Venlafaxine, Paroxetine and Milnacipran for Major Depressive Disorder: A Pragmatic 24-Week Study

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Abstract

Major depressive disorder (MDD), one of the most common psychiatric disorders in the world, is a serious, recurrent and chronic mental disorder, which is associated with significant psychosocial disability and economic burden. Until recently, short-term effectiveness of antidepressants has been measured in terms of patients' response to the medications in significantly reduced depressive symptoms. Remission, a long-term elimination of symptoms and the restoration of normal functioning, has become the primary outcome of therapy. In the current study, the efficacy of three frequently prescribed antidepressants, venlafaxine (75-225 mg/day), paroxetine (20 mg/day) and milnacipran (100 mg/day), used in treating 249 MDD patients with Hamilton Rating Scale of Depression ($HRSD_{17}$) scores higher than 16 was compared. Each patient was evaluated at week 0, 1, 2, 4, 8, 12, 16, 20 and 24 in a 24-week open-label study. Eighty-two patients took venlafaxine, 97 took paroxetine and 70 patients took milnacipran. No significant differences were found between the three groups in the response condition ($HRSD_{17}$ scores decreased more than 50%) after 24 weeks of follow-up. For remission, the paroxetine was the least efficacious medication than either the milnacipran ($HRSD_{17} \leq 7$) or the venlafaxine ($HRSD_{17} \leq 5$) by the last observation carried forward (LOCF) analysis. Our results suggest that the absence of depressive symptoms alone may not be an indicator for MDD remission, but the duration of absent depressive symptoms may be a better indicator.

Key Words: milnacipran, paroxetine, remission, response, venlafaxine

Introduction

Major depressive disorder (MDD), one of the most common psychiatric disorders in the world, is associated with significant psychosocial disability and economic burden (5, 14, 28). Many studies (2, 13) have reported that MDD has high rates of chronicity, relapse, recurrence and suicide. The highest prevalence of MDD over a lifetime is 17% in the U.S. and Europe (17, 20). Most studies evaluating treatment efficacies of antidepressants have reported that patients responded to the tested drugs; however, few studies have ex-

amined remission (8, 15, 23).

Treatment outcome in antidepressant efficacy is most frequently assessed by a response that is defined as a 50% or greater reduction from baseline on the 17-item Hamilton Rating Scale for Depression (HRSD$_{17}$) (8). Remission is usually defined as not manifesting symptoms of MDD and with a score ≤ 7 on the HRSD$_{17}$ symptom severity scale (9). Patients who do not achieve remission often have residual symptoms and continue to experience additional psychosocial impairment. Residual depressive symptoms have been reported as a predictor of relapses and other depressive episodes (13). Therefore, remission for at least 2 months is the principal goal in treating MDD[†]. Many cut-off scores have been used on the HRSD$_{17}$ to define whether remission has been achieved when treated for MDD. Zimmerman *et al.* (36, 37) claimed that a score of ≤ 7 on the HRSD$_{17}$ is too high to define remission. Both Nierenberg *et al.* (23) and Zimmerman *et al.* (37) reported that higher cut-off scores were associated with higher rates of social functional impairment, and Zimmerman *et al.* suggested that a score ≤ 2 on the HRSD$_{17}$ was more valid and should be used as a new standard. Such a low cut-off score, however, may lead to the drawback of having small study populations (35). Other studies (7, 33) have suggested that an HRSD$_{17}$ score ≤ 5 is better for defining the remission state.

No evidences have been reported to show different response rates to different antidepressants (4, 21, 26), and only limited-term of follow-up data was studied for MDD patients (1, 30, 31). Although long-term treatment is required for MDD, in previous studies, researchers have compared the outcome only during weeks 6 through 12 in the acute treatment stage.

Milnacipran is USFDA-approved for treating the pain of fibromyalgia in adult patients. Moreover, milnacipran, an almost equipotent (1:1.6) serotonin and norepinephrine reuptake inhibitor (SNRI), is used, in some countries other than the U.S.A., to treat major depression (18, 22, 25), and is reported to be as effective as and better tolerated than tricyclic antidepressants (19, 32). Milnacipran is also a new antidepressant being used in Taiwan; therefore, we wanted to compare its effect with two other commonly used antidepressants, paroxetine and venlafaxine. Paroxetine is a potent selective serotonin reuptake inhibitor (SSRI) and a weaker norepinephrine reuptake inhibitor (6, 24) often used as a reference drug for comparing medication effects. Venlafaxine is the most widely used SNRI for MDD (27), but it has 30 times the affinity for serotonin transporters than for norepinephrine transporters (32).

In the present observational, open label study, we compared the rates of response, remission, time stayed in remission in three groups of patients taking venlafaxine, paroxetine or milnacipran, respectively, for up to 24 weeks. The prolonged follow-up period was meant to differentiate the response to individual antidepressant.

Materials and Methods

In this observational study of a 24-week drug intervention (non-randomized, open-label), we compared the efficacy of venlafaxine, paroxetine and milnacipran in patients with MDD. The method of assigning consecutive patients to treatments was based on doctors' prescriptions. The protocol was approved by the Human Experiment and Ethics Committees at National Cheng Kung University Hospital (NCKUH). Participants were recruited from the Department of Psychiatry outpatients in NCKUH.

Materials

The 17-item HRSD$_{17}$ (11) was used to measure the severity of depressive symptoms. Inclusion criteria were: an HRSD$_{17}$ score ≥ 16, which fulfils the DSM-IV-TR criterion for MDD, between 18 and 65 years old, and a signed written informed consent. The diagnosis of MDD was confirmed using the Chinese version of the Mini International Neuropsychiatric Interview (MINI), which has good reliability and validity (29). Patients with other DSM-IV-TR Axis I mental illnesses and poorly controlled clinical physical illnesses were excluded. After inclusion, the MDD patients were administered with venlafaxine (an initial dose of 75 mg/day to a maximum dose of 225 mg/day), paroxetine (20 mg/day), or milnacipran (50 mg/twice a day which is the recommended dose for MDD). Participants were evaluated at 0, 1 (± 3 days), 2 (± 3 days), 4 (± 3 days), 8 (± 3 days), 12 (± 7 days), 16 (± 7 days), 20 (± 7 days) and 24 (± 7 days) weeks using the HRSD$_{17}$.

Statistical Analyses

For patients who did not complete the examination on all the visits, the missing data for the incomplete visits were included using the last observation carried forward (LOCF) method, but only for those patients who had completed at least two continuity visits during the study. The baseline characteristics of the three groups were compared using χ^2 tests and *F*-tests. The variables of the testing

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[†]American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am. J. Psychiatry* 157: 1-45, 2000.

Table 1. Characteristics of the venlafaxine, paroxetine and milnacipran groups at the baseline

Characteristic	Venlafaxine (V) n = 82 (%)	Paroxetine (P) n = 97 (%)	Milnacipran (M) n = 70 (%)	F	P	Groups
Age (years), mean (SD)	39.2 (12.2)	42.9 (10.7)	49.5 (9.8)	17.02^a	10^{-7a}	V = P < M
Gender, n (%)						
Female	55.0 (67.1)	65.0 (67.0)	50.0 (71.4)		0.799^b	V = P = M
Male	27.0 (32.9)	32.0 (33.0)	20.0 (28.6)			
BMI (SD)	22.7 (3.7)	22.8 (3.7)	20.8 (5.7)	4.35^a	0.014^a	V = P < M
Baseline HRSD$_{17}$ (SD)	23.3 (4.3)	23.0 (4.9)	19.8 (3.8)	14.32^a	10^{-6a}	V = P > M

[a]ANOVA (Scheffe, Bonferroni); [b] χ^2 test.

Table 2. Changes of HRSD$_{17}$ total scores from the baseline

	LOCF		
	Venlafaxine	Paroxetine	Milnacipran
Week 0	–	–	–
Week 1	–6.61	–6.87	–6.38
Week 2	–8.70	–9.49	–8.45
Week 4	–10.40	–10.51	–9.74
Week 8	–10.89	–11.50	–10.83
Week 12	–10.92	–11.98	–11.47
Week 16	–10.92	–12.26	–12.04
Week 20	–11.58	–12.50	–12.07
Week 24	–11.85	–12.77	–11.94

LOCF, Last-observation carried forward.

Fig. 1. Mixed model analysis of mean score change from the baseline (LOCF).

efficacy were the response rate and whether the patient reached remission, which were used in logistic regression analysis; the baseline score on the HRSD$_{17}$ was set as the covariant. In logistic regression analysis, patients taking paroxetine were the reference group. Scores that declined on the HRSD$_{17}$ from the baseline to week 24 using the LOCF method were analyzed using a mixed-effects model. A general linear model was used for repeated measures and all scoring done on multiple time-points; the covariance set was the age. To determine whether patients stopped treatment because of an improvement (HRSD$_{17}$ ≤ 7) or deterioration in their symptoms, dropout rates were analyzed using Cox proportional hazard regression; the covariant was the baseline score on the HRSD$_{17}$.

Results

Of the 249 participants enrolled in the study, 82 took venlafaxine, 97 paroxetine, and 70 milnacipran. There was a significant difference in the age of the three groups showing that the venlafaxine and paroxetine groups were younger than the milnacipran group. The milnacipran group had a sign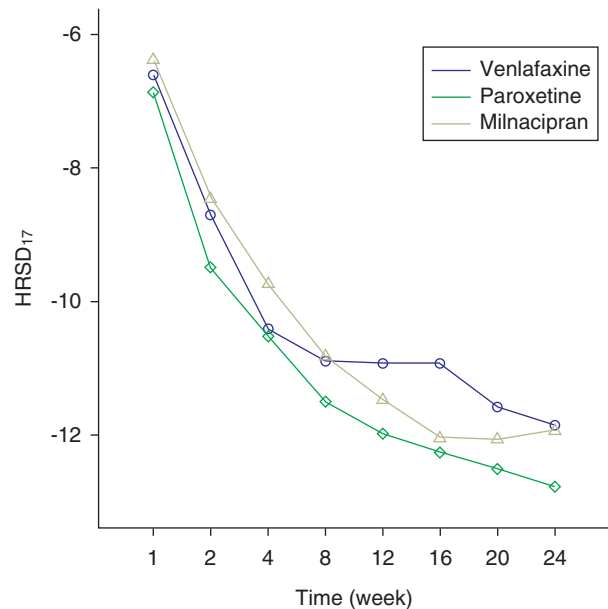ificantly lowest mean score on the HRSD$_{17}$ among the three groups (Table 1). The mean HRSD$_{17}$ total scores by the visits were significant different in all three treatment groups ($P = 0$ .042) (Table 2 and Fig. 1). The results of the logistic regression model are shown in Table 3. There were no significant differences between the three groups in response ($P = 0$ .72); the remission state (cut-off score on the HRSD$_{17}$ was ≤ 7, $P = 0$ .25) and the cut-off score was ≤ 5, $P = 0.09$) in the observed cases. However, using LOCF analysis, a significant difference was shown in the remission state between two differentiate criteria (HRSD$_{17}$ cut-off scores was ≤ 7, $P = 0.004$, and ≤ 5, $P = 0.01$). There were significant differences among the three groups in dropout rates ($P = 0.008$). The odds of the dropout rate was not significant different between the paroxetine and venlafaxine groups (OR = 0.71, CI = 0.43-1.20, $P = 0.20$) but showed significantly higher dropout rate in the milnacipran group (OR = 1.67, CI = 1.05-2.66, $P = 0.03$) (Fig. 2).

Table 3. Logistic regression analysis of the three treatment groups

| | Remission (OC) | | | | | | Remission (LOCF) | | | | | | Response | | |
| | HRSD $\leq$ 7 | | | HRSD $\leq$ 5 | | | HRSD $\leq$ 7 | | | HRSD $\leq$ 5 | | | | | |
treatment	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Vanlafaxine	0.78	0.36-1.70	0.52	0.38	0.14-1.07	0.07	0.68	0.33-1.39	0.29	0.38	0.15-0.99	0.048	0.56	0.29-1.10	0.09
Milnacipran	1.58	0.75-3.34	0.23	1.35	0.55-3.29	0.51	2.46	1.22-4.94	0.01	1.82	0.82-4.05	0.14	1.41	0.62-3.21	0.41

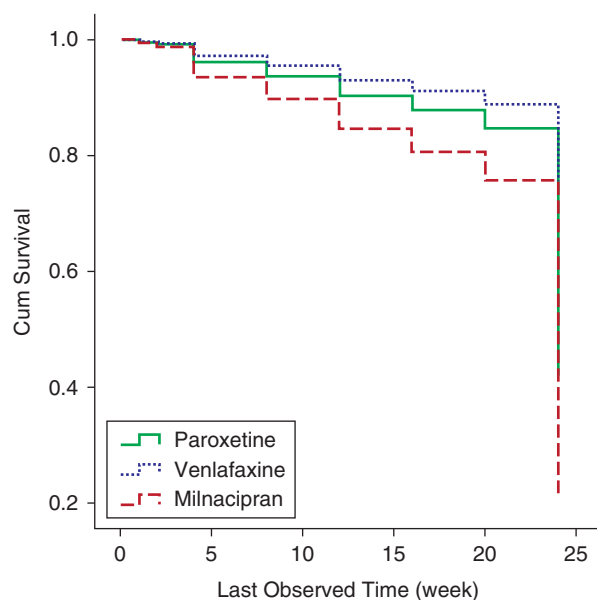OC: Observed cases; LOCF: Last-observation carried forward.

Fig. 2. Cox proportional hazard regression analysis of drop-out rates.

Discussion

We found no significant differences in the response rates between the three groups, which is consistent with our previous study (33). There were no significant differences in remission rates between the three groups when the criterion for remission was an $HRSD_{17}$ score $\leq$ 5. However, we found that milnacipran was more efficacious than paroxetine in relieving the symptoms of MDD when the remission criterion was an $HRSD_{17}$ score $\leq$ 7, and, using LOCF analysis, paroxetine was more efficacious than venlafaxine when the remission criterion was an $HRSD_{17}$ score $\leq$ 5. These findings are consistent with our previous study (33), but the definition of remission used in the present study was more stringent: $HRSD_{17}$ scores $\leq$ 7 and $\leq$ 5 for two months rather than the undefined remission duration in the earlier study. The absence of depressive symptoms is not necessarily an indicator of being in remission: it is only an indicator of the patient's initial response to treatment. The duration of the eliminated depressive symptoms, however, may very well be a better indicator of remission (16).

All three groups were at a moderate level of MDD when treatment began, but the initial mean $HRSD_{17}$ scores was significantly lower in the milnacipran group (Table 1). However, the milnacipran group not only reached an $HRSD_{17}$ score of $\leq$ 7 or $\leq$ 5 much earlier, and were in remission for a longer period of time than the other groups. This may be explained by that the less severe the MDD is, the more efficacious the treatment is. Previous studies (12) reported similar results, but additional investigations with larger populations and longer treatment and observation periods are necessary to affirm that when MDD patients are at the same level of severity, the lower $HRSD_{17}$ score is a critical predictor of whether they will reach remission post-treatment.

Additionally, there were significant differences in dropout rates between the three groups. The dropout rate in the milnacipran group (n = 39, 55.7%) was higher than in the venlafaxine (n = 32, 39%) and paroxetine (n = 40, 41.2%) groups. The reason some patients stopped taking milnacipran and stopped returning to the clinic could be that their depressive symptoms had been sufficiently relieved that they believed they were no longer depressed and in need of treatment. Perhaps because patients with mild depressive symptoms have less discomfort and fewer daily functional disabilities, they are more prone to spontaneously stopping treatment than are patients with more severe depressive symptoms. This suggests that public education about mental health needs to be improved.

Our study has some limitations. First, our study population was small. Second, information on some clinical characteristics was not collected, e.g. comorbidities, previous antidepressant treatment, and the duration of previous depression, which might confound the treatment and finding (3, 10, 17). Third, this study used an open-label design instead of blind assessments which might limit the results for generalization. For future studies, we recommend larger study populations, longer follow-ups, and a standard procedure for assessing remission.

In conclusion, milnacipran is more efficacious than venlafaxine and paroxetine for relieving the symptoms of MDD and for prolonging the remission of MDD. In addition, fewer side effects were found in patients treated by milnacipran than by paroxetine,

consistent with previous finding (34). Although the drop-out rate in the milnacipran group was higher than the in the other groups, continued taking milnacipran would be suggested as having a good performance in maintaining remission. Furthermore, following up on MDD is necessary in future studies.

Acknowledgments

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