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

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ARTICLE INFO

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.

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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

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 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%)