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Evaluation of Simultaneous Effect of Lovastatin Plus Fluoxetine on Depression Using Linear Mixed Model with LASSO Penalty

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Abstract

The effect of lovastatin plus fluoxetine on depression has been investigated in many studies, but ignoring other effective factors has decreased the accuracy of the results. The aim of this study was to assess the simultaneous effect of lovastatin plus fluoxetine on depression while controlling a large number of potential covariates using penalized linear mixed model in a longitudinal study. 60 patients with major depressive disorder according to DSM-IV diagnostic criteria were enrolled. The sample was randomly allocated into fluoxetine (up to 40 mg/day) plus lovastatin (30 mg/day) group and fluoxetine (up to 40 mg/day) plus placebo group. Hamilton depression rating scale was used to measure the depression score at baseline, week 2, and week 6. We used linear mixed model (LMM) with least absolute shrinkage and selection operator (LASSO) penalty. Among 60 patients, 39 (65%) were female with a mean age of 31.93 (9.8) years; 51.7% of the patients were married, a majority (73%) lived in village, and 45% of them had high school education. Both groups showed a significant decrease in depression score using Hamilton Depression scale. However, depression score in the treatment group decreased more than the placebo group (Mean=12.8(SD=6.3) vs. Mean=8.2(SD=4.0), t=3.4, P<.001).The proposed model revealed that in the presence of the other covariates, lovastatin plus fluoxetine could play a key role in the reduction of depression. It was also shown that all of the covariates except blood pressure had a significant effect on depression. Linear mixed model with LASSO penalty revealed that sex, age, education, physical illness had the most significant effect on depression.

Keywords: fluoxetine, LASSO, lovastatin, major depressive disorder, mixed model

1. Introduction

Depression is a major public health problem, with a substantial morbidity, mortality and health-care cost related to it. According to the world health organization (WHO), by the year 2030 depression may become one of the most important causes of disability in the world (Mathers, Fat, & Boerma, 2008). In epidemiological studies, the estimated lifetime prevalence of major depression ranges between 10% and 20% (Patten, 2003). At the individual level, disability from major depressive disorder (MDD) is greater than that for subclinical or mild and moderate depression because of its greater prevalence, and associated increased risk of mortality and coronary heart disease.

Many randomized clinical trials have examined the effectiveness of the existing treatments for major depression. Despite the development of new antidepressant medications, they are only helpful for approximately 60% of patients (Al-Harbi, 2012). Thus, the detection of new methods for the management of depressive disorders is considerable. Statins are primarily used for the treatment of depression and have been recommended to be used for primary prevention of some problems in patients with psychiatric disorders (Andrade, 2013). Many studies have shown the relationship between statins and depression, but there are contradictory results about its effect on depression (Judd et al., 2014; Morales et al., 2006; Otte, Zhao, & Whooley, 2012).

Fluoxetine and lovastatin are two most popular drugs that are widely used in psychiatry and numerous studies have confirmed their impact on depression (Judd et al., 2014; Tao et al., 2012).

Because depression and some related factors are variable during the time, the results of drug effectiveness are

unreliable. To demonstrate the effectiveness over time, we implemented a longitudinal study in which the patients were interviewed at baseline, week 2, and week 6.

Mixed models are one of the best statistical methods for management of longitudinal data. By taking into account the correlation between the observations of an individual, we can increase the accuracy of parameter estimates by using mixed models (Groll & Tutz, 2014). However, like other regression models, these methods suffer from high dimensionality. It means that when the number of independent variables relative to sample size is great, the efficiency of traditional mixed models decreases. In order to overcome this deficiency, we implemented penalized mixed model. One of the best advantages of penalized mixed model versus traditional mixed models is that the former is applicable without any limitation on the number of covariates or sample size (Groll & Tutz, 2014). The key feature of the penalized models is simultaneous processing of various selections and estimations, which leads to higher precision compared to traditional variable selection methods in high-dimensional settings (Tibshirani, 1996). In our study, because of some problems in the follow-up, costs and ethical issues, it was not possible to take further samples. Thus, small sample size relative to the number of variables does not reduce the accuracy of our results.

The univariate effect of statins on depression has been shown in many studies without controlling other confounders (Feng, Tan, Merchant, & Ng, 2008; Otte et al., 2012; Renshaw et al., 2009; Stafford & Berk, 2011) and the effect of some potential factors on depression has been determined using cross-sectional studies (Chang-Quan, Zheng-Rong, Yong-Hong, Yi-Zhou, & Qing-Xiu, 2010; Du et al., 2015; Schillerstrom, Royall, & Palmer, 2008).

Also, in many longitudinal studies the effect of statins on depression was considered using traditional statistical methods like independent T and Chi- square tests (Ghanizadeh & Hedayati, 2013; Ghanizadeh, OmraniSigaroodi, Javadpour, Dabbaghmanesh, & Shafiee, 2014; Gougol et al., 2015; Judd et al., 2014). Moreover, there are many studies assessing the factors affecting depression by common mixed models, but in all of them just a few confounders have been controlled (Bastos, Guimarães, & Trentini, 2013; Detke, DelBello, Landry, & Usher, 2015; Morales et al., 2006; Otte et al., 2012; Roose et al., 2015; Tao et al., 2012; Uher et al., 2014).

The aim of this study was to determine the most effective factors on depression among a huge number of potential variables using penalized mixed model in a longitudinal study. To the best of our knowledge, it is the first study on the effects of the fluoxetine plus lovastatin on MDD while controlling more than 10 confounding variables.

2. Method & Materials

This is a randomized, double-blind, controlled clinical trial, investigating the effect of lovastatin as an adjuvant therapy for treating individuals with major depressive disorder. Written informed consent was provided by the patients. The trial was approved by the Ethics Committee of Shiraz University of Medical Sciences.

The participants of this study were a clinical sample of 60 patients with the major depressive disorder diagnosed according to a face to face interview using DSM-IV diagnostic criteria. The patients received oral doses of fluoxetine (up to 40 mg/day)+lovastatin (30 mg/day) or fluoxetine (up to 40 mg/day)+placebo for six weeks. The history of taking fluoxetine was asked. The patients received non-steroidal anti inflammatory drugs (NSAIDs) concurrently. Those patients with increased SGPT serum glutamic pyruvic transaminase (SGPT; more than 2 times), a positive history of cancer, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and hypothyroidism were excluded. The patients were blind to taking lovastatin or placebo, but not to fluxotine.

Clinical efficacy and tolerability were assessed. The primary outcome measure was the total score with Hamilton depression scale (Hamilton, 1960). Moreover, Clinical Global Impression (CGI) scale was filled out by the raters. The assessment occurred at the baseline, week 2, and week 6.

The outcome was measured using the 17-item Hamilton Depression (HAMD). HAMD is one of the first rating scales developed to quantify the severity of depressive symptomatology which was introduced by Max Hamilton in 1960. It has become the most widely used and accepted outcome measure for evaluating depression severity since then. The scores of 0-7 are generally accepted to be within the normal range (or in clinical remission) and the score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial. The 17 items included are rated on either a 5-point (0-4) or a 3-point (0-2) scale. In general, the 5-point scale items use a rating of 0=absent; 1=doubtful to mild; 2=mild to moderate; 3=moderate to severe; 4=very severe. A rating of 4 is usually reserved for extreme symptoms. The 3-point scale items used a rating of 0=absent; 1=probable or mild; 2=definite. The Hamilton depression questionnaire has been translated into many European and Asian languages.

2.1 Outcome and Covariates

The covariates in our study included age, weight, sex, marital status, education, group, residence, previous depression, physical illness, systolic blood pressure, and diastolic blood pressure. The outcome was Hamilton Depression Rating Scale (HDRS) score (baseline, first follow-up session, second follow-up session).

2.2 Statistical Methods

The LASSO (least absolute shrinkage and selection operator) which has been proposed by Tibshirani enforces shrinkage and variable selection simultaneously. By adding LASSO penalty on the traditional LMM(linear mixed model), LASSO (LMMLASSO) was introduced in 2014 (Groll & Tutz, 2014). All the statistical methods were performed using SPSS version 18 and *glmmLasso* package in R. 3.1.3 software.

3. Results

Among 60 patients, 39 (65%) were female and the others were male. According to the results, the mean (SD) age of the participants was 31.9 (9.8) years. 51.7% of the patients were married, a majority (73%) lived in village, and 45% of them had high school education. Descriptive statistics of demographic variables and Hamilton depression score categorized by factors subgroups are shown in Table 1.

In order to assess the association between our covariates and depression, for each covariate simple linear mixed model was performed with a random intercept term. The results of the univariate mixed model revealed that only sex had a significant effect on the score of Hamilton depression (P-value=0.001).

Table 1. Descriptive statistics of Hamilton depression score, separated by time and subgroups

Variable	Category	n(%)/Mean±SD	Hamilton Depression Score (Mean±SD)		
			Baseline	Week2	Week6
Sex	Male	21 (35)	31.24±6.54	27.38±5.56	20±6.31
	Female	39 (65)	28.23±5.84	24.23±4.92	17.44±5.13
Marital status	single	29 (48.3)	29.93±5.84	25.72±5.11	18.41±6.5
	married	31 (51.7)	28.68±6.58	24.97±5.58	18.26±4.84
Education	up to secondary school	9 (15)	32.56±6.58	28.67±5.32	20.67±5.1
	High school education	27 (45)	29.04±6.39	25.07±5.75	19.33±5.57
	Post-graduate degree	24 (40)	28.33±5.71	24.38±4.5	16.33±5.51
Group	without lovastatin	30 (50)	28.6±5.92	25.83±5.71	20.4±5.48
	with lovastatin	30 (50)	29.97±6.52	24.83±4.97	16.27±5.11
Residence	city	16 (26.7)	29.44±7.6	24.31±6.1	18.5±6.21
	Village	44 (73.3)	29.23±5.73	25.7±5.05	18.27±5.51
previous depression	No	29 (48.3)	28.86±5.99	24.86±5.14	17.45±5.17
	Yes	31 (51.7)	29.68±6.49	25.77±5.55	19.16±6.03
Physical illness	No	47 (78.3)	29.43±6.13	25.79±5.66	18.53±6.21
	Yes	13 (21.7)	28.77±6.74	23.69±3.64	17.62±2.96
Age		31.9(9.8)	-	-	-
Weight		68.4 (14.2)	-	-	-
Systolic blood pressure		110 (12)	-	-	-
Diastolic blood pressure		68 (9)	-	-	-
HDR score at baseline		29.28 (6.21)	-	-	-
HDR score at first follow-up session		25.33 (5.33)	-	-	-
HDR score at second follow-up session		18.33 (5.65)	-	-	-

The effect of treatment group on depression was investigated by adjustment of other covariates in a linear mixed model with LASSO penalty (LMMLASSO). In this model, the optimum amount of lambda was estimated via BIC criteria. The use of LMMLASSO leads to elimination of diastolic blood pressure from the final model. Therefore, the optimal combination of factors was obtained as follows:

$$\log(p_i/1-p_i)=-1.05X1-0.39X2-0.81X3+1.37X4-0.54X5+0.26X6-0.46X7-1.17X8+1.44X9-0.30X10+0.32X11 \quad (1)$$

The presented model revealed that in the presence of the other covariates, lovastatin can play a key role in the reduction of depression. LMMLASSO also introduced age, education, physical illness and sex as the most covariates that had a significance effect on depression (Table 2).

Both groups showed a significant decrease in depression score on the Hamilton Depression scale. However, the depression score in the treatment group decreased more than the placebo group (Mean=12.8(SD=6.3) vs. Mean=8.2(SD=4.0), t=3.4, P<.001).

Table 2. Coefficients of linear mixed model with LASSO penalty

Variable	Category	Coefficient	Standard Error
Sex(X1)	Male	---	---
	Female	-1.05	0.94
Marital status(X2)	Single	---	---
	Married	-0.39	0.75
Education	Up to secondary school	---	---
	High school education(X3)	-0.81	1.00
	Post-graduate degree(X4)	1.37	1.00
Group(X5)	Without lovastatin	---	---
	With lovastatin	-0.54	0.64
Residence(X6)	City	---	---
	Village	0.26	0.67
Previous depression(X7)	No	---	---
	Yes	-0.46	0.77
Physical illness(X8)	No	---	---
	Yes	-1.17	0.69
Age(X9)		1.44	0.84
Weight(X10)		-0.30	0.98
Systolic blood pressure(X11)		0.32	0.41
Diastolic blood pressure(X12)		0.00	NA

The proposed linear mixed model with LASSO penalty revealed that age and high level of education had a direct association with the score of depression. Moreover, we found that the mean score of depression in females was less than that of males and patients with physical illness had a lower score than the others.

4. Discussion

The aim of this study was to assess the simultaneous effect of lovastatin plus fluoxetine on depression by Hamilton depression rating scale, considering other variable factors. In Iran, the correlation between this scale and Beck depression inventory (second edition BDI-II) was 0.55 and its inter-rater reliability was 0.95 (Ebrahimi, Neshatdoost, Mousavi, Asadollahi, & Nasiri, 2013).

The main finding of this trial was that fluoxetine plus lovastatin decreases MDD symptoms more than fluoxetine plus placebo. This was displayed by the linear mixed model with LASSO penalty while controlling a large number of covariates in a longitudinal study.

Our finding is in accordance with the results of a previous animal study indicating that lovastatin potentiated the efficacy of fluoxetine (Renshaw et al., 2009). Although the earlier studies on humans had reached the same conclusion, the survey performed was implemented without considering other potential factors (Ghanizadeh & Hedayati, 2013). In this study, we tried to assess the effect of treatment after controlling the effect of potential confounders that have been shown to have serious impacts on depression.

Several studies have evaluated the effect of sex, age, education, and physical illness on depression (Bastos et al., 2013; Bekker & van Mens-Verhulst, 2007; Ebrahimi et al., 2013; Kessler et al., 2005; Kraus & Karaman, 2013;

Ladin, 2008; Li, Du, Zhang, Chen, & Zheng, 2015; Regan, Kearney, Savva, Cronin, & Kenny, 2013; Ross & Mirowsky, 2006; Scarinci et al., 2002; Shinkov et al., 2014; Tsang et al., 2008; Uher et al., 2014). By using the appropriate statistical method, our finding indicated that beside the treatment group, age, sex, education and physical illness had significant effects on depression. This is a major difference between the present study and previous ones. Thus using this modern statistical approach has increased the accuracy of the obtained results.

Based on our findings, the mean of the HDR score was very high in both genders. However, the data showing that the males were depressed more than females are inconsistent with the results of other studies. The findings of numerous studies indicate that females are more than twice likely to be afflicted with mood disorders (Bekker & van Mens-Verhulst, 2007; Kessler et al., 2005).

Both men and women get depression, but men can experience it differently compared to women. Depression in men is not always easy to recognize and it is usually diagnosed in more advanced stages. Because many men do not recognize, acknowledge, or seek help for their depression, they may be reluctant to talk about how they are feeling.

Our findings showed that older people are more depressed. As with other studies, the increase in age and higher rates of depression are in the same direction (Li et al., 2015; Shinkov et al., 2014).

Another major difference between this study and other studies was the effect of education on depression. In the present study, the participants with high school education were less depressed than those with primary education, and individuals with postgraduate degrees had higher levels of depression than those with primary education. But as an example, Kraus et al. proved that low education is a risk factor for an unfavorable course of major depression (Kraus & Karaman, 2013). Also, depression decreases more in women than men as the level of education increases (Ross & Mirowsky, 2006) and the odds of depression were approximately twice as high among adults with the education of less than high school compared with those of greater educational background (Ladin, 2008). Other studies indicated that the higher the education level, the lower the scores on depression, and younger women had a higher score on depression (Scarinci et al., 2002). A reasonable justification for this contradiction may be the fact that more educated patients lived in villages in the current study, so depression might be due to socioeconomic status, living conditions and expectations of the society of the educated people in rural areas.

The results showed that the individuals who do not have physical health problems are more depressed while the results of Regan et al. showed that physical illness is associated with depressive symptoms in adults aged 65 years old and chronic pain were stronger predictors of depression (Regan et al., 2013). In another study, there was a higher prevalence of chronic pain conditions among females and older people and chronic pain was similarly associated with depression disorder in developing countries (Tsang et al., 2008). This suggests that psychological problems are independent of physical health.

Our findings should be interpreted in the context of some limitations. First of all, due to the small sample size, a generalization of the results should be done with caution. Although we tried to manage this shortcoming using an appropriate statistical method, further studies with larger sample size are required to confirm the current results. As another limitation, the patients were treated for a short time in this trial (6 weeks).

5. Conclusion

Linear mixed model with LASSO penalty introduced sex, age, education and physical illness as the covariates that had the most significant effect on depression.

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Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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