



Assignment refusal and its relation to outcome in a randomized controlled trial comparing Cognitive Therapy and Fluvoxamine in treatment-resistant patients with obsessive compulsive disorder

Johannes A. Landsheer^{a,*}, Johannes H. Smit^b, Patricia van Oppen^b, Anton J.L.M. van Balkom^b

^a Department of Methodology and Statistics, University of Utrecht, Utrecht, The Netherlands

^b Department of Psychiatry and EMGO⁺ Institute, VU University Medical Center, Academic Outpatient Clinic for Anxiety Disorders, GGZinGeest, Amsterdam, The Netherlands

ARTICLE INFO

Article history:

Received 26 June 2014

Received in revised form

16 December 2014

Accepted 31 December 2014

Available online 12 January 2015

Keywords:

Treatment outcome

Patient compliance

Patient dropouts

Obsessive–compulsive disorder

Cognitive Therapy

Fluvoxamine

ABSTRACT

The effectiveness of Fluvoxamine was compared to that of Cognitive Therapy (CT) in a 12-week randomized controlled trial (RCT) in 48 patients with obsessive–compulsive disorder (OCD), who were treatment-resistant to a previous behavior therapy (BT). A considerable amount of patients did not comply with the assigned treatment and switched treatments. The aim of this study was to identify patient characteristics predictive of assignment compliance and to study whether these characteristics were related to outcome. A logistic model, based on psychological and social patient characteristics, in addition to or in interaction with the assignment, was used for the explanation of compliance with treatment assignment. Especially patients who have a higher score on the Yale–Brown Obsessive Compulsive Scale (Y–BOCS) tend to comply with the effective Fluvoxamine treatment. The same set of variables was related to both compliance and outcome of therapy received. Therefore, the logistic model of compliance could be used to reduce the positive bias of As-Treated analysis (AT). The difference between the results of Fluvoxamine and Cognitive Therapy remained statistically significant after correcting for the positive bias as the result of assignment refusal and after applying the assumption that two drop-out patients needed imputation of lesser results.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

The effectiveness of Fluvoxamine was compared to Cognitive Therapy (CT) in a recently published 12-week randomized controlled trial (RCT) in patients with obsessive–compulsive disorder (OCD) who were treatment-resistant to 12 weeks of behavior therapy (BT) (Van Balkom et al., 2012). A considerable amount of these 48 patients (37.5%) refused to comply with their assignment. These patients form a group to whom the treatment as-assigned could not be applied and these patients defied randomization and control. The current study focused on patient characteristics that were predictive for refusal of assignment and the relationship of these characteristics with outcome of therapy received.

Refusal of an assigned treatment may be dependent on patient characteristics that existed before randomization (Dunn et al., 2005) and therefore are expected to be unrelated to a randomly assigned treatment. Examples of such characteristics are personality factors,

ignorance concerning the beneficial results of treatment, anxiety to change as a consequence of treatment, or lack of motivation (Leventhal and Cameron, 1987; Griffith, 1990). Patients with a high need for treatment and patients who have good insight into their illness have more treatment readiness (Maher et al., 2012) and may tend to comply more often. Patients living in a social environment that provides some pressure towards health may also tend to comply more often (Buchanan et al., 1996). When patient characteristics that exist before therapy assignment would be the sole explanation of assignment refusal, this refusal behavior can be considered as a general characteristic and can be expected to occur equally in randomized groups.

In the current trial we consider the additional assumption that subjects' refusal to cooperate is also dependent on the treatment assignment itself. The decision to refuse a treatment can be related to a specific treatment (Leventhal and Cameron, 1987), based on a lack of perception of benefits, perceived negative effects, perceived undesired side effects, or the perceived burden of the treatment (Janz and Becker, 1984). Specifically, it is known that Selective Serotonin Reuptake Inhibitors (SSRIs) such as Fluvoxamine have side effects that may cause patients to stop treatment (Anderson et

* Corresponding author. Tel.: +31 30 253 4438.

E-mail address: j.a.landsheer@uu.nl (J.A. Landsheer).

al., 2012). In the current study, compliance is defined as compliance with the assignment. Furthermore, non-compliers in this study have been assigned to the other treatment and all patients have received similar treatment, either according to their primary assignment or to their re-assignment. The basis for our model of compliance with the assigned treatment is the assumption that patients with stronger motivation are more inclined to comply with the treatment offered. For several patient characteristics a relationship with motivation to get better was hypothesized: patients who have more severe symptoms may have a higher motivation for treatment, patients with work are more motivated to get better and keep their job. In addition, pre-treatment depression and pre-trial treatment experiences are considered. These personal characteristics are considered next to and in interaction with treatment assignment. The assumption that we tested was that patients with these characteristics tend to comply more often and show a better result. Furthermore, our expectation was that the variables that were predictive of assignment compliance were also related to the outcome of treatment received.

2. Methods

2.1. Design and procedure

The dataset resulted from a RCT which was intended to compare the efficacy of Fluvoxamine versus CT as second-step treatments in a sample of subjects with a main diagnosis of OCD and who were non-responsive to 12 weeks of behavior therapy (BT) as a first-step treatment (van Oppen et al., 2010). Patients with obsessions only, suicidal intent, organic brain disease, past or present psychosis, psychoactive substance use disorder, or severe borderline or antisocial personality disorders were excluded. At baseline, all patients gave informed consent to be randomized to either Fluvoxamine or CT for the second step. Patients who did not respond to the first step were informed of their status and randomized over two conditions: Fluvoxamine ($n=26$) or CT ($n=22$). Patients were individually randomly assigned to one of the treatments when they entered the study. The study was accredited by the Ethics Committee of the VU University Medical Center and is registered in the Netherlands Trial Register (NTR1444; <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1444>). Table 1 presents the flow of the patients in this trial. Complete data could be obtained from 45 subjects (93.75%) after 12 weeks.

A considerable number of patients (18) refused the assigned treatment directly after assignment and before actual treatment had started. These patients are called 'assignment refusers'. Most of these patients (16) could be successfully re-assigned to the alternative treatment. Assignment refusers who were re-assigned to a treatment received the same treatment as the patients who complied with the first assignment. A few (two) dropped out during the re-assigned treatment and these patients are called drop-outs.

2.2. Measurements

Treatment effect was assessed by the difference score between post-measurement and pre-measurement score on the Yale–Brown Obsessive Compulsive Scale (Y–BOCS; Goodman et al., 1989). Depression as a comorbid psychiatric symptom was measured with the Montgomery–Asberg Depression Scale (MADRS; Davidson et al., 1986). A higher score on the Y–BOCS pretest is considered as indicative of symptoms that are more severe. The dichotomous variable 'Treated

Before' indicates whether the patient has been treated before the first phase. The dichotomous variable 'Without Work' is used as an indicator of the inability to remain employed.

2.3. Analysis

2.3.1. Modeling assignment refusal

Assignment compliance (0=refusal; 1=compliance) is modeled using logistic regression with the variables mentioned in Section 2.3 as predictors. To optimally differentiate between the two treatment conditions, special attention was paid to interaction effects. Furthermore, we analyzed whether the same person characteristics were also predictive of outcome using a linear model.

2.3.2. Effect estimation

Several conventional approaches are possible for the analysis of datasets with patients who do not comply with their assigned treatment: Intent-to-Treat (ITT) analysis, Per-Protocol analysis (PP) and As-Treated analysis (AT). Each of these approaches has its drawbacks. ITT analysis includes all patients as assigned and is partly counterfactual, because results are attributed to treatments that have not been received. This may provide a limited estimate of the effect when non-complying subjects remain untreated and dilute the results (Morden et al., 2011). ITT estimates may be lower as more patients from the group that is assigned to the effective treatment refuse their assignment, since these non-compliers actually do not receive this effective treatment. This may result in a non-significant estimation (Heritier et al., 2003). PP analysis includes only those who entered the assigned treatment. It therefore concerns groups that are reduced in number by removing assignment refusers, resulting in differential attrition. Due to selectivity, the reduced groups of patients who have followed protocol may have lost their comparability (Morden et al., 2011). Implicitly, PP-analysis assumes that assignment refusal occurs completely at random and can therefore be ignored. This assumption is rarely justified. AT-analysis uses all data as observed and is the most factual of these three alternatives, because the results are analyzed of the treatments that are actually received. AT-analysis often produces a higher effect estimate when compared to the ITT result, but the AT groups cannot be considered as randomized. Specifically patients who expect small or negative results may not comply, while on the other hand patients who are more motivated or expect beneficial results may tend to comply more often. In that case, AT analysis may be biased and provide an over-estimation of the effect found. In this paper, we focus on the factual treatment received, hence on AT-analysis and we consider the possibilities to reduce this bias.

Propensity score matching (PSM) is a statistical matching technique that attempts to improve the comparability of insufficiently randomized treatment groups with the use of variables that predict whether the treatment has been received or not (Rosenbaum and Rubin, 1983). PSM is used to improve the comparability of the differently treated groups (Little et al., 2009; Ten Have et al., 2008; Joffe et al., 2003). When a raw AT estimate is considered as biased due to the refusers' preference for one of the treatments, PSM may result in better comparable groups and remove some of the bias that results from assignment refusal. Alternatively, propensity scores can be used as a covariate to correct for the bias of assignment refusal. There are some differences between the two approaches for correction. A covariance analysis corrects the dependent variable, while matching improves equality of the treated groups specifically for the predictors of assignment refusal. Matching on the propensity to comply makes no difference between covariates that are highly or weakly predictive of the outcome variable (Rubin and Thomas, 1996), while the use of co-variance analysis may remove the effect partially or produce a spurious treatment effect (Miller and Chapman, 2001). A simulation study demonstrated that PSM with small samples (as small as eight) can perform as good as PSM with moderately large samples (200 or 500) in removing covariate imbalances from observational designs (Kolar, 2013).

In this study, a logistic model was used to calculate the propensity of refusal or compliance with the assigned treatment. The applied matching corrections are

Table 1
Assignments and compliance in the trial of Van Balkom et al. (2012).

| | Fluvoxamine (primary assignment) | Cognitive Therapy (secondary assignment) | Cognitive Therapy (primary assignment) | Fluvoxamine (secondary assignment) | Total |
|------------------------------|----------------------------------|--|--|------------------------------------|------------|
| Random assignment | 26 (100%) | | 22 (100%) | | 48 (100%) |
| Compliers | 13 (50%) | | 17 (77%) | | 30 (62.5%) |
| Re-assigned refuser | | 13 (50%) | | 5 (23%) | 18 (37.5%) |
| Drop out and Missing Outcome | | | | 2 (9%) | 2 (4%) |
| Missing Outcome | | 1 (4%) | | | 1 (2%) |
| Observed Outcomes | 13 (50%) | 12 (46%) | 17 (77%) | 3 (13%) | 45 (94%) |

intended to reduce the positive bias of AT-analysis and are called respectively 'Matched As-Treated' analysis and 'As-Treated with propensity as covariate'.

2.3.3. Handling drop-outs and missing values

Another problem next to assignment refusal was the fact that two of the patients who refused the assigned treatment did not finish the treatment in the re-assigned condition. As a result, and in contrast to the other assignment refusers, these two patients dropped out of the experiment and did not finish their treatment. As a result, post-treatment measurements are unavailable for them. A third patient who refused the assigned treatment and was re-assigned to the alternative treatment did finish the treatment, but was not available for post-treatment measurements. The number of missing outcomes is relatively low in the current study (three out of 48), but especially the results of the two patients who broke off their treatment are not easily imputed. The outcome of the third dropout, with solely unavailable post-measurements, is treated as missing at random (MAR). However, for the first two dropouts we explored the sensitivity of the results for possible validity of the missing not at random (MNAR) assumption (Van Buuren, 2012). We considered the possibility that these missing values are informative about the probability of missingness and are therefore non-ignorable. It is likely that they dropped out because they were dissatisfied with the treatment offered.

The procedure for handling these missing data is based on the detailed recommendations for multiple imputation of non-ignorable missing values from Van Buuren (2012). Earlier, Rubin (2009) recommended the use of a straightforward, easily communicated model. We have used 10 imputations. To study the possible overestimation, we used different scenarios: First, assuming that the missing values are MAR, we imputed scores that are similar to those of comparable patients. Second, we assumed that the drop-outs have a score less than that of comparable patients (0.4 S.D. less improvement: a moderate negative effect size) and lastly a worst case scenario: they have a change score that is considerably less than that of comparable patients (0.8 S.D.: a large negative effect size). One S.D. of the Y-BOCS difference score equals 6.96. These scenarios allow us to show the impact of imputation on the effect estimates when it is assumed that the drop outs would have considerable lesser results than comparable patients would. Most importantly, it shows the sensitivity of the results for this assumption.

3. Results

3.1. Basic results

Descriptive statistics can be found in Table 2. Although differences were small and insignificant in the groups of the primary assignment, there are some differences apparent in Table 2. Most notably: males (43%) are especially underrepresented in the Fluvoxamine group (38%), but are as much inclined towards refusal as females (50%); the two drop outs are young in comparison to the rest of the group; the mean Y-BOCS and the MADRS pre-test scores are relatively high in the group of Fluvoxamine compliers.

Raw, uncorrected outcome results of 45 patients with available posttests are shown in Fig. 1. A first analysis of these patients, without imputation or bias correction, shows a meager effect when applying ITT analysis, and a considerably stronger effect when applying AT analysis (see Table 5, first two rows). Because patients treated with CT showed no effect, while strong effects occurred in the Fluvoxamine condition, the ITT-analysis offers an underestimation. Effectively, in the ITT analysis the outcome of the

Fluvoxamine condition was based on 50% patients treated with Fluvoxamine and 50% patients treated with CT (which proved to be ineffective), while the effect of CT was based on 77% patients treated with CT and 23% patients treated with Fluvoxamine. As a result, the effect of Fluvoxamine is diluted. The results of the AT-analysis are considerably higher, but these were expected to be over-estimated due to selective compliance.

3.2. Logistic model of assignment refusal

Various variables are predictive of compliance (Tables 2 and 3). Treatment assignment itself is the strongest predictor of all: patients who were assigned to CT complied more often (77% versus 50%, $P=0.004$). Sex and age were not relevant as predictors (not shown in Table 3). Patients with higher pre-test Y-BOCS scores complied more often. Patients without work complied less often (40% versus 60%, $P=0.027$). Fifteen out of 16 patients who refused their assignment had received previous treatment (94%), while 24 out of 30 compliers had received previous treatment (80%). As a result, previous treatment experience is a weak predictor of assignment-refusal ($P=0.066$). As patients with strong comorbid conditions had been excluded, comorbid depression hardly had any effect. However, its interaction with treatment assignment contributed significantly to the prediction of compliance: patients with a higher score on MADRS were more often inclined to comply with the Fluvoxamine condition ($P=0.01$). This was the only interaction effect with any impact.

The logistic model offers a reasonably strong prediction of compliance: Nagelkerke's Pseudo- $R^2=0.63$. Using a threshold of 0.5, the correlation between prediction and compliance is $\Phi=0.69$

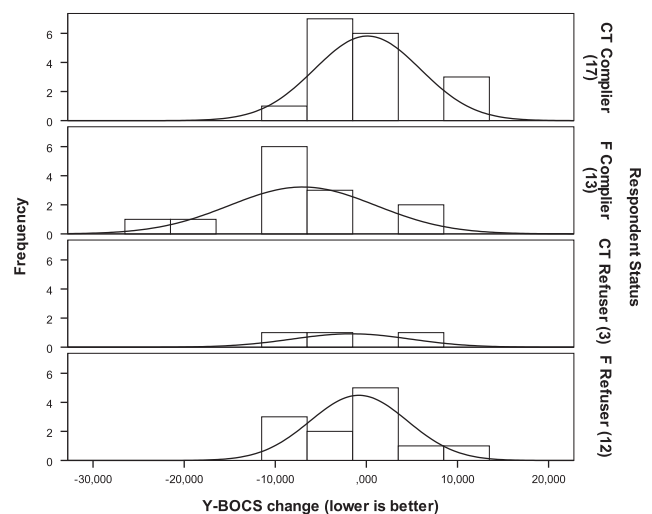


Fig. 1. Effect differences (posttest Y-BOCS – pretest Y-BOCS) in compliers and assignment refusers. Three patients with missing values are not shown.

Table 2
Descriptives.

| Primary assignment Status | Fluvoxamine Complier | CT Complier | CT Refuser | Fluvoxamine Refuser | CT Refuser and Drop-out |
|-----------------------------|----------------------|-------------|------------|---------------------|-------------------------|
| Count | 13 | 17 | 3 | 13 | 2 |
| Sex (male) | 3 | 8 | 1 | 7 | 1 |
| Mean (S.D.) age | 32.6 (7.5) | 38.8 (15.5) | 35.0 (8.5) | 39.5 (9.9) | 30.0 (14.1) |
| Mean (S.D.) Y-BOCS pre-test | 26.2 (6.4) | 23.0 (4.2) | 19.7 (0.6) | 21.5 (2.5) | 25.0 (9.9) |
| Mean (S.D.) MADRS | 43.3 (16.6) | 29.1 (15.7) | 33.7 (3.5) | 24.2 (12.9) | 33.5 (24.7) |
| Without Work | 5 | 7 | 2 | 8 | 2 |
| Treated Before | 11 | 13 | 2 | 13 | 2 |

Y-BOCS: Yale–Brown Obsessive Compulsive Scale.
MADRS: Montgomery–Asberg Depression Scale.

Table 3
Logistic model of compliance.

| | B | S.E. | Wald | P |
|--|--------|-------|-------|-------|
| Constant | −1.197 | 2.774 | 0.186 | 0.666 |
| Primary Treatment Assignment | −8.809 | 3.078 | 8.193 | 0.004 |
| Without Work | −2.290 | 1.034 | 4.907 | 0.027 |
| Y-BOCS pre-test | 0.396 | 0.189 | 4.370 | 0.037 |
| Treated Before | −3.195 | 1.741 | 3.368 | 0.066 |
| MADRS | −0.078 | 0.056 | 1.950 | 0.163 |
| Treatment Assignment × MADRS interaction | 0.238 | 0.093 | 6.600 | 0.010 |

Table 4
Linear regression showing the relevance of patient characteristics for outcome.

| | Estimate | Std. error | t Value | P |
|--|----------|------------|---------|-------|
| (Intercept) | 9.364 | 4.917 | 1.904 | 0.064 |
| MADRS | 0.207 | 0.087 | 2.388 | 0.022 |
| Y-BOCS pre-test | −0.770 | 0.247 | −3.123 | 0.003 |
| Treated Before | 0.577 | 2.757 | 0.209 | 0.835 |
| Without Work | 2.028 | 1.900 | 1.067 | 0.292 |
| Treatment Assignment × MADRS interaction | −0.099 | 0.056 | −1.751 | 0.087 |

(Pearson's Phi-coefficient) for the complete group with seven misclassifications out of 48, $\Phi=0.77$ for the group assigned to the Fluvoxamine condition with three misclassifications out of 26, and $\Phi=0.42$ for the group assigned to the CT condition with four misclassifications out of 22.

3.3. Assignment refusal and outcome

Patients who refused the Fluvoxamine condition and were re-assigned to CT, combined with the patients who were initially assigned to the CT-condition, led to an over representation of patients with lower scores on the Y-BOCS pretest in the CT condition. Because we expected that both less compliance and higher effects have common predictors, we checked which person characteristics that predicted compliance are related to outcome. Table 4 shows that except work and previous treatments all other person characteristics are relevant predictors of outcome.

A large proportion of patients with Fluvoxamine as the primary assignment refused treatment. At the same time, the Fluvoxamine condition is the most effective. Especially patients with relatively severe complaints complied with treatment with Fluvoxamine. The CT-patients were also the patients with limited outcomes and uncorrected AT-analysis therefore provides an over-estimation of the differential causal effect, because the assignment refusers showed a preference for the less effective treatment. The next question we studied is whether we can reduce the bias that resulted from assignment refusal by improving the match of both AT groups.

3.4. Effect estimates

The matched AT effect is the effect difference between the patients who actually have been treated with either Fluvoxamine or CT, but matched on the characteristics that are predictive of assignment refusal. First, all patients were matched on the variables that are predictive of assignment refusal. The group who actually received the CT treatment was the largest and patients from this group were discarded who were least like the patients treated with Fluvoxamine. This matching resulted into two groups equal in size (16).

Table 5 shows the results without imputation. The estimation of the variance of the outcome variable that is explained by the treatment conditions is indicated by η^2 . The uncorrected AT analysis was applied to the 45 observed outcomes. It is executed on two groups who are different because of assignment refusal and this result shows the highest effect estimate. The Matched AT was corrected for the propensity to comply and is therefore lower than the raw AT estimate, as is the last analysis with the propensity score as a covariate. The Matched-As-Treated analysis (MAT), applied to two equal groups of 16 patients, reduces this positive bias and this effect estimate gave 2% less explained variance. The As-Treated analysis with propensity as a covariate (AT.c) uses all available outcomes (45), but the covariate corrects the outcomes. This also results in 14% explained variance.

3.5. Effect estimates and imputations

Table 6 shows the results of multiple imputations, using all data of 48 patients for ITT, AT, MAT and AT.c analysis. Matching after imputation resulted in two equal groups of 18 patients (MAT). The latter analysis is limited by the patients who have been treated with Fluvoxamine (18), while for the CT group the patients who are most like those who received Fluvoxamine were selected. The missing outcomes were imputed under fully conditional specification (Van Buuren, 2012), using R 3.0.3 (R Development Core Team, 2014) and mice package 2.12 (Van Buuren and Groothuis-Oudshoorn, 2011). Under the MAR assumption, the imputed results are similar to those of comparable patients. As the MNAR assumption seems more feasible for the two drop-outs who did not finish their treatment, MNAR imputations are applied with results less than comparable patients, of respectively 0.4 S.D. and 0.8 S.D. of the dependent variable. This sensitivity analysis shows that the results are susceptible to the conditions for imputation. Even though there are only two missing values for which MNAR imputation seems reasonable, these results show a considerable difference in effect. Under the MAR assumption, the results are slightly worse in comparison to the results without imputation, with the ITT outcome as an exception. When the assumption of MNAR is applied, it is noteworthy that the ITT-effects in fact 'improve' strongly when the imputed values represent a lesser effect. This is an artifact (see Section 4). Overall, these few missing data have some influence on the results. The worst case scenario of 0.8 S.D. pushes the results towards non-significance.

4. Discussion

A large meta study (Hollis and Campbell, 1999) showed that 48% of trials dealt with a form of non-compliance, but only a very small minority of studies (4%) explicitly stated that there were no deviations from random allocation. This shows that non-compliance is a relevant and frequent problem. Our study shows that assignment refusal can be partly predicted using patient characteristics that exist before assignment and that these patient characteristics are related to outcome. Furthermore, the assignment itself contributes considerably to the prediction of treatment refusal. Araujo et al. (1996) reported that early compliance is a strong and consistent predictor of outcome of exposure therapy. Regretfully, recent relevant studies of assignment refusal or treatment non-adherence (van Dulmen et al., 2007) are scarce, as are studies of its predictors and its influence on outcome of obsessive-compulsive disorder treatment (Diniz and Fontenelle, 2013).

The results of our logistic model of assignment refusal indicate that especially those with relatively severe complaints tend to comply with treatment with Fluvoxamine. Prior to the second-step treatment, all the therapy-resistant patients had at least one

Table 5
Anova results and effect sizes of treatment.

| Analysis model | Mean effect difference Δ | d.f. | d.f. residual | F | P | η^2 |
|--|---------------------------------|------|---------------|------|-------|----------|
| Without imputation | | | | | | |
| Intent-to-Treat (ITT) | −3.89 | 1 | 43 | 3.68 | 0.060 | 0.08 |
| As-Treated (AT) | −5.72 | 1 | 43 | 8.10 | 0.007 | 0.16 |
| Matched As-Treated (MAT) | −5.19 | 1 | 30 | 4.97 | 0.033 | 0.14 |
| As-Treated with propensity as covariate (AT.c) | −5.59 | 1 | 42 | 6.94 | 0.012 | 0.14 |

ITT: Intention-to-treat analysis; AT: As-Treated analysis; MAT: Matched As-Treated analysis; AT.c: As-Treated with 'propensity to comply' as covariate.

Table 6
Results after multiple imputations.

| Effect | | | | | Effect Confidence Interval (95%) | | | |
|---|-------|------|-------|-------|----------------------------------|-------|-----------|-----------|
| Δ | se | t | d.f. | P | Low | High | λ | η^2 |
| Results after multiple imputation (MAR assumed) | | | | | | | | |
| ITT | −3.88 | 1.95 | −1.99 | 42.56 | 0.05 | −7.83 | 0.06 | 0.03 0.08 |
| AT | −5.00 | 1.97 | −2.54 | 41.82 | 0.02 | −8.98 | −1.02 | 0.04 0.13 |
| MAT | −5.07 | 2.18 | −2.33 | 30.97 | 0.03 | −9.50 | −0.63 | 0.03 0.14 |
| AT.c | −4.87 | 2.07 | −2.35 | 40.49 | 0.02 | −9.06 | −0.68 | 0.05 0.11 |
| Results after multiple imputation (MAR +0.4 S.D.) | | | | | | | | |
| ITT | −4.19 | 1.93 | −2.17 | 43.52 | 0.04 | −8.08 | −0.29 | 0.01 0.09 |
| AT | −4.63 | 1.98 | −2.34 | 43.26 | 0.02 | −8.62 | −0.64 | 0.02 0.11 |
| MAT | −4.70 | 2.20 | −2.13 | 31.68 | 0.04 | −9.19 | −0.21 | 0.01 0.12 |
| AT.c | −4.45 | 2.08 | −2.14 | 41.80 | 0.04 | −8.65 | −0.25 | 0.03 0.09 |
| Results after multiple imputation (MAR +0.8 S.D.) | | | | | | | | |
| ITT | −4.37 | 1.98 | −2.21 | 42.36 | 0.03 | −8.36 | −0.38 | 0.03 0.10 |
| AT | −4.41 | 2.05 | −2.15 | 41.68 | 0.04 | −8.55 | −0.27 | 0.05 0.10 |
| MAT | −4.46 | 2.29 | −1.95 | 30.94 | 0.06 | −9.14 | 0.21 | 0.03 0.10 |
| AT.c | −4.16 | 2.16 | −1.93 | 39.89 | 0.06 | −8.53 | 0.21 | 0.06 0.08 |

Δ : estimate of the mean difference between the two treatments after the use of 10 imputations for the three missing values. λ : the amount of residual variance that results from the imputations. η^2 : the estimate of variance that can be explained by the treatment conditions. ITT: Intention-to-treat analysis; AT: As-Treated analysis; MAT: Matched As-Treated analysis; AT.c: As-Treated with 'propensity to comply' as covariate.

ineffective treatment, but most have experiences with various treatments, including medication. Possibly, this specific group of patients may have relatively well-informed expectations of therapy efficacy. This may indicate that the refusers make a conscious choice to decline Fluvoxamine treatment, possibly related to expected side effects (Anderson et al., 2012). This is an interesting hypothesis for further research, especially since patients with poor insight and greater severity have also displayed higher medication refusal in other studies (Santana et al., 2013).

The methodological challenge caused by drop-out is considerable, as it seems most likely that the drop-out mechanism is missing not at random (MNAR). We therefore followed modern guidelines (Gewandter et al., 2014), by making assumptions for imputation explicit and using multiple imputation. Applying various assumptions concerning lesser results for the drop-out patients provides insight in the sensitivity of the results for drop-out patients. This shows that when imputing moderate lesser results, the matched AT-analysis shows a smaller effect that remains significant. Remarkably enough, the ITT analysis showed results that became more significant when lesser results are assumed. This is because two of the missing values concern patients who were assigned to the CT-condition but did not comply; they were reassigned to the Fluvoxamine condition and then dropped out. In the ITT analysis, their assumed deterioration is allocated to the CT-condition and this leads to an increased estimate when their imputed values are lessened. This illustrates the counterfactual nature of ITT-analysis and underlines the necessity of explicit use of assumptions for analysis and causal inference. It is difficult to say how the missing data can be imputed

best. The results of these patients are unknown and are hard to estimate, given their unfinished treatment. The estimates differ, dependent on the assumptions one is willing to make. In our view, the MNAR assumption is more reasonable for missing data of drop-out patients, in comparison to MAR.

A better outcome of treatment received can be partially predicted with a higher score on the Y-BOCS pre-test. As a result, the effect difference when comparing the two treatments is overestimated in an uncorrected AT-analysis of the current trial: CT results are lower as a result of the influx of patients with lesser complaints, while Fluvoxamine results are probably higher because of the perseverance of patients with relative severe complaints. The propensity to comply allowed us to reduce the positive bias because of assignment refusal. Clearly, this is a better estimate than unmatched AT-analysis, as assignment refusal influences outcome as well. Recently, statisticians have developed various complex methods to improve on causal estimates in trials with limited compliance. This has led to considerable debate (Rubin and Thomas, 1996; West and Thoemmes, 2010; Bareinboim et al., 2014; Pearl, 2014). Clearly, the methods applied in the current study design reduced the AT-estimate, which is considered to be an overestimation. Furthermore, the applied methods allowed us to show that ITT-analysis is susceptible to assumptions concerning the drop-outs. Nevertheless, it is difficult to say whether the applied methods are the most suitable. At this moment, rigorous simulation studies of the various proposed methods are lacking and it is difficult to say which methods would be the best to apply.

Patient beliefs concerning the treatments offered, and expectations of both treatment efficacy and side effects seem relevant. Regretfully, this was not sufficiently measured in the current study. Although all patients of the study gave informed consent to get randomized to either Fluvoxamine or CT in the case of non-response after 12 weeks of BT, the sample of this second step RCT concerned patients who showed a preference for non-medical treatment. The results did provide insight into which patients decided to follow the assigned treatment or not. The effect difference of the two treatments remained statistically significant after correcting for the positive bias that resulted from assignment refusal and assuming moderate worse results for the patients who dropped out from this study.

Acknowledgment

This independent study is sponsored, initiated and funded by VU University Medical Center, Department of Psychiatry and GGZ Ingeest.

References

- Anderson, H.D., Pace, W.D., Libby, A.M., West, D.R., Valuck, R.J., 2012. Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: a retrospective US claims study. *Clinical Therapeutics* 34, 113–123.
- Araujo, L.A.D., Ito, L.M., Marks, I.M., 1996. Early compliance and other factors predicting outcome of exposure for obsessive-compulsive disorder. *The British Journal of Psychiatry* 169, 747–752.

- Bareinboim, E., Tian, J., Pearl, J., 2014. Recovering from selection bias in causal and statistical inference. In: Brodley, C.E., Stone, P. (Eds.), *Proceedings of the Twenty-Eighth Conference on Artificial Intelligence*, AAAI Press, Menlo Park, CA.
- Buchanan, A.W., Soo Meng, K., Marks, I.M., 1996. What predicts improvement and compliance during the behavioral treatment of obsessive compulsive disorder? *Anxiety* 2, 22–27.
- Davidson, J., Turnbull, C.D., Strickland, R., Miller, R., Graves, K., 1986. The Montgomery–Asberg depression scale: reliability and validity. *Acta Psychiatrica Scandinavica* 73, 544–548.
- Diniz, J.B., Fontenelle, L.F., 2013. Obsessive–compulsive disorder: how should we manage treatment nonadherence? *Neuropsychiatry* 3, 451–453.
- van Dulmen, S., Sluijs, E., van Dijk, L., de Ridder, D., Heerdink, R., Bensing, J., 2007. Patient adherence to medical treatment: a review of reviews. *BMC Health Services Research* 7, 55.
- Dunn, G., Maracy, M., Tomenson, B., 2005. Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods. *Statistical Methods in Medical Research* 14, 369–395.
- Gewandter, J.S., McDermott, M.P., McKeown, A., Smith, S.M., Williams, M.R., Hunsinger, M., Farrar, J., Turk, D.C., Dworkin, R.H., 2014. Reporting of missing data and methods used to accommodate them in recent analgesic clinical trials: ACTION systematic review and recommendations. *PAIN[®]* 155, 1871–1877.
- Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale–Brown obsessive compulsive scale: I. Development, use, and reliability. *Archives of General Psychiatry* 46, 1006.
- Griffith, S., 1990. A review of the factors associated with patient compliance and the taking of prescribed medicines. *The British Journal of General Practice* 40, 114–116.
- Heritier, S.R., Gebiski, V.J., Keech, A.C., 2003. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. *Medical Journal of Australia* 179, 438–440.
- Hollis, S., Campbell, F., 1999. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *British Medical Journal* 319, 670–674.
- Janz, N.K., Becker, M.H., 1984. The health belief model: a decade later. *Health Education & Behavior* 11, 1–47.
- Joffe, M.M., Have, T.R.T., Brensinger, C., 2003. The compliance score as a regressor in randomized trials. *Biostatistics* 4, 327–340.
- Kolar, A., 2013. *Sample Size Considerations When Using Propensity Score Methods to Estimate Causal Effect* (Doctoral thesis). Faculty of Social Sciences, University of Ljubljana, Ljubljana.
- Leventhal, H., Cameron, L., 1987. Behavioral theories and the problem of compliance. *Patient Education and Counseling* 10, 117–138.
- Little, R.J., Long, Q., Lin, X., 2009. A comparison of methods for estimating the causal effect of a treatment in randomized clinical trials subject to noncompliance. *Biometrics* 65, 640–649.
- Maher, M.J., Wang, Y., Zuckoff, A., Wall, M.M., Franklin, M., Foa, E.B., Simpson, H.B., 2012. Predictors of patient adherence to cognitive-behavioral therapy for obsessive–compulsive disorder. *Psychotherapy and Psychosomatics* 81, 124.
- Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. *Journal of Abnormal Psychology* 110, 40.
- Morden, J.P., Lambert, P.C., Latimer, N., Abrams, K.R., Wailoo, A.J., 2011. Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. *BMC Medical Research Methodology* 11, 4.
- Pearl, J., 2014. Reply to commentary by Imai, Keele, Tingley, and Yamamoto, concerning causal mediation analysis. *Psychological Methods* 19, 488–492.
- R Development Core Team, 2014. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.
- Rosenbaum, P.R., Rubin, D.B., 1983. The central role of the propensity score in observational studies for causal effects. *Biometrika* 70, 41–55.
- Rubin, D.B., 2009. *Multiple Imputation for Nonresponse in Surveys*. Wiley, New York.
- Rubin, D.B., Thomas, N., 1996. Matching using estimated propensity scores: relating theory to practice. *Biometrics* 52, 249–264.
- Santana, L., Fontenelle, J.M., Yucel, M., Fontenelle, L.F., 2013. Rates and correlates of nonadherence to treatment in obsessive–compulsive disorder. *Journal of Psychiatric Practice* 19, 42–53.
- Ten Have, T.R., Normand, S.-L.T., Marcus, S.M., Brown, C.H., Lavori, P., Duan, N., 2008. Intent-to-treat vs. non-intent-to-treat analyses under treatment non-adherence in mental health randomized trials. *Psychiatric Annals* 38, 772–783.
- Van Balkom, A., Emmelkamp, P.M., Eikelenboom, M., Hoogendoorn, A.W., Smit, J.H., van Oppen, P., 2012. Cognitive therapy versus fluvoxamine as a second-step treatment in obsessive–compulsive disorder nonresponsive to first-step behavior therapy. *Psychotherapy and Psychosomatics* 81, 366.
- Van Buuren, S., 2012. *Flexible Imputation of Missing Data*. CRC Press, Boca Raton.
- Van Buuren, S., Groothuis-Oudshoorn, K., 2011. MICE: multivariate imputation by chained equations in R. *Journal of Statistical Software* 45, 1–67.
- Van Oppen, P., van Balkom, A.J., Smit, J.H., Schuurmans, J., van Dyck, R., Emmelkamp, P.M., 2010. Does the therapy manual or the therapist matter most in treatment of obsessive–compulsive disorder? A randomized controlled trial of exposure with response or ritual prevention in 118 patients. *The Journal of Clinical Psychiatry* 71, 1158–1167.
- West, S.G., Thoemmes, F., 2010. Campbell's and Rubin's perspectives on causal inference. *Psychological Methods* 15, 18.