Time to Rehospitalization in Patients With Major Depressive Disorder Taking Venlafaxine or Fluoxetine

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Objective: The combined serotonin-norepinephrine reuptake inhibitor, venlafaxine, has demonstrated better short-term efficacy than selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine in pooled analyses. This study aimed to compare venlafaxine and fluoxetine treatment in the long-term outcome measure, time to rehospitalization, in patients with major depressive disorder. Other clinical factors that may influence time to rehospitalization were also explored.

Method: Han Chinese patients were admitted to the depression inpatient unit of a major psychiatric center in Taiwan from January 1, 2002, to December 31, 2003. Patients with major depressive disorder (DSM-IV) who showed favorable treatment response to venlafaxine (mean ± SD dose = 116.5 ± 42.5 mg/day; N = 122) or fluoxetine (mean ± SD dose = 25.1 ± 9.0 mg/day; N = 80) during hospitalization were followed up for 1 year after discharge under naturalistic conditions. The 2 treatment groups were similar in demographic and clinical characteristics: sex, age, age at illness onset, comorbid anxiety disorders, personality disorders, nicotine dependence, psychotic features, adjunctive antipsychotics use, duration of index hospitalization, and number of previous hospitalizations. Time to rehospitalization was measured by the Kaplan-Meier method. Possible associations of rehospitalization with other covariates were analyzed using the Cox proportional hazards regression model.

Results: No significant difference for the time to rehospitalization was found between the 2 groups by the log-rank test. The number of previous admissions (hazard ratio = 1.331, 95% CI = 1.153 to 1.538, p = .000), but not other factors, increased the risk of rehospitalization.

Conclusion: The findings suggest that venlafaxine and fluoxetine have similar effects on time to rehospitalization in patients with major depressive disorder. The relatively low dose of venlafaxine may have contributed to the negative finding. Previous hospitalization history may raise the risk of rehospitalization. Longer-term, double-blind, randomized, fixed-dose studies are warranted to better delineate the effectiveness of different pharmacotherapeutic regimens for the outcomes of patients with major depressive disorder.

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Major depressive disorder is a common mental disorder, with lifetime prevalence rates as high as 17% to 19%.[1] Fifty percent or more patients with an initial depressive episode may later experience recurrence.[2] The major goal of treatment is to return patients to their baseline levels of symptomatic as well as functional status and prevent relapse or recurrence of subsequent major depressive episodes.

Antidepressant medication is one of the important treatment modalities for major depressive disorder. Many depressed patients require long-term treatment with antidepressants to maintain remission. The initial selection of an antidepressant medication is based principally on the side effects, tolerability, patient or doctor preference, and cost, rather than on efficacy.[3] On the basis of these considerations, serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, or selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, are among the favorable agents for most patients.[3]

Although there is no consistent evidence of differences in effectiveness between classes of antidepressants,[3] SNRIs, with dual action of inhibiting reuptake of both serotonin and norepinephrine, may be superior to SSRIs in treating severe or treatment-resistant depression and achieving remission.[4–7] The pooled analysis by Thase

et al.[8] indicated that venlafaxine produced a 10% higher rate of remission of depression, and earlier onset of remission, than SSRIs. Another pooled analysis by Shelton et al.[9] demonstrated that venlafaxine is more effective than fluoxetine/paroxetine for sustaining remission of depressive symptoms in 8 weeks of treatment. The meta-analysis by Smith et al.[10] and another pooled analysis by Stahl et al.[11] also suggest that venlafaxine has greater efficacy than SSRIs. However, most efficacy studies of venlafaxine have only assessed the effects of short-term treatment (4–8 weeks) in patients with major depressive episodes.[11] Due to the high rate of relapse or recurrence of depression, it is important to investigate the long-term effectiveness of venlafaxine versus SSRIs under real-world use conditions.

Most patients with major depressive disorder receive treatment in an outpatient setting. Hospitalization is usually indicated for patients who have more severe symptoms, severe functional impairment, psychotic features, and a greater likelihood of being seriously suicidal.[12] Although patients with major depression are admitted as often as patients with schizophrenia,[13] scanty studies[12,14] about rehospitalization for major depressive disorder have been reported.

This study aimed to compare the effects of venlafaxine versus fluoxetine on the time to rehospitalization after discharge in patients with major depressive disorder. Other confounding factors, which may influence time to rehospitalization, were also examined.

METHOD

This study was conducted in Kai-Suan Psychiatric Hospital, a major psychiatric center in Taiwan, under naturalistic conditions. The study was approved by the facility's institutional review board to be exempt from the requirement for written informed consent and was conducted in accordance with the Declaration of Helsinki. Han Chinese patients in Taiwan who were admitted to the Depression Inpatient Unit from January 1, 2002, to December 31, 2003, were screened by experienced psychiatrists, who made the diagnosis using DSM-IV.[15] At admission of new patients, the Mini-International Neuropsychiatric Interview[16] was conducted for clinical diagnosis, and the Mood Disorders Questionnaire[17] was used to exclude bipolarity. Moreover, clinical observation and in-depth interview by psychiatrists and team members during the hospitalization period as well as after discharge, and information from the main supporting caregivers validated the clinical diagnosis. During hospitalization, psychiatrists visited their patients daily and adjusted the dosage according to clinical status, measured by the Clinical Global Impressions-Severity of Illness (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) scales.[18]

Subjects

Subjects consisted of the patients who fulfilled the diagnosis of major depressive disorder and were discharged with a CGI-I score of 1 (very much improved) or 2 (much improved) and tolerability to venlafaxine or fluoxetine treatment. During the study period, a substantial portion of psychiatrists at the hospital favored the newer agent, venlafaxine, and others tended to use the more traditional one, fluoxetine, if there was no specific indication or contraindication. Patients were excluded if they were treatment resistant to at least 2 different classes of antidepressants in adequate doses and treatment duration.[19] We thus supposed and then demonstrated that the 2 treatment groups had similar demographic characteristics and illness course (see Results section). Comorbid anxiety disorders, nicotine dependence, and personality disorders (except antisocial personality disorder) were allowed. However, we excluded patients with comorbidity of alcohol or drug use disorder or major psychiatric disorders, such as schizophrenia-related disorders and bipolar disorder, and those who had received electroconvulsive therapy during hospitalization. Antipsychotics could be added for psychotic features or adjunctive therapy. Benzodiazepines or nonbenzodiazepine hypnotics such as zolpidem, if needed, were allowed but restricted to short-term use of at most 3 weeks.

Procedures

During hospitalization, venlafaxine doses were adjusted in the range from 75 to 225 mg/day and fluoxetine from 20 to 60 mg/day.[3] The optimum dose was individually determined according to treatment response and tolerability.

After discharge, all subjects were followed up at the Outpatient Department usually weekly, biweekly, or monthly, on the basis of their clinical conditions. According to American Psychiatric Association practice guideline,[3] patients continued the same antidepressant at the same dose as used at discharge. The rehospitalization status was monitored for 1 year, up to December 31, 2004. No other specific treatment modalities, such as intensive individual or group psychotherapy, were provided. Rehospitalization was indicated for patients who had more severe symptoms, severe functional impairment, psychotic features, and a greater likelihood of being seriously suicidal that did not respond adequately to outpatient treatment following discharge.[3,12] Clinicians who initiated rehospitalization did not know the background of the study.

Statistical Analyses

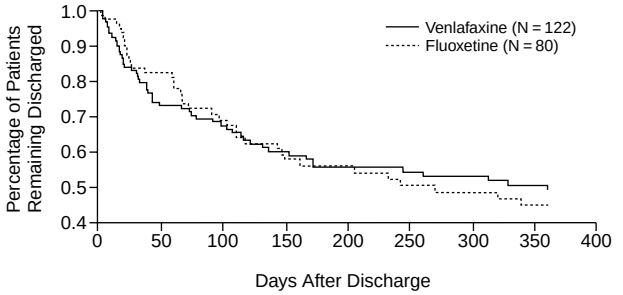
In this study comparing venlafaxine and fluoxetine treatments, time to rehospitalization was regarded as the outcome measure. Covariates included sex, age,[14] comorbid anxiety disorders, personality disorders, nicotine dependence, psychotic features, concomitant antipsychotic

Table 1. Characteristics of Patients With Major Depressive Episodes Discharged While Taking Venlafaxine or Fluoxetine

	Venlafaxine (N = 122)		Fluoxetine (N = 80)		
Variable	N	%	N	%	p[a]
Sex					.997
Male	32	26.2	21	26.3	
Female	90	73.8	59	73.7	
Comorbid anxiety disorders	30	24.6	17	21.3	.583
Comorbid personality disorders	16	13.1	14	17.5	.391
Comorbid nicotine dependence	33	27.0	18	22.5	.441
Psychotic features	14	11.5	10	12.5	.826
Adjunctive antipsychotics use[b]	40	32.8	26	32.5	.966
Short-term benzodiazepine use[c]	96	78.7	64	80.0	.699
	Mean	SD	Mean	SD	p
Age, y	44.4	13.0	43.7	14.5	.718[d]
Age at onset of illness, y	36.0	13.4	38.6	14.7	.201[d]
Duration of index hospitalization, d	27.2	12.2	26.4	14.7	.655[e]
No. of previous admissions within past 5 y	1.7	1.2	1.8	1.5	.771[e]
Daily dose, mg	116.5	42.5	25.1	9.0	…

[a]Pearson χ^2 test.
[b]Two patients in the venlafaxine group and 4 in the fluoxetine group used second-generation antipsychotics; the others used first-generation agents (2-tailed Fisher exact test, p = .202). The mean ± SD chlorpromazine dose equivalent of the first-generation antipsychotics was 96.7 ± 48.7 mg/day for the venlafaxine group and 114.8 ± 72.7 mg/day for the fluoxetine group (t = –1.15, df = 58, p = .254).
[c]Benzodiazepines or nonbenzodiazepine hypnotics such as zolpidem, if needed, were restricted to short-term use of at most 3 weeks.
[d]Independent t test.
[e]Mann-Whitney U test.
Symbol: … = not applicable.

Figure 1. Time to Rehospitalization for Patients Discharged While Taking Venlafaxine or Fluoxetine[a]



[a]Log-rank = 0.01, df = 1, p = .914.

use,[20,21] age at onset of the first major depressive episode,[22,23] duration of index hospitalization,[14] and number of previous hospitalizations within the past 5 years.[24,25]

The Pearson χ^2 test, independent t test, and nonparametric tests were applied to compare demographic variables and risk factors between groups. Kaplan-Meier survival analysis was used to determine time to rehospitalization and time to discontinuation due to loss of follow-up or switch to other antidepressants within 1 year after discharge. The significance of between-group difference was measured by the log-rank test. The Cox proportional hazards regression model was used to analyze covariates thought to affect time to rehospitalization. All tests were 2-tailed, and significance was defined as an α of less than .05. Data were analyzed with the SPSS version 10.0 for Windows (SPSS Inc., Chicago, Ill.).

RESULTS

Three hundred one patients with major depressive disorder were screened, and 99 of them were not included in the study due to the noninclusion criteria. Therefore, a total of 202 patients taking venlafaxine (N = 122) or fluoxetine (N = 80) were recruited (Table 1). The 2 treatment groups were very similar in demographic and clinical variables such as sex (χ^2 = 0.00, df = 1), age (t = 0.36, df = 200), comorbid anxiety disorders (χ^2 = 0.302, df = 1), comorbid personality disorders (χ^2 = 0.735, df = 1), comorbid nicotine dependence (χ^2 = 0.5932, df = 1), psychotic features (χ^2 = 0.048, df = 1), concomitant antipsychotics use (χ^2 = 0.002, df = 1), short-term use of benzodiazepines or nonbenzodiazepine hypnotics (χ^2 = 0.150, df = 1), age at illness onset (t = –1.28, df = 200), duration of index hospitalization (t = 0.48, df = 200), and number of previous admissions (Mann-Whitney U test, due to asymmetrical distribution) (Table 1). In addition, none of the venlafaxine patients and 4 of the fluoxetine-treated individuals received concurrent mood stabilizers (2 used valproate and 2 used carbamazepine).

Fifty-three (43.4%) of the venlafaxine-treated patients and 37 (46.2%) of the fluoxetine-treated patients were rehospitalized within 360 days after discharge (χ^2 = 0.154, df = 1, p = .695). The 2 groups did not differ in the time to rehospitalization within 360 days after discharge (venlafaxine, mean ± SD survival time = 223 ± 15 days; fluoxetine, mean ± SD survival time = 222 ± 17 days; Figure 1).

Thirty-three (27.0%) venlafaxine recipients and 19 (23.8%) fluoxetine-treated individuals were lost to follow-up or shifted from the drug being used within 1 year after discharge (χ^2 = 0.275, df = 1, p = .600). Specifically, only 3 of the 122 venlafaxine-treated patients and none of the 80 fluoxetine recipients shifted to other antidepressants (Fisher exact test, p = .279). The 2 groups were also similar in time to discontinuation (venlafaxine, mean ± SD follow-up time = 270 ± 14 days; fluoxetine, mean ± SD follow-up time = 275 ± 17 days; log rank = 0.29, df = 1, p = .588).

The forward Cox proportional hazards regression analysis showed that the number of previous admissions,

but not other variables, affected the time to rehospitalization within 1 year after discharge ($\beta = .286$, hazard ratio = 1.331, 95% CI = 1.153 to 1.538, p = .000).

DISCUSSION

Our findings do not support the notion that venlafaxine, a dual reuptake inhibitor, is associated with less relapse/tachyphylaxis.[26] The relatively low dose of venlafaxine in this study may have contributed to the negative finding. The mean doses (venlafaxine, 116.5 ± 42.5 mg/day; fluoxetine, 25.1 ± 9.0 mg/day) in our Han Chinese patients are similar to those in a portion of previous studies[27–29] in Western populations. In these studies,[27–29] venlafaxine and fluoxetine showed equal short-term efficacy. In contrast, in studies[30–32] that utilized venlafaxine at mean doses higher than 150 mg/day, this SNRI revealed better treatment response than fluoxetine. Venlafaxine's serotonin reuptake inhibition is approximately 3-fold higher than its noradrenergic reuptake inhibition.[33] Harvey et al.[34] suggest that venlafaxine is a potent serotonin reuptake inhibitor, and it is also a potent inhibitor of norepinephrine reuptake if at a daily dose higher than 150 mg. In the current study, venlafaxine treatment, at lower doses, may have yielded inadequate noradrenergic activity, thus lacking the advantage of "dual action."[35] Of note, the dose had been individually titrated to the optimum in this real-world study, and suitable doses of antipsychotics have been reported to be lower in Han Chinese subjects than in white subjects[36,37] due to the lower activity of drug-metabolizing enzymes such as CYP2D6 or other isozymes in Chinese subjects.[38] Whether the appropriate dosage of venlafaxine, fluoxetine, or other newer antidepressants is also lower in Han Chinese subjects requires investigation. Nonetheless, although the mean dose of venlafaxine in the current study is similar to that used in another Han Chinese population,[39] it remains unclear whether higher doses can bring better long-term outcomes.

In this study, a disproportionately larger percentage of patients received venlafaxine (60%) than fluoxetine (40%). As the follow-up was limited only to patients who responded to therapy, it was important to examine whether venlafaxine was a more widely used medication or, if the medications were prescribed with similar frequency, whether venlafaxine was more effective for the acute treatment. In addition, it is of interest to examine the outcomes for the patients treated with SSRIs other than fluoxetine. We found that venlafaxine was a more widely used medication. A total of 268 patients started treatment with venlafaxine (N = 123), fluoxetine (N = 83), or other SSRIs (N = 61: 26 fluvoxamine, 19 paroxetine, 13 sertraline, 3 citalopram) during hospitalization. The majority of them (98%), including 122 venlafaxine-treated patients (99%), 80 fluoxetine receivers (96%), and 61 patients using other SSRIs (98%), were discharged with a CGI-I score of 1 (very much improved) or 2 (much improved) and were recruited into the 1-year follow-up. The 3 groups did not differ significantly in the time to rehospitalization (venlafaxine, mean ± SD survival time = 223 ± 15 days; fluoxetine, 222 ± 17 days; other SSRIs, 202 ± 19 days; log rank = 0.74, df = 2, p = .692). Thirty-three venlafaxine recipients (27.0%), 19 fluoxetine-treated individuals (23.8%), and 12 patients using other SSRIs (19.7%) were lost to follow-up or discontinued from the drug being used within 1 year after discharge ($\chi^2 = 1.223$, df = 2, p = .542). The 3 groups were also similar in time to discontinuation (venlafaxine, mean ± SD follow-up time = 270 ± 14 days; fluoxetine, 275 ± 17 days; other SSRIs, 302 ± 16 days; log rank = 1.06, df = 2, p = .588).

The rehospitalization rate in our study appears higher than expected.[40,41] One of the main reasons may be that all subjects came from a public mental hospital. It has been suggested that patients with major depression from such hospitals, usually more severe than those in a general hospital, are admitted as often as patients with schizophrenia.[13] In this case, the rehospitalization rate, 44.5% (90/202), in our study appears explicable, for it has been shown that around half of stabilized schizophrenia patients were readmitted to the hospital during 1 year of naturalistic follow-up.[42]

This study also demonstrated that depression patients with more previous admissions tended to be rehospitalized faster. Likewise, an earlier study showed that patients with more previous admissions had more readmissions than those with fewer previous admissions.[14] These findings imply that patients who frequently seek psychiatric services often present with a range of complex, recurring problems and severe psychopathologies that are not easily ameliorated, leaving these individuals vulnerable to further exacerbations in illness and hospitalizations.[25,43] Overall, 90 (44.5%) of the 202 patients were rehospitalized within 360 days after discharge. Mean time to rehospitalization for all subjects was 223 days (SD = 11). This finding supports that rehospitalization is common in depression patients.[14,15]

In this study, concurrent uses of antipsychotics for adjunctive therapy were comparable between the 2 groups (Table 1). In a review article,[21] Thase claims that the use of antipsychotic agents in depressive disorders is not a new idea. Adjunctive therapy with neuroleptics was commonly undertaken in combination with antidepressants for patients with more severe, agitated, or psychotic depressions.[21] Both first-generation[44] and second-generation antipsychotics[45,46] have been used as augmentation strategies in depression.

The limitations of this study are similar to previous studies[47–49] on rehospitalization for psychiatric disorders. First, the patients were not randomly assigned to the drug

treatments, and the doses were not fixed. Additionally, due to patients' recall bias, we did not address other potential confounding factors, such as family history of affective illness, numbers of episodes, noncompliance with medication,[2,15,50–52] or psychosocial stressors. However, the 2 treatment groups were very similar in sex, age, psychotic features, comorbid anxiety disorders, personality disorders, nicotine dependence, duration of index hospitalization, number of previous admissions, and age at illness onset, which has been demonstrated to be correlated with family history of affective illness and number of recurrent episodes.[22,23] Another limitation of the study is the high drop-out rate. Thus, rehospitalization rates were examined merely among the patients who could be followed up for the entire observation period (89 venlafaxine and 61 fluoxetine patients). Finally, this study had a relatively small sample size, and all subjects came from the same psychiatric hospital. Future studies on time to rehospitalization could be conducted in different mental health systems.

The findings of this naturalistic study suggest that venlafaxine and fluoxetine have similar influences on time to rehospitalization in depression patients, and that patients with more previous hospitalizations are more likely to be readmitted. Longer-term, double-blind, randomized, fixed-dose studies are needed to better delineate the effectiveness of different antidepressants for the outcomes of major depression.

Drug names: carbamazepine (Equetro and others), citalopram (Celexa and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zolpidem (Ambien and others).

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