Selective Versus Multi-Transmitter Antidepressants: Are Two Mechanisms Better Than One?

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The issue of selectivity versus efficacy has now reappeared as newer agents have emerged that are less selective than the selective serotonin reuptake inhibitors (SSRIs) but more selective than the tricyclic antidepressants (TCAs). This article provides a critical examination of the clinical literature concerning what evidence there is for differential efficacy. Two broad areas will be discussed: (1) comparisons of SSRIs to TCAs and (2) comparisons of the SSRIs to a somewhat more selective compound (by comparison to the TCAs), venlafaxine. This review should caution one in accepting claims of superiority of any agent based on purported mechanism of action.

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The relatively short history of psychopharmacology has seen an ebb and flow of ideas concerning the mechanisms behind the compounds we use. Hence, it is essential to remind ourselves periodically that we remain largely ignorant of how these medications achieve their desired clinical result. Much of what is discussed under the rubric of "mechanism of action" actually refers to the effects of these substances on cell surface receptors. We remain unable to explain precisely how these receptors produce the desired clinical endpoint of alleviating mood disorders.

The question posed by the title of this article leads directly to other questions, namely, "better for what and better for whom?" Clinical efficacy must be weighed against other issues such as ease of use, adverse event profile, and cost. With the relatively recent arrival of the selective serotonin reuptake inhibitors (SSRIs), considerable time, energy, and scientific effort have been invested in determining how these newer selective agents compare with their less selective predecessors. The success of the SSRIs has been due presumably not to their increased efficacy, but rather to ease of use, minimal need for titration, better tolerability, and improved safety profile in overdose. In the last decade, the SSRIs have largely supplanted the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, despite their greater expense. This profile has led to the virtual domination of SSRIs in the market, as well as a dramatic expansion in the number of patients receiving treatment for depression.

SSRIs VERSUS TCAs

There have been numerous studies suggesting that SSRIs are better tolerated than TCAs (although these differences are surprisingly modest when the data are assembled). This difference in tolerability is presumably due to the fact that drugs affecting multiple receptors, like the TCAs, have the potential to cause more adverse events. Therefore, use of a compound such as amitriptyline, which affects many types of receptors, may result in a rich milieu of potential side effects. The discussion here will focus primarily on comparisons of efficacy.

There have been a large number of comparison studies of TCAs and SSRIs. One way to look at the relative efficacy of the TCAs and SSRIs is to look at placebo-controlled trials of either class of drug, and patient outcome. It should be noted that these are active drug versus placebo comparisons, not TCA versus SSRI direct comparisons.

Walsh et al.[1] selected peer-reviewed, randomized, placebo-controlled trials of outpatients with unipolar major depression that were conducted from 1981 to 2000 and found 43 studies involving TCAs and 33 involving SSRIs. In the trials that were reviewed, clinical response was defined as a reduction of at least 50% on the Hamilton Rating Scale for Depression (HAM-D)[2] and/or a Clinical
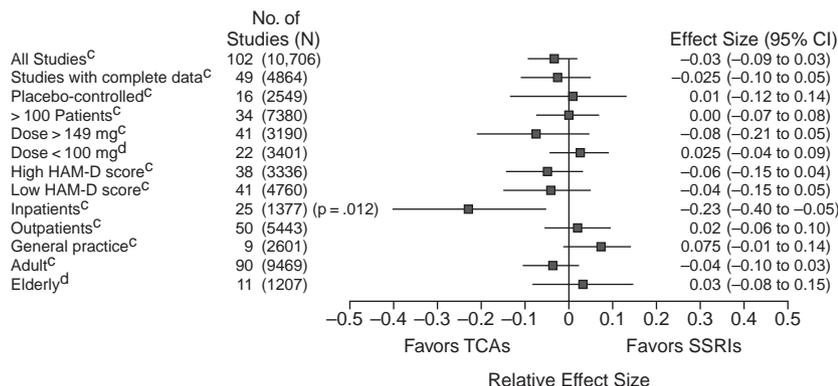
Figure 1. Relative Effect Size of Overall and Subgroup Analyses of Studies Comparing SSRIs and TCAs[a,b]

	No. of Studies (N)	Effect Size (95% CI)
All Studies[c]	102 (10,706)	−0.03 (−0.09 to 0.03)
Studies with complete data[c]	49 (4864)	−0.025 (−0.10 to 0.05)
Placebo-controlled[c]	16 (2549)	0.01 (−0.12 to 0.14)
> 100 Patients[c]	34 (7380)	0.00 (−0.07 to 0.08)
Dose > 149 mg[c]	41 (3190)	−0.08 (−0.21 to 0.05)
Dose < 100 mg[d]	22 (3401)	0.025 (−0.04 to 0.09)
High HAM-D score[c]	38 (3336)	−0.06 (−0.15 to 0.04)
Low HAM-D score[c]	41 (4760)	−0.04 (−0.15 to 0.05)
Inpatients[c]	25 (1377) (p = .012)	−0.23 (−0.40 to −0.05)
Outpatients[c]	50 (5443)	0.02 (−0.06 to 0.10)
General practice[c]	9 (2601)	0.075 (−0.01 to 0.14)
Adult[c]	90 (9469)	−0.04 (−0.10 to 0.03)
Elderly[d]	11 (1207)	0.03 (−0.08 to 0.15)

−0.5 −0.4 −0.3 −0.2 −0.1 0 0.1 0.2 0.3 0.4 0.5
Favors TCAs   Favors SSRIs
Relative Effect Size

[a]Reprinted with permission from Anderson.[5] There are no detectable efficacy differences between TCAs and SSRIs in the overall comparison. Note in particular the lack of difference in the placebo-controlled trials and in the larger (N > 100) trials. Only in a subanalysis of inpatients do the TCAs appear modestly more effective than SSRIs.
[b]Bars indicate 95% CI.
[c]Random-effects model.
[d]Fixed-effects model.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Global Impressions-Improvement scale (CGI-I)[3] score of 1 or 2 (markedly or moderately improved). The mean proportion of patients responding to TCAs was 46.9% (SD = 10.6%; range, 27.5%–65.6%) and to SSRIs was 48.9% (SD = 10.3%; range, 25%–70.4%).

Walsh and colleagues also calculated effect size—the difference between the response to medication and the response to placebo—using an arcsin transformation. The mean (SD) effect size across studies for TCA response was 0.38 (0.22) and SSRI response was 0.40 (0.24). While the differences in effect sizes and proportion of patients exhibiting response are an indirect way of looking at the comparable efficacy of these 2 classes of drugs, the similarity in proportion of response and in effect size is striking.

There have been a number of meta-analyses specifically focused on trials that directly compare the efficacy of SSRIs and TCAs. Geddes et al.[4] in a recent Cochrane review examined randomized controlled trials comparing SSRIs with other kinds of antidepressants in the treatment of patients with depressive disorders. Ninety-eight trials yielded 5044 patients treated with an SSRI and 4510 treated with an alternative antidepressant. Focusing specifically on the SSRI versus TCA comparison, the standardized effect size for SSRIs compared with TCAs was 0.03 using a fixed-effects model (95% CI = −0.018 to 0.092; Q = 88.64, df = 66, p = .03). When a random-effects model was used, the standardized effect size for SSRIs versus TCAs was 0.044 (95% CI = −0.020 to 0.107), leading the authors to conclude, "There was therefore no evidence of statistically or clinically significant differences between the drugs."[4(p4)]

The Cochrane analysis also compared efficacy of SSRIs and TCAs in a subgroup of studies involving inpatients. In these studies, a slightly larger estimate of effect favoring TCAs was found, but according to Geddes et al., "this may be explained merely by chance."[4(p4)] The overall estimate of effect in this subgroup of studies, using a random-effects model, was 0.10 (95% CI = −0.072 to 0.272; Q = 49.1, df = 22, p = .0008). The authors note that this degree of difference is "equivalent to about 1 HAM-D point"[4(p4)] and concluded, "there does not appear to be a clinically significant difference in the effectiveness of SSRIs and any of the older antidepressants including TCAs such as clomipramine that are sometimes believed to be particularly effective."[4(p5)]

Anderson[5] also conducted a meta-analysis of the efficacy and tolerability of SSRIs against TCAs in depressed patients. Efficacy data were taken from 102 randomized controlled trials (10,706 patients) pooled to provide a summary variance-weighted effect size. Variance weighting gives more weight to larger studies in which the effect size can be estimated more precisely. Results were expressed so that a positive effect size indicated an advantage for the SSRI and a negative effect size indicated an advantage for the TCA. The effects of age, treatment setting, severity, and TCA dose were examined, as well as the performance of individual SSRIs and TCAs.

Looking at the overall comparison of SSRIs and TCAs, Anderson[5] concluded that there was no overall difference in efficacy (effect size = −0.03, 95% CI = −0.09 to 0.03). Subanalyses (Figure 1) show the small differences in the placebo-controlled trials and in the larger studies (N > 100), which presumably would have the most preci-

Figure 2. Effect of Citalopram Compared With Clomipramine on HAM-D-17 Scores[a]
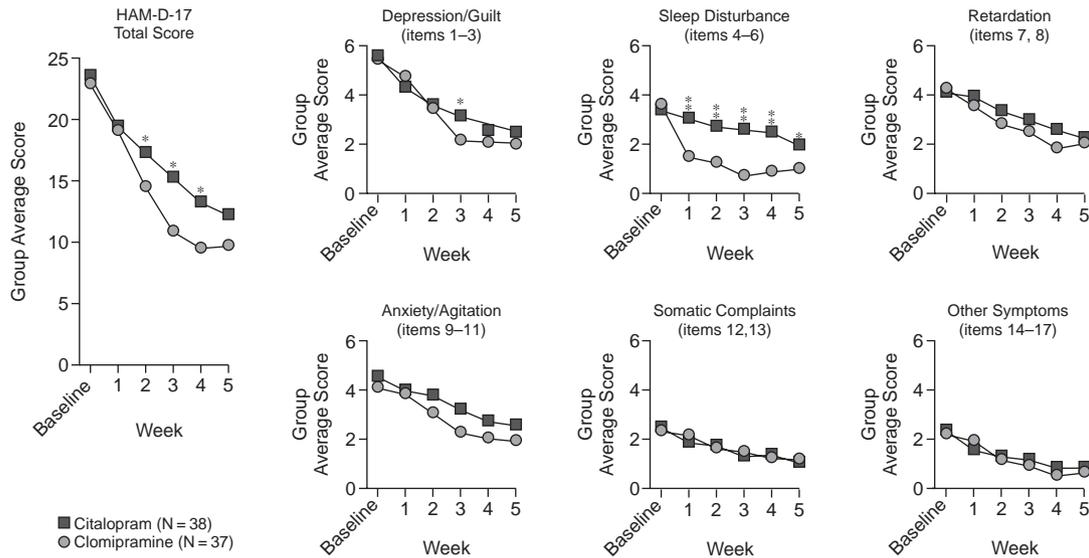
[a]Reprinted with permission from references 6 and 7. Figure shows change over time in HAM-D-17 total score and 6 clusters of HAM-D-17 items in inpatients with endogenous depression treated for 5 weeks with citalopram (40 mg/day) or clomipramine (150 mg/day). Significant between-group differences (p < .05) in HAM-D-17 total score were apparent at weeks 2, 3, and 4, but not at endpoint.
*p < .05.
**p < .01.
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

sion. Inpatients appeared to respond modestly better with TCAs in this meta-analysis (effect size = –0.23, 95% CI = –0.40 to –0.05), but the author notes that publication bias might explain this difference.[5]

Interestingly, while the TCAs demonstrated greater efficacy in hospitalized patients, a similar advantage was not observed in patients with more severe forms of depression (as measured by the HAM-D). Additionally, there was no statistically significant difference in efficacy between what the author classified as dual action and noradrenergic TCAs.[5] In looking at individual agents, amitriptyline did show some advantage while clomipramine did not. However, this potential advantage with amitriptyline was accompanied by a significantly higher rate of treatment discontinuation due to side effects. Interestingly, imipramine did not demonstrate any efficacy advantage, though it is the most balanced TCA in terms of affecting serotonin and norepinephrine. SSRIs were thought to be better tolerated with significantly lower discontinuation rates overall and as a result of side effects.

The failure of clomipramine to distinguish itself in this meta-analysis is in contrast to the results of the Danish University Antidepressant Group[6,7] trials, which often are cited as evidence for the superiority of clomipramine compared to SSRIs. In these trials, clomipramine was found to be statistically superior to both paroxetine and citalopram.

For example, the clomipramine versus citalopram study was a 5-week trial including inpatients who scored > 18 on the HAM-D-17.[6] One hundred two patients who completed at least 2 weeks of treatment were enrolled at 5 centers. Clomipramine was initiated at 75 mg/day, and the dose reached 150 mg on day 3; citalopram was dosed at 40 mg/day. Approximately three quarters (N = 75) of the patients had endogenous depression, and a "complete response" was defined as a HAM-D-17 score of < 7. After 5 weeks, 60% of clomipramine-treated patients and 28% of citalopram-treated patients met this criterion. There was no difference between groups in the total number of "complete" plus "partial" responders.

As mentioned, this study often has been cited as evidence of the superiority of clomipramine over SSRIs. While it is possible that clomipramine has an advantage when used to treat inpatients, alternative explanations for the outcome should be considered. One possible explanation resides in the rating scale used and the differential effect of the 2 drugs on sleep. If the response pattern of the patients with endogenous depression is examined, clomipramine had the greatest impact on the 3 items of the HAM-D that measure sleep disturbance, as shown in Figure 2.

A limitation of the HAM-D as a rating scale is that a drug that is inherently sedating, like clomipramine, may enjoy at least a short-term advantage when compared with a drug that is less sedating. Furthermore, this trial lasted only 5 weeks. While the slope of response trends downward for the citalopram group throughout the study, it is relatively flat in the last weeks for the clomipramine group.

Figure 3. Relative Effectiveness for Agents With "Single," "Dual," or "Triple" Action[a,b]
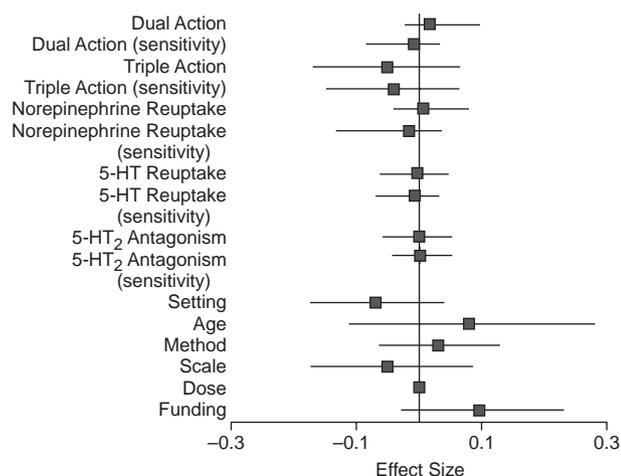
[a]Reprinted with permission from Freemantle et al.[8] Estimated effect sizes are shown for agents with a primary effect on serotonin and/or norepinephrine reuptake inhibition and/or 5-HT$_2$ antagonism. For pharmacologic activity, a value less than zero implies an advantage. Neither pharmacologic activity nor structural factors such as trial setting, patient age, or dose of comparator agent were predictive of greater efficacy.
[b]Bars indicate 95% CI.

There was no significant difference between groups on the HAM-D total score at week 5. The question is raised as to what the response rates would have been after 8 weeks.

A meta-analysis that has particular bearing on the issue of mechanism of action as it relates to differential efficacy is the study by Freemantle et al.[8] These investigators reported a "meta-regression analysis" of 105 randomized clinical trials that compared SSRIs with drugs affecting more than one presumed pharmacologic site. These trials included 5937 patients treated with an SSRI and 5600 patients treated with an alternative antidepressant. No difference in efficacy was found when drugs were analyzed by purported mechanism of action. There was also no increase in effectiveness for agents with "dual-action" or "triple-action" in the model (Figure 3). The authors offer 2 important caveats. "The results of our reviews suggest that great caution needs to be taken when ascribing any possible efficacy advantages of particular antidepressants over SSRIs to acute pharmacologic properties."[8(p294)] They also note that "acute pharmacology, even if it can be known, therefore stands as a crude proxy for as yet unknown changes that are crucial for antidepressant action."[8(p298)]

SSRIs VERSUS VENLAFAXINE

There would be less interest in this topic were it not for an analysis of all of the SSRI versus venlafaxine trials conducted by the clinical research and development group at Wyeth-Ayerst Laboratories during the development of the immediate release (IR) and extended release (XR) formulations of venlafaxine.[9] This analysis has attracted considerable attention because of its suggestion that remission rates with venlafaxine were higher than with comparison SSRIs or placebo. Furthermore, the proposed superiority was suggested to be a result of the "dual action" of venlafaxine. Because this manuscript often is presented as evidence for the superiority of "dual mechanism" drugs, it is important to examine the basis for this conclusion.

The analysis included data from patients with depression who participated in 8 double-blind, randomized clinical trials comparing venlafaxine with SSRIs. These 8 studies include 4 studies of 8-week duration, 1 study of 12-week duration, and 3 studies of 6-week duration. Four of these studies were placebo-controlled. Seven included outpatients (N = 1977), and the remaining study was a small (N = 68) inpatient study conducted by Clerc et al.[10] Dosages of venlafaxine ranged from 75 to 375 mg/day of the IR preparation and 75 to 225 mg/day of the XR preparation. Fluoxetine was the comparator SSRI in 5 of these trials, paroxetine in 2, and fluvoxamine in 1. Data from these disparate studies were pooled and analyzed in a modified intent-to-treat sample with remission rates calculated using the last-observation-carried-forward (LOCF) method. Final remission rates calculated were 45% for venlafaxine, 35% for the SSRIs overall, and 25% for placebo.

The advantage of a pooled analysis is that an increased sample size provides additional statistical power to detect differences between treatments that may not be apparent in smaller studies, yet the strength of an overall conclusion is only as good as the constituent studies. In the venlafaxine analysis,[9] however, there are problems in trying to evaluate the results of the individual studies. Lack of access to the underlying data is a major barrier since only 4 of the trials have been published, another 2 have been presented only as abstracts, and 2 have never been published. Additionally, the fact that only 4 of the trials are placebo-controlled is problematic for at least 2 reasons. First, placebo controls are an important barometer of the sensitivity of the individual studies. Trials in which a study drug fails to separate from placebo are considered negative studies, and those in which an active comparator drug fails to separate from placebo are considered "failed" trials. Hence, the placebo group helps to calibrate a study. In drug-drug comparison trials that lack a placebo comparator, there is no way to gauge the quality of the trial or whether one or both drugs might have separated from placebo.

Second, response rates in trials that lack a placebo comparator tend to be higher, sometimes markedly so. Pooling placebo-controlled studies with those that do not include a placebo control thus runs the risk of producing misleading results. Indeed, in the analysis by Thase et al., "the com-

parison of venlafaxine and SSRIs that included only the 4 studies that were not placebo-controlled was not statistically significant."[9(p237)]

Therefore, it seems appropriate for further analysis to focus on the 4 studies that were placebo-controlled. Of these trials, only 2 have been published. The study conducted by Rudolph and Feiger[11] was a randomized, double-blind, placebo-controlled trial in depressed outpatients using venlafaxine XR and fluoxetine. Doses used were venlafaxine XR, 75 to 225 mg/day, and fluoxetine, 20 to 60 mg/day. Primary efficacy outcome measures were the final rating of the HAM-D-21 total score, the HAM-D-21 depressed mood item, the Montgomery-Asberg Depression Rating Scale (MADRS)[12] total score, and the CGI scores. As a post hoc analysis, remission rates were calculated.

During weeks 4 through 8, the mean daily doses were venlafaxine XR, 175 mg/day, and fluoxetine, 47 mg/day. On the HAM-D total score LOCF analysis, neither venlafaxine nor fluoxetine was statistically superior to placebo. Venlafaxine was superior to placebo on the MADRS total score and the CGI-Severity of Illness score. Fluoxetine was not superior to placebo on either measure. Given the lack of separation between the active comparator, fluoxetine, and placebo on all 3 measures, this should be considered a "failed" trial. One reason that it may have failed is that 24% of the randomized patients had a history of fluoxetine use, while only 2% had a history of using venlafaxine IR or venlafaxine XR. Unfortunately, response to prior antidepressant treatment was not recorded. Since these patients were evenly distributed across the 3 treatment groups, it is possible that patients with a prior history of nonresponse to fluoxetine could have been included in the fluoxetine treatment group, which could bias any proposed comparison between venlafaxine and fluoxetine.

The second published placebo-controlled trial was conducted by Silverstone and Ravindran,[13] who studied 359 outpatients with major depression and concomitant anxiety. This trial lasted 12 weeks, and patients received venlafaxine XR, 75 to 225 mg/day; fluoxetine, 20 to 60 mg/day; or placebo. Primary efficacy variables were final scores on the HAM-D-21, the Hamilton Rating Scale for Anxiety (HAM-A),[14] and the CGI. Response was defined as a 50% decrease from baseline on the HAM-D and HAM-A or a score of 1 or 2 on the CGI-I. Remission was defined as a final score of < 8 on the first 17 items of the HAM-D among patients classified as responders. The mean doses at week 12 were 140.8 mg/day of venlafaxine and 39.9 mg/day of fluoxetine.

The proportion of responders as defined by the HAM-D was significantly higher with venlafaxine XR and fluoxetine than with placebo at weeks 2, 8, and 12 and at the final on-therapy evaluation. HAM-D remission rates for both venlafaxine XR and fluoxetine at week 12 and final on-therapy evaluation were significantly higher than those for

placebo. Remission rates did not differ between venlafaxine XR and fluoxetine. The authors note that a "limitation of this study is that no information was available on previous use of SSRI antidepressants. Inclusion of SSRI nonresponders may have biased the results toward venlafaxine XR."[13(p27)]

Although the 4 non–placebo-controlled trials included in the venlafaxine analysis will not be examined in detail given the lack of differences in remission rates as noted by Thase et al.,[9] it is worth noting that the design of the study by Dierick and colleagues[15] was structured so that venlafaxine, 37.5 mg twice a day, was compared with fluoxetine, 20 mg once a day, for 8 weeks. If the response was inadequate after 2 weeks of treatment, the dosage of venlafaxine could be increased to 75 mg twice daily, but the dose of fluoxetine could not be increased. This is a less than ideal design for elucidating a clinically relevant difference between antidepressants.

One conclusion that can be reached from examining these individual trials is that while each was designed with a particular purpose, none was specifically designed or powered to compare venlafaxine to any comparator drug with remission as the primary outcome. Considering the concerns noted above, any proposed advantage for venlafaxine over the SSRI should be recognized as a hypothesis, not a fact. The need for prospective trials aimed at evaluating remission as a specific outcome is clear.

Thase et al.[9] also summarized 9 other venlafaxine versus SSRI trials not conducted by Wyeth-Ayerst. In 4 of these studies,[16–19] there were nonsignificant differences between venlafaxine and the comparator. Two studies[20,21] reported inconsistent findings, with significant results favoring venlafaxine over fluoxetine using a global definition of remission, but not when looking at the final HAM-D score. Additionally, 3 studies were described in which venlafaxine was superior to paroxetine (in 2 studies) and sertraline. The dose of venlafaxine was 75 to 150 mg/day in 2 of the studies and 200 to 300 mg/day in the other.

Dosage should be noted as a relevant variable in these studies. Venlafaxine is usually not considered to have substantial effects on norepinephrine until the dose is greater than 150 mg/day. Of the placebo-controlled trials reviewed by Thase et al.,[9] only the Rudolph and Feiger[11] study of venlafaxine IR had a mean dose of venlafaxine greater than 175 mg/day. In the 4 studies lacking a placebo control, only the small inpatient study[10] adjusted the dose above 150 mg/day.

An analysis of response rates using the same pooled data included in the report by Thase et al.[9] has also been published.[22] Both of these articles report that 3 additional Wyeth-supported, placebo-controlled comparisons of venlafaxine and SSRIs have been conducted for which "data analyses are not complete."[9(p239), 22(p1167)] These studies may contribute important information on this topic because differential rates of remission were presumably among the

Table 1. Venlafaxine Versus Other Antidepressants in the Treatment of Depression[a]

Study	Comparator	Change in Depression Rating From Baseline	Response Rate	Remission Rate
Costa e Silva	Fluoxetine	No difference	No difference	No difference
Silverstone	Fluoxetine	No data	No difference	No difference
Mehtonen	Sertraline	No difference	Venlafaxine superior[b]	Venlafaxine superior
Ballus	Paroxetine	No difference	No difference	No difference
Tzanakaki	Fluoxetine	No difference	Venlafaxine superior	No difference
Clerc	Fluoxetine	Venlafaxine superior	No difference	No data
Poirier	Paroxetine	No difference	No difference	Venlafaxine superior
Dierick	Fluoxetine	No difference	No difference	No data

[a]Adapted from Olver et al.[24] Response was defined (depending on the study) as ≥ 50% improvement from baseline in HAM-D or MADRS scores. Remission was defined (depending on the study) as HAM-D or MADRS score ≤ 8 to 10.
[b]HAM-D only; no difference between the drugs was observed on the MADRS or CGI.
Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

prospective outcomes studied. At least 1 of these studies, a comparison of venlafaxine IR and fluoxetine in geriatric outpatients, appears to have been presented as a poster and published in abstract form.[23] In this study, neither drug was significantly different from placebo in overall effect or in remission rate. Results from the remaining 2 trials have yet to be made public.

There have been at least 2 subsequent attempts to look at a broader range of studies comparing venlafaxine with the SSRIs. Olver et al.[24] used a MEDLINE literature search to identify reports of double-blind, controlled trials of venlafaxine versus other antidepressants in the treatment of depression. Nine of those trials compared venlafaxine with SSRIs. Of these, the Rudolph and Feiger[11] study cited above was eliminated because the comparator drug was not more effective than placebo. The remaining 8 studies were compared with respect to remission rates (when available), response rates, and the change in depression rating scale scores from baseline (Table 1).

In 4 of these 8 studies, there was no difference between the drugs on any of the outcome measures. Four studies did show a difference in at least 1 outcome measure, but in none of the studies was venlafaxine superior on all 3 outcome measures. Of the 5 studies comparing venlafaxine with fluoxetine, 3 showed no difference on any parameter.

Olver et al. offered the summary view that "no study has shown convincing improvements of efficacy in all 3 reviewed outcome measures. When differences were reported, the magnitude was small and while they may have been statistically significant, they are unlikely to be clinically significant."[24(p946)]

Smith et al.[25] conducted the most thorough study to date of randomized, double-blind trials of venlafaxine compared with other antidepressants. In this meta-analysis, the outcome measure was pooled, standardized difference in mean treatment effect. This analysis included 20 trials comparing venlafaxine with SSRIs, 9 trials comparing venlafaxine with TCAs, and 3 trials comparing venlafaxine with other drugs. The authors concluded that the size of the effect was approximately 1.2 points on the HAM-D in favor of venlafaxine. This conclusion was based on an overall effect size estimate of –0.14 (95% CI = –0.22 to –0.07) in favor of venlafaxine. For the venlafaxine versus SSRI comparison, the effect-size estimate was –0.17 (95% CI = –0.27 to –0.08). The results appeared consistent across the SSRIs (although there have been no published trials to date of venlafaxine vs. citalopram or escitalopram). Interestingly, there were differences in the TCA studies such that venlafaxine seemed to be significantly better than imipramine (effect size = –0.38, 95% CI = –0.57 to –0.19). In the context of the "dual mechanism" theory, this finding is ironic given that imipramine is the most balanced TCA with respect to its effects on serotonin and norepinephrine. Looking specifically at remission rates, 16 of the trials reported remission rates of venlafaxine versus an SSRI. Venlafaxine enjoyed an advantage in this analysis (odds ratio = 1.43, CI = 1.21 to 1.71). There was no effect of dose on the size of the advantage of venlafaxine over SSRIs.

It should be noted that there have been no published comparison trials between venlafaxine and citalopram, and only preliminary data from studies comparing venlafaxine XR and escitalopram have been presented as abstracts.[26,27] In one study,[26] outpatients with major depression were randomly assigned to receive 8 weeks of double-blind treatment with flexible doses of escitalopram, 10 to 20 mg/day, or venlafaxine XR, 75 to 150 mg/day. Escitalopram and venlafaxine XR were not statistically different on the primary efficacy measure, the mean change from baseline in MADRS scores. After 8 weeks, there were no differences in response (50% or greater reduction in MADRS score) or remission rates (MADRS score ≤ 12). A reanalysis of week 8 remission rates from this study defining remission as a MADRS score ≤ 10 showed remission rates of 64.3% for escitalopram and 64.8% for venlafaxine in an observed cases analysis and 56.2% for escitalopram and 60.6% for venlafaxine in an LOCF analysis (Andrew Korotzer, Ph.D., written communication, May 2003). Both drugs were reasonably well tolerated, although significantly more venla-

faxine XR patients experienced constipation, sweating, and nausea.

One strength of this study was that it prospectively defined remission as an outcome measure. It also used dosages of both medications that are commonly used clinically, as well as doses of venlafaxine comparable to the doses used in most of the studies from the Thase et al.[9] pooled analysis. However, this study was not designed to answer the key question of interest that is the focus of the current article. There was no placebo group, and the doses of venlafaxine used were not high enough to have an impact on norepinephrine uptake.

A comparative study of higher doses of escitalopram and venlafaxine XR in the treatment of major depression has now been reported.[27] In this double-blind trial, patients were randomly assigned to receive 20 mg/day of escitalopram or 225 mg/day of venlafaxine XR, the maximum recommended doses of these agents, for 8 weeks. Patients were titrated, in accordance with labeling information, from starting doses of escitalopram, 10 mg/day, and venlafaxine XR, 75 mg/day. On the primary efficacy measure of mean change from baseline in MADRS score, there was no statistically significant difference between treatment groups. Analysis of rates of response and remission, defined as a decrease of at least 50% from baseline in MADRS score and a MADRS score of ≤ 10, respectively, showed escitalopram and venlafaxine XR to be similarly efficacious. At endpoint (LOCF), 58.8% of escitalopram-treated patients met criteria for response, compared with 48.0% of venlafaxine-treated patients, and 41.2% of escitalopram-treated patients met criteria for remission, compared with 36.7% of venlafaxine-treated patients.

Although this study lacked a placebo control, there was no evidence that the ascribed "dual action" of venlafaxine on serotonin and norepinephrine transporters was superior to the highly selective effect of escitalopram on serotonin reuptake. However, the high dose of venlafaxine XR was less well tolerated than the high dose of escitalopram. While there were no discontinuations in either treatment group for lack of efficacy, 16% of venlafaxine-treated patients discontinued due to adverse events, compared with 4% of escitalopram-treated patients, a difference that was statistically significant (p < .01).

SSRIs VERSUS SSRIs

It is worthwhile to remember that there has been very little effort to compare available SSRIs in placebo-controlled randomized trials. These compounds all inhibit the reuptake of serotonin, but structurally, pharmacologically, and pharmacokinetically, they are quite distinct. Each of the SSRIs has a distinct receptor-activity profile and may have different utility.

Among 4 published SSRI versus SSRI placebo-controlled trials,[28–31] one was a fluoxetine versus paroxetine study in which neither drug separated from placebo.[28] A placebo-controlled comparison of sertraline and citalopram lasting 24 weeks showed an earlier separation from placebo for citalopram compared with sertraline.[29] The remission rates (HAM-D score < 8) reported in that study were citalopram 45%, sertraline 37%, and placebo 28%. These rates are similar to those reported in the Thase et al. pooled analysis.[9] More recently, 2 placebo-controlled trials of escitalopram compared with racemic citalopram have suggested that at comparable doses, escitalopram may be more potent than citalopram (i.e., 10 mg/day of escitalopram was shown to be at least as effective as 40 mg/day of citalopram)[30] and that escitalopram separates from placebo at an earlier timepoint than does citalopram.[30,31]

Clearly, there still is much to be learned about potential differences between available antidepressants, including the SSRIs. There have not been adequately powered trials to detect differences between active drugs. Rather, the data that have been used to compare drugs in the literature too often consist of post hoc analyses and lumped data gathered in very different ways.

CONCLUSION

This review should caution one in accepting claims of superiority of any agent based on purported mechanism of action. The great majority of head-to-head trials (and even pooled analyses) suggest comparable efficacy between classes of antidepressants. In the few instances in which a difference is suggested, this difference seems to consistently hover around 1 HAM-D point, a difference too small to be clinically significant.

Although most medication trials have been conducted in outpatients with mild-to-moderate depression, there are suggestions from the literature that a subgroup of patients, such as inpatients or patients with endogenous depression, may respond better to TCAs than to SSRIs. This possible difference should be adequately evaluated. However, few of these types of patients are currently enrolled in clinical trials.

A great deal of attention has been devoted to the pooled analysis of venlafaxine versus SSRIs. However, as the above critique notes, there are substantial limitations to the individual trials that are included in this analysis. Remission in these trials was defined post hoc, and the trials were a mixture with varying design, duration, population type, dose, and preparation. A number of these trials have not been published or have been published only in abstract form, severely limiting the ability to judge the quality of the individual studies. Five of the individual trials used fluoxetine as a comparator. In the 2 published placebo-controlled trials of venlafaxine versus fluoxetine, difficulties in interpreting the data arise because of the inclusion of patients who had already had a trial of fluoxetine prior

to entering the studies (24% of patients in the Rudolph and Feiger[11] study). This is relevant because fluoxetine nonresponders may well have been randomized to receive fluoxetine.

Doses of venlafaxine used in these studies were generally not high enough to have any impact on norepinephrine, as noted by Harvey et al.[32] In this regard, venlafaxine is probably not the ideal compound to use in testing the "dual mechanism" hypothesis. A better comparison may be with a compound like duloxetine that has relatively balanced noradrenergic and serotonergic effects across its dosage range.

Several areas of research could help evaluate the "dual mechanism" hypothesis. Additional placebo-controlled trials of candidate drugs, for example, should be a priority. Perhaps the ideal comparison would be between a drug like escitalopram, which is highly selective for the serotonin transporter, and a drug like duloxetine.

Regardless of the outcomes of such trials, agents that work less selectively may have a broader range of adverse events because more receptors are affected. Therefore, in comparison studies it will be essential to examine the adverse event profiles carefully. At one level, it seems obvious that a drug that impacts both serotonergic receptors and adrenergic receptors would have the potential to cause all of the adverse events of the SSRIs in addition to the adverse events associated with noradrenergic stimulation. For example, venlafaxine at low doses produces side effects typically associated with serotonin uptake inhibition. At higher doses, where noradrenergic stimulation occurs, hypertension can occur. However, because of cross-talk between transmitter systems, this is not a certainty.

On another level, does it really make sense to talk about "remission" of depression at the end of 6 to 8 weeks and to do so on the basis of a specific score from any single rating scale? Major depression by definition affects social and occupational functioning, dimensions of the illness that are largely ignored in most clinical trials and not well captured by commonly used rating scales. While remission is certainly the goal, equating remission with an arbitrary cutoff on a rating scale minimizes the impact that depression has on a person's life. Remission should be seen as a restoration of function, and not a HAM-D score of less than 8. Likewise, 6 to 8 weeks seems an unrealistically short time to declare victory over an episode of depression, particularly since it is now well recognized that treatment should continue well beyond the acute phase to consolidate response. If this controversy allows us to better focus on complete recovery as a goal, we should develop better ways to measure recovery and design trials of adequate length.

Also relevant is the consideration of differential effects of antidepressants on relapse. Geddes et al.[33] reviewed the data for various classes of antidepressants with respect to their ability to prevent relapse of depression. They concluded that ability to prevent relapse was similar for all classes of antidepressants. The similar performance of the various antidepressants to prevent relapse echoes the data from the meta-analyses of the short-term trials: all antidepressants appear to be similarly effective at treating depression and maintaining response.

Given the existing data, is there a compelling reason to choose a drug based on its mechanism of action? The answer probably depends on the characteristics of the individual patient. For the hospitalized person with severe depression, some physicians may choose to use a TCA. For the more typical outpatient with less severe depression, there are many important factors to consider in choosing a drug, such as ease of use, side effect profile, and cost. Another relevant issue in drug selection is titration. The TCAs must be titrated to a therapeutic dose, and the dose of venlafaxine must be titrated upward if one hopes to affect more than serotonin. To a busy clinician, titration often means more visits or phone calls and juggling dosages, and in the case of venlafaxine, more attention must be paid to monitoring blood pressure. Better evidence is needed before purported mechanism of action is elevated to the role of primary selection criteria.

The questions of the relative efficacy of antidepressants and how mechanism of action relates to efficacy are important scientific issues and a challenge to the field. Utilizing large-scale, placebo-controlled, randomized trials designed to detect a difference between active comparators is the only way we will be able to answer this question. Until data from such trials are available, there can be no definitive answer to this intriguing question.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression. JAMA 2002;287:1840–1847
2. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
3. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
4. Geddes JR, Freemantle N, Mason J, et al. Selective serotonin reuptake inhibitors (SSRIs) for depression (Cochrane Review). In: The Cochrane Library, Issue 3 2002. Oxford, England: Update Software; 2002
5. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 2000;58:19–36
6. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacology (Berl) 1986;90:131–138
7. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
8. Freemantle N, Anderson IM, Young P. Predictive value of pharmacology activity for the relative efficacy of antidepressant drugs. Br J Psychiatry 2000;177:292–302

9. Thase ME, Entsuah RA, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241

10. Clerc GE, Ruimy R, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 1994;9:139–143

11. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord 1999;56:171–181

12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389

13. Silverstone PH, Ravindran A. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. J Clin Psychiatry 1999;60:22–28

14. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55

15. Dierick M, Ravissa L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:57–71

16. Tylee A, Beaumont G, Bowden MW, et al. A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. Primary Care Psychiatry 1997;3:51–58

17. McPartlin GM, Reynolds A, Anderson C. A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. Primary Care Psychiatry 1998;4:127–132

18. Diaz-Martinez A, Benassinni O, Ontiveros A, et al. A randomized, open-label comparison of venlafaxine and fluoxetine in depressed outpatients. Clin Ther 1998;20:467–476

19. Alves C, Cachola I, Brandao J. Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. Primary Care Psychiatry 1999;5:57–63

20. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry 1998;59:352–357

21. Tzanakaki M, Guazzelli M, Nimatoudis I, et al. Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. Int Clin Psychopharmacol 2000;15:29–34

22. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;52:1166–1174

23. Schatzberg A. Antidepressant early response and remission of venlafaxine and fluoxetine in geriatric outpatients. Eur Neuropsychopharmacol 2000;10(suppl 3):S225–S226

24. Olver JS, Burrows GD, Normal TR. Third-generation antidepressants: do they offer advantages over the SSRIs? CNS Drugs 2001;15:941–954

25. Smith D, Dempster C, Glanville J, et al. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 2002;180:396–404

26. Montgomery SA, Huusom AKT, Bothmer J. Escitalopram is a new and highly efficacious SSRI in the treatment of major depressive disorder. Eur Neuropsychopharmacol 2002;12(suppl 3):S254–S255

27. Bielski RJ, Ventura D, Chang C-C, et al. A double-blind comparison of escitalopram with venlafaxine XR in the treatment of major depressive disorder. Eur Neuropsychopharmacol 2003;13(suppl 4):S262

28. Fava M, Amsterdam JD, Deltito JA, et al. A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. Ann Clin Psychiatry 1998;10:145–150

29. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry 2000;48:894–901

30. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002;63:331–336

31. Lepola UM, Loft H, Reines EH. Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int J Psychopharmacol 2003;18:211–217

32. Harvey AT, Rudolph RL, Preskorn SH. Evidence of dual mechanisms of action of venlafaxine. Arch Gen Psychiatry 2000;57:503–509

33. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003;361:653–661