Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis*

DAVID SMITH, CARRIE DEMPSTER, JULIE GLANVILLE, NICK FREEMANTLE and IAN ANDERSON

Background In individual studies and limited meta-analyses venlafaxine has been reported to be more effective than comparator antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs).

Aims To perform a systematic review of all such studies.

Method We conducted a systematic review of double-blind, randomised trials comparing venlafaxine with alternative antidepressants in the treatment of depression. The primary outcome was the difference in final depression rating scale value, expressed as a standardised effect size. Secondary outcomes were response rate, remission rate and tolerability.

Results A total of 32 randomised trials were included. Venlafaxine was more effective than other antidepressants (standardised effect size was −0.14, 95% CI −0.07 to −0.22). A similar significant advantage was found against SSRIs (20 studies) but not tricyclic antidepressants (7 studies).

Conclusions Venlafaxine has greater efficacy than SSRIs although there is uncertainty in comparison with other antidepressants. Further studies are required to determine the clinical importance of this finding.

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Depressive disorders are the second most important cause of disability in developed countries (Murray & Lopez, 1997) but a substantial minority of depressed patients fail to respond to antidepressant treatment (Anderson *et al*, 2000). Although newer antidepressants have tolerability and safety benefits over older tricyclic antidepressants (TCAs), similar efficacy generally is reported (Edwards, 1992; Gross & Huber, 1999; Anderson, 2000; Geddes *et al*, 2001). It is potentially of great clinical importance if an antidepressant were to be more effective than comparators, and understanding why may shed light on how antidepressants work. It has been proposed (Nelson *et al*, 1991; Seth *et al*, 1992; Heninger *et al*, 1996) that antidepressants with a dual action of inhibiting the reuptake of both noradrenalin and serotonin (5-hydroxytryptamine, 5-HT) may be more effective than drugs acting on a single monoamine (e.g. selective serotonin reuptake inhibitors, SSRIs). Venlafaxine is the first drug to be marketed that inhibits both noradrenalin and 5-HT reuptake without actions at other receptors (Holliday & Benfield, 1995). We present a systematic review investigating the relative efficacy and tolerability of venlafaxine compared with other antidepressants.

METHOD

Relevant trials were identified from our existing database (Eccles *et al*, 2000) and from systematic searches of electronic databases. The search terms were VENLAFAXINE, EFEXOR or EFFEXOR. Databases searched included Medline, Embase, Biosis, PsychLit, National Research Register, Healthstar, SIGLE, Cochrane Database of Systematic Reviews, DARE, Cochrane Controlled Trials Register and Current Controlled Trials. A total of 2349 trials were identified from our electronic search strategy. We carried out a manual search of reference lists of included studies and requested unpublished data from authors and study sponsors.

Inclusion criteria

Trials were included if they were double-blind, randomised studies comparing venlafaxine with an alternative antidepressant for the treatment of depression. The definition of depression was intentionally broad and included explicit clinical or research criteria for major depression (such as DSM–IV; American Psychiatric Association, 1994) or if the clinician considered the patient to be depressed and eligible for antidepressant treatment. Two of the researchers (D.S. and C.D.) made an independent assessment of each potentially eligible study and disagreements were resolved through discussion within the team.

Data abstraction

Design characteristics and quality assessment

We abstracted data on the inclusion and exclusion criteria for each study, the dose and regimen of venlafaxine and alternative antidepressants, the adequacy of randomisation and concealment of allocation (as reported in the paper), number of patients randomised, loss to follow-up, form of analysis (completer analysis or last observation carried forward), relevant clinical outcomes reported, age and gender of participants and length of follow-up. When specific variables were not reported within a given trial, the authors of the paper were contacted to obtain the missing data. If this was unsuccessful, we contacted the sponsors. Data were abstracted on all available patients randomised in the trials and patients were analysed on the basis of initial random allocation to treatment group (intention to treat) whenever possible.

Clinical outcomes

The primary outcome was the mean depression severity measure assessed by the final

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Table 1 Description of included trials[1]

Drug class	Comparator	Trial	Citation	No. of studies	No. of patients	Venlafaxine dose	Mean age	Female (%)	Method	Setting
TCA				9	1508	131[5]	50	68[5]		
	Amitriptyline	Gentil *et al*, 2000	23	1	116	103	39	81	LOCF	Out-patient
	Clomipramine	Smeraldi *et al*, 1998	24	2	113	83	72	73	LOCF	Out-patient
		Samuelian & Hackett, 1998	25		102	105	47	62	LOCF	Out-patient
	Dothiepin (dosulepin)	Mahapatra & Hackett, 1997	26	2	92	100	74	70	LOCF	Out-patient
		Stanley *et al*, 1998	14		86	75	NA	NA	Completers	Out-patient
	Imipramine	Shrivastava *et al*, 1994	27	4	381	165	43	54	LOCF	Out-patient
		Benkert *et al*, 1996	28		167	233	47	68	LOCF	In-patient
		Lecrubier *et al*, 1997	29		153	111	40	69	LOCF	Out-patient
		Schweizer *et al*, 1994	30		146	182	42	66	LOCF	Out-patient
SSRI				20	3989	150[5]	47	67[5]		
	Fluoxetine	Costa & Silva, 1998	31	13	382	91	40	79	LOCF	Out-patient
		Tylee *et al*, 1997	15		341	75	45	71	Completers	Out-patient
		Dierick *et al*, 1996	32		314	111	44	65	LOCF	Out-patient
		Rudolph *et al*, 1998	33		308	300			Not clear	Out-patient
		Silverstone & Ravindran, 1999	34		249	141	42	60	Completers	Out-patient
		Schatzberg & Cantillon, 2000	35		204	150	71	50	LOCF	Out-patient
		Rudolph & Feiger, 1999	36		203	175	40	70	LOCF	Out-patient
		Unpublished data[2]	37		196	150	NA	NA	LOCF	Out-patient
		Unpublished data[3]	38		156	150	NA	NA	LOCF	Out-patient
		Geerts *et al*, 1999	39		146	102	43	68	LOCF	Out-patient
		Tzanakaki *et al*, 2000	40		109	225	48	79	LOCF	In-patient
		Alves *et al*, 1999	41		87	113	NA	NA	LOCF	Out-patient
		Clerc *et al*, 1994	42		68	200	51	68	LOCF	In-patient
	Fluvoxamine	Unpublished data[4]	43	2	92	150	NA	NA	LOCF	Out-patient
		Zanardi *et al*, 2000	44		28	225	51	64	LOCF	In-patient
	Paroxetine	McPartlin *et al*, 1998	45	4	361	75	45	68	LOCF	Out-patient
		Salinas, 1997	46		246	113	47	63	LOCF	Out-patient
		Poirier & Boyer, 1999	47		123	269	43	72	LOCF	Out-patient
		Ballus *et al*, 2000	48		84	113	NA	NA	LOCF	Out-patient
	Sertraline	Mehtonen *et al*, 2000	49	1	147	114	43	66	LOCF	Out-patient
Other				3	418	166[5]	53	64[5]		
	Mirtazapine	Guelfi, 1999	50	1	157	255	45	64	LOCF	In-patient
	Trazodone	Cunningham *et al*, 1994	51	2	149	160	41	55	LOCF	Out-patient
	Trazodone	Smeraldi *et al*, 1998	24		112	83	72	72	LOCF	Out-patient
Total				32	5562	147[5]	48	67[5]		

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; LOCF, last observation carried forward.

1. Multiple comparisons were made in a number of trials. As a quality criterion, and a rule of thumb, we cite the total number of patients in the trials, rather than the comparisons included, because there is good empirical evidence that the quality of studies is affected directly by the overall size.
2. Unpublished data: Nemeroff, C & Amchin, J. (1998) Placebo-controlled trial of the efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression (abstract P.1.066). 11th European Congress of Neuropsychopharmacology, Paris, France.
3. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.
4. Unpublished data: Hackett D., Salinas, E. & Desmet, A. (1998) Efficacy and safety of venlafaxine vs. fluvoxamine in outpatients with major depression (abstract P.1.210). 11th European Congress of Neuropsychopharmacology, Paris, France.
5. Weighted mean.

(end of trial) Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), the Montgomery and Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979) or the Clinical Global Impression (Guy, 1976), with preference given in that order if more than one scale was reported. Secondary outcome variables were response rate (typically 50% or greater drop in depression rating scale from baseline) and remission rate (depression rating scale below a certain score, e.g. HRSD <8). Data on tolerability were abstracted by collecting 'all cause' withdrawals from each treatment group and also the attributed reason for withdrawal from therapy (lack of efficacy and adverse effects).

Statistical analysis

The primary efficacy outcome was the pooled standardised difference in mean treatment effect. For this measure, standardised effect sizes (difference in final rating scale means divided by the within-study standard deviation) were estimated from the efficacy data for each treatment group. Where an estimate of study variance was not available, this was imputed by taking the average for the studies using the same outcome measure. Secondary binary outcomes of response and remission, as well as tolerability data, were calculated as the odds ratio and absolute risk difference.

A simulation method was used to estimate pooled treatment effects using Gibbs sampling in BUGS software (Smith *et al*, 1995; Freemantle *et al*, 1999). This method is analogous to standard methods but does not require large sample assumptions, making it superior in meta-analysis where these assumptions frequently are not met. It has the additional advantage that the predictive value of different factors, such as patient severity or dose, may be examined using meta-regression approaches (Freemantle *et al*, 1999). Absolute risk differences were calculated using standard methods (DerSimonian & Laird, 1986) and interpreted as 'number needed to treat' (NNT). Negative NNTs are often described as 'number needed to harm'.

Fixed effects approaches to meta-analysis assume that each trial contributes an estimate of a constant population effect for a treatment, whereas random effects approaches assume that there is no single population effect but a *distribution* (range)

Table 2 Effect size analysis

Class	Comparator	Effect size	95% CI	Study
TCA	Amitriptyline	0.26	−0.10 to 0.63	Gentil *et al*, 2000
	Pooled amitriptyline	0.26	−0.10 to 0.63	
	Clomipramine	0.05	−0.32 to 0.42	Smeraldi *et al*, 1998
	Clomipramine	−0.11	−0.51 to 0.28	Samuelian & Hackett, 1998
	Pooled clomipramine	−0.03	−0.29 to 0.24	
	Dothiepin	−0.02	−0.44 to 0.4	Mahapatra & Hackett, 1997
	Dothiepin	−0.18	−0.71 to 0.36	Stanley *et al*, 1998
	Pooled dothiepin	−0.08	−0.40 to 0.24	
	Imipramine	−0.4	−0.64 to −0.16	Shrivastava *et al*, 1994
	Imipramine	−0.32	−0.65 to 0.02	Schweizer *et al*, 1994
	Pooled imipramine	−0.38	−0.57 to −0.19	
	Pooled TCA	−0.13	−0.33 to 0.09	
SSRI	Fluoxetine	−0.02	−0.22 to 0.19	Costa & Silva, 1998
	Fluoxetine	0.18	−0.07 to 0.43	Tylee *et al*, 1997
	Fluoxetine	−0.18	−0.40 to 0.04	Dierick *et al*, 1996
	Fluoxetine	−0.14	−0.37 to 0.09	Rudolph *et al*, 1998
	Fluoxetine	−0.12	−0.37 to 0.14	Silverstone & Ravindran, 1999
	Fluoxetine	−0.48	−0.76 to −0.2	Schatzberg & Cantillon, 2000
	Fluoxetine	−0.21	−0.49 to 0.07	Rudolph & Feiger, 1999
	Fluoxetine	−0.22	−0.50 to 0.06	Unpublished data[1]
	Fluoxetine	0.02	−0.30 to 0.35	Unpublished data[2]
	Fluoxetine	−0.5	−0.85 to −0.15	Geerts *et al*, 1999
	Fluoxetine	−0.08	−0.46 to 0.3	Tzanakaki *et al*, 2000
	Fluoxetine	−0.34	−0.77 to 0.1	Alves *et al*, 1999
	Fluoxetine	−0.58	−1.06 to −0.09	Clerc *et al*, 1994
	Pooled fluoxetine	−0.14	−0.22 to −0.06	
	Fluvoxamine	0.56	−0.23 to 1.34	Zanardi *et al*, 2000
	Pooled fluvoxamine	0.56	−0.23 to 1.34	
	Paroxetine	−0.1	−0.31 to 0.12	McPartlin *et al*, 1998
	Paroxetine	−0.46	−0.73 to −0.19	Salinas, 1997
	Paroxetine	−0.07	−0.42 to 0.29	Poirier & Boyer, 1999
	Paroxetine	−0.07	−0.50 to 0.37	Ballus *et al*, 2000
	Pooled paroxetine	−0.19	−0.34 to −0.05	
	Sertraline	−0.31	−0.67 to 0.06	Mehtonen *et al*, 2000
	Pooled sertraline	−0.31	−0.67 to 0.06	
	Pooled SSRI	−0.17	−0.27 to −0.08	
Other	Mirtazapine	0.23	0.55 to −0.09	Guelfi, 1999
	Pooled mirtazapine	0.23	0.55 to −0.09	
	Trazodone	−0.11	−0.44 to 0.23	Cunningham *et al*, 1994
	Trazodone	−0.37	−0.74 to 0.01	Smeraldi *et al*, 1998
	Pooled trazodone	−0.23	−0.47 to 0.02	
	Pooled 'other drug'	−0.09	−0.42 to 0.23	
Overall pooled		−0.14	−0.22 to −0.07	

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
1. Unpublished data: Nemeroff, C & Amchin, J. (1998) Placebo-controlled trial of the efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression (abstract P.I.066). IIth European Congress of Neuropsychopharmacology, Paris, France.
2. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.

of effects. Random effects models were used where venlafaxine was compared with a variety of agents (e.g. in comparison with SSRIs) but fixed effects models were used where venlafaxine was compared with individual agents.

Meta-regression was used to examine the predictive value of potentially important explanatory factors on the primary efficacy outcome measure (Freemantle *et al*, 1999). This hierarchical approach to data modelling enables examination of the effect of trial characteristics while preserving the structure of individual trials. The factors that we identified *a priori* were: size of trial; in-patient *v.* out-patient status; design criteria (last observation carried forward *v.* completer analysis). The analysis on size of trial is a particularly helpful method of identifying potential publication bias and is analogous to using a funnel plot. Other factors also investigated were age and gender, comparator drug class, length of follow-up, rating scale used (e.g. HRSD or Montgomery and Åsberg Depression Rating Scale), dose of venlafaxine and if the variance was imputed.

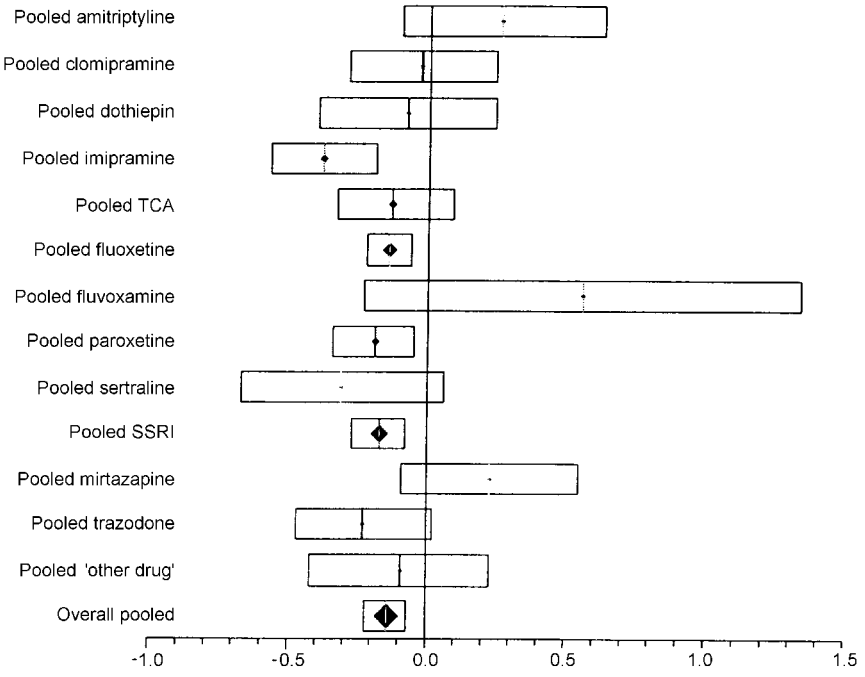

Fig. 1 Plot of pooled efficacy of venlafaxine compared with other antidepressants. The bars show the effect size (difference in final rating scale score divided by pooled final standard deviation) and the 95% CI. Results falling to the left of the line of no effect (zero) indicate an advantage to venlafaxine.

RESULTS

Included trials

A total of 32 studies met the inclusion criteria (Table 1), with comparisons of venlafaxine with TCAs (clomipramine, imipramine, dothiepin (dosulepin) and amitriptyline), SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline) and other drugs (trazodone and mirtazapine). There were 5562 patients in total[1]: 3844 in the twenty trials comparing venlafaxine with SSRIs (SSRI n=1857); 1356 in the nine trials comparing venlafaxine with TCAs (TCA n=579); and 418 in the three trials comparing venlafaxine with other drugs (other n=212). The average trial size was 179 patients (range 28–382). The average length of follow-up was 10 weeks (range 4–48). Most trials used the last observation carried forward for the primary analysis (see Table 1). For three of the trials, we imputed the measure of variance because the data were not available and could not be obtained from the authors or sponsors. None of the trials indicated whether concealment of allocation was conducted appropriately.

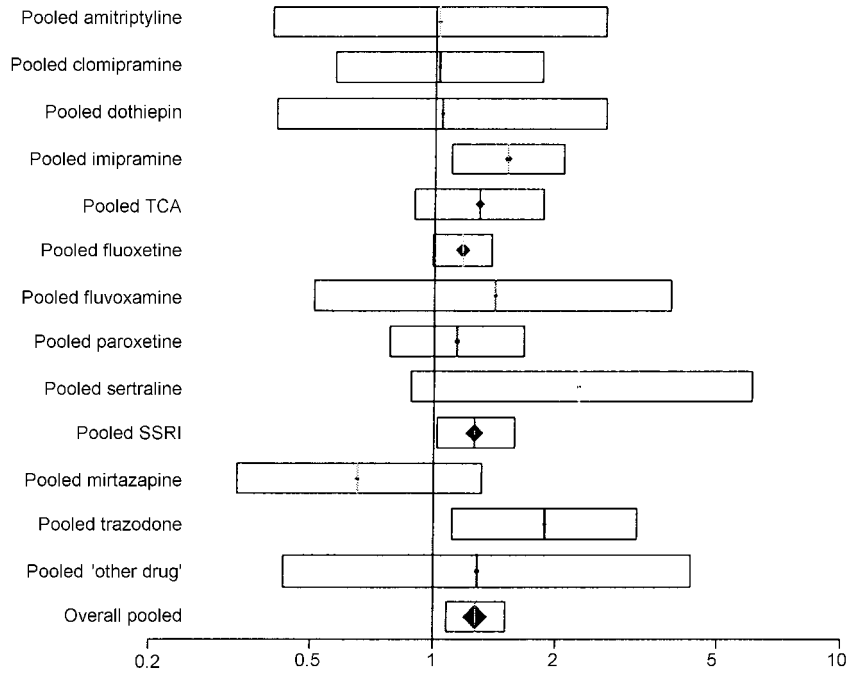

Fig. 2 Plot of pooled response rate to venlafaxine compared with other antidepressants. The bars show the odds ratio and the 95% CI. Results falling to the right of the line of no effect (1) indicate an advantage to venlafaxine.

Primary outcome

There were 29 comparisons in the effect size analysis of clinical efficacy (Table 2). The overall effect size estimate was −0.14

1. Multiple comparisons were made in a number of trials. As a quality criterion, and a rule of thumb, we cite the total number of patients in the trials, rather than the comparisons included, because there is good empirical evidence that the quality of studies is affected directly by the overall size.

(95% CI −0.22 to −0.07) in favour of venlafaxine. The size of effect (given a pooled standard deviation of 8.3) is equivalent to the final HRSD score, being about 1.2 points lower on venlafaxine. For the SSRIs, the effect size estimate was −0.17 (95% CI −0.27 to −0.08). Effect sizes for the TCAs and the 'other drug' categories were similar but not significantly different from venlafaxine (Table 2, Fig. 1).

The results appeared consistent across the SSRIs but there were differences between the TCA studies, notably imipramine: the effect size was −0.38 (95% CI −0.57 to −0.19), favouring venlafaxine, whereas there was no benefit in studies against other TCAs (Table 2, Fig. 1).

Response rates

Table 3 shows the estimated response rates. The overall odds ratio for response was 1.27 (95% CI 1.07–1.52). The risk difference was 0.05 (95% CI 0.02–0.09), with an NNT of 19 (95% CI 11–63). The pooled results for different drug classes were similar to this overall effect (Fig. 2).

Remission rates

Table 4 and Fig. 3 display the pooled remission results. The overall odds ratio for remission rate was 1.36 (95% CI 1.14–1.61), favouring venlafaxine. The overall risk difference was 0.07 (95% CI 0.03–0.11), giving an NNT of 14 (95% CI 9–29).

Remission rates were measured in only 18 of the trials and, of these, 16 used an SSRI agent as the comparator. The result for the pooled SSRI comparison was similar to the overall effect.

None of the factors that were hypothesised to influence the estimate of primary outcome were significantly predictive of greater efficacy in meta-regression analyses (analysis not shown).

Meta-regression analysis and visual inspection of funnel plots provided no evidence of publication bias, although did not exclude the possibility of the existence of such bias.

Treatment discontinuation

Table 5 shows an analysis of drop-outs by reason and comparator drug class. The overall risk difference of −0.004 (95% CI −0.029 to 0.020) indicates that there are 0.4% fewer drop-outs overall in the venlafaxine group, and the difference is not statistically or clinically significant. The only statistically significant drop-out comparison exists for drop-outs due to side-effects compared with the 'other drug' category, where there is a risk difference of 0.221 (95% CI 0.065–0.376), giving an NNT of 5 (95% CI 3–15) in favour of

Table 3 Response analysis

Class	Comparator	Odds ratio	95% CI	Study
TCA	Amitriptyline	1.02	0.4–2.62	Gentil *et al*, 2000
	Pooled amitriptyline	1.02	0.4–2.62	
	Clomipramine	0.54	0.21–1.36	Smeraldi *et al*, 1998
	Clomipramine	1.92	0.8–4.64	Samuelian & Hackett, 1998
	Pooled clomipramine	1.02	0.57–1.83	
	Dothiepin	1.04	0.41–2.63	Mahapatra & Hackett, 1997
	Pooled dothiepin	1.04	0.41–2.63	
	Imipramine	1.72	1.04–2.87	Shrivastava *et al*, 1994
	Imipramine	0.76	0.39–1.47	Benkert *et al*, 1996
	Imipramine	2.55	1.1–6.14	Lecrubier *et al*, 1997
	Imipramine	2.18	0.79–6.14	Schweizer *et al*, 1994
	Pooled imipramine	1.51	1.10–2.07	
	Pooled TCA	1.29	0.89–1.85	
SSRI	Fluoxetine	0.99	0.55–1.78	Costa & Silva, 1998
	Fluoxetine	0.82	0.47–1.43	Tylee *et al*, 1997
	Fluoxetine	0.54	0.33–0.87	Dierick *et al*, 1996
	Fluoxetine	1.59	0.96–2.61	Rudolph *et al*, 1998
	Fluoxetine	1.29	0.74–2.27	Silverstone & Ravindran, 1999
	Fluoxetine	1.42	0.79–2.56	Schatzberg & Cantillon, 2000
	Fluoxetine	1.32	0.73–2.39	Rudolph & Feiger, 1999
	Fluoxetine	0.97	0.47–1.97	Unpublished data[1]
	Fluoxetine	2.63	1.2–5.82	Geerts *et al*, 1999
	Fluoxetine	1.44	0.6–3.5	Tzanakaki *et al*, 2000
	Fluoxetine	2.26	0.64–9.05	Alves *et al*, 1999
	Fluoxetine	2.67	0.86–8.45	Clerc *et al*, 1994
	Pooled fluoxetine	1.17	0.99–1.38	
	Fluvoxamine	1.41	0.51–3.82	Unpublished data[2]
	Pooled fluvoxamine	1.41	0.51–3.82	
	Paroxetine	1.01	0.58–1.75	McPartlin *et al*, 1998
	Paroxetine	1.49	0.68–3.29	Poirier & Boyer, 1999
	Paroxetine	1.15	0.43–3.07	Ballus *et al*, 2000
	Pooled paroxetine	1.14	0.78–1.67	
	Sertraline	2.27	0.88–6.08	Mehtonen *et al*, 2000
	Pooled sertraline	2.27	0.88–6.08	
	Pooled SSRI	1.26	1.02–1.58	
Other	Mirtazapine	0.65	0.33–1.31	Guelfi, 1999
	Pooled mirtazapine	0.65	0.33–1.31	
	Trazodone	1.7	0.78–3.75	Cunningham *et al*, 1994
	Trazodone	2.06	0.89–4.78	Smeraldi *et al*, 1998
	Pooled trazodone	1.88	1.11–3.17	
	Pooled 'other drug'	1.28	0.43–4.31	
	Overall pooled	1.27	1.07–1.52	

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
1. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.
2. Unpublished data: Hackett D., Salinas, E. & Desmet, A. (1998) Efficacy and safety of venlafaxine vs. fluvoxamine in outpatients with major depression (abstract P.I.210). IIth European Congress of Neuropsychopharmacology, Paris, France.

other drugs. However, because the overall difference in drop-out is equivalent, this result is countered by drop-out for all other causes.

DISCUSSION

Efficacy

This meta-analysis provides evidence that in the treatment of depressive disorders all antidepressants are not equal. Pooling data from all currently available studies reveals that venlafaxine carries an advantage of about 1.2 HRSD points over other antidepressants. The majority of comparisons were with SSRIs, where the effect appeared consistent across the different drugs. In contrast, it is less clear that the advantage is consistent across other antidepressants such as TCAs, where imipramine is the only individual drug that clearly demonstrates lesser efficacy. This does not, however, reduce the importance of the findings for the primary outcome measure – venlafaxine *v.* any other antidepressant in reducing symptoms of depression – in which a clear advantage was identified.

The results are of probable clinical significance, with an NNT of 19 (95% CI 11–63) for response and 14 (95% CI 9–29) for remission. The two data-sets do not include all of the same studies and are not as comprehensive as the data used in primary analysis of effect sizes, so the absolute figures must be viewed as approximate. However, this magnitude of advantage for venlafaxine over other antidepressants is potentially of considerable importance, given the often prolonged or even chronic nature of depressive episodes. It is increasingly recognised that improvement of depression on antidepressants is often incomplete or partial so that remission rates are relatively low (Ferrier, 1999) and only 42% of patients in the studies that we included achieved remission by the end of the study. Patients who fail to reach remission have significantly greater continuing morbidity and higher relapse rates than those who do experience remission (Cornwall & Scott, 1997). If only one extra person reaches remission when treated with venlafaxine instead of an SSRI for every 14 patients treated, then this is a potentially important health benefit. It suggests that even if not used first line, venlafaxine should be considered for

Table 4 Remission analysis

Class	Comparator	Odds ratio	95% CI	Study
TCA	Amitriptyline	1.03	0.46–2.32	Gentil *et al*, 2000
	Pooled amitriptyline	1.03	0.46–2.32	
	Pooled TCA	1.03	0.46–2.32	
SSRI	Fluoxetine	1.15	0.52–2.57	Costa & Silva, 1998
	Fluoxetine	1.06	0.61–1.85	Tylee *et al*, 1997
	Fluoxetine	1.49	0.9–2.47	Rudolph *et al*, 1998
	Fluoxetine	1.02	0.6–1.75	Silverstone & Ravindran, 1999
	Fluoxetine	1.8	0.97–3.35	Schatzberg & Cantillon, 2000
	Fluoxetine	2.03	1.04–3.99	Rudolph & Feiger, 1999
	Fluoxetine	1.43	0.59–3.51	Unpublished data[1]
	Fluoxetine	2.17	1.02–4.62	Geerts *et al*, 1999
	Fluoxetine	1.23	0.52–2.89	Tzanakaki *et al*, 2000
	Fluoxetine	1.5	0.57–3.92	Alves *et al*, 1999
	Pooled fluoxetine	1.42	1.17–1.73	
	Fluvoxamine	0.36	0.05–2.44	Zanardi *et al*,
	Pooled fluvoxamine	0.36	0.05–2.44	
	Paroxetine	1.09	0.69–1.71	McPartlin *et al*, 1998
	Paroxetine	1.59	0.89–2.82	Salinas, 1997
	Paroxetine	2.68	1.08–6.87	Poirier & Boyer, 1999
	Paroxetine	1.47	0.57–3.85	Ballus *et al*, 2000
	Pooled paroxetine	1.4	1.05–1.88	
	Sertraline	2.57	1.15–5.82	Mehtonen *et al*, 2000
	Pooled sertraline	2.57	1.15–5.82	
	Pooled SSRI	1.43	1.21–1.71	
Other	Mirtazapine	0.69	0.33–1.43	Guelfi, 1999
	Pooled mirtazapine	0.69	0.33–1.43	
	Pooled 'other drug'	0.69	0.33–1.43	
	Overall pooled	1.36	1.14–1.61	

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
1. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.

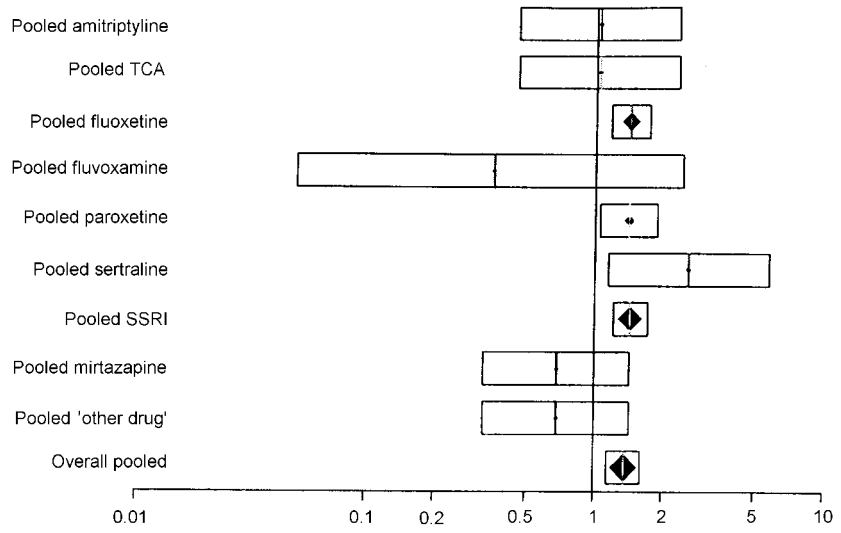

Fig. 3 Plot of pooled remission rate on venlafaxine compared with other antidepressants. The bars show the odds ratio and the 95% CI. Results falling to the right of the line of no effect (1) indicate an advantage to venlafaxine.

Table 5 Drop-out analysis by cause and drug class

	Risk difference (venlafaxine minus comparator)	Lower CL	Upper CL	NNT[1]	Lower CL	Upper CL
All causes						
All drugs	−0.004	−0.029	0.020	−224	−34	49
SSRI	0.002	−0.025	0.029	494	−40	34
TCA	−0.028	−0.089	0.033	−36	−11	30
Other drug	−0.080	−0.196	0.035	−12	−5	28
Unsatisfactory response						
All drugs	−0.006	−0.016	0.004	−159	−62	275
SSRI	−0.008	−0.019	0.003	−123	−52	350
TCA	0.003	−0.020	0.026	341	−50	39
Other drug	−0.032	−0.123	0.059	−31	−8	17
Side-effects						
All drugs	0.010	−0.007	0.026	105	−141	38
SSRI	0.017	−0.006	0.040	60	−161	25
TCA	−0.025	−0.070	0.020	−40	−14	51
Other drug	0.221	0.065	0.376	5	15	3

CL, confidence limit; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
1. A negative number needed to treat (NNT) represents the number of people that, when treated with venlafaxine, will lead to one fewer expected drop-outs *v.* the comparator (e.g. for all drugs and all causes of drop-out, it is expected that for every 224 people treated with venlafaxine there will be one fewer drop-outs compared with other therapies). A positive NNT represents the number of people that, when treated with venlafaxine, will lead to one more expected drop-out *v.* the comparator (e.g. for SSRI, all causes, it is expected that when 494 people are treated with venlafaxine, there will be one more drop-out in the venlafaxine-treated patients).

patients having an inadequate response to other antidepressants.

Our study confirms the more limited meta-analysis recently reported by Thase *et al* (2001), which only included a small subset (eight) of studies against SSRIs and therefore cannot be considered systematic. It only assessed efficacy using remission rates with an odds ratio of 1.5 (95% CI 1.3–1.9) in favour of venlafaxine. The NNT was not calculated formally but appears to be about 10 from the difference in remission rates (45% *v.* 35%); this is a greater advantage to venlafaxine than we found with a larger data-set.

Our analysis of the tolerability of venlafaxine as measured by total treatment drop-outs and those due to side-effects did not suggest that greater efficacy was offset by poorer tolerability overall or against SSRIs or TCAs. More patients dropped out of treatment owing to side-effects on venlafaxine than trazodone or mirtazapine, suggesting poorer tolerability than these drugs, but the small number of studies makes it difficult to draw conclusions.

Mechanism underlying venlafaxine's greater efficacy

We have reported previously being unable to identify a relationship between pharmacology and efficacy using a meta-regression analysis of a variety of antidepressants compared with SSRIs (Freemantle *et al*, 2000). There were, however, considerable problems in that analysis, relating to being able to identify accurately the acute pharmacology of many antidepressants *in vivo*. In this study some of these problems are overcome through using a single agent and it appears that the most plausible mechanism by which venlafaxine may exert increased efficacy in comparison with SSRIs is its ability to inhibit not only 5-HT reuptake but also the reuptake of noradrenalin (Holliday & Benfield, 1995). Whether this is the mechanism in the case of venlafaxine has yet to be confirmed, however. The profile of its binding to human monoamine transporters suggests a weak affinity for the noradrenalin transporter compared with the 5-HT transporter (Owens *et al*, 1997; Tatsumi *et al*, 1997). At lower doses, venlafaxine appears to act as an SSRI and it is unclear at what dose significant noradrenalin effects occur. Preliminary evidence suggests that, at least outside the brain, this is somewhere between 75 and 225 mg, with one study suggesting that it may occur by 150 mg (Abdelmawla *et al*, 1999). It is of interest that previous meta-analyses have suggested superior efficacy for amitriptyline against other antidepressants, particularly SSRIs (Anderson, 2000; Barbui & Hotopf, 2001), which adds some support to dual action conferring greater efficacy than occurs when blocking the reuptake of a single transmitter.

We did not find an effect of dose on the size of the advantage to venlafaxine over SSRIs, raising some question as to the mechanism underlying its greater efficacy. However, the studies in this meta-analysis were not designed to detect dose–response effects, most employing flexible dosing. The lack of an association between efficacy and a venlafaxine dose below or above 150 mg is probably against a strong linear dose–response over the range used but cannot rule out a non-linear relationship. Two fixed-dose studies of venlafaxine against placebo have suggested a dose–response over the range 60–225 mg (Kelsey, 1996; Rudolph *et al*, 1998), but the differentiation between doses has not been statistically significant and the dose at which any possible greater efficacy may arise is not clear.

Methodological considerations

The major methodological challenge to all systematic overviews is publication bias – the selective availability of trials with positive results. The comprehensive search strategies used to identify trials, the

systematic attempts to identify unpublished trials and unpublished data and examination of the distribution of the results from included trials all mediate against the importance of this threat to the validity of the results of this overview. However, it has to be acknowledged that the majority of studies were sponsored by the company that markets venlafaxine and sponsorship has been suggested as a potential factor influencing the outcome of the trials (Stewart & Parmar, 1996; Freemantle *et al*, 2000).

Although over 5000 patients were included in the trials identified for this meta-analysis, this number is small against other clinical areas where this number of patients commonly may be included in a single trial. Further randomised trials, including those of a naturalistic design, involving larger numbers of patients in different clinical settings (particularly primary care, where the majority of treatment for major depressive disorder is conducted) are required to find out how generalisable this result is to different settings and whether venlafaxine has increased effectiveness in usual clinical practice.

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APPENDIX

Studies included in the meta-analysis

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CLINICAL IMPLICATIONS

- The findings from this systematic review and meta-analysis provide some confidence that venlafaxine is more effective than selective serotonin reuptake inhibitors (SSRIs) with comparable tolerability.
- The size of this advantage is of probable clinical importance when the prolonged or chronic nature of depression is taken into account.
- Venlafaxine should be considered for patients in whom efficacy needs to be maximised and in those failing to respond to an SSRI.

LIMITATIONS

- Apart from the comparison with fluoxetine, there are insufficient comparisons between venlafaxine and individual SSRIs and other antidepressants to draw strong conclusions with regard to specific comparisons.
- Meta-analysis is dependent on the quality of individual studies included in the analysis.
- Drop-outs are a relatively crude proxy for tolerability.

DAVID SMITH, PhD, Kaiser Center for Health Research, Portland, Oregon, USA; CARRIE DEMPSTER, MSc, University of Dumfries and Galloway, Scotland; JULIE GLANVILLE, MSc, NHS Centre for Reviews and Dissemination, University of York; NICK FREEMANTLE, PhD, Department of Primary Care & General Practice, University of Birmingham; IAN ANDERSON, MD, Neuroscience and Psychiatry Unit, University of Manchester, UK

Correspondence: Nick Freemantle, Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Tel: +44 (0)121 414 7943; fax: +44 (0)121 414 6571; e-mail: N.Freemantle@bham.ac.uk

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