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Citalopram Pulse-Loading for Severe Treatment-Resistant OCD: A Case Series of Acute Response, One Year Follow-Up and Tolerability

Giacomo Grassi[1]* and Stefano Pallanti[1,2]

[1]Department of Neuroscience, University of Florence, Italy
[2]Mount Sinai School of Medicine, New York, USA

Abstract

Background: Treatment resistance is a frequent situation in Obsessive Compulsive Disorder (OCD), occurring in 40-60% of patients. However, in the current literature there are only a few evidence-based options for treatment-resistant patients. Pulse-loading treatment consists in a rapid titration of the pharmacological agent in the first days of treatment. A few studies suggested that this kind of titration with intravenous clomipramine could result in a greater and faster response than with a standard titration in OCD resistant patients. The main aim of this case series was to investigate the effectiveness and tolerability of a citalopram pulse-loading protocol in severe treatment-resistant OCD patients. **Methods:** We treated 5 severe treatment-resistant OCD patients with intravenous citalopram starting with 40 mg for 3 days and increasing the dose up to 80 mg from the fourth day. The patients continued the treatment with 80 mg of intravenous citalopram for 18 days (a total of 21 days of intravenous treatment), then they switched to oral treatment (80 mg of oral citalopram). We assessed acute and one-year follow-up efficacy and tolerability.

Results: During the pulse-loading treatment no patients showed significant adverse events. Two of five patients had a full response and one of these had remission. Furthermore, these two patients did not have any relapse of OC symptoms during the 1-year follow-up. One of five patients had a partial response after 12 weeks and a full response during the 1-year follow-up period after switching from quetiapine to aripiprazole and after a CBT trial. Two of five patients did not respond. No patients showed clinical significant changes of the QTc interval. No patients showed significant changes of the sodium levels.

Conclusion: Taking into account the very limited sample size, this case series suggests that this treatment approach deserves further controlled studies.

Keywords: Obsessive compulsive disorder; CBT

Introduction

Treatment resistance is a frequent situation in Obsessive Compulsive Disorder (OCD), occurring in 40-60% of patients, which may occur at different stages during all the course of illness, having a strong impact on the long-term prognosis of the disease [1]. Treatment-response is actually a symptom reduction of 35% (or more) of the initial Yale – Brown Obsessive-Compulsive Scale (Y-BOCS) total score [1-3]. With regards to other psychiatric disorders, patients with this slight grade of clinical improvement might be still considered non-responders. Considering these issues, even if some important progresses have been made in last few years, many questions still remain open and represent a notable limit for an optimal intervention. Firstly, the treatment for non-responders is largely not evidence-based; secondly, the research on predictors of response has not provided clear treatment recommendations for resistant patients, even if some elements (early onset, poor insight, hoarding symptom dimension) have been individuated [4].

While there are several guide-lines based on expert opinion, in the current literature there are only a few evidence-based options for treatment-resistant patients. The most evidence-based option is the augmentation strategy with antipsychotics (e.g. haloperidol and risperidone). However, only a third of resistant-patients respond to this treatment [5]. Another option is the combination of CBT and pharmacotherapy that may be superior to pharmacological or non-pharmacological therapy alone, although literature data is still inconsistent [6]. After that a third option, mostly based on guide-lines and again with limited evidences of efficacy, is to combine serotonin reuptake inhibitors (SRIs) or increase the SRIs doses at supratherapeutic doses [6].

A promising approach is the infusive therapy strategy. A few controlled studies indicate that infusion therapy can be considered as a valid therapeutic strategy for treatment-resistant cases [7-12]. Two molecules are currently available for this kind of treatment of OCD, clomipramine and citalopram.

The rationale for using this way of administration is provided by both phamacokinetical and clinical considerations. On the one hand, the absorption of an intravenous administered drug is rapid, constant, and complete and is not affected by malabsorption, gastric pH modifications, intestinal motility, simultaneous administration of other drugs, etc. Moreover, intravenous administration allows to by-pass the hepatic first pass, that considerably influences the biodisponibility of the drug (in other words, the amount of active drug that reaches the systemic circulation). On the other hand, from a clinical point of view infusion therapy may improve treatment compliance, reinforce the therapeutic alliance and reduce the frequency of adverse events [13].

Clomipramine is partially converted by first pass metabolism into the metabolite desmethyl-clomipramine, which has a weaker serotoninergic effect. Intravenous administration may therefore

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increase the plasmatic clomipramine/desmethyl-clomipramine ratio and enhance the therapeutic effect. Fallon et al. [7] conducted a double-blind placebo controlled study on 54 non-responders patients (in a previous 8 weeks-long trial with clomipramine per os) and reported a greater efficacy of clomipramine i.v. versus placebo.

Clomipramine can be administered with a gradual increase of the dose or with a "pulse loading" strategy. Pulse-loading treatment is a rapid titration of the pharmacological agent in the first days of treatment. Several studies suggested that this kind of titration with intravenous clomipramine could result in a greater and faster response than with a standard titration in OCD resistant patients [8-10]. Furthermore, intravenous treatments seem to have a stronger long-term efficacy, as supported by clinical observation and by a follow-up study [11]. Ross et al. [11] conducted a follow-up study examining a sample of treatment-resistant OCD patients 4-11 years after they were treated with intravenous clomipramine. This study revealed that almost half of these patients reported to be much improved or very much improved compared to their state prior to treatment with intravenous clomipramine, and nearly one third no longer met criteria for OCD. These results suggest that a substantial percentage of treatment-resistant OCD patients treated with intravenous clomipramine improve symptomatically with time [11].

The combined evidence from head-to-head trials and meta-analysis does not appear to support the superiority of clomipramine over selective serotonin reuptake inhibitors (SSRIs). Furthermore, SSRIs have a greater tolerability than clomipramine, mainly because of the absence of anti-cholinergic effects, offering considerable advantages for the long-term treatment of OCD [14,15]. Citalopram is the only SSRI available for infusion therapy. Pallanti et al. [12] administered for three weeks intravenous citalopram (followed by oral administration for other 9 weeks) to treatment-resistant OCD patients that were non-responders in at least two adequate trials with SSRI but not citalopram: 59% of the patients showed a reduction of at least 25% of the initial Y-BOCS score after the first 3 weeks of therapy, and improved more at the end of the 12 weeks [12].

Infusive treatment with citalopram with a pulse-loading titration could represent an effective alternative to pulse-loaded clomipramine. However, up to date there are no studies investigating this kind of treatment. Thus, the main aim of this case series was to investigate the effectiveness of a citalopram pulse-loading protocol in severe treatment-resistant OCD patients.

On 2011, a US Food and Drug Administration (FDA) Safety Announcement informed health care professionals and patients that citalopram should no longer be used at doses above 40 mg/day because in higher doses the drug can unfavorably alter the electrical activity of the heart. FDA reported that clinicians could expect citalopram administration at doses of 20 mg, 40 mg, and 60 mg to lengthen the QTc interval by 8.5 msec, 12.6 msec, and 18.5 msec, respectively. However a recent review on the American Journal of Medicine found no cases of citalopram-induced sudden cardiac death among patients taking up to 60 mg/day of citalopram and free of risk factors for QTc interval prolongation and torsade de pointes [16].

Indeed, the second aim of this case series was to investigate cardiac tolerability of high intravenous doses of citalopram.

Methods

Patients

We selected 9 consecutive severe treatment-resistant OCD outpatients, fulfilling our inclusion criteria, in charge to the OCD unit of the University of Florence. Of these, 5 patients accepted to enter the study. To be included in the study all the patients had to meet DSM-IV criteria for OCD, established with the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) [17] and had treatment-resistant OCD. Treatment-resistance was defined as non-response to 2 SRIs trials (clomipramine, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram), 1 antipsychotic augmentation trial (haloperidol, risperidone, olanzapine, quetiapine, aripiprazole) and a non-response to 16 sessions CBT trial [1]. We excluded potential patients with any of the following conditions: a concurrent DSM-IV Axis I diagnosis of major depressive disorder as indicated by a SCID-I interview or score of > 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D) [18], schizophrenia or other psychotic syndromes; substance dependence or substance abuse, including alcohol, in the last year; Tourette's disorder or other tic syndromes; bipolar I or II disorder; mental disorder due to a general medical condition; serious suicide risk; pregnancy or nursing of an infant. No cognitive or behavioral psychotherapy was allowed during the intravenous or oral citalopram treatment period.

Study design

After a 2-week washout period from previous SRIs medications and after having obtained informed consent the patients have been treated with intravenous citalopram starting with 40 mg for 3 days and increasing the dose up to 80 mg from the fourth day. The patients continued the treatment with 80 mg of intravenous citalopram for 18 days (a total of 21 days of intravenous treatment), then switched to oral treatment (80 mg of oral citalopram).

The patients treated with an antipsychotic augmentation, continued their antipsychotic treatment without any change during all the treatment protocol.

Assessment

At baseline all patients were assessed with the SCID-I diagnostic interview, the Y-BOCS Checklist, the Y-BOCS, the CGI-Improvement (CGI-I) and CGI-Severity of Illness (CGI-S) [19] and the HAM-D.

We assessed treatment response using the Y-BOCS and the CGI-I at baseline, week 3 and week 12. Treatment response was also assessed at months 6, 9 and 12 during the follow-up visits.

The pulse-loading protocol incorporate standard criteria for treatment response (>35% improvement in baseline Y-BOCS scores and a CGI-I of 1 or 2), partial response (≥ 25% improvement in baseline Y-BOCS scores), and non-response (<25% improvement in baseline Y-BOCS scores) [1].

Tolerability was assessed with a clinical report form. We assessed putative cardiac side effects with an electrocardiography at baseline, after the fourth day of infusion and before switching to oral therapy, monitoring any QTc change. We also monitored sodium levels during all the course of treatment.

Case Series

Patient 1

Mr. P.P. is a 59 years old caucasian male with a severe treatment-resistant OCD (doubting and checking subtype) with an onset at the age of 15. Before entering the protocol Mr. P.P. failed to respond to a combination therapy of fluvoxamine up to 300 mg and aripiprazole 5 mg. The patient had a baseline Y-BOCS of 35 and a HAM-D score of 12.

After 3 weeks of treatment the patient showed a dramatic improvement of OC symptoms and had a Y-BOCS total score of 16 (a 54.3 % reduction of a Y-BOCS baseline score) and CGI-I of 1. At week 12 (after 9 weeks of oral treatment) the patient remitted having a Y-BOCS total score of 12 (a 65.7% reduction of a Y-BOCS baseline score) and a CGI-I of 1.

During the infusive treatment the patient did not show any side effect and any significant prolongation of the QTc interval. The baseline QTc interval was 435ms. After the fourth day of infusion therapy there was no change on the QTc interval. After 21 infusions the QTC interval was 443 ms (a 8 ms prolongation respect to the baseline). Sodium hematic levels were in the normal range (135-146 mEq/L) during all the course of treatment.

During the one year follow-up the patient continued his therapy with citalopram 80 mg and aripiprazole 5 mg. No changes to this therapy were needed during the follow-up and the patient did not have any recurrence. At month 6 the patient had a Y-BOCS total score of 13; at month 9 the patient had Y-BOCS total score of 14 and at month 12, again, he had a Y-BOCS total score of 14 (Figure 1).

Patient 2

Mr. G.C. is a 56 years old caucasian male with a severe treatment-resistant OCD (washing subtype) with an onset at the age of 14. Before entering the protocol Mr. G.C. failed to respond to a combination therapy of fluvoxamine up to 300 mg and olanzapine 10 mg. The patient had a baseline Y-BOCS of 38 and a HAM-D score of 14. After 3 weeks of treatment the patient showed an improvement of OC symptoms and had a partial response with a Y-BOCS total score of 28 (a 26.3% reduction of a Y-BOCS baseline score) and CGI-I of 2. At week 12 (after 9 weeks of oral treatment) the patient had a full response having a Y-BOCS total score of 24 (a 36.8% reduction of a Y-BOCS baseline score) and a CGI-I of 1.

During the infusive treatment the patient did not show any side effect and any significant prolongation of the QTc interval. The baseline QTc interval was 442 ms. After the fourth day of infusion therapy there was no change on the QTc interval. After 21 infusions the QTc interval was 421 ms. Sodium hematic levels were in the normal range (135-146 mEq/L) during all the course of treatment.

During the one year follow-up the patient continued his therapy

Figure 1. Y-BOCS changes during time

Figure 1: Y-BOCS total score changes from the baseline to month 12. On the x-axis, time (Baseline, week 3, week 12, month 6, month 9, month 12). On the y-axis, Y-BOCS total scores.

with citalopram 80 mg and olanzapine 10 mg. At month 6 the patient had a Y-BOCS total score of 24. At month 6 the patient started a CBT trial and at month 9 he had a Y-BOCS total score of 22 (a 42.1% reduction of a Y-BOCS baseline score). Finally, at month 12 he had a Y-BOCS total score of 21 (a 44.7% reduction of a Y-BOCS baseline score) (Figure 1).

Patient 3

Mr. N.B. is a 20 years old caucasian male with a severe treatment-resistant OCD (checking subtype) with an onset at the age of 12. Before entering the protocol Mr. N.B. failed to respond to a combination therapy of fluoxetine 60 mg, clomipramine 75 mg and aripiprazole 10 mg. The patient had a baseline Y-BOCS of 32 and a HAM-D score of 8. After 3 weeks of treatment the patient did not show any improvement of OC symptoms and had the same baseline Y-BOCS total score of 32 and a CGI-I of 3. At week 12 (after 9 weeks of oral treatment) the patient showed only a minimal change of the Y-BOCS total score (from 32 at baseline to 31, with a 1point reduction on the obsessions distress item) and a CGI-I of 3.

During the infusive treatment the patient did not show any side effect and any significant prolongation of the QTc interval. The baseline QTc interval was 428 ms. After the fourth day of infusion therapy there was no change on the QTc interval. After 21 infusions the QTC interval was 412 ms. Sodium hematic levels were in the normal range (135-146 mEq/L) during all the course of treatment.

Due to the non-response to treatment after 12 weeks, the patient left the maintenance protocol (Figure 1).
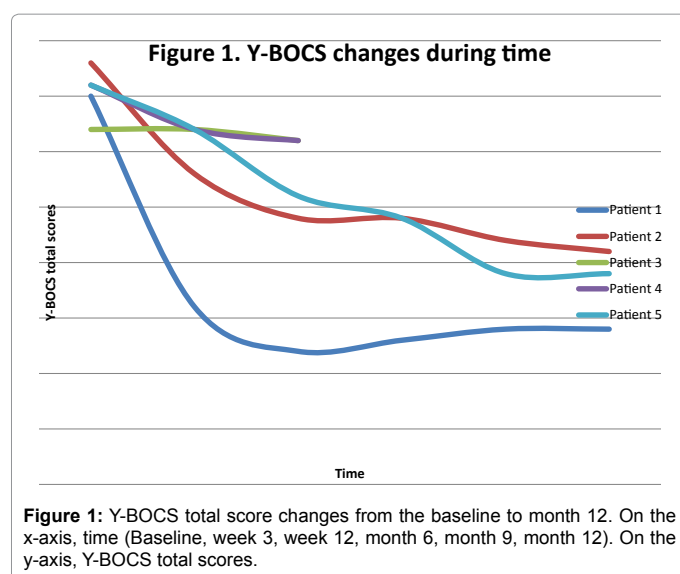
Patient 4

Miss R.B. is a 21 years old caucasian female with a severe treatment-resistant OCD (doubting and checking subtype) with an onset at the age of 15. Before entering the protocol Miss. R.B. failed to respond to a combination therapy of sertraline 200 mg and risperidone 1 mg. The patient had a baseline Y-BOCS of 36 and a HAM-D score of 6. After 3 weeks of treatment the patient showed a slight improvement of OC symptoms and had a Y-BOCS total score of 32 (a 11.1% reduction of a Y-BOCS baseline score) and a CGI-I of 2. At week 12 (after 9 weeks of oral treatment) the patient showed a Y-BOCS total score of 31 (a 13.8 % reduction of a Y-BOCS baseline score) and a CGI-I of 3.

During the infusive treatment the patient reported a minimal sedation that disappeared after 5 days. The baseline QTc interval was 450 ms. After the fourth day of infusion therapy the QTc interval was 449 ms. After 21 infusions the QTC interval was 466 ms (a 16 ms prolongation respect to the baseline). Due to this QTc interval prolongation we performed an electrocardiography at the end of the oral treatment phase and we found a QTc interval of 454 ms (a 4ms prolongation respect to the baseline). Sodium hematic levels were in the normal range (135-146 mEq/L) during all the course of the treatment.

Due to the non-response to treatment after 12 weeks, the patient left the maintenance protocol (Figure 1).

Patient 5

Miss. L.P. is a 31 years old caucasian female with a severe treatment-resistant OCD (checking and ordering/symmetry subtype) with an onset at the age of 17. Before entering the protocol Miss. L.P. failed to respond to a combination therapy of clomipramine up to 100 mg and quetiapine 200 mg. The patient had a baseline Y-BOCS of 36 and a HAM-D score of 12. After 3 weeks of treatment the patient showed

a slight improvement of OC symptoms and had a Y-BOCS total score of 32 (a 11.1% reduction of a Y-BOCS baseline score) and CGI-I of 2. At week 12 (after 9 weeks of oral treatment) the patient had a partial response having a Y-BOCS total score of 26 (a 27.7% reduction of a Y-BOCS baseline score) and a CGI-I of 2.

During the infusive treatment the patient did not show any side effect and any significant prolongation of the QTc interval. The baseline QTc interval was 450 ms. After the fourth day of infusion therapy the QTc interval was 448. After 21 infusions the QTC interval was 459 ms (a 9 ms prolongation respect to the baseline). Sodium emetic levels was between the normal range (135-146 mEq/L) during all the course of the treatment.

During the one year follow-up the patient continued his therapy with citalopram 80 mg. Due to the partial response obtained after 12 weeks of treatment, we decided to switch from quetiapine to aripiprazole 10 mg and to start a CBT trial. At month 6 the patient had a Y-BOCS total score of 24 (a 33.3% reduction of a Y-BOCS baseline score). At month 9 he had a full response with a Y-BOCS total score of 19 (a 47.2% reduction of a Y-BOCS baseline score). At month 12 he maintained symptoms improvement and he had a Y-BOCS total score of 19 (Figure 1).

Conclusions

This brief case series shows that citalopram pulse-loading may be a tolerable and effective treatment approach for severe treatment-resistant OCD patients. During the pulse-loading treatment no patients showed adverse events, expect for one patient having a transitory sedation.

Two of five patients had a full response and one of these two had remission. One of five patients had a partial response after 12 weeks and a full response during the 1-year follow-up period after switching from quetiapine to aripiprazole and after a CBT trial.

Pulse-loading treatment seemed to induce a faster improvement respect to a standard titration, since the responder patients showed a significant improvement already after 3 weeks. Two of five patients did not respond.

Another important result is that the two responder patients did not have any relapse of OC symptoms during the 1-year follow-up, suggesting that citalopram pulse loading could have not just an acute but also a long-term effectiveness.

No patients showed clinical significant change of the QTc interval. Three of five patients had a slight prolongation of the QTc interval (respectively 8, 4 and 9 ms respect to the baseline). No patients showed significant change of the sodium levels.

Despite the limited sample size, we observed a higher than expected response in patients with a severe OCD and a history of treatment resistance to 2 SSRIs trials and 1 augmentation trial with an atypical antipsychotic. Due to our simple study design we can only speculate some putative explanations for this effect that deserve further studies in order to be elucidated.

The first hypothesis is that the high intravenous doses and the rapid titration of citalopram may be related to a rapid attainment of high plasma levels and consequently, high brain tissue levels, more strongly affecting the expression of genes involved in obsessive-compulsive disorder's pathophysiology than do the brain levels associated with standard oral dosing. We can't support this hypothesis because of the absence of citalopram plasma levels during the treatment. Thus, future studies must clarify this hypothesis through measuring citalopram plasma levels and their relation to plasma level changes of neurotrophic factors such as BDNF.

A second hypothesis is that this unexpected response has been due to citalopram itself rather than to the higher parenteral doses and to the rapid titration. However, this hypothesis is unlikely, because both a responder (patient 5) and a non-responder (patient 3) had a history of non-response to 60 mg of oral citalopram. Furthermore, all the five patients had a history of non-response to at least to SRIs and the current literature shows that the estimated chance of responding to a second SRI after failing one SRI trial is 40%, and to a third is even less [15].

The third hypothesis is that the responder patients' respect to non-responder patients had a favorable pharmacogenomic profile to citalopram. In fact, in a recent study, Vulink et al. [20], found that the Met/Met genotype of the COMT polymorphism receptor gene was associated with response to 10 weeks of treatment with citalopram in OCD patients. Therefore, future studies must address this issue by investigating the genotype role in the effectiveness of treatment-resistance approaches.

Finally, taking into account the very limited sample size of this case series and the methodological limitations, we suggest that this treatment approach deserves further controlled studies.

References

1. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, et al. (2002) Treatment non-response in ocd: methodological issues and operational definitions. Int J Neuropsychopharmacol5:181-191.

2. Goodman W, Price L, Rasmussen S, Fleischmann R, Hill C, et al. (1989) The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), part I: development, use, and reliability. Arch Gen Psychiatry46:1006-1011.

3. Goodman W, Price L, Rasmussen S, Mazure C, Delgado P, et al. (1989) The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), part II: validity. Arch Gen Psychiatry 46:1012-1016.

4. Erzegovesi S, Cavallini M, Cavedini P, Diaferia G, Locatelli M, et al. (2001) Clinical predictors of drug response in obsessive-compulsive disorder. J ClinPsychopharmacol 21:488-492.

5. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, et al. (2006) A systematic review: antipsychotic augmentation with treatment refractory obsessivecompulsive disorder. Mol Psychiatry 11:622-632.

6. Abudy A, Juven-Wetzler A, Zohar J (2011) Pharmacological Management of Treatment-Resistant Obsessive-Compulsive Disorder. CNS Drugs 25: 585-596.

7. Fallon B, Liebowitz M, Campeas R, Schneier F, Marshall R, et al. (1998) Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. Archives of General Psychiatry 55: 918-924.

8. Koran LM, Sallee FR, Pallanti S (1997) Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. Am J Psychiatry 154: 396-401.

9. Koran LM, Pallanti S, Paiva RS, Quercioli L (1998) Pulse loading versus gradual dosing of intravenous clomipramine in obsessive-compulsive disorder. EurNeuropsychopharmacol 121-26.

10. Koran LM, Aboujaude E, Ward H, Shapira NA, Sallee FR, et al. (2006) Pulse-loaded intravenous clomipramine in treatment-resistant obsessive-compulsive disorder. J ClinPsychopharmacol 26: 79-83.

11. Ross S, Fallon BA, Petkova E, Feinstein S, Liebowitz MR (2008) Long-term follow-up study of patients with refractory obsessive-compulsive disorder. J Neuropsychiatry ClinNeurosci 20: 450-457.

12. Pallanti S, Quercioli L, Koran LM (2002) Citalopram intravenous infusion in resistant obsessive-compulsive disorder: an open trial. J Clin Psychiatry 63: 796-801.

13. Moukaddam NJ, Hirschfeld RMA (2004) Intravenous antidepressants: a review. Depression and Anxiety 19: 1-9.

14. Minle RJ, Goa L (1991) CitalopramA review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 41: 450-477.

15. Fineberg NA, Raghunandanan S, Brown A, Pampaloni I (2013) Pharmacotherapy of obsessive-compulsive disorder: evidence-based treatment and beyond. Aust N Z J Psychiatry 47: 121-141

16. Vieweg V, Hasnain M, Howland RH, Hettema JM, Kogut C, et al. (2012) Citalopram, QTc Interval Prolongation, and Torsade de Pointes. How Should We Apply the Recent FDA Ruling? Am J Med 859-868.

17. First MB, Spitzer RL, Gibbon L, Janet BWWilliams (1995) Structured clinical interview for DSM-IV Axis-I disorders- patient (edn SCID-I/P, Version 2.0). Biometric Research, Psychiatric Institute, New York, USA.

18. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23: 56-62.

19. Guy W (2000) Clinical Global Impressions (CGI) Scale. Modified From: Rush J, et al.: Psychiatric Measures, APA, Washington DC, USA.

20. Vulink NC, Westenberg HG, van Nieuwerburgh F, Deforce D, Fluitman SB, et al. (2012) Catechol-O-methyltranferase gene expression is associated with response to citalopram in obsessive-compulsive disorder. Int J Psychiatry Clin Pract 16: 277-283.