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ORIGINAL PAPER

Michael Bauer · Puvan Tharmanathan · Hans-Peter Volz · Hans-Juergen Moeller · Nick Freemantle

The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression

A meta-analysis

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Abstract *Objective* Meta-analysis of all available trials of Venlafaxine in the treatment of major depressive disorders, including treatment resistant depression and long-term relapse prevention. *Methods* We conducted a meta-analysis comparing venlafaxine and tricyclics, or selective serotonin reuptake inhibitors (SSRIs), in major depression. We also included trials comparing venlafaxine and alternative antidepressants in subjects with treatment resistant depression, or compared with placebo in long-term relapse prevention. Trials were identified through searches of Medline, Embase, Cochrane Library and through accessing unpublished trials held by the manufacturer. Results based on intention to treat analyses where available, were pooled using theoretically exact conditional maximum likelihood methods for fixed effects (primary analyses), and numerical simulation using a Gibbs sampler for full random effects. *Results* Compared to all SSRIs for the treatment of major depression (fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine), venlafaxine was associated with a greater response [odds ratio 1.15 (95% CI 1.02–1.29)] and remission [odds ratio 1.19 (95% CI 1.06–1.34)]. Overall drop out rates appeared similar for SSRIs and venlafaxine. Compared to tricyclics, response to venlafaxine was estimated to be greater by exact method, odds ratio 1.21 (95% CI 1.03–1.43), but not statistically significantly different, using a full random effects method odds ratio 1.22 (95% CI 0.96–1.54). We observed no difference in remission rates (odds ratio 1.06 (95% CI 0.74–1.63)). Tricyclics were less well tolerated with higher overall drop out rates. Compared to alternative antidepressants in treatment resistant depression (trials included comparison with sertraline, bupropion, fluoxetine, citalopram, and one with a range of agents—mostly SSRIs), the odds ratio for response was 1.35 (95% CI 1.19–1.54). The odds ratio for remission was 1.35 (95% CI 1.20–1.52). Compared to placebo the odds ratio for relapse prevention with venlafaxine was 0.37 (95% CI 0.27–0.51). *Conclusion* This meta analysis provides evidence of the clinical efficacy of venlafaxine in achieving therapeutic response and remission in patients with major depression. Venlafaxine appears more effective than SSRIs, and at least as effective as tricyclic antidepressants, in the treatment of major depressive episode. Venlafaxine appeared more effective than comparators in treatment resistant depression. In addition, venlafaxine effective in reducing relapse when given long term after major depressive episode.

Key words venlafaxine · meta analysis · selective serotonin reuptake inhibitors · tricyclic antidepressants · treatment resistant depression

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M. Bauer
Department of Psychiatriy and Psychotherapy
University Hospital Carl Gustav Carus
Technical University Dresden
Fetscherstr. 74
01307 Dresden, Germany

H.-P. Volz
Hospital for Psychiatry
Psychotherapy and Psychosomatic Medicine
Schloss Werneck
Balthasar-Neumann-Platz 1
97440 Werneck, Germany

H.-J. Moeller
Department of Psychiatry
Ludwig-Maximilians-University
Nussbaumstrasse 7
80336 Munich, Germany

P. Tharmanathan · N. Freemantle, PhD (✉)
School of Health and Population Sciences
University of Birmingham
Edgbaston, Birmingham B15 2TT, UK
E-Mail: N.Freemantle@bham.ac.uk

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Introduction

Clinical depression, characterised by a high rate of chronic disease, relapse and recurrence, causes significant physical and social impairment. It is prevalent in developed as well as developing societies [33]. The development of newer antidepressants has focused on improving efficacy and tolerability. Though there is still no full understanding of a common mechanism of action for all antidepressants, newer agents are generally considered more targeted agents. There appears to be no major difference in efficacy of the most commonly used among newer agents, selective serotonin reuptake inhibitors (SSRIs) and among conventional agents (tricyclics and monoamine oxidase inhibitors). Venlafaxine, the first in a class of agents that inhibit both noradrenalin and serotonin reuptake, has been estimated to achieve a greater efficacy than SSRIs in pooled analysis of relevant clinical trials [50].

A number of trials and meta-analyses have demonstrated the efficacy and tolerability of venlafaxine in the treatment of major depression (MDD) [77]. The aim of this study was to obtain a comprehensive updated overview of the relative efficacy of venlafaxine compared with alternative antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclics (TCAs). We also examined efficacy in terms of relapse and recurrence prevention and in patients with treatment resistance when venlafaxine was used second line. Treatment resistance refers to stage one (non-response to one adequate antidepressant trial) according to Thase and Rush [52].

Methods

Study identification

Randomised controlled trials completed up to April 2007 comparing venlafaxine with other antidepressant drugs in the treatment of major depression were identified through systematic searches of the databases Medline, Embase, the Cochrane Library and our own database of trials [50]. Further searches were conducted to identify trials of venlafaxine in comparison with placebo in the prevention of relapse in previously treated patients with MDD. Additionally, all available unpublished study data were included. These results were provided by Wyeth, the manufacturer of venlafaxine, and were identified through searches of the company archives

Data extraction and quality assessment

Data were extracted by one and checked for accuracy by a second author. The following information was abstracted: length of follow up; loss to follow up; concealment of allocation; blinding.

Outcome measures

Predefined outcome measures were response as defined in trial publication, (usually defined as a 50% reduction in Hamilton Depression Rating Scale Score), remission (defined as achieving a Hamilton Score of ≤7), drop out rate for all causes, drop out rate due to side effects or drop out rate due to inefficacy.

Statistical methods

Trial results were pooled using a theoretically exact conditional likelihood method for fixed effects analysis included in the Software Package StatsDirect. The exact method estimates the odds ratio on the basis of all possible permutations of a (conditional) hypergeometric response and is an extension of Fisher's exact test. For random effects analysis, studies were pooled using the empirically Bayesian numerical simulation approach in WinBugs, which has the advantage of including heterogeneity and its uncertainty in the estimate of treatment effect, rather than the standard methods which presume that the observed heterogeneity is the true heterogeneity.

The number needed to treat (NNT) was calculated using the DerSimonian and Laird Risk Difference method. Heterogeneity was assessed using Breslow-Day, Cochran Q and the I^2 test.

Treatment effect asymmetry was assessed using Begg-Mazumdar, Egger and Horbold-Egger methods. Analyses were conducted in StatsDirect (Ver 2.6.1, Cambridge, Camcode) and Winbugs (Cambridge, MRC).

Results

Overall, 63 trials were identified meeting the inclusion criteria (see Fig. 1 and Table 1). Data from the trials are included Tables 2, 3, 4 and 5 in Appendix

(i) Venlafaxine versus SSRIs in Major Depressive Episode

Thirty-four trials with 7,155 randomised subjects were identified comparing venlafaxine with SSRIs.

Treatment response

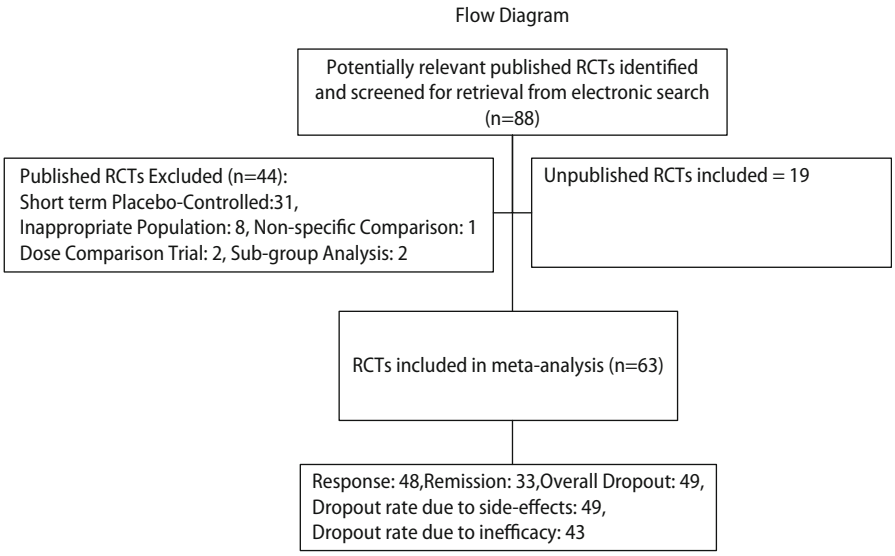
Twenty-nine trials provided data for the analysis of relative response in the treatment of major depressive episode (Fig. 2). Fifteen trials compared venlafaxine with fluoxetine, 7 trials compared venlafaxine with paroxetine. The remaining trials compared venlafaxine with sertraline (3), citalopram (2) and escitalopram (2). Overall, venlafaxine was significantly more effective compared to SSRI treatment (random effects odds ratio 1.15, 95% CI 1.02–1.29). The NNT with venlafaxine rather than a SSRI to achieve response was 36 (95% CI 19–763).

There was no evidence of heterogeneity of treatment effect (Breslow-Day = 32.1, df = 28, $P = 0.27$), $I^2 = 11.2\%$ (95% CI = 0–43.9%), and no evidence of asymmetry of treatment effect (Begg-Mazumdar: Kendall's tau = 0.07, $P = 0.62$; Egger: bias = 0.47, 95% CI = −0.68–1.63, $P = 0.41$; Horbold-Egger: bias = 0.47, 92.5% CI = −0.60–1.53, $P = 0.43$).

Remission

Twenty-three trials provided data for estimating the effect of venlafaxine versus SSRIs on remission (Fig. 3). Eleven trials compared venlafaxine with

Fig. 1 Study flow



fluoxetine, six trials compared venlafaxine with paroxetine. The remaining trials compared venlafaxine with sertraline (3), escitalopram (2) or citalopram (1). Overall, venlafaxine was significantly more effective than SSRI treatment (random effects odds ratio 1.19, 95% CI 1.06–1.34). There was some evidence of heterogeneity of treatment effect (Breslow-Day = 36.1, df = 22, $P = 0.03$), $I^2 = 38\%$ (95% CI = 0–61.5%). The NNT with venlafaxine rather than with a SSRI to achieve remission was 19 (95% CI 12–57).

There was some evidence of asymmetry of treatment effect (Fig. 4. Begg-Mazumdar: Kendall's tau = 0.24, $P = 0.11$; Egger: bias = 1.44, 95% CI = 0.13–2.76, $P = 0.03$, Horbold-Egger: bias = 1.44, 92.5% CI = 0.20–2.68, $P = 0.04$). However, a similar result was obtained when trials above the median size were pooled using the conditional maximum likelihood method (1.27, 95% CI 1.06–1.53, $P = 0.01$).

Treatment tolerability

Thirty-one trials provided data for the assessment of the overall drop out rate, 30 for the assessment of the drop out rate due to side effects and 25 for the assessment of the drop out rate due to lack of efficacy. The overall drop out rate was not significantly different for venlafaxine and SSRIs, exact odds ratio 1.06 (95% CI 0.95–1.19; $P = 0.26$). The pooled Risk Difference 0.013, 95% CI −0.011 to 0.037. The drop out rate due to side effects was significantly higher in the venlafaxine trials, exact odds ratio 1.45 (95% CI 1.23–1.70; $P < 0.0001$), with a pooled risk difference of 0.032, (95% CI 0.013–0.052). Drop out was less due to inefficacy, exact odds ratio 0.70 (95% CI 0.55–0.90; $P = 0.005$), and pooled risk difference −0.007 (95% CI −0.016 to 0.001).

(ii) Venlafaxine versus tricyclic antidepressants in Major Depressive Episode

Eighteen trials were identified with 2,769 randomised subjects comparing venlafaxine with tricyclic antidepressants.

Treatment response

Sixteen trials provided data for the analysis of the relative response in the treatment of major depressive episode (Fig. 2). Venlafaxine was compared with imipramine in 7 trials, with clomipramine (3 trials), amitriptyline (2 trials), dothiepin (2 trials), amineptine (1 trial) and maprotiline (1 trial). The odds ratio for response was 1.22 (95% CI 0.96–1.54) by full random effects method, and 1.21 (95% CI 1.03–1.43) by conditional maximum likelihood method in favour of venlafaxine. There was some evidence of heterogeneity of treatment effect (Breslow-Day = 24.2, df = 15, $P = 0.06$), $I^2 = 37.4\%$ (95% CI = 0–64.4%). The NNT to achieve response with venlafaxine compared to tricyclic antidepressants was 23 (95% CI 11 to ∞). There was no evidence of asymmetry of treatment effect (Begg-Mazumdar: Kendall's tau = −0.1, $P = 0.56$; Egger: bias = 0.07, 95% CI = −3.15 to 3.29, $P = 0.96$; Horbold-Egger: bias = −0.07, 92.5% CI = − 2.99–2.85, $P = 0.96$).

Remission

Seven trials provided data for the analysis of relative remission in the treatment of major depressive episode (Fig. 3). Venlafaxine was compared with clomipramine in 2 trials, and with amineptine (1 trial), amitriptyline (1 trial), dothiepin (1 trial), maprotiline (1 trial) and nortriptyline (1 trial). The odds ratio for remission was 1.06 (95% CI 0.74–1.63) by full random effects method, and 1.05 (95% CI 0.77–1.43) by conditional maximum likelihood method. The NNT to achieve remission with venlafaxine rather than

Table 1 Included trials

Study	Comparison	Population #	Depression scale baseline score	Number randomised (*N*)	Length of follow-up (days)	Drop-out (loss to follow-up)	Concealment	Blinding
Tricyclics								
0600A-319, Wyeth-Ayerst France 1991 [75]	Amineptine	Adult, DSM-III-R	MADRS (min.24)	105	43	39	NK	Single
0600A1-300, Wyeth research Philadelphia 2002 [64]	Amytriptyline	Adult, DSM-III-R	NA	160	14	56	NK	Double
Samuelian [39]	Clomipramine	Adult, DSM-III-R	MADRS (min.24)	102	43	36	NK	Double
0600A-326, Wyeth-Ayerst France 1991 [76]	Clomipramine	Adult, DSM-III-R	MADRS (min. 24)	121	43	35	NK	Double
Mahapatra [27]	Dothiepin	Adult, DSM-III-R	HAM-D (min.18)	92	43	16	NK	Double
Schweizer [42]	Imipramine	Adult, DSM-III-R	HAM-D (min.21)	146	43	59	NK	Double
0600A-303, Wyeth-Ayerst USA [72]	Imipramine	Adult, DSM-III-R	HAM-D (min.21)	155	43	62	NK	Double
Benkert [7]	Imipramine	Adult, DSM-III-R (with melancholia)	NA	167	43	52	NK	Double
0600A1-343, Wyeth-research Philadelphia [62]	Imipramine	Adult, DSM-III-R	HAM-D (min.21)	208	43	90	NK	Double
Lecrubier [24]	Imipramine	Adult, minor/intermittent/ major depression	NA	153	91	46	NK	Double
0600B1-384, Wyeth-Ayerst USA [69]	Imipramine	Adult, DSM-III-R	MADRS (min.27)	359	42	114	NK	Double
0600A-321, Wyeth-Ayerst France [73]	Maprotiline	Adult, DSM-III-R	HAM-D (min.20)	129	43	16	NK	Double
Shrivastava [44]	Imipramine	Adult, DSM-III-R	NA	381	365	276	NK	Double
Gentil [19]	Amitriptyline	Over 65, DSM-IV	HAM-D (min 20)	116	56	17	NK	Double
Smeraldi [49]	Clomipramine, trazodone	Over 65, DSM-III-R	MADRS (min.24)	170	43	7	NK	Double
Sauer [40]	Amitriptyline ER	Adults, DSM-IV (moderate severity)	HAM-D (20–26)	160	42	NK	NK	Double
Gasto [18]	Nortriptyline	Over 65, DSM-IV	HAM-D (min.21)	68	168	11	NK	Single
Trick [55]	Dothiepin	Over 60, DSM-IV (moderate severity)	MADRS (min.19)	88	182	34	NK	Double
SSRIs								
Allard [2]	Citalopram	Over 65, DSM-IV	MADRS (min.20)	151	168	33	NK	Double
Hua [16] (Chinese)	Citalopram	Adult, DSM-IV.	HAM-D (min.16)	60	56	3	NK	Open-label
Bielski [9]	Escitalopram	Adult, DSM-IV	HAM-D (min.20)	198	42	60	NK	Double
Montgomery [31]	Escitalopram	Adult, DSM-IV	MADRS (min.18)	293	56	40	NK	Double
600A-332, Wyeth-Ayerst USA [70]	Fluoxetine	Adult, DSM-III-R	HAM-D (min. 20)	51	43	14	NK	Double
Diereck [15]	Fluoxetine	Adult, DSM-III-R.	HAM-D (min 21)	314	56 + 6 ?? (tapering)	78	NK	Double
0600A1-372, Wyeth research Philadelphia [63]	Fluoxetine	Adult, DSM-IV.	MADRS (min.26)	460 (156 + 152)??	42 + 12 (tapering)	80	NK	Double
Rudolph [37]	Fluoxetine	Adult, DSM-IV	HAM-D (min.20)	301 (95 + 103)??	56	47	NK	Double
Silverstone [46]	Fluoxetine	Adult, DSM-IV	HAM-D (min.20)	368 (128 + 121)??	84 + 7 (tapering)	69	NK	Double
0600A-626, Wyeth-Ayerst [68] (Poster)	Fluoxetine	Adult, DSM-IV (moderate severity)	HAM-D (18–25)	156	56	39	NK	Double
0600A-654, Wyeth-Ayerst [66]	Fluoxetine	Adult, DSM-IV.	MADRS (min. 20)	266	84	98	NK	Double
0600B-100469, Wyeth-Ayerst USA [71] (acute phase)	Fluoxetine	Adult, DSM-IV.	HAM-D (min.18)	1,096	70	381	NK	Double
Costa e Silva [45]	Fluoxetine	Adult, DSM-III-R	HAM-D (min.20)	382	56	47	NK	Double
Tylee [56]	Fluoxetine	Adult, DSM-IV	NA	341	84	93	NK	Double
Schatzberg [41]	Fluoxetine	Adult, DSM-IV.	HAM-D (min.20)	300 (104 + 100)??	56	67	NK	Double
DeNayer [13]	Fluoxetine	Adult with moderate depression	HAM-D (18–25)	146	84	53	NK	Double
Tzanakaki [57]	Fluoxetine	Adult, DSM-IV (with melancholia)	MADRS (min 25)	109	42	21	NK	Double
Alves [3]	Fluoxetine	Adult with major depression	HAM-D (min.20)	87	84	19	NK	Double
Clerc [10]	Fluoxetine	Adult, DSM-III-R (with melancholia)	MADRS (min.25)	68	42	18	NK	Double
Diaz-Martinez [14]	Fluoxetine	Adult, DSM-III-R	HAM-D (min 20)	145	56	35	NK	Open-label

Table 1 continued

Study	Comparison	Population #	Depression scale baseline score	Number randomised (*N*)	Length of follow-up (days)	Drop-out (loss to follow-up)	Concealment	Blinding
Zanardi [78]	Fluvoxamine	Adult, DSM-IV	NA	28	42	2	NK	Double
0600A-347, Wyeth research Philadelphia [59]	Fluvoxamine	NK	NA	92	NK	14	NK	Double
0600A-349, Wyeth research Philadelphia [61]	Paroxetine	Adult, DSM-III-R	NA	167	56	52	NK	Double
0600B1-367, Wyeth-Ayerst France [74]	Paroxetine	Adult, DSM-III-R	HAM-D (min.20)	332 (165 + 81)??	56	74	NK	Double
0600B 428, Wyeth-Ayerst [67]	Paroxetine	Adult, DSM-III-R	NA	114	56	20	NK	Double
Ballus [5]	Paroxetine	Adult, ICD-10 (mild to moderate depression or dysthymia)	HAM-D (min 17)	84	168	27	NK	Double
McPartlin [29]	Paroxetine	Adult, DSM-IV	MADRS (min.19)	361	84	99	NK	Double
Poirier [36]	Paroxetine	Adult, DSM-III-R	HAM-D (min.18)	123	28	NK	NK	Double
Li [25] (Chinese)	Paroxetine	Adult, with depression	NA	60	56	1	NK	NK
Hwang [22]	Paroxetine	Over 65, DSM-IV	NA	105	28	6	NK	Open
Mehtonen [30]	Sertraline	Adult, DSM-IV	HAM-D (min.18)	147	56	28	NK	Double
Oslin [35]	Sertraline	Over 65, DSM-IV	NA	52	70	20	NK	Double
Sir [48]	Sertraline	Adult, DSM-IV	HAM-D (min.18)	163	56 + 14 (taper)	38	NK	Double
0600B1-402, Wyeth research Philadelphia [58]	Sertraline	Adult, DSM-IV	HAM-D (min.20)	688	70	187	NK	Double
Miscellaneous								
Thase [54]	Bupropion	Adult, DSM-IV	HAM-D (min.17)	348	84	153	NK	Double
Guelfi [20]	Mirtazapine	Adult, DSM-IV	HAM-D (min.25)	157	56	46	NK	Double
Benkert [8]	Mirtazapine	Adult, DSM-IV	HAM-D (min.21)	242	42	86	NK	Double
0600A1-351, Wyeth Research Philadelphia [60]	Moclobemide	Adult, DSM-III-R	NA	142	43	8	NK	Double
Akkaya [1]	Reboxitine	Adults with DSM-IV-TR	HAM-D (min.16)	107	70	14		Open-label
Cunningham [12]	Trazodone	Adult, DSM-III-R	HAM-D (min.20)	227 (72 + 77)??	42	49	NK	Double
Florkowski [17] (Polish)	Trazodone	Adult, ICD-10	HAM-D (min.20)	115	42	12	NK	NK
Treatment resistant trials								
Rush [38]	Bupropion sertraline	Adult, non-psychotic major depressive disorder	NA	727	1,095 (3 years)	NA	NK	Open-label
Corya [11]	Fluoxetine	Adult, DSM-IV	CGI-S (≤4)	119	84	27	NK	Double
Baca [4]	Conventional antidepressant, mostly SSRIs	Adult, DSM-IV	HAM-D (min.17)	3,502	168	1,065	NK	Open-label
0600B 671, Wyeth-Ayerst [65]	Citalopram	Adult, DSM-IV	HAM-D (min.20)	406	84	92	NK	Double
Long-term trials								
Simon [47]	Placebo	Adult, DSM-IV	CGI-S (≤3) HAM-D (≤10)	490 (292)	Up to 6 months	NA	NK	Double-blind
0600B-100469 (maintenance phase), Wyeth-Ayerst USA [71]	Placebo	Adult, DSM-IV		258	24 months	NA	NK	Double-blind
Montgomery 2004 (maintenance phase) [32]	Placebo	Adult, DSM-IV	HAM-D (≤12)	225	12 months	NA	NK	Open-label

DSM diagnostic and statistical manual of mental disorders, *NA* not available or applicable, *HAM-D* Hamilton rating scale for depression, *MADRS* montgomery-Asberg depression rating scale, *CGI-S* clinical global impressions-severity of illness, *NK* not known

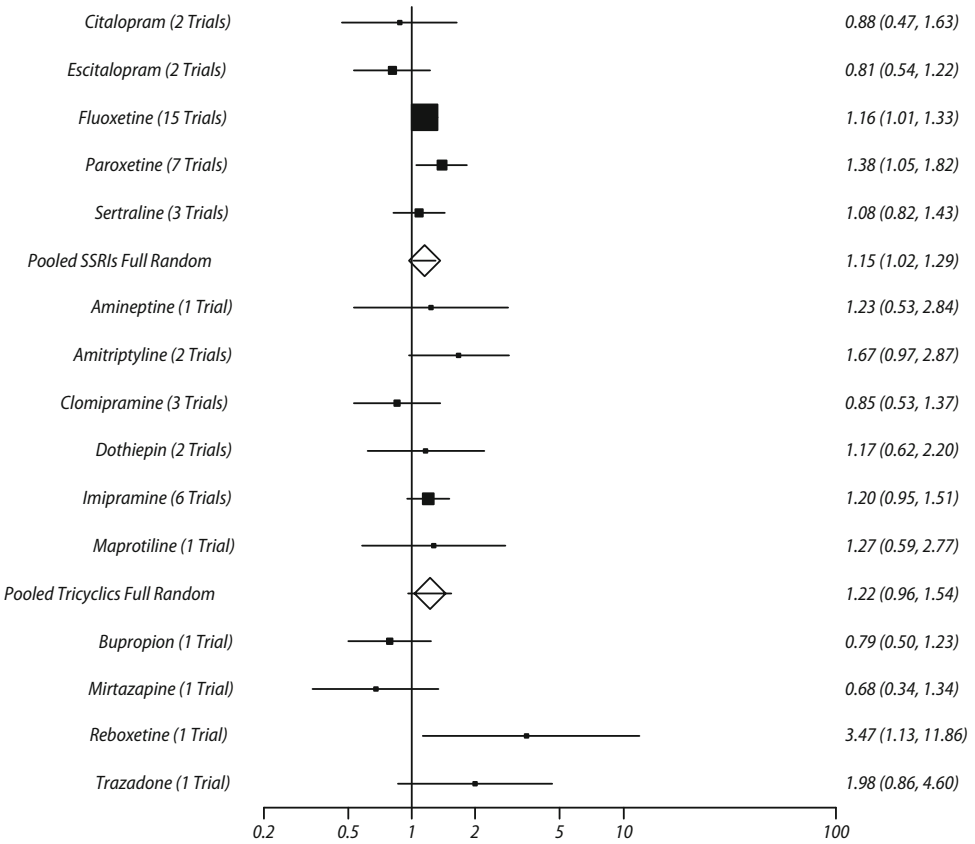


Fig. 2 Venlafaxine versus active comparator—response (odds ratio and 95% confidence intervals)

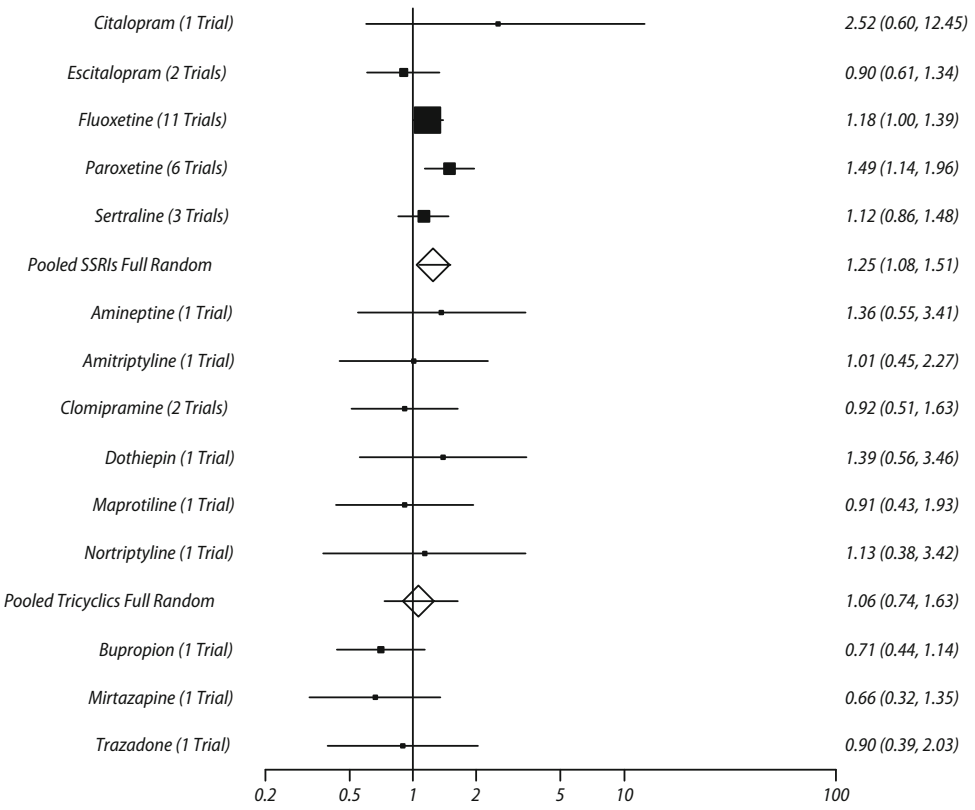


Fig. 3 Venlafaxine versus active comparator—remission (odds ratio and 95% confidence intervals)

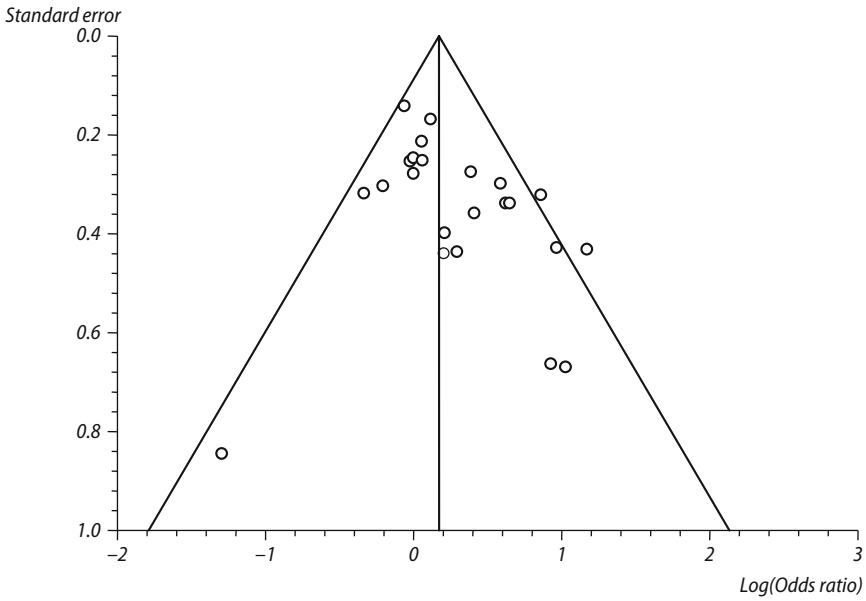


Fig. 4 Bias assessment plot for venlafaxine versus SSRIs—remission

with tricyclic antidepressants was 73 (95% CI 12 to ∞).

There was no evidence of heterogeneity of treatment effect (Breslow-Day = 4.35, df = 6, $P = 0.63$), $I^2 = 0\%$ (95% CI = 0–58.5%). Similarly there was no evidence of asymmetry of treatment effect (Begg-Mazumdar: Kendall's tau = 0.33, $P = 0.38$; Egger: bias = 4.01, 95% CI = − 3.36 to 11.38, $P = 0.22$; Horbold-Egger: bias = 4.06, 92.5% CI = − 2.37–10.49, $P = 0.22$) although the small number of contributing studies reduces the available statistical power to detect differences.

Treatment tolerability

Fifteen trials provided data for the overall drop out rate and the drop out rate due to inefficacy. Sixteen trials provided data for the drop out rate due to side effects. The overall drop out rate was less for venlafaxine compared to TCAs, exact odds ratio 0.77 (95% CI 0.65–0.90; $P = 0.003$), with a pooled risk difference of −0.03 (95% CI 0.00 to −0.07). The drop out rate due to side effects was higher in the TCA trials, exact odds ratio 0.76 (95% CI 0.61–0.94; $P = 0.013$), with a pooled risk difference of −0.01 (95% CI −0.04 to 0.01). There was no difference for the drop out rate due to inefficacy, exact odds ratio 1.07 (95% CI 0.78–1.47; $P = 0.673$) with a pooled risk difference of 0.00 (95% CI −0.02 to 0.02).

(iii) Venlafaxine versus other antidepressants in a Major Depressive Episode

Four trials (5 comparisons) compared venlafaxine with antidepressants with other pharmacological characteristics. There was one trial each comparing venlafaxine with buproprion, mirtazapine, moclobemide, reboxetine and trazadone. The results of these individual comparisons are described in Figs. 2 and 3 for response and remission, although small numbers of subjects available for each comparison prevent conclusive results on these comparisons.

(iv) Venlafaxine versus alternative antidepressants in Treatment Resistant Depression

Five trials provided data for the comparison of venlafaxine and other antidepressants in treatment resistant depression, mostly defined as second line treatment after failure of pre-treatment. One trial compared venlafaxine with sertraline and bupropion, one each with fluoxetine, citalopram and paroxetine, and one with several agents (mostly SSRIs).

Treatment response

Four trials provided data for the comparison of venlafaxine with other antidepressants in treatment resistant depression for treatment response. The odds ratio for response was 1.35 (95% CI 1.19–1.54) by conditional maximum likelihood, and 1.38 (95% CI 0.67–3.38) by full random effects analysis. The wide confidence intervals for the random effects analysis reflect the sparse number of trials available for this comparison, and thus uncertainty on the degree of between study variability in treatment effect. There was no evidence of heterogeneity of treatment effect (Breslow-Day = 5.17, df = 3, $P = 0.16$). Asymmetry of the treatment effect could not be assessed due to insufficient strata. The NNT to achieve response with venlafaxine in comparison with other antidepres-

sants in treatment resistant depression was 15 (95% CI 8–138).

Remission

Five trials provided data for the analysis of remission in patients with treatment resistant depression. The odds ratio for remission was 1.35 (95% CI 1.20–1.52) by conditional maximum likelihood method, and 1.36 (95% CI 0.99–2.10) for the full random effects method, again both in favour for venlafaxine. Again the wide confidence intervals for the random effects analysis reflect the sparse number of trials available for this comparison and thus the uncertainty in the degree of variability in the results of the trials. There was however no evidence of heterogeneity of treatment effect (Breslow-Day = 3.75, df = 4, $P = 0.44$), or asymmetry of treatment effect: Begg-Mazumdar: Kendall's tau = 0, $P = 0.82$; Egger: bias = 0.35, 95% CI = − 2.14 to 2.85, $P = 0.68$; Horbold-Egger: bias = 0.36, 92.5% CI = − 1.75 to 2.46, $P = 0.61$). The NNT to achieve remission with venlafaxine rather than other antidepressants was 15 (95% CI 11–24).

Treatment tolerability

Three trials provide data for the comparison of the overall drop out rate, the drop out rate due to side effects and the drop out rate for inefficacy. Drop out was lower for venlafaxine, exact odds ratio 0.85 (95% CI 0.74–0.97; $P = 0.018$), and pooled risk difference 0.00, 95% CI −0.07 to 0.06, Drop out rate for side effects was higher among subjects taking venlafaxine, exact odds ratio 1.66 (95% CI 1.34–2.08; $P < 0.0001$) with a pooled risk difference of 0.02 (95% CI = − 0.02 to 0.06). Drop out rate due to inefficacy as similar between the groups, odds ratio 0.91 (95% CI 0.75–1.10; $P = 0.3146$), and the risk difference was 0.00 (95% CI = − 0.03 to 0.03).

(v) Venlafaxine versus placebo in long-term maintenance trials

Three trials provided data comparing venlafaxine with placebo in the prevention of relapse or recurrence after major depressive episode. The odds ratio for relapse prevention with venlafaxine was 0.37 (95% CI 0.27–0.51) by conditional maximum likelihood method, and 0.36 (95% CI 0.03–3.48) by full random effects analysis, both in favour for venlafaxine. The wide confidence intervals for the full random effects analysis reflect the sparse number of studies available for comparison, and thus uncertainty on the variability in treatment effects. There was no evidence of heterogeneity of treatment effect (Breslow-Day = 4.28, df = 2, $P = 0.12$). There were too few strata to assess asymmetry of treatment effect. The NNT to prevent relapse or recurrence with venlafaxine compared to placebo was 5 (95% CI 4–10).

Discussion

The presented data result from the most comprehensive systematic review to date of the efficacy of venlafaxine in comparison with SSRIs, tricyclic antidepressants and other antidepressant agents in the treatment of major depression, and in comparison with placebo in the prevention of relapse. The present analysis includes more than ten thousand patients and is to our knowledge the first giving a complete overview of the existing data which informs the clinical use of venlafaxine. Most of the existing meta-analyses focus on only one comparison [28, 34, 43, 51, 53]. Additional analyses applied also to "special" indications such as treatment-resistant depression and long-term treatment in regard to the prevention of recurrence, of which both aspects have not been systematically evaluated with a meta-analytical approach.

Many trials of antidepressant therapy are too small to provide precise estimates of treatment effects, emphasising the importance of gaining best available estimates of treatment effects from meta analyses of randomised controlled trials. In particular, this applies to trials with active comparators. Although we only observed little evidence of heterogeneity of treatment effect in the meta analysis, variability in the dosage of venlafaxine or comparator (e.g. 150 mg/d instead of the maximum between 225–375 mg/d [31]) the use of the different formulations such as the the immediate release (IR)-formulation of venlafaxine instead of the potentially better tolerated sustained release (SR), or inappropriately rapid dose escalation of venalfaxine [5, 9, 30] or comparator could have contributed to confounding of treatment effect at the individual study level.

Although the primary outcome of most trials is the difference in mean depression rating score, this outcome may be difficult to interpret clinically. Response and remission are increasingly widely accepted as providing clinically relevant outcome measurements. However, sustained remission is the preferred goal of treatment and is associated with a better long-term prognosis [6, 23]. Thus there has been considerable interest and standardisation of dichotomous scores describing response or remission. These are the data presented here.

Venlafaxine was estimated to be more effective than SSRIs in terms of response, and remission, and compared to tricyclic antidepressants in terms of response using the theoretically exact fixed effects method, which is consistent with previous reports

demonstrating the beneficial effects of venlafaxine in the treatment of MDD [28, 34, 43, 51, 53]. Venlafaxine was estimated to be more effective for both response and remission than other antidepressants in treatment resistant depression. In addition, compared to placebo, venlafaxine was effective in preventing relapse and recurrence. These results confirm and broaden the findings of our previous review [50], which demonstrated similar effects albeit with wider confidence intervals due to the limitations of data available at that time.

The number needed to treat is an easily comprehensible epidemiological measure that indicates how many patients would require treatment with a medication to reduce/or to increase by one the expected number of cases of a defined endpoint. The cut off of NNTs as being clinical relevant is difficult to interpret. In the presented meta-analysis a NNT of 19 for achieving remission in the comparison of venlafaxine vs. SSRI treatment means that 19 patients must be treated with venlafaxine over the mean duration of the included studies to achieve one additional remission compared to treatment with SSRI. This NNT of 19 is consistent with previous meta-analyses showing NNTs for venlafaxine achieving remission between 14 and 17 [34, 50, 53]. When comparing two effective treatments the NNT will be higher than where the comparison is with placebo. However, since sustained remission, not simply response, is the strongly preferred goal of treatment it may be appropriate to prefer a treatment by which one additional patient benefits out of every 19 treated. In this context it can be noted that NNTs above 20 are considered acceptable for other indications, although there is no clear rationale for judgements on the clinical significance of such differences [21].

Further analysis compared the relative efficacy between venlafaxine and TCAs which were limited to some degree by the smaller number of patients randomised to available trials. Although we did not identify a statistically significant difference in respect to tolerability, there is evidence that TCAs have poorer tolerability and safety (e.g. anticholinergic side-effects, cardiotoxicity) compared to modern antidepressants, including venlafaxine [26], and TCAs are usually regarded as second line treatment options in depression (e.g. NICE-guidelines). While we found superiority for venlafaxine as regards response and remission when compared to SSRIs, for TCAs this was only the case for response and there only for the fixed effects analysis. One reason for this might be that fewer studies (and patients) could be included in the comparison of venlaxine versus TCAs when compared with venlafaxine versus SSRIs. This smaller database of studies for venlafaxine versus TCAs reflects changing views of standard therapy during the period of development of the compound. In the comparison of venlafaxine versus SSRIs, 27 studies with 6,360 patients have been included; in the comparison of venlafaxine versus TCAs the respective numbers are 18 studies with 2,880 patients. Alternatively rather than a lack of statistical power, the similarity in action between at least some of the TCAs and venlafaxine (i.e. reuptake inhibition of serotonin and noradrenaline) could also be the reason why clear differences on other outcomes were not identified.

Marketing authorisation for venlafaxine was based upon established superiority over placebo in the acute management of major depressive disorder. As our main question regarded the appropriate choice of antidepressant therapy once a decision to prescribe had been taken, the short-term placebo trials were not considered further. However the longer term use of venlafaxine in the prevention of relapse and recurrence was a new indication, asking the question of whether treatment should be continued. For this aim, placebo controlled trials are relevant, and have been included. The results from these long-term studies up to 2 years confirm the clinical benefit for MDD patients, which typically experience a chronic course of the disease.

We used sophisticated fixed and random effects methods to summarise the results of contributing trials. Both methods preserve randomisation and its benefits in summarising trials. Fixed effects methods assume that there is a single treatment effect which is estimated across the contributing trials, which random effects approaches consider a range of treatment effects which are distributed among the contributing studies. The full random effects approach taken is particularly helpful in that, unlike standard random effects approaches, it does not assume that observed heterogeneity in treatment effects is the true heterogeneity, but instead this is estimated with error from the contributing trials and that measurement error (e.g. uncertainty on the degree of heterogeneity) is incorporated in the estimates of treatment effect. This has the consequence that in meta analyses of small numbers of studies, even when little evidence of heterogeneity is observed, the uncertainty on the degree of true heterogeneity (e.g. the inadequacy of the measurement of heterogeneity from the trials) will lead to a full random effects analysis with wide confidence intervals. While it is statistically appropriate to present both fixed and full random effects analyses, we must recognise that the random effects estimates presented in this paper will not be directly comparable to those using standard approximate methods. Our principal analyses utilised a random effects approach because of the potential for differences in the magnitude of treatment effects between different trials.

Our analysis has a number of strengths. First, we conducted a careful systematic literature search in order to identify all published randomised trials relevant to our questions. Second, we were able to gain

access to several randomised trials, which have not been published so far, conducted by Wyeth, the manufacturer of venlafaxine. Third, we used appropriate statistical methods to pool relevant data from all trials, and to assess heterogeneity of treatment effect and asymmetry of treatment effect.

However, the following limitations have to be considered: First, we cannot ensure to have included all unpublished data. However, we found no difference in the results when analysing published and unpublished trials separately. For example, the odds ratio for response with venlafaxine versus SSRIs was 1.14 (95% CI 1.00–1.30) for published trials and 1.13 (95% CI 0.95–1.35) for the unpublished trials (*P* value for difference = 0.95), providing no evidence of a selection bias between unpublished and published trials. Second, we were limited to the analysis of published summary data, rather than individual patient data, which hindered an adequate exploration of homogeneity of treatment effects across relevant subgroups of patients. Third, in a number of trials we were unable to pool results because of poor data reporting. Limitations in the reporting of outcome measures undermine the validity of the study. Although we have no evidence of bias in reporting of outcome measures, such a bias if it existed would also lead to bias in the pooled estimates of treatment effect (a form of publication bias which we found no evidence of). Fourth, while we were able to describe potential differences in treatment effects between agents through describing the pooled results for each agent in subgroup analyses (Figs. 2 and 3), it was not possible to examine other potential sources of heterogeneity such as differences in dosages and dose escalation of the different comparator agents and differences in settings. This is because of poor understanding on what constitutes an adequate dose of different agents or lack of consistency on the definitions of treatment settings. Fifth, the results of comparisons between venlafaxine and SSRIs or tricyclic antidepressants are necessarily driven by the agents for which randomised trials are available for pooling. Thus for example 52% of trials comparing venlafaxine with SSRIs for the outcome of response were comparisons with fluoxetine, and 24% were comparisons with paroxetine. The comparison of venlafaxine and specific antidepressants is described by the point estimates and 95% confidence intervals in Figs. 2 and 3.

In conclusion

There is considerable data on the comparative effectiveness of venlafaxine. Venlafaxine appears superior to SSRIs for both response and remission, with similar overall tolerability, derived from a lower rate of drop out for inefficacy and a higher rate of drop out from side effects. Further, there is some evidence for the superiority of venlafaxine over tricyclic antidepressants for the outcome of response. In addition, venlafaxine may have an important role in the long-term prevention of depressive relapse and recurrence, and in patients with treatment resistant depression who have failed to respond previously to antidepressant therapy.

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Appendix

Table 2 Data from trials comparing venlafaxine and SSRIs

Study	*N* (Ven)	*N* (Con)	Remit (Ven)	Remit (Con)	Resp (Ven)	Resp (Con)	Drop out (Ven)	Drop out (Con)	Side effects (Ven)	Side effects (Con)	Inefficacy (Ven)	Inefficacy (Con)
Allard [2]	73	75			49	54			6	3		
Hua [16]	34	32	9	4	24	22	2	1	1			
Bielski [9]	100	98	31	35	48	60	34	26	16	4		
Montgomery [31]	145	148	99	102	113	113	19	21	16	11	3	6
0600A-332, Wyeth-Ayerst USA [70]	27	24			14	15	8	6	7	1	1	0
Diereck [15]	153	161			107	100	38	40	14	7	9	14
0600A1-372, Wyeth research Philadelphia [63]	156	152			86	74	43	37	21	11	1	3
Rudolph [37]	95	103	37	22	57	50	19	28	6	9	3	7
Silverstone [46]	128	121	38	36	82	74	37	32	13	8	6	6
0600A 626 Wyeth-Ayerst [68]	79	77	26	19	38	36	15	24	10	13	1	2
0600A 654 Wyeth-Ayerst [66]	131	135					55	43	36	17	3	0
0600B 100469 Wyeth-Ayerst USA [71]	821	275	380	132	232	78	291	90	72	22	56	26
Costa e Silva [45]	196	186	44	42	119	114	29	18	14	7	5	2
Tylee [56]	171	170	44	42	79	84	47	46	36	24	4	7
Schatzberg [41]	104	100	44	29	59	48	37	30	28	19	2	6
DeNayer [13]	73	73	38	27	46	33	24	29	8	9	5	10
Tzanakaki [57]	55	54	22	19	38	33	10	11	3	5	4	4
Alves [3]	40	47	19	19	32	34	7	9				
Clerc [10]	34	34			24	17	6	12	1	5	3	6
Diaz-Martinez [14]	70	75			37	45	15	20	8	6	0	0
Zanardi [78]	14	14	7	11			2	0	2	0	0	0
0600A-347 Wyeth research Philadelphia [59]	63	29					13	9	5	3	3	3
0600A-349 Wyeth research Philadelphia [61]	82	85					28	24	17	8	7	5
0600B1-367 Wyeth-Ayerst France [74]	165	81	85	34	98	44	46	28	15	7	15	13
0600B 428 Wyeth-Ayerst [67]	58	56	47	32	43	29	10	10	2	3		
Ballus [5]	41	43	23	22	27	26	16	11	6	3	2	4
McPartlin [29]	183	178	98	93	139	128	47	52	22	29	2	5
Poirier [36]	61	62	22	11	27	18			5	3	3	3
Li [25]	30	30	9	4	24	22	1					
Hwang [22]	52	53			46	51	3	3				
Mehtonen [30]	75	72	40	27	49	41	16	12	12	5	6	4
Oslin [35]	25	27					15	5	13	5		
Sir [48]	84	79	43	47	56	56	25	13	5	3		
0600B1-402 Wyeth research Philadelphia [58]	295	293	130	121	174	167	92	95	33	31	7	8

Remit remittance, *Resp* response, *Inefficacy* drop out due to inefficacy, *Drop out* overall drop out, *Ven* venlafaxine, *Side effects* drop out due to side effects, *Con* control treatment

Table 3 Data from trials comparing tricyclics and venlafaxine

Study	*N* (Ven)	*N* (Con)	Remit (Ven)	Remit (Con)	Resp (Ven)	Resp (Con)	Drop out (Ven)	Drop out (Con)	Side effects (Ven)	Side effects (Con)	Inefficacy (Ven)	Inefficacy (Con)
0600A-319 Wyeth-Ayerst France [75]	55	50	19	14	27	22	18	21	11	12	5	5
Gentil [19]	57	59	34	35	43	44	9	8	6	4	0	0
Sauer [40]	79	77			51	35			4	6		
0600A1-300 Wyeth research Philadelphia [64]	58	52					28	28	7	9	14	9
Samuelian [39]	52	50	21	15	30	20	18	18	7	10	4	3
0600A-326 Wyeth-Ayerst France [76]	60	61	20	28	32	41	22	13	6	6	12	3
Smeraldi [49]	55	58			37	46	20	44	3	8	3	12
Mahapatra [27]	44	48	21	19	26	28	9	7	3	4	2	1
Trick [55]	45	43			22	18	20	14	17	14	0	0
Schweizer [42]	73	73			42	33	26	33	12	18	3	1
0600A-303 Wyeth-Ayerst USA [72]	79	76			31	29	31	31	15	12	7	4
Benkert [7]	85	82			44	48	21	31	8	10	14	14
6001A-343 Wyeth-research Philadelphia [62]	139	69			66	28	54	36	21	19	6	4
Lecrubier [24]	78	75			65	50	23	23	11	10	2	8
0600B1-384 Wyeth-Ayerst USA [69]	176	183			75	83	55	59	23	30	14	6
Shrivastava [44]	290	91			157	37	203	73	81	31	17	9
0600A-321 Wyeth-Ayerst France [73]	64	65	32	34	42	39	5	11	1	4	1	1
Gasto [18]	34	34	22	21			5	6	1	1		

Remit remittance, *Resp* Response, *Drop out* overall drop out, *Side effects* drop out due to side effects, *Inefficacy* drop out due to inefficacy, *Ven* venlafaxine, *con* control treatment

Table 4 Treatment resistant trials

Study	*N* (Ven)	*N* (Con)	Remit (Ven)	Remit (Con)	Resp (Ven)	Resp (Con)	Drop out (Ven)	Drop out (Con)	Side effects (Ven)	Side effects (Con)	Inefficacy (Ven)	Inefficacy (Con)
Rush [38]	250	477	62	93								
Corya [11]	59	60	13	10	29	19	15	12	1	3	7	4
Baca [4]	1,830	1,672	967	755	1,262	1,034	517	548	220	122	225	234
0600B 671 Wyeth-Ayerst [65]	200	206	94	93	123	129	49	43	10	9	17	12
Poirier [36]	61	62	22	11	27	18			5	3	3	3

Remit remittance, *Resp* response, *Drop out* overall drop out, *Side effects* drop out due to side effects, *Inefficacy* drop out due to inefficacy, *Ven* Venlafaxine, *Con* control treatment

Table 5 Long term relapse prevention trials

Study	*N* (Ven)	*N* (Placebo)	Relapse (Ven)	Relapse (Placebo)
0600A-335 [32]	109	116	24	64
0600B1-370- [47]	154	138	40	64
0600B-100469 Wyeth-Ayerst USA [71]	129	129	29	46

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