Journal of Psychiatric Research 47 (2013) 1700–1707

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Can early improvement be an indicator of treatment response in obsessive-compulsive disorder? Implications for early-treatment decision-making☆

Daniel Lucas da Conceição Costa [a,*], Roseli Gedanke Shavitt [a], Raony Cassab Castro Cesar [b], Marinês Alves Joaquim [a], Sonia Borcato [a], Carolina Valério [a], Eurípedes Constantino Miguel [a], Juliana Belo Diniz [a]

[a] Department and Institute of Psychiatry, School of Medicine, Universidade de São Paulo (USP), São Paulo, Brazil
[b] Department of Statistics, Institute of Mathematics and Statistics, Universidade de São Paulo, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 17 February 2013
Received in revised form
3 July 2013
Accepted 5 July 2013

Keywords:
Obsessive-compulsive disorder
Treatment
Prognosis
Clinical pharmacology
Serotonin reuptake inhibitor

ABSTRACT

In major depression, early response to treatment has been strongly associated with final outcome. We aimed to investigate the ability of early improvement (4 weeks) to predict treatment response at 12 weeks in DSM-IV-defined obsessive-compulsive disorder (OCD) patients treated with serotonin reuptake inhibitors (SRI). We conducted an SRI practical trial with 128 subjects. Inclusion criteria: age range 18–65 years-old, baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score $\geq$ 16, and absence of previous adequate pharmacological treatment. Systematic assessments were performed at baseline, 4 and 12 weeks of treatment. Treatment response at 12 weeks was defined as a 35% or greater reduction in baseline Y-BOCS score. Stepwise logistic regression was used to test the relationship between early improvement and treatment response at 12 weeks, taking into account additional potential predictive factors. Different thresholds of early improvement were tested and their predictive power was calculated. Early improvement, defined as a 20% or greater reduction from baseline Y-BOCS score at 4 weeks, predicted response at 12 weeks with 75.6% sensitivity and 61.9% specificity. According to a logistic regression including demographic and clinical features as explaining variables, early improvement was the best predictor of treatment response (OR = 1.05, $p < 0.0001$). Only 19.8% of patients who did not improve at 4 weeks were responders after 12 weeks. In contrast, 55.3% of the individuals who showed early improvement were responders at 12 weeks (Pearson Chi-Square = 17.06, $p < 0.001$). Early improvement predicted OCD treatment response with relatively good sensitivity and specificity, such that its role in early decision-making warrants further investigation in wider samples.

Trial registration: clinicaltrials.gov Identifier NCT00680602.

1. Introduction

The efficacy of both cognitive-behavior therapy (CBT) (Belotto-Silva et al., 2012; Foa et al., 2005; Greist et al., 2002; Lindsay et al., 1997) and serotonin reuptake inhibitors (SRI) (Soomro et al., 2008) for obsessive-compulsive disorder (OCD) treatment has been well established in controlled studies. Although most patients benefit from these treatments, up to 60% may not respond to a first trial with any of these options in effectiveness studies (Belotto-Silva et al., 2012).

Prediction of response to treatment in OCD individuals is an extensive area of research. However, to date, pharmacotherapy studies have focused mainly on demographic and clinical features present at baseline as potential predictors, such as age at OCD onset (Ackerman et al., 1994; Erzegovesi et al., 2001), marital status (Shavitt et al., 2006), type of symptoms content (Alarcon et al., 1993; Ferrão et al., 2006; Mataix-Cols et al., 1999), presence of sensory phenomena (Shavitt et al., 2006), specific axis I or II comorbidities (Baer et al., 1992; Carrasco et al., 1992; Jakubovski et al., 2012; Jenike

☆ The data of the present study were presented at the 25th ECNP Congress, 13–17 October 2012, Vienna, Austria, and at the 6th ICOCS Annual Scientific Meeting, 18th October 2012, Vienna, Austria.

* Corresponding author. Department and Institute of Psychiatry, Faculdade de Medicina da Universidade de São Paulo, R. Dr. Ovídio Pires de Campos, 485, 3° andar, CEAPESQ, sala 7, CEP 05403-010 São Paulo, SP, Brazil. Tel.: +55 11 2661 6972; fax: +55 11 2661 7895.
E-mail addresses: dlccosta@usp.br, danielcosta228@yahoo.com.br (D.L. da Conceição Costa).

0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.07.006

et al., 1986; Shavitt et al., 2010), family history of OCD (Erzegovesi et al., 2001), illness duration (Alarcon et al., 1993; Ravizza et al., 1995; Stein et al., 2001), level of insight (Erzegovesi et al., 2001), socioeconomic status (Ferrão et al., 2006; Tükel et al., 2006) and family functioning (Ferrão et al., 2006; Tükel et al., 2006).

In OCD, as in other psychiatric disorders (Quitkin et al., 1987, 1996), pharmacological treatment is not expected to yield full response immediately following its initiation (March et al., 1997), proving an opportunity to assess early improvement as a possible predictor of outcome. OCD treatment guidelines (American Psychiatric Association, 2007; March et al., 1997) consider 8–12 weeks an adequate duration for a trial before switching drugs or augmenting therapy with another agent. Continuous improvement has been shown for periods longer than 12 weeks (Diniz et al., 2011; Jakubovski et al., 2012; Tollefson et al., 1994), suggesting that treatment response in OCD is rather slow and progressive than abrupt and stable.

In major depression, early response to treatment has been strongly associated with final outcome (Henkel et al., 2009). In one study investigating OCD patients treated with clomipramine, improvement at weeks 1 and 4 was determined to be the best predictor of treatment response at 12 weeks among other predictors, such as age at onset and severity of depressive symptoms (Ackerman et al., 1996).

Early identification of individuals less likely to respond could minimize exposure to ineffective drugs and optimize the use of medical resources (Szegedi et al., 2009). Therefore, predicting treatment outcome sooner could diminish the exposure of patients to ineffective treatments and guide sequential interventions.

Considering the lack of replication on early improvement as a possible predictor of outcome in OCD treatment, we aimed to investigate the predictive value of improvement at 4 weeks regarding treatment response 12 weeks after pharmacological treatment initiation.

2. Materials and methods

We performed a secondary analysis of the results of a trial conducted on OCD patients seeking treatment at the OCD Spectrum Disorders Program, at the Institute of Psychiatry, School of Medicine, University of São Paulo, Brazil between February 2005 and October 2009. The protocol was approved by the local Research Ethics Committee and written informed consent was obtained from all participants following a detailed description of the study procedures.

2.1. Study design

Patients included in this study were admitted to a randomized practical trial and were sequentially allocated to fluoxetine monotherapy or group cognitive-behavioral therapy (GCBT) (Belotto-Silva et al., 2012; Valerio et al., 2012). Four hundred and fifty-nine individuals were submitted to psychiatric screening; 304 met the inclusion criteria and were randomized to receive fluoxetine ($n = 199$), or GCBT ($n = 105$). Non-responders among those allocated to receive GCBT or those who withdrew from GCBT were given the option to initiate fluoxetine. Given that this protocol consisted of a practical clinical trial, patients who experienced intolerable side effects of fluoxetine in the first 4 weeks were allowed to switch to another selective serotonin reuptake inhibitor (SSRI). In this study, we included only subjects who were maintained on the same SSRI during the first 4 weeks of the trial. Measures for OCD severity at baseline, 4 and 12 weeks following treatment initiation were available for 102 patients initially allocated to the fluoxetine group. Likewise, measures for OCD severity at baseline, 4 and 12 weeks of pharmacological treatment were available for 26 patients initially allocated in the GCBT group who later switched to SSRI treatment.

2.2. Participants

The study sample consisted of 128 consecutive adult outpatients with primary OCD diagnosis according to DSM-IV criteria treated with an SSRI (mostly fluoxetine). Patients were referred from primary psychiatric services, patient associations and radio/TV/newspaper announcements.

Inclusion criteria: age in the range of 18–65 years-old; DSM-IV primary diagnosis of OCD; absence of previous adequate pharmacological treatment for OCD (defined as the use of an SRI – Clomipramine, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline or Paroxetine – at the maximum recommended or tolerated dose for at least 12 weeks); baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score $\geq$ 16 or Y-BOCS score $\geq$10 for obsessions or compulsions only. Exclusion criteria: any condition that could impair understanding of the protocol and/or interpretation of the results (e.g., history of head trauma with post-traumatic amnesia); current drug abuse or dependence; current psychotic symptoms; suicide risk; clinical or psychiatric comorbidities that precluded the use of the protocol medications (Belotto-Silva et al., 2012). Of note, bipolar disorder (BD) was not considered an exclusion criterion. However, patients with a lifetime history of BD had to be stable and on mood stabilizers in order to be admitted to the study. In our sample, only one individual had a DSM-IV diagnosis of BD and was on stable dosage of divalproate. One individual, with no previous diagnosis of BD, presented an antidepressant-induced mania episode and discontinued the study.

2.3. Treatment

Fluoxetine was used and stable dosage was set as the maximum tolerated up to 80 mg/day (titration: weekly increases of 20 mg/day). Regarding treatment maintenance between weeks 4 and 12, the individuals were divided into 4 groups: patients maintained on fluoxetine ($n = 114$); patients who switched to another antidepressant ($n = 2$); patients who received augmentation agents ($n = 6$); and dropouts who interrupted the SSRI treatment but came back for the 12-week evaluation ($n = 6$).

The mean doses (standard deviations) of fluoxetine used at weeks 4 and 12 by the patients in the first group were 68.9 (SD = 18.8) and 73.9 (SD = 13.0) mg/day, respectively.

Patients following a regime of chronic use of benzodiazepines were allowed to maintain them during the trial, as long as the dosage was not altered. When a complaint of insomnia was registered, our first treatment option was zolpidem 5–10 mg at bedtime. None of the patients were using stimulants.

2.4. Clinical assessments

The interviewers were experienced clinical psychologists or psychiatrists. All assessments, including self-reports, were checked and revised by an interviewer. The following array of standardized instruments was applied (Miguel et al., 2008).

a. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989)
b. Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (Rosario-Campos et al., 2006)
c. Beck Depression and Anxiety Inventories (BDI and BAI, respectively) (Beck et al., 1988; Beck et al., 1961)