

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

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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

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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

Table 1 Description of included trials¹

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		Unpublished data ²	37		203	175	40	70	LOCF	Out-patient
Paroxetine		Unpublished data ³	38		196	150	NA	NA	LOCF	Out-patient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	Unpublished data ⁴	43	2	68	200	51	68	LOCF	In-patient	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

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

- 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.
- 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.
- Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.
- 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.
- 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 <i>et al</i> , 2000	
	Pooled amitriptyline	0.26	-0.10 to 0.63		
	Clomipramine	0.05	-0.32 to 0.42	Smeraldi <i>et al</i> , 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 <i>et al</i> , 1998	
	Pooled dothiepin	-0.08	-0.40 to 0.24		
	Imipramine	-0.4	-0.64 to -0.16	Shrivastava <i>et al</i> , 1994	
	Imipramine	-0.32	-0.65 to 0.02	Schweizer <i>et al</i> , 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 <i>et al</i> , 1997
Fluoxetine		-0.18	-0.40 to 0.04	Dierick <i>et al</i> , 1996	
Fluoxetine		-0.14	-0.37 to 0.09	Rudolph <i>et al</i> , 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 <i>et al</i> , 1999	
Fluoxetine		-0.08	-0.46 to 0.3	Tzanakaki <i>et al</i> , 2000	
Fluoxetine		-0.34	-0.77 to 0.1	Alves <i>et al</i> , 1999	
Fluoxetine		-0.58	-1.06 to -0.09	Clerc <i>et al</i> , 1994	
Pooled fluoxetine		-0.14	-0.22 to -0.06		
Fluvoxamine		0.56	-0.23 to 1.34	Zanardi <i>et al</i> , 2000	
Pooled fluvoxamine		0.56	-0.23 to 1.34		
Paroxetine		-0.1	-0.31 to 0.12	McPartlin <i>et al</i> , 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 <i>et al</i> , 2000	
Pooled paroxetine	-0.19	-0.34 to -0.05			
Sertraline	-0.31	-0.67 to 0.06	Mehtonen <i>et al</i> , 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 <i>et al</i> , 1994	
	Trazodone	-0.37	-0.74 to 0.01	Smeraldi <i>et al</i> , 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 P1.066). 11th 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). XX1th 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.

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 total¹: 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

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.

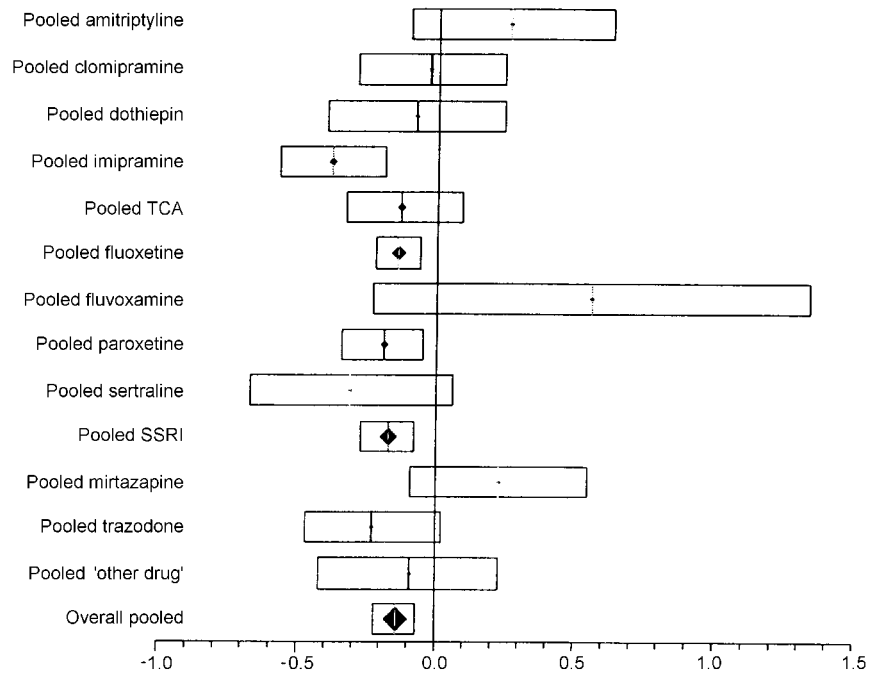


Fig. 1 Plot of pooled efficacy of venlafaxine compared with other antidepressants. The bars show the effect size (difference in final rating scale score divided by pooled final standard deviation) and the 95% CI. Results falling to the left of the line of no effect (zero) indicate an advantage to venlafaxine.

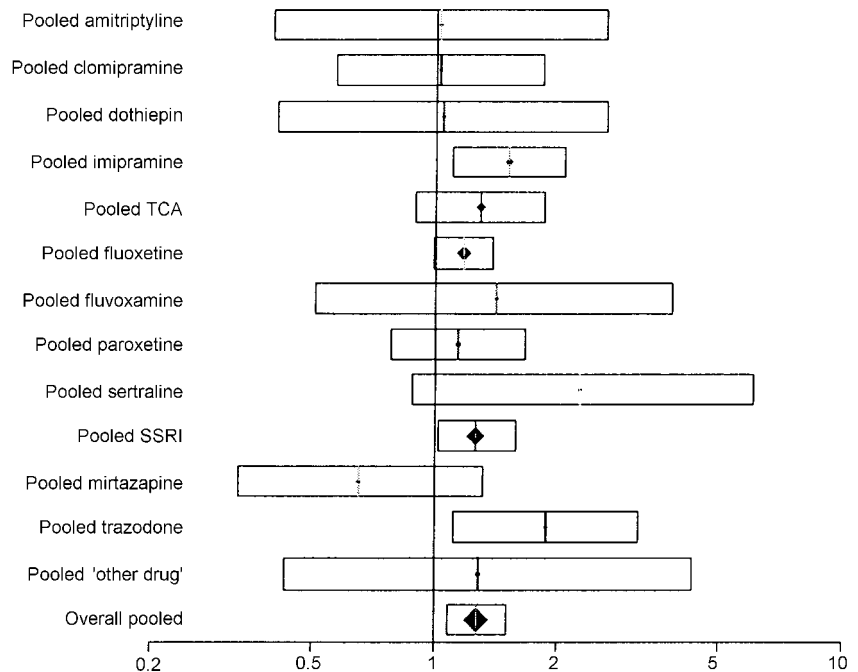


Fig. 2 Plot of pooled response rate to venlafaxine compared with other antidepressants. The bars show the odds ratio and the 95% CI. Results falling to the right of the line of no effect (1) indicate an advantage to venlafaxine.

available and could not be obtained from the authors or sponsors. None of the trials indicated whether concealment of allocation was conducted appropriately.

Primary outcome

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

(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

Table 3 Response analysis

Class	Comparator	Odds ratio	95% CI	Study
TCA	Amitriptyline	1.02	0.4–2.62	Gentil <i>et al</i> , 2000
	Pooled amitriptyline	1.02	0.4–2.62	
	Clomipramine	0.54	0.21–1.36	Smeraldi <i>et al</i> , 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 <i>et al</i> , 1994
	Imipramine	0.76	0.39–1.47	Benkert <i>et al</i> , 1996
	Imipramine	2.55	1.1–6.14	Leclubier <i>et al</i> , 1997
	Imipramine	2.18	0.79–6.14	Schweizer <i>et al</i> , 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 <i>et al</i> , 1997
	Fluoxetine	0.54	0.33–0.87	Dierick <i>et al</i> , 1996
	Fluoxetine	1.59	0.96–2.61	Rudolph <i>et al</i> , 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 <i>et al</i> , 1999
	Fluoxetine	1.44	0.6–3.5	Tzanakaki <i>et al</i> , 2000
	Fluoxetine	2.26	0.64–9.05	Alves <i>et al</i> , 1999
	Fluoxetine	2.67	0.86–8.45	Clerc <i>et al</i> , 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 <i>et al</i> , 1998
	Paroxetine	1.49	0.68–3.29	Poirier & Boyer, 1999
Paroxetine	1.15	0.43–3.07	Ballus <i>et al</i> , 2000	
Pooled paroxetine	1.14	0.78–1.67		
Sertraline	2.27	0.88–6.08	Mehtonen <i>et al</i> , 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 <i>et al</i> , 1994
	Trazodone	2.06	0.89–4.78	Smeraldi <i>et al</i> , 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.1.210). 11th European Congress of Neuropsychopharmacology, Paris, France.

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

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 <i>et al</i> , 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 <i>et al</i> , 1997
	Fluoxetine	1.49	0.9–2.47	Rudolph <i>et al</i> , 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 <i>et al</i> , 1999
	Fluoxetine	1.23	0.52–2.89	Tzanakaki <i>et al</i> , 2000
	Fluoxetine	1.5	0.57–3.92	Alves <i>et al</i> , 1999
	Pooled fluoxetine	1.42	1.17–1.73	
	Fluvoxamine	0.36	0.05–2.44	Zanardi <i>et al</i> ,
	Pooled fluvoxamine	0.36	0.05–2.44	
	Paroxetine	1.09	0.69–1.71	McPartlin <i>et al</i> , 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 <i>et al</i> , 2000
	Pooled paroxetine	1.4	1.05–1.88	
	Sertraline	2.57	1.15–5.82	Mehtonen <i>et al</i> , 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). XXlth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.

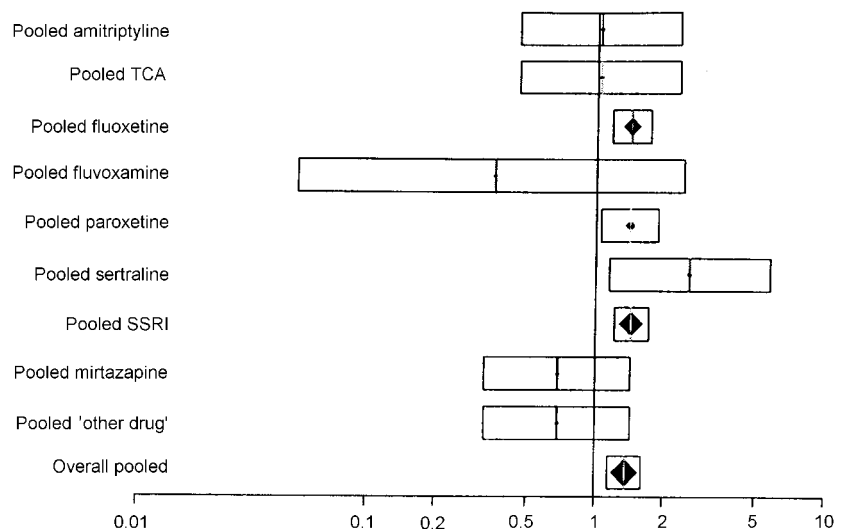


Fig. 3 Plot of pooled remission rate on venlafaxine compared with other antidepressants. The bars show the odds ratio and the 95% CI. Results falling to the right of the line of no effect (1) indicate an advantage to venlafaxine.

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.

REFERENCES

- Abdelmawla, A., Langley, R., Szabadi, E., et al (1999)** Comparison of the effects of venlafaxine, desipramine and paroxetine on noradrenalin and methoxamine evoked constriction of the dorsal hand vein. *British Journal of Clinical Pharmacology*, **48**, 345–354.
- American Psychiatric Association (1994)** *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). Washington, DC: APA.
- Anderson, I. M. (2000)** Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disorders*, **58**, 19–36.
- , **Nutt, D. J. & Deakin, J. F. W. (2000)** Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, **14**, 3–20.
- Barbui, C. & Hotopf, M. (2001)** Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. *British Journal of Psychiatry*, **178**, 129–144.
- Cornwall, P. & Scott, J. (1997)** Partial remission in depressive disorders. *Acta Psychiatrica Scandinavica*, **95**, 265–271.
- DerSimonian, R. & Laird, N. (1986)** Meta-analysis in clinical trials. *Controlled Clinical Trials*, **7**, 177–188.
- Eccles, M., Freemantle, N. & Mason, J. (2000)** The choice of antidepressants for depression in primary care. *Family Practice*, **16**, 103–111.
- Edwards, G. (1992)** Selective serotonin reuptake inhibitors: a modest though welcome advance in the treatment of depression. *BMJ*, **304**, 1644–1645.
- Ferrier, N. (1999)** Treatment of major depression: is improvement enough? *Journal of Clinical Psychiatry*, **60** (suppl. 6), 10–14.
- Freemantle, N., Cleland, J., Young, P., et al (1999)** What is the current place of β -blockade in secondary prevention after myocardial infarction? A systematic overview and meta regression analysis. *BMJ*, **318**, 1730–1737.
- , **Anderson, I. M. & Young, P. (2000)** Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs. Meta-regression analysis. *British Journal of Psychiatry*, **177**, 292–302.
- Geddes, J. R., Freemantle, N., Mason, J., et al (2001)** SSRIs versus alternative antidepressants for depressive disorders. *Cochrane Library*, issue 1. Oxford: Update Software.
- Gross, G. & Huber, G. (1999)** How far are newer antidepressants an advance compared with classical antidepressants? *Neurology, Psychiatry and Brain Research*, **7**, 79–86.
- Guy, W. (1976)** *ECDEU Assessment Manual for Psychopharmacology*. Revised DHEW Pub. (ADM). Rockville, MD: National Institute for Mental Health.
- Hamilton, M. (1960)** A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.
- Heninger, G., Delgado, P. & Charney, D. (1996)** The revised monoamine theory of depression: a modulatory role of monoamines, based on new findings from monoamine depletion experiments in humans. *Pharmacopsychiatry*, **29**, 2–11.
- Holliday, S. M. & Benfield, P. (1995)** Venlafaxine. A review of its pharmacology and therapeutic potential in depression. *Drugs*, **49**, 280–294.
- Kelsey, J. (1996)** Dose–response relationship with venlafaxine. *Journal of Clinical Psychopharmacology*, **16** (suppl. 2), 21S–26S.
- Montgomery, S. A. & Åsberg, M. (1979)** A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, **134**, 382–389.
- Murray, C. & Lopez, A. (1997)** Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet*, **349**, 1436–1442.
- Nelson, J., Mazure, C., Bowers, M., et al (1991)** A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Archives of General Psychiatry*, **48**, 303–307.
- Owens, M., Morgan, W., Plott, S., et al (1997)** Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *Journal of Pharmacological Experimental Therapies*, **283**, 1305–1322.
- Rudolph, R., Fabre, L., Feighner, J., et al (1998)** A randomised, placebo-controlled, dose–response trial of venlafaxine hydrochloride in the treatment of major depression. *Clinical Psychiatry*, **59**, 116–122.
- Seth, R., Jennings, A. L., Bindman, J., et al (1992)** Combination treatment of noradrenalin and serotonin reuptake inhibitors in resistant depression. *British Journal of Psychiatry*, **161**, 562–565.
- Smith, T., Spiegelhalter, D. & Thomas, A. (1995)** Bayesian approaches to random-effects meta-analysis: a comparative study. *Statistics in Medicine*, **14**, 2685–2699.
- Stewart, L. A. & Parmar, M. K. B. (1996)** Bias in the analysis and reporting of randomized controlled trials. *International Journal of Technology Assessment in Health Care*, **12**, 264–275.
- Tatsumi, M., Groshan, K., Blakely, R., et al (1997)** Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *European Journal of Pharmacology*, **340**, 249–258.
- Thase, M. E., Entsuah, A. R. & Rudolph, R. L. (2001)** Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *British Journal of Psychiatry*, **178**, 234–241.

APPENDIX

Studies included in the meta-analysis

- Alves, C., Cachola, I. & Brandao, J. (1999)** Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. *Primary Care Psychiatry*, **5**, 57–63.
- Ballus, C., Quiros, G., de-Flores, T., et al (2000)** The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder of dysthymia. *International Clinical Psychopharmacology*, **15**, 43–48.
- Benkert, O., Gruender, G., Wetzel, H., et al (1996)** A randomised, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. *Journal of Psychiatric Research*, **30**, 441–451.
- Clerc, G. E., Ruimy, P. & Verdeau, P. J. (1994)** A double-blind comparison of venlafaxine and fluoxetine in patients hospitalised for major depression and melancholia. *International Clinical Psychopharmacology*, **9**, 139–143.
- Costa, E. & Silva, J. (1998)** Randomised, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *Journal of Clinical Psychiatry*, **59**, 352–357.
- Cunningham, L., Borison, R., Carman, J., et al (1994)** A comparison of venlafaxine, trazodone and placebo in major depression. *Journal of Clinical Psychopharmacology*, **14**, 99–106.
- Dierick, M., Ravizza, L., Realini, R., et al (1996)** A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **20**, 57–71.
- Geerts, S., Lacante, P. & Migon, A. (1999)** Venlafaxine versus fluoxetine in the treatment of depressed patients with concomitant anxiety. *Journal of the European College of Neuropsychopharmacology*, **9** (suppl. 5), S224.
- Gentil, V., Kerr-Correa, F., Moreno, R., et al (2000)** Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. *Journal of Psychopharmacology*, **14**, 61–66.
- Guelfi, J. D. (1999)** *Efficacy and Tolerability of Mirtazapine versus Venlafaxine in Hospitalised, Severely Depressed Patients with Melancholia* [Abstract]. London: Association of Clinical Neuropsychopharmacology.
- Leclercq, Y., Bourin, M., Moon, C.-A.L., et al (1997)** Efficacy of venlafaxine in depressive illness in general practice. *Acta Psychiatrica Scandinavica*, **95**, 485–493.
- McPartlin, G. M., Reynolds, A., Anderson, C., et al (1998)** A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. *Primary Care Psychiatry*, **6**, 127–132.
- Mahapatra, S. N. & Hackett, D. (1997)** A randomised, double-blind, parallel-group comparison of venlafaxine and dothiepin in geriatric patients with

major depression. *International Journal of Clinical Practice*, **51**, 209–213.

Mehtonen, O., Sogaard, J., Roponen, P., et al (2000) Randomised, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. *Journal of Clinical Psychiatry*, **61**, 95–100.

Poirier, M. F. & Boyer, P. (1999) Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *British Journal of Psychiatry*, **175**, 12–16.

Rudolph R., Fabre, L., Feighner, J., et al (1998) A randomised, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. *Clinical Psychiatry*, **59**, 116–122.

— & Feiger, A. (1999) A double-blind, randomised, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *Journal of Affective Disorders*, **56**, 171–181.

Salinas, E. (1997) Once-daily venlafaxine XR versus paroxetine outpatients with major depression. *Biological Psychiatry*, **42** (suppl. 1), 297S.

Samuelian, J. C. & Hackett, D. (1998) A randomised, double-blind, parallel-group comparison of venlafaxine and clomipramine in outpatients with major depression. *Journal of Psychopharmacology*, **12**, 273–278.

Schatzberg, A. & Cantillon, M. (2000) Antidepressant early response and remission with venlafaxine or fluoxetine in depressed geriatric patients. *International Journal of Neuropsychopharmacology*, **3** (suppl. 1), S191.

Schweizer, E., Feighner, J., Mandos, L. A., et al (1994) Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. *Journal of Clinical Psychiatry*, **55**, 104–108.

Shrivastava, R. K., Cohn, C., Crowder, J., et al (1994) Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression. *Journal of Clinical Psychopharmacology*, **14**, 322–329.

Silverstone, P. H. & Ravindran, A. (1999) Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. *Journal of Clinical Psychiatry*, **60**, 22–28.

Smeraldi, E., Rizzo, F. & Crespi, G. (1998) Double-blind, randomised study of venlafaxine, clomipramine and trazodone in geriatric patients with major depression. *Primary Care Psychiatry*, **4**, 189–195.

Stanley, N., Kimber, S., Fairweather, D., et al (1998) Venlafaxine and dothiepin in depressed patients: a comparison of efficacy and effect on cognition and subjective sleep [Abstract P1044]. *11th European Congress of Neuropsychopharmacology*. Paris, France.

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.

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Tylee, A., Beaumont, G., Bowden, M. W., et al (1997) A double-blind, randomised, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe depression in general practice. *Primary Care Psychiatry*, **3**, 51–58.

Tzanakaki, M., Guazzelli, M., Nimatoudis, I., et al (2000) Increased remission rates with venlafaxine

compared with fluoxetine in hospitalised patients with major depression and melancholia. *International Clinical Psychopharmacology*, **15**, 29–34.

Zanardi, R., Franchini, L., Serretti, A., et al (2000) Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study. *Journal of Clinical Psychiatry*, **61**, 26–29.