dependent on the DUI. More specifically, we aimed at confirming results of a poor response in subjects with a longer DUI to the current pharmacological treatment and we aimed at expanding the knowledge examining response to the first ever adequate pharmacological treatment.

Methods

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.

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 (e.g. Albert et al., 2015), 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, 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.

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 and were prospectively and naturalistically treated according to International Guidelines (clomipramine and/or SSRIs, for at least 12 weeks, at adequate doses) (Bandelow et al., 2008; 2012). We enrolled patients who were assessed at baseline (prior to the administration of our prospective treatment) with a baseline Y-BOCS in order to determine the current severity of their OCD symptoms and who were administered the same scale after 12 weeks of treatment; response rates at week 12 were calculated, defining response as a reduction in the Y-BOCS total score over the 12-week period greater or equal to 25% with respect to baseline. Treating psychiatrists were free of choosing the drug provided that their choice was among first-line compounds (clomipramine or SSRIs) according to guidelines. No patient was excluded due to comorbid disorders as long as his/her principal diagnosis was OCD.

We separately considered response rates to the current, prospectively administered adequate treatment (the one we prescribed and followed-up for at least 12 weeks) and response rates to the first ever adequate pharmacological treatment patients received. For those patients for whom the current treatment prescribed was their first ever treatment, we could prospectively evaluate of course the response to the first ever adequate treatment. Through chart reviews we tried to retrospectively determine response rates to the first ever adequate pharmacological treatment for patients whenever it was possible to retrieve a baseline Y-BOCS and a second Y-BOCS administered at least 12 weeks after receiving the treatment.

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 longer), using two different cut-offs: 1. The median value in our sample, 2. The previously used (Dell'Osso et al., 2010) cut-off of 24 months. 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.

Results

Patients' characteristics

Two-hundred fifty-one patients were enrolled in the study; 25 individuals (9.9%) dropped out before completing 12 weeks of pharmacological treatment, leaving 226 subjects who completed a prospectively evaluated adequate pharmacological treatment for their OCD.

One hundred thirty-four of these patients received an adequate pharmacological treatment for the first time in their lives; moreover, we managed to retrospectively determine response to the first ever adequate treatment for additional 106 individuals, giving a total sample of 240 subjects for the evaluation of response rates to the first ever adequate pharmacological treatment (see Figure 1).

Baseline socio-demographic and clinical characteristics of patients included are reported in Table 1.

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 Figure 2 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, 2010) of 24 months (brief DUI: ≤24 months) and to our median value (brief DUI: ≤60 months). Using both cut-offs, a significant percentage of our patients reported a longer DUI (that is received a first adequate pharmacological treatment years after the onset of the full-blown impairing disorder – OCD onset).

Response rates according to Duration of Untreated Illness

Table 3 reports mean DUI (in months) in responders versus non-responders to the currently administered, prospectively evaluated, adequate pharmacological treatment and to the first ever adequate pharmacological treatment; a significant longer mean DUI is associated with non-response to the first ever treatment.

Figure 3 presents responder rates (reduction ≥25% in the Y-BOCS total score) according to the type of DUI (brief versus longer) with the two different cut-offs used; response rates were significantly reduced in subjects with longer DUI, independently of the cut-off used, both to the current and to the first ever treatment.

The magnitude of the difference is greater when the first ever adequate treatment is considered.

Discussion

The aim of the present study was to estimate the mean duration of untreated illness in a huge 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 (Dell'Osso et al., 2010), examining response rates to the current prospectively evaluated adequate pharmacological treatment and to the first ever adequate treatment (retrospectively examined and/or prospectively evaluated when possible).

An *adequate* pharmacological treatment for OCD requires the use of clomipramine or a SSRI, given for at least 12 weeks at adequate doses in order to elicit a response, which is usually measured and defined as a reduction in the total score on the Y-BOCS at least equal to or greater than 25% with respect to baseline; response for OCD is then slow and usually the degree of reduction of symptoms is small in the first 3 months. 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 (2010), 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 the minimum effective doses are at least moderate, while others (namely the WFSBP) seem to suggest that even low doses are indicated. When deciding which minimum dose to consider in order to examine response rates according to the DUI in the present study, we reviewed previous papers dealing with the same issue. We found that the group by Dell'Osso and coworkers used the WFSBP guidelines (Bandelow et al., 2008; 2012) in defining an *adequate* treatment for OCD, while Poyraz and colleagues (2015) did not specify to which minimum effective dose they referred to when considering *adequate* the pharmacological treatment. We then decided to refer to the lower threshold and 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.

Even when considering this lower threshold, we found that the mean interval elapsing from onset of the disorder (that means onset of symptoms interfering with functioning and/or occupying a significant amount of time per day) 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 other Italian sample – Dell'Osso et al., 2010, 2013, 2015, 2017; Altamura et al. 2010; Benatti et al., 2016- and 7 years in the Turkish sample – Poyraz et al., 2015).

This impressive long duration of untreated illness is mainly to be attributed to the delay of patients in seeking help (the mean interval between the onset of the disorder and when patients sought professional help for the first time is 82 months – approximately 7 years).

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 (Garcia-Soriano et al., 2014; Robinson et al., 2017). 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 diagnosing appropriately OCD (indeed high rates of OCD symptom misidentification by mental health professionals were found – Glazier et al., 2013), 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 in 2018 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.

We added to the existing but scarce evidence in the literature (Dell'Osso et al., 2010) in showing that response rates are significantly reduced when the DUI is longer (or, which is specular, that the mean DUI is significantly longer in subjects not responding to the first ever adequate treatment); this may imply that even for OCD the longer the DUI the greater could be the biological damage associated with the duration of severe symptoms. In favor of this "neuroprogressive/neurodegenerative" hypothesis are results of studies finding reduced hippocampal and amygdalar volumes associated with longer DUI (Atmaca et al., 2008) and reduced N-acetyl aspartate among others neurochemical measures (using magnetic resonance spectroscopy) in several cerebral areas in OCD (Gnanavel et al., 2014). It is then possible that even the duration of untreated OCD (as the duration of untreated psychosis) has an effect on neurodegeneration as hypothesized for psychosis (Anderson et al., 2014). An old study from our research group (Maina et al., 2001) supports this conclusion: we found that relapses after discontinuation of drug in OCD are associated with increased resistance to the same pharmacological treatment (same compound given exactly at the same dosage), suggesting that each episode of untreated illness may carry a "toxic" nature. However, these conclusions are very speculative to date and further studies are strongly needed in order to deepen our understanding of this hypothesized mechanisms of increased resistance to treatments.

An alternative hypothesis that could explain why subjects with longer DUI are more resistant to pharmacological treatments is that the effect is mediated by greater family accommodation. The term family accommodation has been proposed to refer to family responses specifically related to obsessive-compulsive symptoms: it encompasses behaviours such as directly participating to compulsions and/or assisting a relative with OCD when he/she is performing a ritual (e.g. controlling that the patient with OCD is "*correctly*" taking a shower without touching nothing "*dirty*" or potentially "*contaminating*"; having to pass towels to the patient

taking particular care that they don't touch "*contaminated*" surfaces) or helping him/her avoiding triggers that may precipitate obsessions and compulsions (the relative has to respect rules that OCD imposes on the patient; e.g. for a patient with contamination obsessions, having to undress before entering the home and putting the "*dirty*" clothes in a specific place at home, avoiding to "*contaminate*" the house with these "*dirty clothes*" and having to immediately wash themselves before entering "*uncontaminated*" rooms)(see for a review on the argument Albert et al., 2017). Family accommodation is associated with lower perceived quality of life of family members and greater burden (Albert et al, 2007; 2010) but also with some degree of resistance to treatments, both CBT and pharmacological ones. According to the cognitive-behavioural model, accommodation results in a negative reinforcement cycle, in which patients are more likely to continue engaging in avoidance and compulsive behaviours because accommodation by a relative is immediately associated with a decrease in anxiety/distress; moreover, this prevents patients from developing more adaptive appraisals and behaviours to cope with their OCD-related distress (Wu et al., 2016). From a theoretical point of view, then, accommodating behaviours counteract the goal of exposure and response prevention technique. Indeed, several reports found that the higher is family accommodation among family members (mainly parents of children/adolescents) the higher is the degree of treatment resistance/refractoriness to CBT and to pharmacological treatment (Barrett et al., 2005; Ferrao et al., 2006; Storch et al., 2008; Garcia et al., 2010; Cherian et al., 2014). It could then 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. Indeed, a very interesting study found that OCD rates are significantly increased not only among first-degree relatives of OCD patients, but also among spouses/partners (not genetically related) of individuals with OCD (Mataix-Cols et al., 2013). This may be explained as a sort of assortative mating but it may also be that living several years with an individual with untreated OCD is associated with the development of a "secondary" OCD.

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 (Aguglia et al., 2018). It could be that persistent avoidance of medical consultations associated with untreated fear of contamination, for example, may lead to failure to get appropriate diagnosis and treatment of medical problems (Albert et al., 2010), adding burden to the existing psychiatric disorder.

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 (Menchon et al., 2016).

Strengths and limitations

Strengths of our study are, firstly, the inclusion of a larger sample of OCD patients (N=251) as compared to that of the previous study by Dell'Osso et al. (2010). Moreover, we could be able to prospectively follow patients for the first 12 weeks of the acute phase in order to determine response rates; for many patients, this was the first ever treatment, while for another 104 individuals we could be able to retrospectively determine response rates to the first ever pharmacological treatment they received because we could have access to a baseline Y-BOCS and a 12-week Y-BOCS. We could then be able to investigate whether the DUI was associated with poorer response to the first ever treatment patients received.

Among possible limitations is the retrospective investigation of AAO, which is subject to recall bias. However, following the same methodology used in previous researches (Albert et al., 2015), 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.

Conclusions

Despite limitations, we confirmed in a greater sample and using both the first ever treatment and the current treatment, that a longer 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.

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