Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors

MICHAEL E. THASE, A. RICHARD ENTSUAH and RICHARD L. RUDOLPH

Background  It had been suggested that the antidepressant venlafaxine, which inhibits reuptake of both serotonin and (at higher doses) noradrenaline, may result in better outcomes than treatment with selective serotonin reuptake inhibitors (SSRs).

Aims  To compare remission rates during treatment with SSRIs or venlafaxine.

Method  Data from eight comparable randomised, double-blind studies of major depressive disorder were pooled to compare remission rates (Hamilton Rating Scale for Depression score ≤7) during treatment with venlafaxine (n=851), SSRIs (fluoxetine, paroxetine, fluvoxamine; n=748) or placebo (four studies; n=446).

Results  Remission rates were:
- venlafaxine, 45% (382/851); SSRIs, 35% (260/748); placebo, 25% (110/446) (P < 0.001; odds ratio for remission is 1.50 (1.3–1.9), favouring venlafaxine v. SSRIs).
- The difference between venlafaxine and the SSRIs was significant at week 2, whereas the difference between SSRIs and placebo reached significance at week 4.
- Results were not dependent on any one study or the definition of remission.

Conclusions  Remission rates were significantly higher with venlafaxine than with an SSRI.

Declaration of interest  M.E.T. is a paid consultant to Wyeth–Ayerst Laboratories, the employer of A.R.E. and R.L.R.

The more commonly used measure of antidepressant efficacy in clinical trials has been a 50% reduction from baseline total scores on the Hamilton Rating Scale for Depression (HRSD) (Prien et al, 1991; Depression Guideline Panel, 1993). A more stringent measure of antidepressant efficacy is the ability to induce remission, a clinical state characterised by minimal residual symptoms (e.g. 17-item HRSD total scores of ≤7; Frank et al, 1991). Patients treated to full remission are less likely to relapse (Thase et al, 1992; Fava et al, 1996) and have more normal psychosocial and vocational functioning (Miller et al, 1998) when compared with incompletely remitted patients. This report presents the results of a pooled analysis of remission rates comparing venlafaxine and three selective serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine and fluvoxamine. It includes original data from 2045 patients with depression, drawn from eight related randomised controlled trials. We undertook this analysis to test the hypothesis that patients treated with venlafaxine, a serotonin–noradrenaline reuptake inhibitor (SNRI) (Muth et al, 1986), are significantly more likely to achieve remission than those treated with SSRIs.

METHOD

This analysis included data from the patients with depression who participated in the eight double-blind, randomised clinical trials comparing venlafaxine and SSRIs conducted by the Clinical Research and Development department at Wyeth–Ayerst Laboratories during the development of the immediate-release (IR) and extended-release (XR) formulations of venlafaxine. Results from four of these studies have been published (Clerc et al, 1994; Dierick et al, 1996; Silverstone et al, 1998; Rudolph & Feiger, 1999). Results from two studies have been presented as posters and published in abstract form (Salinas et al, 1997; Rudolph et al, 1998a). The remaining two studies are unpublished (Studies 347 and 349; data on file, Wyeth–Ayerst Laboratories, Philadelphia, PA). The doses employed were: venlafaxine IR, 75–375 mg/day; venlafaxine XR, 75–225 mg/day; fluoxetine, 20–80 mg/day; paroxetine, 20–40 mg/day; and fluvoxamine, 100–200 mg/day. Four studies included a placebo control group (Salinas et al, 1997; Rudolph et al, 1998a; Silverstone et al, 1998; Rudolph & Feiger, 1999). Each study was approved by the ethics committees of the participating sites and conducted according to the guidelines of the Declaration of Helsinki and its amendments. All patients provided written informed consent. Table 1 summarises the study characteristics.

Patients

Patients could be enrolled if they were at least 18 years old and met the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 1987, 1994) for major depression (DSM–III–R) or major depressive disorder (DSM–IV) for at least 1 month. There were 68 in-patients (one study, Clerc et al, 1994) and 197 out-patients; all patients had minimum scores of either 20 on the HRSD21 (Hamilton, 1960) or 25 on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) at both pre-study and baseline (study day −1), with no greater than a 20% decrease in severity between pre-study and baseline evaluations.

Patients with clinically significant cardiovascular, renal or hepatic disease, seizure disorders, a recent history of alcohol or drug misuse or clinically significant abnormalities on baseline physical examination, electrocardiogram (ECG) or laboratory tests were excluded from participation. Patients who were hypersensitive to the study drugs or had used any investigational or antipsychotic drug within 30 days, a monoamine oxidase inhibitor within 14 days or other antidepressant, anxiolytic, sedative–hypnotic or non-psychopharmacological drugs with psychotropic effects within 7 days of double-blind treatment also were excluded. Chloral hydrate (maximum 2000 mg) or temazepam (20 mg; one study) were permitted as hypnotics. Table 2 summarises the
Table 1  Studies pooled for analysis of the Hamilton Rating Scale for Depression remission (n=8)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Dosage range (mean)</th>
<th>Number of patients per study: all patients (n=2117)/ITT (n=2045)</th>
<th>Treatment duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudolph &amp; Feiger, 1999 (Study 211)</td>
<td>Venlafaxine XR</td>
<td>75–225 mg/day (175)</td>
<td>100/95</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>20–60 mg/day (47)</td>
<td>103/103</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>98/97</td>
<td></td>
</tr>
<tr>
<td>Silverstone et al, 1999 (Study 360)</td>
<td>Venlafaxine XR</td>
<td>75–225 mg/day (141)</td>
<td>128/121</td>
<td>8^</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>20–60 mg/day (40)</td>
<td>121/114</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>118/118</td>
<td></td>
</tr>
<tr>
<td>Salinas et al, 1997 (Study 367)</td>
<td>Venlafaxine XR</td>
<td>75–150 mg/day (75/150)</td>
<td>165/161</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>20 mg/day (20)</td>
<td>81/80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>83/82</td>
<td></td>
</tr>
<tr>
<td>Rudolph et al, 1998e (Study 372)</td>
<td>Venlafaxine IR</td>
<td>75–375 mg/day (318)</td>
<td>156/144</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>20–80 mg/day (NA)</td>
<td>152/146</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>152/149</td>
<td></td>
</tr>
<tr>
<td>Clerc et al, 1994 (Study 340)</td>
<td>Venlafaxine IR</td>
<td>100–200 mg/day (199)</td>
<td>34/33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>20–40 mg/day (NA)</td>
<td>34/34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>34/34</td>
<td></td>
</tr>
<tr>
<td>Study 347^</td>
<td>Venlafaxine IR</td>
<td>75–150 mg/day (NA)</td>
<td>77/77</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>100–200 mg/day (NA)</td>
<td>34/34</td>
<td></td>
</tr>
<tr>
<td>Dierick et al, 1996 (Study 348)</td>
<td>Venlafaxine IR</td>
<td>75–150 mg/day (112)</td>
<td>153/145</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>20 mg/day</td>
<td>161/157</td>
<td></td>
</tr>
<tr>
<td>Study 349^</td>
<td>Venlafaxine IR</td>
<td>75–150 mg/day (NA)</td>
<td>82/75</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>20–40 mg/day (NA)</td>
<td>85/80</td>
<td></td>
</tr>
</tbody>
</table>

1. This study employed 75 and 150 mg fixed doses of venlafaxine XR.
2. This study lasted 12 weeks but results are presented at week 8 for consistency.
4. IR, immediate-release formula; ITT, intention-to-treat patients; XR, extended-release formulation.

Table 2  Baseline characteristics of intent-to-treat patients (pooled studies, n=2045)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venlafaxine (n=851)</th>
<th>SSRI (n=748)</th>
<th>Placebo (n=446)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (s.d.)</td>
<td>42 (12)</td>
<td>42 (13)</td>
<td>41 (11)</td>
</tr>
<tr>
<td>Women/men, %</td>
<td>65/35</td>
<td>64/36</td>
<td>62/38</td>
</tr>
<tr>
<td>Mean (s.d.) HRSD21 total score</td>
<td>26 (5)</td>
<td>26 (4)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Mean (s.d.) MADRS total score</td>
<td>31 (5)</td>
<td>31 (5)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>CGI–S score &gt; 4 (%)</td>
<td>53</td>
<td>53</td>
<td>36^</td>
</tr>
</tbody>
</table>

1. Studies utilising placebo enrolled significantly fewer patients with CGI–S scores > 4 (P < 0.01). Across the placebo-controlled studies there was no difference between groups.
2. CGI–S, Clinical Global Impression – Severity of Illness; HRSD21, 21-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; SSRI, selective serotonin reuptake inhibitor.

socio-demographic and pre-treatment clinical characteristics of the pooled study groups.

### Study drugs

Patients were randomly assigned to treatment with venlafaxine (n=865), an SSRI (fluoxetine, n=563; paroxetine, n=160; or fluvoxamine, n=34) or placebo (four studies only, n=450) during the double-blind treatment period at the daily dosages shown in Table 1.

### Efficacy and safety assessments

The HRSD, MADRS and Clinical Global Impression – Severity of Illness (CGI–S) (National Institute of Mental Health, 1985) were performed at study day –1, prior to double-blind therapy. These measures (along with the CGI improvement score) were reassessed on study days 7, 14, 21, 28, 42 and, if available, 56. Remission was defined as a total score of ≤7 on the first 17 items of the HRSD (Frank et al, 1991).

Safety and tolerability were evaluated on the basis of adverse events that were recorded throughout the study evaluation period and changes that occurred in the physical examination, vital signs, 12-lead ECG recordings and clinical laboratory tests during treatment. For this report, only the proportions of patients withdrawn from double-blind therapy because of side-effects and lack of efficacy were compared.

### Statistical analyses

The analyses were performed on data from a modified intent-to-treat sample, which included all patients who received at least one dose of study medication and had at least one HRSD evaluation during therapy. Remission rates were calculated using the last-observation-carried-forward (LOCF)
method, which allowed the inclusion of patients who were withdrawn early. Pairwise comparisons of remission rates were made with Fisher’s exact test. All tests of hypotheses were two-sided. Results of statistical analyses were considered significant when P was ≤ .05. The 95% confidence intervals (CIs) for differences in remission rates between groups were calculated for the pooled data at each interval. The odds ratios for remission with a 95% CI (Rothman, 1986) were also calculated for venlafaxine or an SSRI v. placebo and for venlafaxine v. the SSRIs. Homogeneity of the odds ratios across studies was tested with the Breslow–Day test (Breslow & Day, 1980).

Analyses of various subgroups were performed to corroborate the overall findings, including studies using the extended-release or immediate-release formulations, active-controlled studies, placebo-controlled studies, the single in-patient study, the seven out-patient studies and studies utilising fluoxetine v. those using other SSRIs. Additional analyses compared alternative definitions of remission to ensure the robustness of the findings. The following additional definitions were examined: HRSD\textsubscript{21} ≤ 7, HRSD\textsubscript{21} ≤ 8, HRSD\textsubscript{21} ≤ 10, HRSD\textsubscript{17} ≤ 10 plus CGI=1, MADRS < 10, and ≥ 50% decrease from baseline HRSD\textsubscript{21} scores. Finally, a sensitivity analysis was performed by removing each individual study from the pooled analysis, one at a time (Thase et al., 1997).

**RESULTS**

Among the 2117 patients enrolled, 2045 (96.6%) were included in the intent-to-treat analyses of venlafaxine XR and venlafaxine XR (n=851), the SSRIs (n=748) and placebo (n=446). Results from one investigational site (27 patients in total) were excluded prior to the analysis because the validity of the data could not be verified. The treatment groups had similar characteristics at baseline (see Table 2). However, patients enrolled in the four placebo-controlled studies were significantly less severely depressed than those enrolled in the other studies.

Final remission rates were 45% for venlafaxine (382/851), 35% for the SSRIs (260/748) and 25% for placebo (110/446). The differences for venlafaxine v. SSRIs, venlafaxine v. placebo and SSRIs v. placebo were highly statistically significant (P < 0.001 for all comparisons).

Week-by-week comparisons are illustrated in Fig. 1. Venlafaxine was statistically significantly more effective than the SSRIs from week 2 onwards and versus placebo from week 3 onwards. The SSRI group had a significantly higher remission rate.

**Table 3** Remission rates (%) and odds ratios for comparison of intent-to-treat 17-item Hamilton Rating Scale for Depression (HRSD\textsubscript{21}) remission by treatment\textsuperscript{1}

<table>
<thead>
<tr>
<th>Study</th>
<th>Remission rate (%)</th>
<th>Odds ratio</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Venlafaxine v. SSRI</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>SSRI</td>
<td>Placebo</td>
</tr>
<tr>
<td>Rudolph &amp; Feiger, 1999 (Study 211)</td>
<td>42</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Silverstone et al, 1999 (Study 360)</td>
<td>29</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Salinas et al, 1997 (Study 367)</td>
<td>49\textsuperscript{2}</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Rudolph et al, 1998a (Study 372)</td>
<td>44</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Clerc et al, 1994 (Study 340)</td>
<td>55</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Study 347\textsuperscript{3}</td>
<td>51</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Dierick et al, 1996 (Study 348)</td>
<td>52</td>
<td>45</td>
<td>–</td>
</tr>
<tr>
<td>Study 349\textsuperscript{3}</td>
<td>35</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Pooled data</td>
<td>45</td>
<td>35</td>
<td>25</td>
</tr>
</tbody>
</table>

\textsuperscript{1} The remission rates reported here reflect the intent-to-treat, HRSD\textsubscript{21} ≤ 7 method used in this paper. The results may therefore differ from those reported in the source manuscripts.

\textsuperscript{2} Unpublished data on file, Wyeth–Ayerst Research, Philadelphia, PA.

\textsuperscript{3} The intent-to-treat remission rate on 75 mg/day of venlafaxine XR was 47% and on 150 mg/day it was 51%. SSRI, selective serotonin reuptake inhibitor.
than the placebo group from week 4 onwards.

The results of the eight individual studies are summarised in Table 3. Odds ratios for remission ranged from 1.0 to 3.5, with an overall odds ratio of 1.5 (95% CI 1.3–1.9). Thus, there was a 50% greater chance of remission during venlafaxine treatment than during SSRI treatment. Testing for homogeneity of the odds ratios revealed no significant difference ($\chi^2 = 8.63$, d.f. = 7, $P = 0.28$). The sensitivity analysis similarly found that the significant difference between venlafaxine and the SSRIs was not dependent on any one study.

Figure 2 illustrates the results for various subgroup comparisons. The differences between venlafaxine and the SSRIs were statistically significant for all but one of the subgroup analyses. The comparison of venlafaxine and SSRI that included only the four studies that were not placebo-controlled was not statistically significant ($P = 0.053$).

Figure 3 summarises the results according to multiple alternative outcome criteria. Regardless of the definition used, venlafaxine was significantly more effective than the SSRIs, and the SSRIs were significantly more effective than placebo.

In total, 83 (9%) patients were withdrawn from venlafaxine therapy because of side-effects, compared with 57 (7%) SSR1-treated patients and 10 (2%) patients given placebo (Fisher’s exact test, $P = 0.001$, venlafaxine v. placebo and SSRI v. placebo; the venlafaxine v. SSRI comparison was not significant, $P = 0.185$). A total of 33/895 (4%) of the venlafaxine-treated patients were withdrawn because of lack of efficacy, compared with 46/769 (6%) of patients given an SSRI and 63/453 (14%) of patients given placebo (Fisher’s exact test, $P = 0.037$, venlafaxine v. SSRI; $P = 0.001$, venlafaxine v. placebo; $P = 0.001$, SSRI v. placebo).

**DISCUSSION**

**Are all antidepressants equally effective?**

It is often stated that the various different classes of antidepressant medication are equally effective (American Psychiatric Association, 1993; Depression Guideline Panel, 1993). However, the methods used to conduct randomised clinical trials render them relatively insensitive to possible differences between active antidepressants (Thase, 1999). Studies seldom compare groups larger than 120 patients, which does not afford the statistical power to detect modest but still clinically meaningful differences. In addition, multi-site trials may have relatively lower statistical power because of greater patient heterogeneity and lower reliability of diagnoses or dependent measures (Thase, 1999). Moreover, the composition of study groups can have a marked influence on the apparent efficacy of a treatment (Quitkin et al., 1993; Thase et al., 1997).

Meta-analysis provides useful alternative methods to compare active treatments. For example, meta-analyses comparing tricyclic antidepressants and
SSRIs found differences in subgroup comparisons not apparent in qualitative reviews (Anderson & Tomenson, 1994; Edwards & Anderson, 1999). However, because the statistical power of a conventional meta-analysis is determined by the number of studies included, a large number of comparative trials must be available. For comparisons between newer antidepressants, meeting this requirement is often difficult. A second type of meta-analysis, using the data of individual patients participating in a series of related clinical trials, permits powerful comparisons to be made with a much smaller number of studies. Such pooled analyses have been used to document the efficacy of monoamine oxidase inhibitors in the treatment of atypical depression (Quitkin et al., 1993), to examine the association between fluoxetine and suicidality (Beasley et al., 1991), to examine the effects of venlafaxine treatment on blood pressure (Thase, 1998) and to compare psychotherapy and pharmacotherapy (Thase et al., 1997; DeRubeis et al., 1999).

The clinical significance of the magnitude of the differences between venlafaxine and the SSRIs warrants comment. In a conventional antidepressant clinical trial, the size of the study groups is such that statistically significant effects parallel relatively large differences in response rates (i.e. 20–23%) that are clearly clinically significant. An analysis of pooled data from an extremely large group of patients, by contrast, would have the statistical power to detect differences in remission rates so small that they would be considered trivial by most (i.e. 3–5%). The difference in remission rates observed in our pooled analysis is roughly halfway between these extremes. Given the high prevalence of depression and the staggering associated illness burden, a 10% advantage in remission rates could have substantial public health implications, particularly if costs and tolerability are comparable. From another perspective, we observed that venlafaxine–treated patients had a 50% greater chance of attaining remission than patients treated with an SSRI. In terms of the number of patients needed to treat to realise a difference, ten patients would need to be treated with venlafaxine in order to obtain one extra case of remission when compared with the SSRIs. When considered together, these various indicators point to a clinically meaningful difference.

**Relationships to pharmacological mechanisms**

It is proposed that the greater efficacy of venlafaxine is the result of reuptake inhibition of both serotonin and noradrenaline. Of course, reuptake inhibition is not essential to therapeutic action and it is possible that medications that potently and selectively affect either serotonergic or noradrenergic neurotransmission may initiate cascades of intracellular events that ultimately modulate the same changes in gene activity (Duman et al., 1997). Nevertheless, several previous studies found clomipramine, another potent dual reuptake inhibitor, to have a significant advantage relative to SSRIs (see Anderson &

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**Table 4 Summary of intent-to-treat remission rates of nine venlafaxine–SSRI comparative studies of non-psychotic depression not included in pooled analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Duration (weeks)</th>
<th>Treatment (n)</th>
<th>Dosage (mg/day)</th>
<th>Remission criterion</th>
<th>ITT remission rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylee et al., 1997</td>
<td>PC</td>
<td>12</td>
<td>Venlafaxine IR (171) Fluoxetine (170)</td>
<td>75</td>
<td>MADRS ≤ 6</td>
<td>35</td>
</tr>
<tr>
<td>McPartlin et al., 1998</td>
<td>PC</td>
<td>12</td>
<td>Venlafaxine XR (183) Paroxetine (178)</td>
<td>75</td>
<td>HRSD ≤ 6</td>
<td>54</td>
</tr>
<tr>
<td>Diaz-Martinez et al., 1998</td>
<td>OP</td>
<td>8</td>
<td>Venlafaxine IR (70) Fluoxetine (75)</td>
<td>75–150</td>
<td>CGI=1</td>
<td>41</td>
</tr>
<tr>
<td>Costa e Silva, 1998†</td>
<td>OP</td>
<td>8</td>
<td>Venlafaxine IR (196) Fluoxetine (186)</td>
<td>75–150</td>
<td>CGI=1</td>
<td>58</td>
</tr>
<tr>
<td>Poirier &amp; Boyer, 1999</td>
<td>OP/IP</td>
<td>6</td>
<td>Venlafaxine IR (61) Paroxetine (62)</td>
<td>75–300</td>
<td>HRSD &lt;10</td>
<td>37</td>
</tr>
<tr>
<td>Alves for the Venlafaxine</td>
<td>OP</td>
<td>12</td>
<td>Venlafaxine IR (40) Fluoxetine (47)</td>
<td>75–150</td>
<td>HRSD ≤ 8</td>
<td>30</td>
</tr>
<tr>
<td>Study Group (1999)</td>
<td>OP</td>
<td>8</td>
<td>Venlafaxine IR (75) Sertraline (72)</td>
<td>75–150</td>
<td>HRSD &lt;10</td>
<td>53</td>
</tr>
<tr>
<td>Mehtonen et al., 2000</td>
<td>OP</td>
<td>8</td>
<td>Venlafaxine IR (41) Paroxetine (43)</td>
<td>75–150</td>
<td>HRSD &lt;8</td>
<td>59</td>
</tr>
<tr>
<td>Ballús et al., 2000</td>
<td>OP</td>
<td>12</td>
<td>Venlafaxine IR (55) Fluoxetine (54)</td>
<td>75–150</td>
<td>HRSD &lt;7</td>
<td>41</td>
</tr>
<tr>
<td>Tzanakaki et al., 2000†</td>
<td>IP/PHP</td>
<td>6</td>
<td>Venlafaxine IR (55) Fluoxetine (54)</td>
<td>225</td>
<td>HRSD &lt;7</td>
<td>36</td>
</tr>
</tbody>
</table>

1. Results reported according to two definitions of remission.

CGI, Clinical Global Impression (improvement) scale; HRSD, Hamilton Rating Scale for Depression; IP, psychiatric in-patient; IR, immediate-release formulation; ITT, intent to treat; MADRS, Montgomery–Åsberg Depression Rating Scale; OP, psychiatric out-patient; PC, primary care; PHP, partial hospitalisation programme; XR, extended-release formulation.
Tomenson, 1994). It appears that relatively higher doses of venlafaxine may be necessary to achieve significant noradrenergic effects, as inferred from in vitro (Muth et al., 1986; Owens et al., 2000), animal (Redrobe et al., 1998) and human (Thase, 1998; Harvey et al., 2000) studies. Consistent with this, there is a clear dose–response relationship for venlafaxine (Rudolph et al., 1998b) and patients who fail to benefit from 75 mg/day often respond to higher doses (Dierick et al., 1996; Costa e Silva, 1998; Diaz-Martinez et al., 1998; Mehtonen et al., 2000). Therefore, it is likely that the difference in efficacy between venlafaxine and SSRIs is dose dependent. Unfortunately, the flexible dose schedules utilised in five of the studies included in our meta-analysis precluded a valid examination of dose–response relationships. Research using modern molecular biological techniques would help to confirm that the greater antidepressant efficacy of venlafaxine is directly linked to a dual reuptake–inhibitory mechanism of action.

Review of other comparative studies

The most important limitation of a pooled analysis is that the results can be biased by selection of a non-representative group of studies. Our data set included all eight comparative studies conducted by the Wyeth–Ayerst Clinical Research and Development department; no studies were excluded. However, there are at least 12 other studies comparing venlafaxine and SSRIs for treatment of non-psychotic depression. Among these, three recently completed studies (double-blind, placebo- and fluoxetine-controlled trials in out-patients with melancholia, in-patients with melancholia or elderly patients) could not be included because data analyses were not complete. The remaining nine published studies were not included because we did not have access to the original data sets (see Table 4).

It is possible that the inclusion of these additional trials would have affected the findings of the current pooled analysis. We therefore conducted a qualitative review of the nine published studies. Two studies found no evidence of differences in response or remission rates (Tylee et al., 1997; McPartlin et al., 1998). These studies were conducted in primary care clinics and compared the minimum therapeutic dosages of venlafaxine (75 mg/day) and fluoxetine (20 mg/day) (Tylee et al., 1997) or paroxetine (20 mg/day) (McPartlin et al., 1998).

Two studies reported non-significant differences (Diaz-Martinez et al., 1998; Alves et al., 1999). Diaz-Martinez et al. (1998) reported that 41% of 70 patients treated with venlafaxine (75–150 mg/day) remitted during an open-label but randomised 8-week trial, as compared with 36% of 75 patients treated with fluoxetine (20–40 mg/day). The difference was 30% (i.e. 50% v. 20%) among those who received either 150 mg/day of venlafaxine (n=18) or 40 mg/day of fluoxetine (n=15). However, this numerically large difference was not statistically significant (P=0.07) in such a small subsample. Alves et al. (1999) found a 19% difference (30% v. 11%) in remission rates favouring venlafaxine (75–150 mg/day) over fluoxetine (20–40 mg/day), which again was not statistically significant in a relatively small study (n=87).

Two studies reported inconsistent findings, with significant results favouring venlafaxine over fluoxetine using a global definition of remission but not according to the final HRSD score (see Table 4). Costa e Silva (1998) observed remission rates of 58% for venlafaxine (75–150 mg/day) and 35% for fluoxetine (20–40 mg/day) using a CGI numeric score of 1 to define remission, although 60% of the patients in each group remitted when an HRSD score of ≤7 was the criterion. Tzanakaki et al. (2000) similarly found that the groups were comparable using an HRSD criterion (<7) but significantly different according to the CGI definition (see Table 4).

The three remaining studies found significant differences favouring venlafaxine; these studies all utilised maximum doses of ≥150 mg/day. Ballus et al. (2000) observed remission rates of 59% for venlafaxine (75–150 mg/day) and 31% for paroxetine (20–40 mg/day). Mehtonen et al. (2000), defining remission as a score of <10 on the 21-item version of the HRSD, reported rates of 68% for venlafaxine (75–150 mg/day) and 45% for sertraline (50–100 mg/day) among completers at week 8. Poirier & Boyer (1999) enrolled only patients who had failed to respond to at least two previous trials of antidepressants. About 75% had not responded to a prior course of SSRI therapy. They found a 19% advantage (37% v. 18%) in remission rates in favour of venlafaxine (200–300 mg/day) relative to paroxetine (20–40 mg/day).

Although these studies used various durations of treatment and definitions of remission, two conclusions are evident. First, there is no evidence that venlafaxine is more effective than the SSRIs at minimum therapeutic doses. Second, among the studies that permitted a venlafaxine dosage of ≥150 mg/day, there was a 14.4% average difference (range 5–23%) in remission rates favouring venlafaxine. It appears that the results of our pooled analysis would not have changed if we could have included these studies.

Other limitations

The generalisability of the results of a group of controlled clinical trials, like those of the individual studies, is limited by the exclusion of patients with more complex conditions, such as significant psychiatric and medical comorbidities. Although this lessens the relevance of these results to clinical practice, there is no reason to suspect that this exclusivity favours venlafaxine over the SSRIs. Other potential shortcomings of pooled analyses include problems with the reliability of dependent measures and the possibility that the results may be influenced by the data from one or two particularly large studies. We found significant differences between SSRIs and placebo, however, which indicates that the ‘assay sensitivity’ (Leber, 1991) of the pooled analysis was, at the least, sufficient to overcome measurement error. We also confirmed that the differences were not attributable to any particular study and extended across multiple definitions of remission.

Three more specific limitations can be considered. First, the SSRIs were lumped together as a class. Although there is no evidence that any SSRI is more effective than another, they are not truly interchangeable and some patients respond poorly to one SSRI but well to another (Edwards & Anderson, 1999). In this respect, our pooled analysis included a disproportionate number of patients treated with fluoxetine. The studies listed in Table 4 provide a broader range of comparisons and, in aggregate, yielded similar results. Nevertheless, among the 17 comparative studies included in the pooled analysis or summarised in Table 4, there is only one study each utilising fluvoxamine or sertraline and, to date, there are no studies of citalopram.
Second, all of the studies were short term. It is possible that a longer treatment period could have resulted in comparable remission rates.

Third, none of the studies used in the pooled analysis excluded patients who had failed to respond to other SSRIs. Because several SSRIs were already widely available when these studies were conducted, it is possible that the advantage observed for venlafaxine was delimited to a subgroup of patients who had previously failed trials of other SSRIs (see, for example, Poirier & Boyer, 1999).

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