HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2010; **25**: 525–529.
Published online 22 September 2010 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1147

Differences in clinical effect and tolerance between fluvoxamine and paroxetine: A switching study in patients with depression

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Objective We examined whether discontinuation and the responses to fluvoxamine (FLV) administration could predict the subsequent discontinuation and the responses to paroxetine (PRX) in patients with depression.
Methods The subjects comprised 106 outpatients who were diagnosed with depression, and clinical evaluation was conducted every 2 weeks. Patients who discontinued FLV because of side effects or did not achieve remission with 200 mg/day of FLV, the drug was switched to PRX. The maximum dose of PRX was 40 mg/day.
Results Among 10 patients who discontinued FLV, PRX was also discontinued in one patient. Of 33 patients without remission on FLV, PRX was discontinued because of side effects in two patients. There was no statistical difference in the discontinuation rates between the two groups. Four of 10 patients who discontinued FLV achieved remission, while nine of 33 patients without remission with FLV achieved remission with PRX. The remission rate was not significantly different between the two groups.
Conclusion Discontinuation and the responses related to FLV could not serve as a predictor for the subsequent discontinuation and the responses related to PRX. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — depression; discontinuation; fluvoxamine; paroxetine; replacement

INTRODUCTION

In recent years, remission should be the goal of depression treatment (Rush, 2007). However, no differences have been detected in the remission rates of different selective serotonin reuptake inhibitors (SSRIs) during treatments for depression. A remission rate of 30–40% is standard for SSRIs, and these rates were comparable with those of tricyclic antidepressants (TCAs) (Bondolfi *et al*., 2006; Omori *et al*., 2009; Warden *et al*., 2007). Therefore, in daily clinical settings, more often than not, initial administrations of an SSRI do not lead to remission and it becomes necessary to switch to another antidepressant. During treatment for depression, even when there is no response to initial administrations of one SSRI, there is a possibility that responses may be obtained by using another SSRI (Joffe *et al*., 1996; Nurnberg *et al*., 1999; Thase *et al*., 1997; Warden *et al*., 2007). In fact, based on treatment algorithms for depression, even when an SSRI of the first choice is ineffective, another SSRI should be considered as the second choice (TMAP, 2008).

The discontinuation rates for the use of SSRIs due to side effects are as high as 15–30% (Bondolfi *et al*., 2006; Gartlehner *et al*., 2005). In daily clinical settings, when initial administrations of an SSRI are discontinued due to some kind of side effects, it is difficult to decide whether another SSRI should be selected as the next antidepressant. There has been a report that, when switching from fluoxetine (FLOX) to sertraline (SER), discontinuation of FLOX administration serves as a predictor for discontinuation of SER administration (Zarate *et al*., 1996). Another report argues that discontinuation of FLOX administration does not necessarily lead to discontinuation of SER administration (Brown and Harrison, 1995). However, such details have not yet been fully clarified. Fluvoxamine (FLV) and paroxetine (PRX) are, like other SSRIs, widely used in the treatment of depression. Several articles have been published suggesting that there are differences in the side effects induced by these two drugs (Mackay *et al*., 1997; Omori *et al*., 2009; Raeder

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Received 29 June 2010
Accepted 11 August 2010

et al., 2006; Silvestri *et al*., 2001), but the details are unknown. Furthermore, to the extent of our knowledge, there have been no previous reports on substitution between these two drugs to examine whether discontinuation of the initial drug could serve as a predictor for the discontinuation of the subsequent drug treatment.

We, therefore, examine whether the discontinuation and responses related to FLV administered prior to PRX could serve as a predictor for the discontinuation and responses related to PRX administered subsequently.

METHODS

Subjects

The study was conducted with outpatients between 18 and 65 years of age who received treatment for depression at the outpatient clinic of psychiatry service at Niigata University Medical and Dental Hospital and who, based on the Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision, were diagnosed with either major depressive disorder, depressive disorder not otherwise specified, or an adjustment disorder with depression, and whose 17-item Hamilton Rating Scale for Depression (HAMD) score at their initial consultation was 18 or more in total. Any patient also suffering from other Axis I disorders or apparent personality disorders were excluded. Other concomitant drugs except benzodiazepines, FLV, or PRX were not allowed in the study.

This study was conducted with the approval of the Gene Ethics Committee of Niigata University Graduate School of Medical and Dental Sciences. Documents for informed consent were handed to all patients after providing thorough explanations in order to obtain their consent in writing.

Methods for drug administration and evaluation

Following the initial consultation, they were treated with FLV at a starting dose of 25 mg/day with the aim of achieving remission, defined as a HAMD score of 7 or less. The HAMD score and the status of discontinuation of the treatment and the causes thereof were assessed every 2 weeks for up to 12 weeks.

In the cases in which remission was not achieved, the FLV dose was increased to 50, 100, 150, or 200 mg/day based on clinical judgments. Assessments of the cases were concluded when FLV administration was discontinued for unknown reasons (when the patients stopped to come to outpatients clinic) or when patients achieved remission with FLV. In all of the cases in which FLV was discontinued due to side effects or in which no remission was achieved at a FLV dose of 200 mg/day, the drug was switched to PRX. The FLV dose was reduced to 150 mg/day at the same time when PRX administration was started. Thereafter, the FLV dose was reduced by 50 mg/day to zero over a 3-week period following the commencement of PRX administration. Treatment with PRX started at a starting dose of 10 mg/day, and as in the treatment with FLV, assessments were conducted every 2 weeks until remission was achieved. In the cases in which remission was not achieved, the PRX dose was increased to 20, 30, and up to 40 mg/day based on clinical judgments. Patients who were required to take concomitant drugs except benzodiazepine drugs during the assessment period were excluded.

Statistical analysis

We used χ^2 analyses and Fisher's exact test to compare the discontinuation rates and remission rates. The significance level was set to $p < 0.05$ for both rates. SPSS-16.0 (SPSS Japan Inc., Tokyo, Japan) was used for statistical calculations.

RESULTS

There were 106 sample cases and their clinical characteristics and diagnoses are shown in Table 1. Of the 106 cases of treatment with FLV, FLV was discontinued due to side effects or for unknown reasons in 32 cases (30.2%). Of the 43 cases of treatment with PRX, PRX was discontinued due to side effects or for unknown reasons in eight cases (18.6%). There was no significant statistical difference observed in the discontinuation rates of the FLV and PRX groups ($\chi^2 = 2.090$, df = 1, $p = 0.148$) (Table 2).

Of the 106 cases of treatment with FLV, FLV was discontinued due to side effects in 10 cases (9.4%). Of the 43 cases of treatment with PRX, PRX was discontinued due to side effects in three cases (7.0%). There was no significant statistical difference observed in the discontinuation rates of the two groups ($p = 0.758$) (Table 2).

Table 1. Demographic and diagnostic characteristics of cases

Sex (male:female) (*n*)	58:48
Age (mean ± SD)	39.9 ± 13.4
HAMD score at initial visit (mean ± SD)	22.1 ± 4.9
Diagnoses (*n*)	
Major depressive disorder	91
Adjustment disorder with depression	8
Depressive disoreder not otherwise specified	7

Abbreviation: HAMD = 17-item Hamilton rating scale for depression.

DOI: 10.1002/hup

Table 2. Outcomes of fluvoxamine and paroxetine treatment

Outcome of fluvoxamine	Final dose of fluvoxamine (mg)	*n*	(%)	Outcome of paroxetine	n
Remission	119.1 ± 58.2	41	(38.7)		
Non-remission	200	33	(31.1)	Remission	9
				Non-remission	18
				Discontinuation due to side effects	2
				Discontinuation for unknown reasons	4
Discontinuation due to side effects	105.0 ± 36.9	10	(9.4)	Remission	4
				Non-remission	4
				Discontinuation due to side effects	1
				Discontinuation for unknown reasons	1
Discontinuation for unknown reasons		22	(20.8)		

Of the 10 cases in which FLV administration was discontinued due to side effects, PRX was also discontinued due to side effects in one case (10.0%). Of the 33 cases in which no remission was achieved even when the FLV dose was increased to 200 mg/day, PRX administration was discontinued due to side effects in two cases (6.1%). There was no significant statistical difference observed in the discontinuation rates of the two groups ($p = 0.558$) (Table 2).

With regard to the 12 cases in which administrations of either FLV or PRX was discontinued during the course of treatment due to side effects, the reason for discontinuation for each case is shown in Table 3. Drug administration was discontinued for seven out of 10 patients treated with FLV (70%) and two out of three patients treated with PRX (66.7%) due to gastrointestinal symptoms which were the most common cause of discontinuation.

Of the 106 cases of treatment with FLV, remission was achieved in 41 cases (38.7%). Of the 43 cases in which no remission was achieved at an FLV dose of 200 mg/day or in which FLV was discontinued due to side effects and switched to PRX thereafter, remission was achieved in 13 cases (30.2%) (Table 2). There was no significant statistical difference observed in the remission rates of the two groups ($\chi^2 = 0.945$, df = 1, $p = 0.331$).

Of the 10 cases in which FLV administration was discontinued due to side effects, remission was achieved in four cases (40.0%). Of the 33 cases in which no remission was achieved even when the FLV dose was increased to 200 mg/day, remission was achieved in nine cases (27.3%)(Table 2). There was no significant statistical difference observed in the remission rates of the two groups ($p = 0.458$).

DISCUSSION

The results of this study demonstrated that, during treatment for depression, discontinuation of the initial drug, FLV, as well as the responses, do not serve as a predictor for discontinuation and responses related to PRX administered subsequently. Previous reports have examined the discontinuation rates and responses related to the use of SSRIs using randomized controlled trials (Dewan and Anand, 1999; Gartlehner

Table 3. Details of cases in which fluvoxamine or paroxetine was discontinued due to side effects

Case			Fluvoxamine			Paroxetine		
number	Sex	Age	Final dose (mg)	Reason for discontinuation	Outcome	Final dose (mg)	Reason for discontinuation	Outcome
1	M	34	100	Nausea	Discontinued	10	Nausea	Discontinued
2	F	60	100	Nausea, headache	Discontinued	30	—	Remission
3	F	27	100	Nausea	Discontinued	30	Unknown	Discontinued
4	F	43	50	Nausea	Discontinued	20	—	Remission
5	M	23	100	Diarrhea	Discontinued	40	—	Non-remission
6	M	30	150	Gastralgia	Discontinued	40	—	Non-remission
7	M	34	150	Hand tremors, leg tremors	Discontinued	40	—	Remission
8	F	23	100	Drowsiness	Discontinued	40	—	Non-remission
9	M	45	150	Malaise	Discontinued	40	—	Remission
10	M	56	50	Nausea, vomiting	Discontinued	40	—	Non-remission
11	M	53	200	—	Non-remission	30	Nausea	Discontinued
12	M	57	200	—	Non-remission	20	Headache, dizziness	Discontinued

DOI: 10.1002/hup

et al., 2005; Rapaport *et al*., 1996). However, there have been few reports comparing the discontinuation rates and responses related to different SSRIs in a single sample of patients; moreover, to the extent of our knowledge, this is the first study to directly compare FLV and PRX.

Brown and Harrison (1995) reported that SER was prescribed for 8 weeks for 113 patients with major depression for whom FLOX was discontinued due to side effects and found that the SER administration was discontinued due to side effects in only 11 patients (9.8%). They concluded that discontinuation of FLOX administration due to side effects does not predict discontinuation of SER administration due to side effects. On the other hand, another report has demonstrated that, when switching from FLOX to SER, discontinuation of FLOX administration serves as a predictor for discontinuation of SER administration (Zarate *et al*., 1996). However, the study by Zarate *et al.* (1996) was retrospective, whereas the study by Brown and Harrison (1995) was prospective, which may be responsible for the different results obtained.

In this study, most of the side effects which led to discontinuation of FLV administration were gastrointestinal side effects such as nausea. As indicated in previous reports (Bignamini and Rapisarda, 1992; Dunbar *et al*., 1991; Farbe, 1988), gastrointestinal side effects are the most common cause for the discontinuation of treatment. All SSRIs induce side effects related to the digestive system. However, as every SSRI has a different chemical structure, there are considerable individual variations in the ways in which side effects are expressed. We have previously reported that the gastrointestinal side effects that are induced by FLV are associated with 5-HT2A receptor gene polymorphism (Suzuki *et al*., 2006), while those that are induced by PRX are associated with 5-HT3B receptor gene polymorphism (Sugai *et al*., 2006), and this suggests that there may be differences, even between SSRIs, in the mechanisms underlying the gastrointestinal side effects. Such differences in pharmacodynamic characteristics may be the reason for the differences in the ways in which FLV-induced and PRX-induced side effects are expressed in a single sample of patients.

The overall discontinuation rate of this study was 31.1% in the case of FLV administration and 18.6% in the cases of PRX administration. The rate of discontinuation due to side effects was 9.4% for FLV administration and 7.0% for PRX administration. In comparison to previous reports which reported the discontinuation rates for SSRI administration due to side effects to range between 15 and 30% (Bondolfi *et al*., 2006; Gartlehner *et al*., 2005; Machado *et al*., 2006) or 60% and over (Bondolfi *et al*., 2006), the discontinuation rates identified in our study were lower. In this study, the starting dose of FLV was set low at 25 mg/day, and this may have been one of the factors behind the low discontinuation rates for FLV administration.

There was no significant difference between the rate of remission achieved with FLV and the rate of remission achieved with PRX in patients who had not achieved remission with FLV and switched to PRX. This indicates that if remission is not achieved with the FLV that is prescribed initially, administering PRX as the second-choice drug is appropriate. When patients who did not achieve remission with FLOX were switched to treatment with SER, there was no significant difference observed in the rates of remissions achieved with these two SSRIs (i.e., FLOX and SER) (Thase *et al*., 1997). The results of our study, therefore, confirmed the findings of the previous report.

There are several limitations in this study. First, there was no period set for washing out FLV when the treatment was switched from FLV to PRX, and there were no comparative samples using a placebo or other antidepressants. Secondly, although there was no significant statistical difference observed in the overall discontinuation rates for FLV administration and PRX administration, the rate of discontinuation due to unknown reasons was 7.0% for PRX administration and 21% for the previously prescribed FLV, the latter being higher. It is, therefore, possible that the cases in which FLV administration was discontinued for some unknown reasons may include those cases in which FLV was discontinued due to side effects. Thirdly, gastrointestinal side effects induced by SSRIs, even when expressed immediately after the administration of the drug, are gradually reduced in many cases (Dunbar, 1992; Leyman *et al*., 1995). In this study, exposure to the initially prescribed FLV may have affected the susceptibility to side effects induced by the subsequently prescribed PRX, resulting in a reduction in the discontinuation rate for PRX administration.

CONCLUSION

Currently, based on the established treatment algorithms for depression, it is recommended that the administration with one SSRI be switched to another SSRI even when the first SSRI proves to be ineffective. The results of this study indicate that the established treatment algorithms for depression are valid.

CONFLICT OF INTEREST

None declared.

DOI: 10.1002/hup

AUTHORSHIP

All authors fulfill the criteria of authorship based on their substantial contribution to the conception and design, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; or the final approval of the version to be published. No one who fulfils these criteria has been excluded as an author. Dr Toshiyuki Someya is the guarantor for the present manuscript; he accepts full responsibility for the finished article, since he had access to all data, and controlled the decision to submit for publication.

ACKNOWLEDGEMENTS

The study was funded by Health and Labour Sciences Research Grants (Research on Psychiatric and Neurological Diseases and Mental Health) (H17-kokoro-002), a Grant-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Research (JSPS) (no. 17591199), and an intramural grant from Niigata University to Dr Someya. The funding sources played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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