A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care

Alan J Lenox-Smith, Alan Reynolds

SUMMARY

Background: *Generalised anxiety disorder (GAD) is one of the commonest anxiety disorders and is treated almost entirely in primary care. Most recent studies performed in GAD have excluded depression for regulatory reasons. As GAD is usually a co-morbid disease, often co-existing with depression, the results from recent studies have only limited relevance to the naturalistic population. This study was set up to investigate venlafaxine XL in a more naturalistic population of patients with GAD.*

Aim: *To assess the efficacy of venlafaxine XL in patients with generalised anxiety disorder with and without co-morbid depression.*

Design of study: *Double-blind, randomised, placebo controlled, parallel-group, 24–week study.*

Setting: *Primary care in the UK.*

Methods: *Patients enrolled in the study were over 18 years old, met DSM-IV criteria for GAD, and had a score of 20 or more on the Hamilton Anxiety Scale (HAM-A). A score of more than 23 on the Montgomery Asberg Depression Rating Scale (MADRS) excluded patients. Eligible patients were randomised to receive 75 mg of venlafaxine or a matching placebo. After 2 weeks the dose could be doubled if the physician considered the response to be poor. The study duration was 24 weeks.*

Results: *244 patients were enrolled, with 122 randomised to the placebo and 122 to venlafaxine. Baseline characteristics were similar for both groups, each having a mean total HAM-A score at baseline of 28. The difference from the placebo group at 24 weeks on the total HAM-A score was 2.1 points (95% 0 to 4.2), which was statistically significant (*P = *0.05). Remission rates at week 24 were 27.9% for the venlafaxine XL group and 18.9% for placebo group (*P = *0.11).*

Conclusion: *Venlafaxine was efficacious in the treatment of patients with GAD with and without depression over a 24–week period.*

Keywords: *venlafaxine XL; generalised anxiety disorder; randomised controlled trial; depression.*

A J Lenox-Smith, MRCP, FFPM, senior medical adviser; A Reynolds, scientific affairs manager, Wyeth Pharmaceuticals, UK.

Address for correspondence:

Alan Lenox-Smith, Medical Department, Wyeth Pharmaceuticals, Huntercombe Lane South, Taplow, SL6 0PH. E-mail: Lenoxsa@wyeth.com

Submitted: 19 August 2002; Editor's response: 2 January 2003; final acceptance: 24 June 2003.

Introduction

AS currently defined in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[1], generalised anxiety disorder (GAD) is a chronic and disabling disorder which is dangerous for the sufferer in terms of suicidal ideation and life choices, and not, as it is often perceived, a trivial illness. In the DSM-IV, GAD is characterised as a chronic state of anxiety and uncontrollable worry (apprehensive expectation) concerning multiple daily-life events or activities, accompanied by at least three symptoms belonging to a list of six common manifestations of psychic or motor tension. The pathological worry that characterises and differentiates GAD is different from normal: patients with GAD worry about minor things that normal people do not worry about.[2] The anxiety and worry are distressing and/or disabling and are recognised by the sufferer and others as excessive compared to the thoughts and feelings of most other people in similar situations.

The prognosis of patients with GAD is unfavourable. Its course is chronic, frequently beginning in patients' early twenties,[3-5] persisting over years[6] or even decades,[7] and being either constant or fluctuating with spontaneous improvement and relapse.[8-10] The remission rate would appear to be low, of the order of 15% at 1 year and increasing to 25% at 2 years.[3]

Patients with GAD tend to have poor social functioning. In the Harvard–Brown Anxiety Research Programme (HARP) study,[3] more than a third of the patients with GAD never married. Patients were also under-employed, compared with the general population, and 37% were receiving social security.

In the HARP study, 13% of the patients with GAD had made a suicide attempt or gesture.[11] The presence of suicidal ideation has also been shown to be closely related to the presence of GAD — as it is for depression.[12] A study by Allgulander and Lavori[13] looked at the effect of 'pure anxiety' on mortality in a group of patients who had been hospitalised with 'pure' anxiety neurosis. Using record-linkage, a significant excess of deaths from suicide was found in these patients, leading the investigators to conclude that the risk of suicide is just as high for inpatients with anxiety disorders as it is for patients with depression. The prevalence of GAD in the general population appears to be of the order of 3% in the UK.[14] GAD is associated with a wide spectrum of other mental disorders, and co-morbid diagnoses are common.

Venlafaxine is a selective serotinergic and noradrenergic

HOW THIS FITS IN

What do we know?

It has already been established that venlafaxine XL is efficacious in generalised anxiety disorder (GAD) and separately in depression in rigidly controlled studies.

What does this paper add?

This is the first study to show that venlafaxine XL is effective in a more naturalistic population suffering primarily from GAD with or without depression drawn from a population from primary care in the UK.

re-uptake inhibitor (SNRI) that has been licensed for depression in the UK since 1995. More recently, in 2001, a licence for venlafaxine was approved for GAD. This licence was based on five studies, all of which, for regulatory reasons, excluded patients who had concurrent depression. Four[15-18] of the five studies have been published in full, and the fifth[19] has been presented as a poster.

Most patients with GAD will have some co-morbid mental illness, the commonest form being depression, and this study was set up to study typical patients with GAD in the UK primary care setting, who might or might not have associated depression.

Method

The research was structured around a double-blind, randomised, multi-centre, placebo controlled parallel group, with patients recruited from primary care. All included patients were required to have a principal diagnosis of GAD (DSM-IV criteria), a minimum score of 20 on the HAM-A, and to be able and willing to give informed consent. Males and females aged 18 years and over were allowed to participate. Exclusion criteria included mania or psychotic illnesses, post-traumatic stress disorder (PTSD), a history of alcoholism or drug abuse, pregnancy, a Montgomery Asberg Depression Rating Scale (MADRS) score equal to or more than 23, and suicidal ideation. Other psychopharmacologically active drugs (antipsychotics, antidepressants, other anxiolytics, and lithium) were not allowed during the duration of the study, with the exception of zopiclone and zolpidem for insomnia. Sumatriptan (and other $5HT_1$ agonists) were not allowed. Formal psychotherapy; for example, cognitive behavioural therapy, was not allowed.

Intervention

At the baseline visit (there was no single-blind lead-in phase) suitable patients were randomised to receive venlafaxine XL or a placebo in a double-blind fashion. The dose of venlafaxine XL was initially 75 mg daily (or one placebo), although this could be increased any time after 2 weeks to 150 mg (or two placebos), and then reduced again if there were any tolerability issues. At the end of 24 weeks all patients on 150 mg of venlafaxine were reduced to 75 mg daily for a week, and then all patients received a placebo for a second week.

Efficacy assessments

Efficacy was assessed by the HAM-A (primary endpoint), the Hospital Anxiety Depression (HAD), the MADRS, and the Clinical Global Impression (CGI) scales, which were administered at baseline, 2, 4, 8, 16 and 24 weeks. In addition, the SF36 (quality of life) scale was administered at baseline, 8 and 24 weeks. Safety was assessed by routine physical examinations, which included pulse and blood pressure readings at every visit. A pregnancy test was performed at the baseline visit in women of child-bearing potential. Adverse events were recorded at every visit after the baseline visit.

Statistics

Analyses were performed on an intention-to-treat basis with last observations carried forward. Power calculations suggested that 172 patients would be required to detect a four-point difference in the HAM-A total score between the two groups, with 90% power using a two-sided test at 5% level. To allow for non-evaluable patients, the aim was to recruit 200 patients in total. Randomisation was by randomly permuted blocks that had been generated centrally. The study was double-blind with matching placebos and active medication. All analyses/summaries were produced using SAS® Version 6.12 for Windows. Analysis of continuous efficacy data was performed using analysis of co-variance (ANCOVA) via the general linear models (GLM) SAS procedure. Type III sums of squares were used for all significance tests. ANCOVA models had baseline value, centre (pooled) and treatment fitted. In order to determine the heterogeneity of the treatment effect across centre, the treatment-by-centre (pooled) interaction term was investigated. The interaction term was dropped from the model if found not to be statistically significant at the 5% level. In the presence of a significant interaction, further analysis/summary was performed in order to find a suitable explanation. Residual plots were used to check normality assumptions. If these were not satisfied, then for those analyses a suitable transformation or non-parametric procedure was sought.

Ethics

The study was performed in accordance with Good Clinical Practice, the Declaration of Helsinki, and local regulations. It was approved by the Anglia and Oxford Multiple Research Ethics Committee and all local research ethics committees.

Results

Demographics

A total of 244 patients were randomised into the study from 31 centres, with 122 assigned to venlafaxine and 122 assigned to the placebo, and all of the above are included in the intention-to-treat analysis. The main demographics are shown in Table 1.

All the patients randomised to venlafaxine received active medication, but only 121 patients on the placebo received medication, as one patient did not take any medication after the second week, although this patient completed the study. All 244 patients are included in the intention-to-treat analysis; 204 patients completed the study (Figure 1).

Table 1. Baseline demographics

	Venlafaxine XL group *n* = 122	Placebo group *n* = 122
Mean age in years (range)	48 (21–79)	46 (19–76)
Mean duration of episode in months	61	63
Female/male	75/47	69/53
Mean HAM-A total	28	28
Mean MADRS total	16	16

Efficacy

The primary efficacy rating scale was the total HAM-A. These results are shown in Figure 2, and it can be seen that although venlafaxine had superior efficacy to the placebo early on, this only became statistically significant by the end of the study with a difference of 2.1 (95% confidence interval [CI] = 0 to 4.2; $P = 0.05$) points at week 24.

The patient-completed total HAD scores showed a size of effect (difference between venlafaxine and placebo) favouring venlafaxine of 2.7 (95% CI = 0.8 to 4.5) points at week 8 ($P = 0.005$) and 2.6 (95% CI = 0.6 to 4.7) points at week 24 ($P = 0.013$). The MADRS was also analysed, even though patients were not that depressed (they should have been excluded if their MADRS was more than 23) and showed only a modest size of effect favouring venlafaxine of 1.5 (95% CI = 0.1 to 3.1) at week 8 ($P = 0.072$) and 1.8 (95% CI = 0 to 3.7) at week 24 ($P = 0.053$).

As patients with GAD primarily suffer from 'worry' and 'anxiety', the HAM-A psychic anxiety (items 1 to 6 and 14) scores were analysed and are shown in Figure 3.

It can be seen from Figure 3 that the core symptoms of anxiety have improved by week 8 ($P = 0.038$), and this improvement is maintained and increases further as time goes on, for up to 6 months ($P = 0.07$).

Clinical interpretation

In order to put the above into a clinical context, response (50% reduction in rating scale) and remission (HAM-A total score 7) rates were analysed. Response rates were not statistically significant at weeks 8 or 24, and by week 24, 52.5% of patients on venlafaxine had responded, compared with 48.4% on the placebo ($P = 0.61$). With regards to remission, even though there were around 50% more patients in remission at weeks 8 and 24 on venlafaxine than on the placebo, these were not statistically significant. Remission rates were 13.1% and 8.2% (giving a number needed to treat [NNT] of 20) for week 8 ($P = 0.24$), and 27.9% and 18.9% (NNT of 11) for week 24 ($P = 0.11$) for venlafaxine and the placebo, respectively. The CGI was originally developed as a 'clinically relevant' scale, and response is often defined as a value of 1 (very much improved) or 2 (much improved). Using this definition, 59% of patients on venlafaxine had responded by week 8, compared to 37% patients on the placebo ($P = 0.001$), and by week 24, 65% of patients had responded on venlafaxine compared to 46% on the placebo ($P = 0.003$).

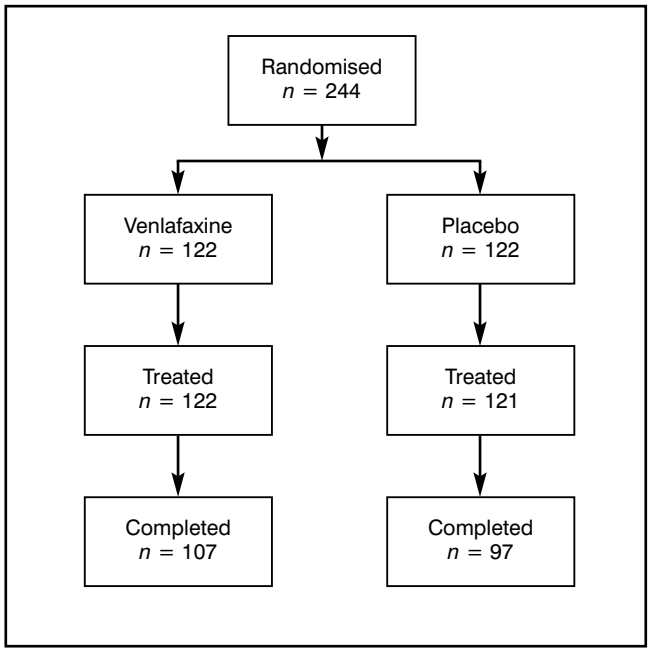

Figure 1. Flow chart describing progress of patients through the trial.

Dose of medication

The mean dose at the end of the study was 110 mg of venlafaxine for those on the active drug, and the equivalent of 129 mg venlafaxine for those on the placebo. More patients on the placebo (80/121 [66%]) had their dose increased than those on venlafaxine (54/122 [44%]), which was statistically significant ($P < 0.001$) and is a further indicator of efficacy.

Quality of life

The SF36 questionnaire can be divided into the following items: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. The only domains in which venlafaxine came out consistently statistically significantly superior to the placebo at weeks 8 and 24 were vitality and mental health. In all the other areas, except for physical functioning, venlafaxine produced more favourable scores than the placebo, which either approached or reached statistical significance at either week 8 or 24. See Table 2.

Safety

The majority of patients (92% of patients on venlafaxine and 90% of patients on the placebo) reported at least one adverse event, and a total of 874 adverse events were reported in total. The commonest adverse events are shown in Table 3.

As can be seen, the profile of adverse events in patients with GAD is very similar to that seen in depression, with nausea and sweating being seen more commonly with venlafaxine compared to the placebo.

There were nine serious adverse events in this study: four in the patients on venlafaxine and five in the patients on the placebo. None of the serious adverse events was consid-

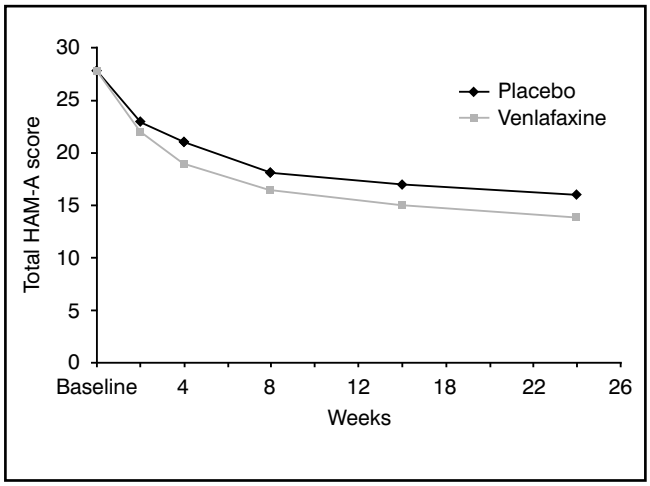

Figure 2. HAM-A score ITT. P = *0.1 at 8 weeks, and* P = *0.05 at 24 weeks.*

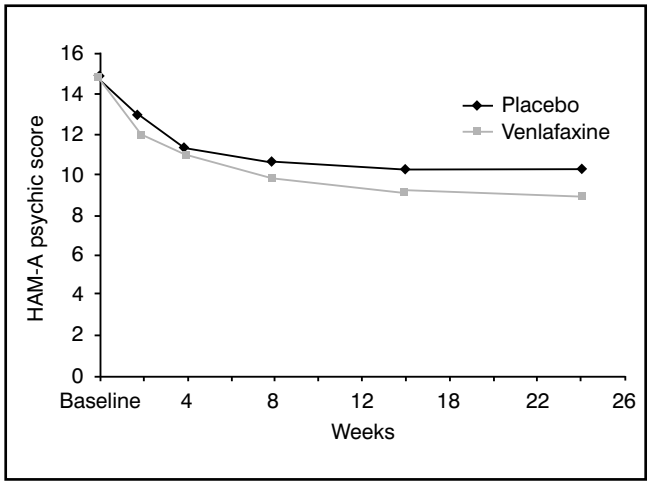

Figure 3. HAM-A psychic score ITT. P = *0.038 at 8 weeks, and* P = *0.07 at 24 weeks.*

ered to be related to the medication. The serious events in patients on venlafaxine were: collapse (with recovery within 24 hours), elective varicose vein surgery, overdose, and chest pain. The serious events in patients on the placebo were: overdose, abdominal pain, carcinoma of the breast, breathlessness, and fractured jaw.

Discussion

Strengths

Most of the recent studies in patients with GAD have excluded patients who have had co-morbid depression. While this has been necessary for regulatory purposes, it does mean that the population studied may not have been typical of that seen in general practice. The purpose of this study was primarily to study a 'typical' patient population in primary care that was primarily suffering from GAD, and that might also be suffering from symptoms of depression. The main strength of this study is that it is a prospective randomised study in a population representative of that seen commonly in primary care in the UK.

Limitations

The main weakness of this study is that it still had the constraints of a formal randomised study, with fixed visit times and standardised entry criteria. Thus, although this study contained a representative population, the treatment the patients received was less flexible than in normal practice.

In retrospect, the four points used in our power calculation were probably not appropriate owing to the fact that the characterisation of GAD has changed over time. More emphasis is now placed on the long-term nature of the disease in modern definitions, which would lead to smaller changes being seen in recent studies. Also, as mentioned above, older studies generally used less robust ways of analysing data (using observed cases instead of last observation carried forward), which would tend to increase the size of effect.

Comparison of magnitude of effect with previous literature

The mainstay of treatment of GAD prior to the use of antidepressants was diazepam and buspirone. At the time of licensing venlafaxine for GAD, a literature search was performed to compare the size of effect with previous studies. MEDLINE was searched for published reports on GAD, according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III or DSM-III-R or DSM-IV), and for placebo controlled studies. Reports were rejected if they did not provide access to randomised parallel comparisons, or if they contained a purely experimental compound in early development. Eighteen reports on abecarnil, alprazolam, bromazepam, buspirone, chlorprothixene, clobazam, diazepam, hydroxyzine, imipramine, ipsaperone, ketazolam, lorazepam, ritanserin, suriclone, and trazodone were identified. Of the 18 reports, 15 were conducted using the DSM-III diagnostic criteria, which only require a 1–month duration of symptoms for diagnosis. Only three studies used either the DSM-III-R or DSM-IV criteria, which require a 6–month duration of symptoms for diagnosis, and in one of these studies[20], this requirement was in itself restricted to the observed-case analysis, which is less robust than the last-observation-carried-forward analysis now considered to be the gold standard.

Eight of the 18 reports above explicitly used a last-observation-carried-forward analysis, and the size of effect ranged from 0.8 to 6.8 on the total HAM-A scale, although because many of these studies used DSM-III criteria (more akin to acute anxiety) it is not appropriate to make direct comparisons.

Of the more recent studies using a DSM-III-R or DSM-IV diagnosis, the study by Ansseau *et al* (1991)[20] using suriclone, a benzodiazepine-like anxiolytic, showed an estimated difference from the placebo of 6.5 for diazepam using a repeated-measures analysis performed with the intention-to-treat population. However, despite the quoted DSM-III-R criteria, over 70% of these patients in fact had episodes of less than 6 months and almost 40% of patients had a duration of illness of less than 2 months. In a DSM-III-R study by Pollack *et al* (1997)[21] comparing abecarnil, a partial benzodiazepine-receptor agonist, with buspirone,

Table 2. SF36 scores.

Quality of life category	Week	Treatment	*n*	Arithmetic mean (SD)[a]	LS mean[b]	Difference (V–P) (95% CI)	*P*-value[c]
Physical functioning	8	Venlafaxine	122	73.1 (24.69)	72.3	-0.07 (4.1 to -4.2)	0.975
		Placebo	122	71.8 (28.40)	72.4		
	24	Venlafaxine	122	71.8 (27.65)	71.0	0.03 (-4.9 to 5.0)	0.990
		Placebo	122	70.5 (29.34)	71.0		
Physical role	8	Venlafaxine	122	49.8 (42.70)	50.8	7.4 (-2.4 to 17.1)	0.139
		Placebo	121	43.7 (41.95)	43.4		
	24	Venlafaxine	122	54.9 (42.35)	55.6	9.0 (-0.7 to 18.7)	0.070
		Placebo	121	47.1 (42.84)	46.6		
Bodily pain	8	Venlafaxine	122	68.4 (24.63)	68.4	6.2 (0.8 to 11.7)	0.024
		Placebo	122	62.2 (28.20)	62.2		
	24	Venlafaxine	122	66.9 (27.20)	66.9	4.2 (-1.7 to 10.1)	0.164
		Placebo	122	62.8 (29.66)	62.8		
General health	8	Venlafaxine	122	58.3 (23.64)	57.2	4.0 (-0.2 to 8.2)	0.064
		Placebo	121	52.7 (23.13)	53.2		
	24	Venlafaxine	122	58.5 (23.14)	57.5	3.9 (-0.5 to 8.3)	0.086
		Placebo	121	53.1 (23.13)	53.7		
Vitality	8	Venlafaxine	122	48.0 (21.16)	47.5	7.9 (2.9 to 12.9)	0.002
		Placebo	122	39.1 (23.74)	39.6		
	24	Venlafaxine	122	47.7 (22.52)	47.2	5.6 (0.3 to 10.9)	0.039
		Placebo	122	41.1 (24.51)	41.6		
Social functioning	8	Venlafaxine	122	61.0 (30.89)	59.7	3.3 (-3.6 to 10.1)	0.347
		Placebo	122	55.1 (27.64)	56.4		
	24	Venlafaxine	122	62.8 (31.76)	61.5	3.6 (-3.5 to 10.8)	0.316
		Placebo	122	56.6 (29.07)	57.9		
Emotional role	8	Venlafaxine	122	47.0 (42.15)	45.8	8.0 (-1.9 to 18.0)	0.112
		Placebo	121	36.4 (40.60)	37.8		
	24	Venlafaxine	122	56.3 (40.67)	54.9	11.3 (0.7 to 21.8)	0.036
		Placebo	121	42.7 (43.30)	43.7		
Mental health	8	Venlafaxine	122	56.7 (21.69)	56.1	9.5 (4.7 to 14.2)	<0.001
		Placebo	122	46.0 (20.64)	46.6		
	24	Venlafaxine	122	58.1 (22.26)	57.6	8.3 (3.3 to 13.4)	0.001
		Placebo	122	48.7 (21.23)	49.2		

SD = standard deviation; [a]From raw data; [b]LS = least square mean from ANCOVA (adjusted for baseline); [c]V–P = venlafaxine – placebo; [d]From ANCOVA for difference between least square means. With the exception of week 8 'physical functioning' analysis, venlafaxine produced more favourable (higher) scores than the placebo. Differences between the treatment groups were either approaching statistical significance or were statistically significant for all but the 'physical functioning' and 'social functioning' scales.

the estimated drug–placebo difference for buspirone was 3.1. In a study comparing abecarnil with alprazolam by Lydiard *et al* (1997),[22] in which patients were excluded if they discontinued within 2 weeks for a non-pharmacological reason, the difference versus placebo using last-observation-carried-forward analysis for the remaining patients with at least one efficacy evaluation, was 4.5 for alprazolam. In the only DSM-IV study[23] exploring the efficacy of

Table 3. Common adverse events experienced during the trial.

Part of the body affected	Adverse event	Venlafaxine XL group (%)	Placebo group (%)
Body as a whole	Influenza syndrome	6.6	5.8
	Headache	15.6	11.6
	Infection	13.1	9.9
	Pain	10.7	7.4
Digestive system	Nausea	31.1	9.9
	Diarrhoea	9.0	11.6
	Vomiting	9.0	5.0
Nervous system	Anxiety	17.2	17.4
	Depression	11.5	11.6
	Dizziness	13.1	6.6
	Insomnia	13.1	7.4
Respiratory system	Pharyngitis	15.6	14.9
Skin	Sweating	13.1	1.7

hydroxyzine in GAD, the magnitude of effect found for the buspirone 20 mg/day control versus placebo was 1.6. This is comparable to the 2.1 seen in our study.

Looking to compare the effect size with other studies against venlafaxine, there are only two other long-term studies,[17,18] the first of which had an effect size at 6 months of 4.6 (95% CI = 2.4 to 6.8) for 75 mg and 5.2 (95% CI = 3.0 to 7.3) for 150 mg. The second variable dose study (which is more similar in design to the GP study,[17] had an effect size of 3.5 (95% CI = 1.67 to 5.35), which is again comparable to our study.

We are not aware of any other recent randomised long-term studies in GAD, and from the information above it would appear that the figure of 2.1 points seen in our study is analogous to that seen in other similar studies when like is compared to like.

Implications for further study

Further studies are required to investigate the effects and interactions of drugs and psychotherapy on patients with GAD in a totally naturalistic manner in order to assess the full effectiveness of antidepressants in this area.

Summary of main findings

This is the first study to demonstrate that patients in primary care with GAD, with and without depression, can be treated successfully with the antidepressant venlafaxine. The clinical relevance of these findings is demonstrated in the trends seen in response and remission rates that attain statistical significance in the CGI scores.

As GAD is a long-term disease with a minimum duration of symptoms of 6 months, it is likely to require long-term treatment. It is reassuring to see that there was no sign of tolerance in this study as demonstrated by the fact that there was no reduction in efficacy over time, which is consistent with the previous findings of Gelenberg[17] in another 6–month, variable dose study of venlafaxine in GAD. This is in contrast to treatment with benzodiazepines, which are often used to treat anxiety in the UK, but which should not be used for longer than 4 weeks owing to the possibility of tolerance and dependence, especially when given at higher doses and for longer durations.

This double-blind, randomised, multi-centre, parallel-group, placebo controlled study in GAD demonstrates that venlafaxine offers physicians another option to treat this difficult disease.

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Acknowledgements

This study was fully funded by Wyeth. We would like to acknowledge the following who participated in the study: Dr C Aitchison (Houston), Dr P Bishop (Warrington), Dr M Blagden (Chesterfield), Dr R Bowen (Cardiff), Dr A Burton (Glasgow), Dr G Canning (Glasgow), Dr J Cecil (St Austell), Dr R Cook (Saltash), Dr A Cooper, (Crawley), Dr A Cowie (Corsham), Dr M C Free (Sutton), Dr T Gooding (Atherstone), Dr J Hutchison (Glasgow), Dr G Jackson (Aylesbury), Dr T Khong (Leicester), Dr R Kneen (Saltash), Dr K Korlipara (Bolton), Dr R Lal-Sarin (Coventry), Dr A Lane (Cardiff), Dr C Langdon (Maidenhead), Dr G McLaren (Houston), Dr A Mishra (Bolton), Dr P Mooney (Sheffield), Dr I Patchett (Leicester), Dr A Rotheray (Falmouth), Dr J Ryan (Penzance), Dr B Silvert (Bolton), Dr D Sutherland (Glasgow), Dr R Symons (Maidenhead), Dr A Wall (Woking), Dr M Whitehead (Thornton Heath) and Dr A Wijnberg (Birmingham).