

# Response to Fluvoxamine in the Obsessive-Compulsive Disorder Patients: Bayesian Ordinal Quantile Regression

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## Abstract

**Purpose:** Aim of study is identifying the predictors of fluvoxamine therapy in OCD patients. Obsessive-Compulsive Disorder (OCD) is a chronic neuropsychiatric disorder associated with unpleasant thoughts or mental images making the patient repeat physical or mental behaviors to relieve discomfort. 40-60% of patients do not respond to Serotonin Reuptake Inhibitors, including fluvoxamine therapy. Here, we identify the predictors of fluvoxamine therapy in OCD patients by Bayesian Ordinal Quantile Regression Model.

**Design/methodology/approach:** This study was performed on 109 patients with OCD. Three methods including bayesian ordinal quantile, probit and logistic regression models were applied to identify predictors of response to fluvoxamine. The accuracy and weighted kappa were used to evaluate these models.

**Findings:** Our result showed that rs3780413 (mean=-0.69, sd=0.39) and cleaning dimension (mean=-0.61, sd=0.20) had reverse effects on response to fluvoxamine therapy in bayesian ordinal probit and logistic regression models. In the 75th quantile regression model, marital status (mean=1.62, sd=0.47) and family history (mean=1.33, sd=0.61) had a direct effect, and cleaning (mean=-1.10, sd=0.37) and somatic (mean=-0.58, sd=0.27) dimensions had reverse effects on response to fluvoxamine therapy.<sup>[1]</sup>

**Originality/value:** Response to fluvoxamine is a multifactorial problem and can be different in the levels of socio-demographic, genetic and clinical predictors. Marital status, familial history, cleaning and somatic dimensions associated with response to fluvoxamine therapy.

## Keywords:

Obsessive compulsive disorder; Fluvoxamine, Ordinal variables; Quantile regression

## Introduction

Obsessive Compulsive Disorder (OCD) is a chronic neuropsychiatric disorder associated with unpleasant thoughts or mental images that force the patient to repeat physical or mental behaviors to relieve discomfort.

The prevalence of OCD in the world is estimated to be 1.5-3% independent of ethnicity and cultural groups. It is predicted that OCD could be one of the top ten disorders lead to disability in the next twenty years.

The first line medication to treat this disorder is a class of selective serotonin reuptake inhibitors (SSRIs) which 40-60%

of patients do not usually respond to. Therefore, the researchers have focused on the relationship between genetic, clinical and environmental factors responding to SSRIs.<sup>[2]</sup>

The results of previous studies showed inconsistencies in the relationship between demographic, clinic and genetic factors with response to SSRIs therapy in OCD patients. Store et al. found association between the response to fluoxetine in a longer period of illness, older age, and more severe symptoms

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in OCD patients. On the other hand, Denys et. al. revealed that patients with no previous history of treatment, moderate severity of OCD and a low score on the Hamilton Depression Scale were more likely to respond positively to treatment.

Hollander et. al. showed that left-sided visuospatial soft signs significantly increased in the non-responders compared to the responders. Nakatani et. al. indicated that patients with lower baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and without the cleansing compulsion responded better to treatment. A meta analysis confirmed the relationship between hoarding, a dimension of OCD symptoms, and poor response to treatment.<sup>[3]</sup>

Although, Bella et al. could not show the relationship between 5-HTTLPR genotypes and response to fluvoxamine, response to SRIs therapy in OCD patients has been revealed to associate with 5-HTTLPR, 5-HTT, 5HT2A, 5HT1B, BDNF genes in other studies. In the present study, we aimed to investigate the association between demographic, clinic and genetic factors with Fluvoxamine therapy in Iranian OCD patients. Here, response to treatment was considered an ordinal variable by three categories: refractory, non-responder and responder.

The ordinal probit or logistic models have been usually proposed for modeling the ordinal outcomes. Both models focus on the cumulative probabilities of the ordinal response variable to take into account the ordinality between the categories in the modeling.

We know the validity of these models depends on the assumptions made on the underlying distribution of the latent variable. The two mentioned models do not provide sufficient information about the underlying distribution of the latent variable. In addition to these two models, we used bayesian quantile ordinal regression model to find predictors of fluvoxamine therapy in Iranian OCD patients.<sup>[4]</sup>

## Materials and Methods

### Study Population

In present study, we used information of 109 OCD patients referred to Imam Hossein Hospital in Tehran, Iran between 2014 and 2017 and they have given consent for their information to be used in the research. More information about dataset is available in the article of Hasanpour and et. al.

In this project, after twelve weeks of taking fluvoxamine, based on the degree of reduction in the severity of OCD compared to the severity of pre-treatment severity of symptom, patients were categorized into three groups: refractory, non-responder, responder. Hence, response to pharmacotherapy has three ordered categories.

### Data Variables

The socio-demographic variables were age, gender, educational status, occupation, marital status, ethnicity and the clinical variables included family history of OCD or other mental illnesses, age of disorder onset (under or over 18 years old), and duration of illness.

Moreover, we used five dimensions including aggression/checking, contamination/cleaning, symmetry/ordering/repeating/counting/hoarding, which have been explored from Y-BOCS checklist by Asadi et. al.

In each dimension, the positive and greater values indicate greater severity of the obsession and compulsion in an OCD patient. The genetic variables included 5-HTTLPR polymorphism of SLC6A4 gene, HTR2A gene SNPs (rs6311, rs6313) and SLC1A1 gene SNPs (rs301430, rs3780413 and rs2228622).<sup>[5]</sup>

### Statistical Analysis

Statistical analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and Matlab 2016b. The continuous variables were expressed as mean and standard deviation, and the categorical variables were expressed as frequency and percentages.

In order to identify the predictors of pharmacotherapy in OCD patients (ordinal response variable), we used bayesian ordinal quantile regression, bayesian ordinal probit regression and bayesian ordinal logistic regression models (For more information see supplementary file).

Bayesian approach could cover the lack of information due to the small sample size by using prior information on the regression coefficients. In all of the mentioned models, the normal prior distribution with large variance (non-informative prior distribution) is considered for estimating the regression coefficients.

Inference was done based on 12000 iterations after 3000 were burned. The performance of all the models was evaluated using the Akaike Information Criteria (AIC), weighted kappa and accuracy.<sup>[6]</sup>

## Results

This indicates the distribution of the socio-demographic, clinical variables and polymorphisms of the selected genes by three categories of the pharmacotherapy results in OCD patients. 64% of patients in the study were female, 72 of patients reported undergraduate education, 57% reported unemployed patients, 83% reported family history of OCD or other mental diseases, 64% of patients had more than 5 years of disease duration, 66% of patients have been diagnosed after the age of 18[Table 1].

**Table 1. Demographic and Genetic Factors by Classification of Response to Fluvoxamine Pharmacotherapy**

Variable	Total (Frequency)	Sub groups (Frequency)		
		Refractory	Non-Responder	Responder
Male	39	7	10	22
Female	70	12	18	40
Marital status				
Married	75	13	16	46
Single	34	6	12	16
occupation				
Unemployed	62	13	15	34
Employed	47	6	13	28
Age of onset				
early	37	9	8	20
late	72	10	20	42
Familial history				
Yes	91	16	21	54
No	18	3	7	8
Ethnicity				
Persian	62	11	16	35
Other	47	8	12	27
Education				
Academic	30	2	10	18
Under academic	79	17	18	44
Illness duration				
Under 5 years	41	4	12	25
Upper 5 years	68	15	16	37
5-HTTLPR				
LL, LS	69	12	18	39
SS	40	7	10	23
rs6311				
CC, CT	77	15	15	47
TT	32	4	13	15
rs6313				
CC, CT	81	15	22	44
TT	28	4	6	18
rs301430				
CC, TC	51	9	16	26
TT	58	10	12	36
rs3780413				
CC, CG	56	3	19	34
GG	53	16	9	28

		rs2228622			
GA, AA	77	14	18	45	
GG	32	5	10	17	

This indicates the posterior means and standard deviations of parameters in three simple bayesian ordinal regression models: logistic, probit and quantile for P=0.25 0.50 and 0.75[Table 2].

**Table 2. The Results of Simple Bayesian Quantile, Probit and Logistic Models.**

parameters	25th Quantile			50thQuantile			75th Quantile			Ordinal Probit			Ordinal Logistic		
	Mean	STD	P	Mean	STD	P	Mean	STD	P	Mean	STD	P	Mean	STD	P
Marital Status (married)	0.43	0.5	0.39	1.39	0.46	<0.01	1.79	0.5	<0.01	0.24	0.24	0.32	0.43	0.39	0.27
Occupation (unemployed)	0.04	0.5	0.93	0.9	0.5	0.7	1.29	0.55	0.02	-0.19	0.23	0.41	-0.28	0.38	0.46
Age of onset (late)	0.55	0.49	0.26	1.19	0.48	0.01	1.52	0.51	<0.01	0.21	0.24	0.38	0.31	0.4	0.24
Familial history (positive)	0.4	0.67	0.55	1.4	0.63	0.03	1.46	0.57	0.01	0.23	0.29	0.44	0.41	0.47	0.38
Ethnicity (other)	0.32	0.53	0.55	1.09	0.52	0.03	1.48	0.55	<0.01	0.03	0.23	0.9	0.04	0.38	0.9
Education (Academic)	0.7	0.54	0.2	1.25	0.57	0.03	1.72	0.62	<0.01	0.27	0.25	0.29	0.37	0.42	0.38
Illness duration (>5)	-0.06	0.49	0.9	0.86	0.48	0.07	1.25	0.52	0.02	-0.27	0.19	0.24	0.4	0.39	0.3
5-HTTLPR (ss)	0.14	0.7	0.84	0.45	0.62	0.47	0.53	0.55	0.34	0.03	0.23	0.95	0.03	0.39	0.94
rs6311 (TT)	0.17	0.68	0.8	-0.24	0.61	0.7	-0.17	0.52	0.72	-0.14	0.24	0.56	-0.31	0.4	0.43
rs6313 (TT)	0.47	0.75	0.53	0.79	0.67	0.24	0.87	0.6	0.15	0.23	0.26	0.38	0.39	0.44	0.37
rs301430 (TT)	0.38	68	0.58	1.04	0.58	0.07	1.06	0.54	0.05	0.19	0.22	0.39	0.35	0.37	0.34

rs3780413 (GG)	-1.1	0.64	<0.01	0.08	0.6	0.89	0.23	0.53	0.66	-0.46	0.23	0.04	-0.66	0.38	0.08
rs2228622 (GG)	0.13	0.7	0.86	0.14	0.64	0.83	0.21	0.57	0.71	-0.06	0.25	0.83	-0.12	0.4	0.76
Age	0.003	0.03	0.92	0.08	0.03	<0.01	0.12	0.04	<0.01	-0.01	0.01	0.59	-0.01	0.02	0.72
Aggression/Checking	0.2	0.39	0.61	-0.14	0.37	0.7	-0.12	0.31	0.69	0.01	0.1	0.92	-0.01	0.18	0.95
Contamination/Cleaning	-1.05	0.45	0.02	-1	0.36	<0.01	-0.83	0.3	<0.01	-0.36	0.12	<0.01	-0.6	0.2	<0.01
Symmetry/Ordering/...	0.42	0.41	0.31	0.11	0.45	0.81	0.09	0.28	0.75	0.1	0.11	0.37	0.13	0.18	0.46
Somatic	-0.64	0.44	0.15	-0.58	0.35	0.09	-0.35	0.25	0.16	-0.19	0.1	0.06	-0.32	0.17	0.07

In order to find the final model in each approach, all the covariates by p-value less than 0.2 were included in the model at the beginning and were removed one by one

according to a significance criterion (p-value< 0.10). The performance indexes AIC, weighted kappa and accuracy of each model are reported [Table 3].

**Table 3. The Results of Multiple Bayesian Quantile, Probit and Logistic Models**

parameter s	25th Quantile			50thQuantile			75th Quantile			Ordinal Probit			Ordinal Logistic		
	Mean	STD	P	Mean	STD	P	Mean	STD	P	Mean	STD	P	Mean	STD	P
Marital status (married)	-	-	-	1	0	0	2	0	<0.01	-	-	-	-	-	-
Familial history (positive)	-	-	-	1	1	0.1	1	1	0	-	-	-	-	-	-
rs3780413 (GG)	-1	1	0	-	-	-	-	-	-	-0	0	0	-1	0.39	0.1
Contamination/Cleaning	-1	0	0	#	0	<0.01	-1	0	<0.01	-0	0	<0.01	-1	0.2	<0.01
Somatic	-	-	-	-	-	-	-1	0	0	-	-	-	-	-	-
AIC		207		207.17	204.18	210.59	211.37								
Weighted kappa		0.13		0.1	0.23	0.3	0.29								

Accuracy	0.587	0.587	0.614	0.614	0.614
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In bayesian ordinal quantile regression models, contamination/cleaning dimension has negative effect on the probability of response to fluvoxamine treatment in the OCD patients, especially in the upper half of the distribution, therefore individuals with compulsive washing responded less to this treatment. The bayesian ordinal probit and logistic regression models confirmed this subject.<sup>[2]</sup>

In the upper quartile of the distribution, somatic obsessions had a negative effect on the probability of response to fluvoxamine treatment in the OCD patients which means this treatment was not beneficial for patients with somatic obsessions. Although bayesian ordinal probit and logistic regression models could not show any relationship between marital status and family history with response to fluvoxamine treatment in the OCD patients, in the upper half of the distribution, marriage and in the upper quartile of the distribution, family history had a positive effect on this treatment. Results show that rs3780413 has a negative effect on the response to fluvoxamine treatment in OCD patients in bayesian ordinal probit and logistic regression models. Choosing the best model in this dataset was not easy. Although, the bayesian ordinal probit and logistic regression models (included rs3780413, Contamination/ Cleaning) have the biggest values of the accuracy and weighted kappa and were the simplest models, they could not find any relationship between socio-demographic variables and the response to fluvoxamine treatment in the OCD patients.<sup>[5]</sup>

## Discussion

Considering the simultaneous effect of environmental, genetical and clinical factors on the fluvoxamine therapy and using three ordinal regression models to detect the predictors of fluvoxamine therapy are exploited in the present study. Although, we could not see the significant difference among the performance characteristics of these model included accuracy and weighted kappa, the predictors staying in each model were not similar. The socio-demographic predictors played important roles in quantile regression models that could be a proxy of inequality distribution of these predictors in the population. The ordinal probit and logistic identified rs3780413 had significant effect on fluvoxamine therapy in OCD patients. Our results could not confirm the findings of Rahman 2016 that shows the bayesian quantile ordinal regression models provide a better model fit relative to the ordinal probit model. We observed in the model included marital status, familial history, contamination/cleaning and somatic dimensions, 75<sup>th</sup> quantile regression model had a better performance than ordinal logistic and probit regression models, and in the model included rs3780413 and contamination\cleaning dimensions ordinal logistic and probit regression models had performance better than 75<sup>th</sup> quantile regression model.<sup>[3]</sup>

**Cumulative logistic and cumulative probit models:**

Consider the following regression model

Where  $X$  is a vector of explanatory variables,  $\beta$  is a vector of unknown regression coefficients,  $\epsilon$  follows an normal distribution with mean 0 and variance  $\sigma^2$ ,  $n$  is number of observations.  $Y^*$  is unobserved latent variable that relates to the observed ordinal variable  $Y$ , which has  $J$  categories, via the cut-point vector  $k$  as follows:

Above model represent an ordinal probit model.

In the above model, if  $\epsilon$  follows an logistic distribution with mean 0 and variance  $\pi^2/3$ , ordinal logistic regression model is obtained.

Quantile regression in ordinal model

Consider the following regression model

Where  $X$  is a vector of explanatory variables,  $\beta$  is a vector of unknown quantile regression coefficients,  $\epsilon$  follows an asymmetric laplace distribution with location parameter, scale parameter and skewness parameter  $0, 1, p$  respectively,  $n$  is number of observations.  $Y^*$  is unobserved latent variable that relates to the observed ordinal variable  $Y$ , which has  $J$  categories, via the cut-point vector  $k$  as follows:

Nakatani et al. and Mataix-Cols et al. showed the patients without contamination/cleaning and hording dimension had better response to treatment with fluvoxamine/SSRIs in separate studies. Living with a partner and age of symptom onset were not associated with better response to clomipramine pharmacotherapy in Shavitt et. al. Having the family history of anxiety disorders has been shown to have a positive effect on response to drug. Based on these studies it will be difficult to choose a model just with two predictors as the final model.<sup>[4]</sup>

Based on previous studies, the several genetic markers were found to be significantly associated with antidepressant response: CYP2D6, CYP2C19, SLC6A4 (5HTTLPR and STin2), HTR1A (rs6295), HTR2A (rs7997012, rs6311, rs6313 and rs6314), SLC6A2 (rs5569), TPH1 (rs1800532). In this study we investigated the effect of 5-HTTLPR polymorphisms of SLC6A4 gene, HTR2A gene SNPs (rs6311, rs6313) and SLC1A1 gene SNPs (rs301430, rs3780413 and rs2228622) and our study revealed that SLC1A1 polymorphism, rs3780413, is associated with response to fluvoxamine therapy.<sup>[6]</sup>

## Conclusion

Response to fluvoxamine is a multifactorial problem and can be different in the levels of socio-demographic, genetic and clinical predictors. Marital status, familial history, cleaning and somatic dimensions associated with response to fluvoxamine therapy.

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