

Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline

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Background Few studies have examined the relative risks of switching into hypomania or mania associated with second-generation antidepressant drugs in bipolar depression.

Aims To examine the relative acute effects of bupropion, sertraline and venlafaxine as adjuncts to mood stabilisers.

Method In a 10-week trial, participants receiving out-patient treatment for bipolar disorder (stratified for rapid cycling) were randomly treated with a flexible dose of one of the antidepressants, or their respective matching placebos, as adjuncts to mood stabilisers.

Results A total of 174 adults with bipolar disorder I, II or not otherwise specified, currently in the depressed phase, were included. All three antidepressants were associated with a similar range of acute response (49–53%) and remission (34–41%). There was a significantly increased risk of switches into hypomania or mania in participants treated with venlafaxine compared with bupropion or sertraline.

Conclusions More caution appears indicated in the use of venlafaxine rather than bupropion or sertraline in the adjunctive treatment of bipolar depression, especially if there is a prior history of rapid cycling.

Declaration of interest None.

Bipolar disorder occurs in 1–3% of the population (Angst & Sellaro, 2000; Akiskal *et al*, 2000). Despite naturalistic treatment in the community or intensive treatment at academic centres, patients remain symptomatic approximately half of the year, and the time depressed exceeds the time manic or hypomanic by a factor of three (Judd *et al*, 2002; Post *et al*, 2003a; Kupka *et al*, 2005). Bipolar disorder is potentially lethal, with a 10–20% lifetime risk of dying by suicide (Goodwin & Jamison, 1990).

Despite these staggering human and public health statistics, there have been relatively few controlled studies of the use of antidepressants in the treatment of acute bipolar depression (Cohn *et al*, 1989; Himmelhoch *et al*, 1991; Young *et al*, 2000; Nemeroff *et al*, 2001) compared with numerous controlled trials in unipolar depression. There has been one moderately sized ($n=60$) randomised, single-blind study comparing the efficacy of paroxetine and venlafaxine (Vieta *et al*, 2002) in bipolar depression. A small comparative trial by Sachs *et al* (1994) suggested that bupropion – which increases brain dopamine levels in the dorsal and ventral striatum upon acute and chronic administration (Nomikos *et al*, 1989, 1992) and also possesses some effects on noradrenaline – showed comparable acute efficacy to the noradrenergic tricyclic antidepressant desipramine, when added to ongoing treatment with a mood stabiliser for acute treatment of bipolar depression. However, the rate of switching into mania or hypomania on desipramine during acute and continuation treatment was considerably higher (37.5%) compared with bupropion (13.3%) (Guille *et al*, 1999). These data suggested the possibility that either the anticholinergic effects associated with the older tricyclic compounds in general or the potent selective effects of desipramine on noradrenaline re-uptake could account for these differences. Gijssman *et al* (2004) in a meta-analysis found comparable efficacy but higher

switch rates for tricyclic antidepressants compared with the newer antidepressants in acute trials for bipolar depression.

Based on the early study of Sachs *et al* (1994), we predicted that the three antidepressants bupropion, sertraline and venlafaxine would achieve equal rates of response, but that venlafaxine (like desipramine) would show a higher rate of switching into hypomania or mania because of its additional noradrenergic effects. Consistent with the latter hypothesis, the study of Vieta *et al* (2002) found an increased rate of switching on venlafaxine (13.3%) in a single-blind, randomised comparison with paroxetine (3.0%) for 6 weeks in bipolar depression.

METHOD

This study was a 10-week randomised trial of 184 patients comparing bupropion, sertraline and venlafaxine as adjuncts to one or more mood stabilisers. Because of the anticipated prolonged unavailability of one set of masked compounds at study outset, the first 28 patients were randomised by a data-coordinating centre in Bethesda but were treated with open medications at each site; the next 156 patients were studied in a randomised, double-blind fashion. Each of the three drugs had an identically matched placebo and all patients took two sets of compounds throughout this study (one active and one placebo).

The study method has been previously described for a smaller subgroup of these patients in an interim analysis of the overall response and switch rates into hypomania or mania of the antidepressants as a group prior to unmasking the data (Post *et al*, 2001a,b). This is the report of the response and switch rates of each of the three separate antidepressants, and it includes the entire cohort of patients randomised to the first acute phase of adjunctive treatment of bipolar depression.

Patients were included when they met criteria for DSM-IV bipolar depression (American Psychiatric Association, 1994) and had an Inventory of Depression Symptomatology (IDS; Rush *et al*, 1986, 1996) scale score of at least 16; a Clinical Global Impression scale for Bipolar Disorder (CGI-BP; Spearing *et al*, 1997) depression severity score of at least 3; or the decision on the part of the physician of a need to treat the depressive episode because of its functional impact. Most of these patients

were also rated for severity of depression and mania on a daily basis on the National Institute of Mental Health – Life Chart Method (NIMH–LCM), as described by Leverich *et al* (2006).

Patients who showed clinically relevant levels of mania – a Young Mania Rating Scale (YMRS; Young *et al*, 1978) score of at least 14 or a CGI–BP mania severity score of at least 3 – at baseline were excluded from the study, leaving a sample of 174 patients. The antidepressants were added to an average of 1.4 other mood stabilisers or antimanic agents. These medications included lithium (64 patients), valproate (93 patients), carbamazepine (16 patients), lamotrigine (8 patients), typical antipsychotics (8 patients) and atypical antipsychotics (30 patients). The maintenance medications were distributed equally among all three antidepressants except for lithium, which was present in 21.6% of those taking bupropion, 36.2% of those taking sertraline and 47.7% of those taking venlafaxine ($P=0.01$).

All the patients who were randomised had a depressive episode despite ongoing treatment with one or more mood stabilisers within specified dosage and therapeutic blood level guidelines. The minimum blood level guidelines for the mood stabilisers were 0.7 mmol/l for lithium, 50 µg/ml for valproate and 4 µg/ml for carbamazepine. Dosages of these drugs, as well as of typical or atypical antipsychotics, or ongoing benzodiazepines in prophylaxis, were held steady during the course of the protocol except for dose reductions because of side-effects. However, acute augmentation with benzodiazepines or chloral hydrate for a maximum of 7 days was allowed for relief of initial treatment-emergent insomnia or anxiety.

All patients were participants in the Stanley Foundation Bipolar Network at a time when it was funded by the Stanley Medical Research Institute, the National Institute for Mental Health and each local academic site (Leverich *et al*, 2001; Post *et al*, 2001b; Suppes *et al*, 2001). All patients provided written informed consent for participation in the Network in general, and additional specific written informed consent for participation in this randomised clinical trial as approved by each local institutional review board. In the randomisation, the patients were stratified on the basis of presence or absence of a prior history of DSM–IV-defined rapid cycling in the year prior to study entry. At the

European sites in The Netherlands and Germany, patients were randomised only between sertraline and venlafaxine because bupropion was not approved or available in these countries.

The antidepressants were titrated towards maximum dosages based on side-effects tolerability and clinical discretion during the 10-week acute trial. Starting and maximal dosages respectively for each compound were: bupropion 75–450 mg/day, sertraline 50–200 mg/day and venlafaxine 37.5–375 mg/day.

Patients were seen weekly for 2 weeks and then every 2 weeks for the duration of the 10-week acute-treatment trial. Symptom assessments were conducted using the IDS, the YMRS and the CGI–BP at each visit. The CGI–BP part I, or severity scale, parallels that of the original CGI, but the new format allows separate ratings for severity of depression, mania and overall illness. The scale ranges are 1 not ill, 2 minimally ill, 3 mildly ill, 4 moderately ill, 5 markedly ill, 6 severely ill and 7 very severely ill.

Although those not responding to antidepressant therapy were subsequently offered re-randomisation to another antidepressant (Post *et al*, 2001a; Leverich *et al*, 2006), the analysis in this report only considered the first parallel-group randomised phase, so that all patients would be represented only once and data would be suitable for independent statistics. All data presented represent the intention-to-treat analysis.

Three outcome variables were assessed: antidepressant response, antidepressant remission and antidepressant-related switch into mania or hypomania. Response was operationalised as either a 50% or greater improvement in IDS score, or a decrease in the CGI–BP depression score of at least 2 points. Response rates were reported at the study end-point and the time to response was calculated for each drug. Remission criteria included an IDS score below 12 and/or a CGI–BP depression severity score of 1 (normal, not ill) at study end-point. A switch into hypomania or mania was operationalised as either a 2-point increase at any point in the trial on the CGI–BP (suggesting a clinically meaningful switch), or a CGI–BP manic severity score of at least 3 (i.e. at least mildly manic) or a YMRS score above 13 at any visit.

Statistical analysis

The Stanley Foundation Bipolar Network ended in 2002 and the analysis of these

data was supported by the Stanley Research Medical Institute. The core data repository was transferred from the data coordinating centre in Bethesda to the University of California at Los Angeles where analyses for this study were conducted. The patients were entered into this study at the seven different sites beginning in March 1996 and ending in November 2002.

When demographic data, response rates and switch rates were analysed separately for the 27 open and 147 masked randomisations, they were not found to be statistically significantly different (details available in the data supplement to the online version of this paper). Therefore, the data are presented for the combined analysis of the 174 patients for simplicity of presentation and in order to have maximum power for detecting differences in switch rates among the three antidepressant drugs. This was felt to be justified because our initial hypothesis was that there would be no significant difference in initial degrees of acute responsiveness among these three antidepressants, but as in the Sachs *et al* (1994) data for desipramine, venlafaxine would have a higher switch rate than the other two drugs.

Kaplan–Meier curves were used to construct survival curves among the treatment arms in time-to-event data. Differences in strata were assessed using the log-rank test. Chi-squared tests were used to assess significance for categorical data.

RESULTS

Patient characteristics are summarised in Table 1 and the flow of patients is shown in Fig. 1. Participants showed balanced gender distribution, were an average of 41.7 years of age and had 19.1 years of illness, averaging 14.3 prior episodes of depression and 12.2 prior episodes of mania. The majority (73%) of diagnoses were bipolar I disorder, 26% were bipolar II disorder and 1% bipolar disorder not otherwise specified. More than a quarter (27%) had a prior history of rapid cycling. Fifty-one patients were randomised to receive bupropion, 58 to sertraline and 65 to venlafaxine. Patients were treated with an average maximum daily dosage of 286 (s.d.=132) mg for bupropion, 192 (s.d.=104) mg for sertraline or 195 (s.d.=112) mg for venlafaxine.

About a third of the patients withdrew from the trial prematurely, for lack of

Table 1 Demographic factors and course of illness data

Variable	Randomised drug			All (n=174)	Test statistic	P
	Bupropion (n=51)	Sertraline (n=58)	Venlafaxine (n=65)			
Gender						
Female, %	54.9	44.8	50.8	50	$\chi^2=1.13$, d.f.=2	0.57
Age, years: mean (s.d.)						
Age at study entry	41.0 (11.8)	43.4 (14.2)	40.6 (12.1)	41.7 (12.7)	$F=0.82$, d.f.=2	0.44
Age at onset of illness ¹	19.3 (12.7) n=45	25.1 (14.6) n=51	23.2 (12.2) n=59	22.7 (13.3) n=155	$F=2.38$, d.f.=2	0.10
Type of disorder, n (%)						
Bipolar I	35 (69)	41 (71)	50 (77)	126 (73)		
Bipolar II	16 (31)	16 (28)	14 (22)	46 (26)		
Bipolar NOS	0 (0)	1 (1)	1 (1)	2 (1)	$\chi^2=2.80$, d.f.=4	0.59
Rapid cycling	16 (31)	13 (22)	18 (28)	47 (27)	$\chi^2=1.14$, d.f.=2	0.57
Prior depression history:						
mean (s.d.)						
Episodes ¹	16.1 (5.8) n=45	13.3 (7.6) n=52	13.7 (7.5) n=49	13.7 (7.1) n=146	$F=2.131$, d.f.=2	0.12
Hospitalisations ¹	1.4 (2.7) n=45	1.6 (2.0) n=52	2.6 (4.5) n=49	1.9 (3.2) n=146	$F=1.92$, d.f.=2	0.15
Prior mania history:						
mean (s.d.)						
Episodes ¹	13.3 (7.3) n=45	10.9 (8.1) n=52	12.5 (7.3) n=48	12.2 (7.3) n=145	$F=1.22$, d.f.=2	0.30
Hospitalisations ¹	1.3 (2.3) n=45	1.6 (3.2) n=48	2.6 (5.0) n=48	1.8 (3.7) n=141	$F=1.64$, d.f.=2	0.20
Severity of depression at baseline:						
mean (s.d.)						
IDS	30.6 (10.6)	35.8 (9.7)	34.08 (10.2)	33.6 (10.3)	$F=3.67$, d.f.=2	0.03
CGI-BP	4.25 (0.99)	4.71 (0.88)	4.65 (1.01)	4.55 (0.98)	$F=3.49$, d.f.=2	0.03

CGI-BP, Clinical Global Impression – Bipolar Disorder; IDS, Inventory of Depression Symptomatology; NOS, not otherwise specified.
1. Not reported by several patients in each group.

improvement or worsening mood, including 29% of those taking bupropion ($n=15$), 28% taking sertraline ($n=16$) and 38% taking venlafaxine ($n=25$) (Table 2). Other withdrawals for side-effects or administrative reasons did not differ among the three drugs.

Overall, the percentage of patients who left the study prior to 10 weeks for any reason was 31% of those taking bupropion, 41% of those taking sertraline and 45% of those taking venlafaxine.

Response and remission rates

At week 10, using the IDS or CGI-BP criterion, response rates were 49% for bupropion, 53% for sertraline and 51% for venlafaxine; remission rates (either IDS

score ≤ 12 or CGI-BP score=1) were 41%, 36% and 34% respectively (Table 3). There was no significant difference between the groups. To evaluate if co-treatment with lithium influenced these results a log linear model was fitted to the data. The inclusion of a relationship between lithium and response or remission did not improve the fit of the log linear model (response: $\Delta\chi^2=0.196$, d.f.=1, $P>0.5$; remission: $\Delta\chi^2=0.112$, d.f.=1, $P>0.5$).

Switch rates

Most patients did not switch into hypomania or mania when prescribed acute adjunctive antidepressant therapy, regardless of the antidepressant prescribed. However,

on most measures and analyses venlafaxine showed a higher risk of patients switching into hypomania or mania than bupropion or sertraline. Using the requirement of a 2-point or greater increase on the CGI-BP mania severity rating, switching occurred in 10% of patients taking bupropion, 9% taking sertraline, and 29% taking venlafaxine. To control for the effect of withdrawals on the relative risk of switching, these data were analysed using survival analysis (Fig. 2). Results revealed a significant overall difference between the three groups (log rank $\chi^2=12.462$, d.f.=2, $P=0.002$). Controlling for lithium yielded the same result (log rank $\chi^2=11.99$, d.f.=2, $P<0.01$). *Post hoc* analysis of this result demonstrated that the effect was mainly driven by a significant difference in the risk of switching

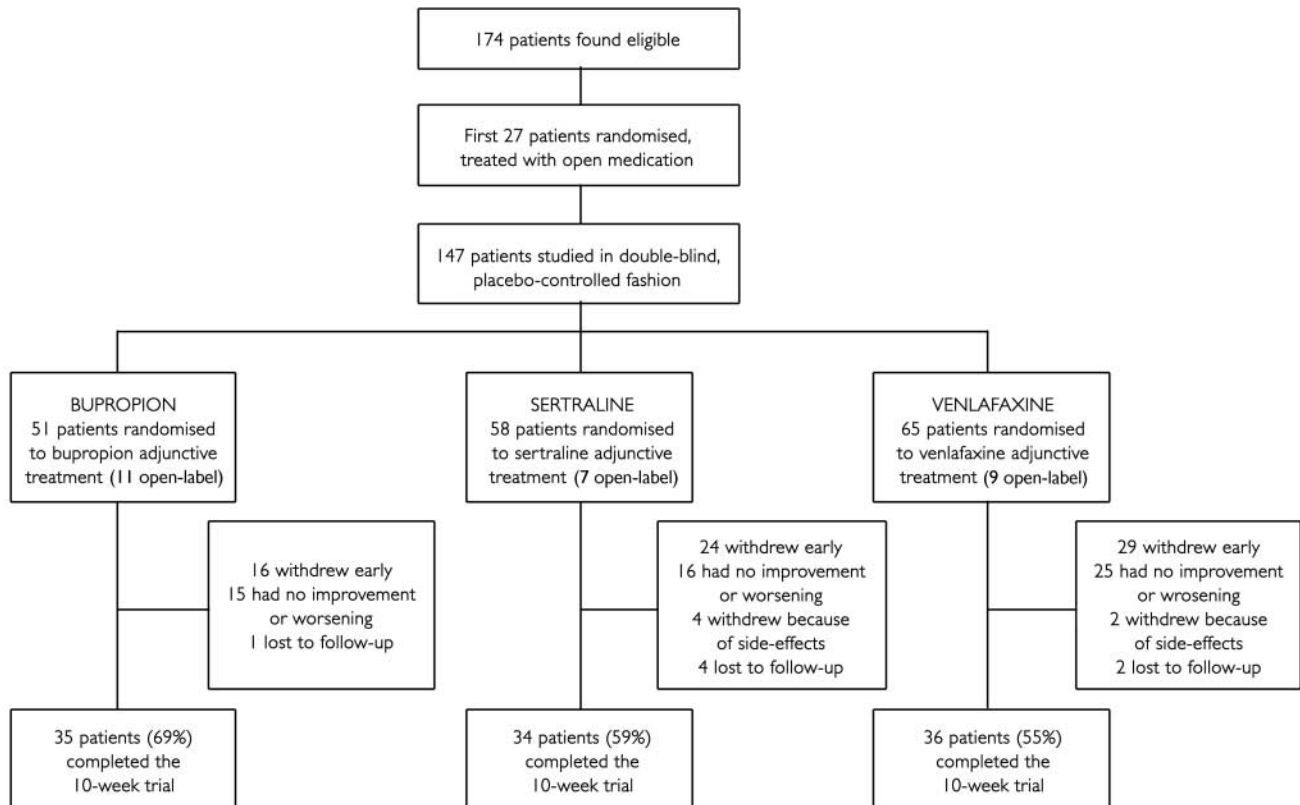


Fig. 1 Study profile.

time between venlafaxine and both sertraline and bupropion (venlafaxine *v.* sertraline, adjusted for lithium: log rank $\chi^2=6.70$, d.f.=1, $P=0.01$; venlafaxine *v.* bupropion, adjusted for lithium: log rank $\chi^2=8.16$, d.f.=1, $P<0.01$), whereas there

was no significant difference between sertraline and bupropion (adjusted for lithium: log rank $\chi^2=0.02$, d.f.=1, $P=0.90$).

Using the more conservative YMRS threshold score of >13, only 4% of

patients on bupropion and 7% of patients on sertraline switched into hypomania or mania by study end-point, but 15% of patients on venlafaxine had switched by study end-point (log rank $\chi^2=5.91$, d.f.=2, $P=0.052$; Fig. 3). The effect of medication

Table 2 Early discontinuation from 10-week adjunctive antidepressant trial

Reasons	Early discontinuation, n (%)				Test statistic	P
	Bupropion (n=51)	Sertraline (n=58)	Venlafaxine (n=65)	Total (n=174)		
All reasons	16 (31)	24 (41)	29 (45)	69 (40)	$\chi^2=2.24$, d.f.=2	0.33
No improvement/worsening ¹	15 (29)	16 (28)	25 (38)	56 (32)	$\chi^2=1.92$, d.f.=2	0.39
Hypomania	2	1	6	9		
Mania	2	1	1	4		
Hospitalised	0	0	2	2		
Depression	8	9	10	27		
Hospitalised	0	3	3	6		
Suicide attempt	0	0	1	1		
Psychosis	0	1	1	2		
Cycle acceleration	2	0	2	4		
Other unspecified	1	1	0	2		
Side-effects	0 (0)	4 (7)	2 (3)	6 (3)	$\chi^2=5.23$, d.f.=2	0.07
Administrative	1 (2)	4 (7)	2 (3)	7 (4)	$\chi^2=1.88$, d.f.=2	0.39

1. Multiple symptoms were possible.

Table 3 Rates of antidepressant response, remission and switching into hypomania or mania

Outcome	Bupropion (n=51) n (%)	Sertraline (n=58) n (%)	Venlafaxine (n=65) n (%)	All (n=174) n (%)	Test statistic	P
Response						
IDS (50% improvement)	17 (33)	24 (41)	24 (37)	65 (37)	$\chi^2=0.76$, d.f.=2	0.68
Either IDS or CGI-BP (2-point improvement)	25 (49)	31 (53)	33 (51)	89 (51)	$\chi^2=0.22$, d.f.=2	0.90
Remission						
IDS \leq 12	19 (37)	20 (34)	16 (25)	55 (32)	$\chi^2=2.49$, d.f.=2	0.29
Either IDS \leq 12 or CGI-BP=1	21 (41)	21 (36)	22 (34)	64 (37)	$\chi^2=0.67$, d.f.=2	0.72
Switching into hypomania or mania						
YMRS > 13	2 (4)	4 (7)	10 (15)	16 (9)	log rank $\chi^2=5.93$, d.f.=2	0.05
Either CGI-BP \geq 3 or YMRS > 13	7 (14)	9 (16)	20 (31)	36 (21)	log rank $\chi^2=7.33$, d.f.=2	0.03
CGI-BP increase of 2	5 (10)	5 (9)	19 (29)	29 (17)	log rank $\chi^2=12.46$, <0.01 d.f.=2	
Rapid cycling and switching						
Using YMRS > 13						
RC (switch/total)	0/21 (0)	1/12 (8)	4/14 (29) ¹	5/47 (11)	log rank $\chi^2=9.658$, <0.01 d.f.=2	
Non-RC (switch/total)	2/30 (7)	3/46 (6)	6/51 (12)	11/127 (9)	log rank $\chi^2=1.197$, d.f.=2	0.55
Using either CGI-BP \geq 3 or YMRS > 13						
RC	3/21 (14)	1/12 (8)	6/14 (43)	10/47 (21)	log rank $\chi^2=7.898$, d.f.=2	0.02
Non-RC	4/30 (13)	8/46 (17)	14/51 (27)	26/127 (20)	log rank $\chi^2=3.133$, d.f.=2	0.21

CGI-BP, Clinical Global Impression – Bipolar Disorder; IDS, Inventory of Depression Symptomatology; RC, rapid cycling; YMRS, Young Mania Rating Scale.

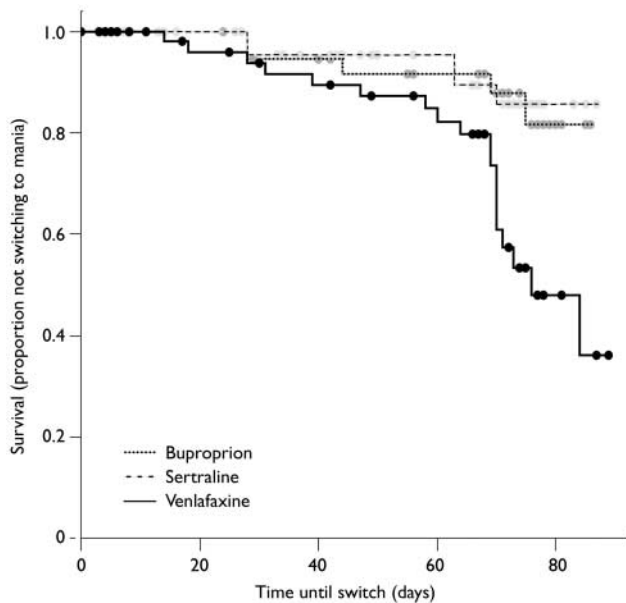


Fig. 2 Increased switch rate (defined as a 2-point increase in manic severity score on the Clinical Global Impression – Bipolar Disorder scale) for venlafaxine compared with bupropion and sertraline.

on the survival rates was not significant. In addition, controlling for possible effects of lithium did not influence the results (log rank $\chi^2=5.80$, d.f.=2, $P=0.055$).

Using the combined switch criterion of CGI-BP severity of mania \geq 3 or YMRS > 13, the switch rate of the bupropion group was 14%, the switch rate of the sertraline group was 16% and the switch rate for venlafaxine was 31%. This difference was significant both when lithium was not included (log rank $\chi^2=7.33$, d.f.=2, $P=0.03$) and when lithium was included (log rank $\chi^2=7.55$, d.f.=2, $P=0.02$). The results of a *post hoc* analysis again showed that the difference was driven by venlafaxine. The hazard for switching was not significantly different between bupropion and sertraline after adjustment for lithium (log rank $\chi^2=0.38$, d.f.=1, $P=0.54$), whereas the patients treated with venlafaxine experienced significantly higher switch rates than the patients

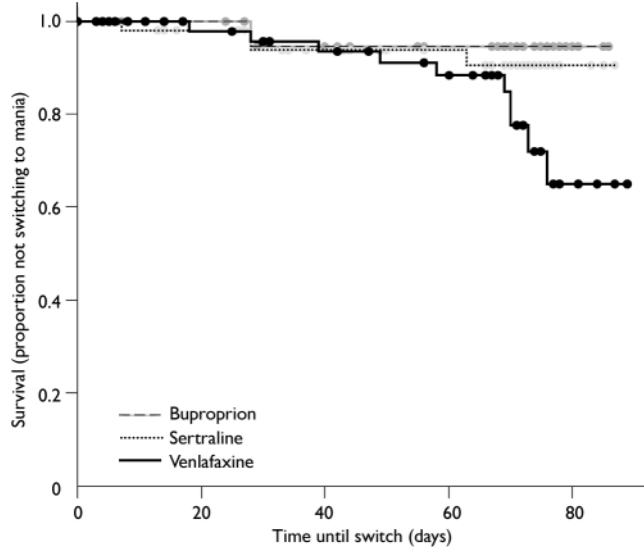


Fig. 3 Increased switch rate, defined more conservatively by Young Mania Rating Scale scores >13 , on venlafaxine compared with bupropion and sertraline.

treated with bupropion (adjusted for lithium, log rank $\chi^2=6.35$, d.f.=1, $P=0.01$). The difference in the risk for switching between venlafaxine and sertraline was not significant at $\alpha=0.05$, but the data suggest a trend towards a difference (adjusted for lithium, log rank $\chi^2=3.18$, d.f.=1, $P=0.07$).

Rapid cycling

There was a strong interaction between the rapid-cycling status of patients and the relative risk of switching for the three medication groups. In those without rapid-cycling disorder the risk of switching was identical for all three medication groups (log rank $\chi^2=1.197$, d.f.=2, $P=0.55$), but the difference between the three medications was highly significant among rapid-cycling patients (log rank $\chi^2=9.66$, d.f.=2, $P<0.01$). The pattern of this difference for the rapid-cycling group was the familiar result that bupropion had a significantly lower risk for switching than venlafaxine (log rank $\chi^2=9.07$, d.f.=1, $P<0.01$), whereas there was no significant difference between bupropion and sertraline (log rank $\chi^2=1.9$, d.f.=1, $P=0.17$) or between sertraline and venlafaxine (log rank $\chi^2=2.1$, d.f.=1, $P=0.15$).

DISCUSSION

Overall response and switch rates on antidepressant augmentation

To our knowledge, this is the largest randomised comparative study of the response

and switch rates of modern (i.e. non-tricyclic) antidepressants in the adjunctive treatment of acute bipolar depression. All of these unimodal antidepressants are approved by the US Food and Drug Administration (FDA) for the treatment of major depression, but are not FDA-approved for use in bipolar depression and are not widely studied by European authorities.

The three agents with different mechanisms of action were assessed for their relative magnitude of acute antidepressant response when added to ongoing treatment with mood stabilisers in this 10-week trial. Overall response (49–53%) and remission rates (34–41%) were similar to those often seen in antidepressant monotherapy trials in unipolar illness, using the traditional 50% improvement and absolute criteria respectively. Substantial numbers of patients (31–45%) withdrew prematurely from the trial because of lack of improvement or worsening of either depressed or manic mood, indicating a continuing need to find more effective agents for even the acute treatment of bipolar depression.

Most patients in this acute treatment trial did not switch into hypomania or mania with the addition of an antidepressant to their ongoing mood stabiliser regimen. Overall, across all medication groups, 9% switched by the more stringent criteria of YMRS score >13 (Table 3), whereas more than double that (21%) switched using the CGI-BP severity score (≥ 3) of at least mild mania.

The CGI-BP cut-off of mild mania is a more permissive measure than the YMRS

score, and this two-fold difference in what is categorised as a switch depending on which scale or cut-off score is used needs to be considered by investigators in the future when designing trials and specifying outcome measures. Use of different threshold criteria may account for some of the large discrepancies in the field regarding reported switch rates. Similarly, the inclusion or exclusion of patients with rapid-cycling disorder in a study also contributes to these differences in switch rates.

Switch rates among the three antidepressants

Venlafaxine had a greater risk for inducing switching than the other two agents, i.e. bupropion as a dopamine-active agent and sertraline as a representative serotonin selective reuptake inhibitor (SSRI) (Nomikos *et al*, 1989, 1992; Ascher *et al*, 1995).

Venlafaxine's dual actions on serotonin and noradrenaline reuptake (Montgomery *et al*, 1993), which may account for its greater efficacy in patients with unipolar depression compared with SSRIs in recent meta-analyses (Thase *et al*, 2001; Stahl *et al*, 2002), could have contributed to the higher rate of switching with this agent compared with the other two agents.

These data are consistent with those from the single-blind randomised study of Vieta *et al* (2002), who found a greater switch risk for venlafaxine (mean dosage 180 mg) compared with the SSRI paroxetine (mean dosage 30 mg), although patients were only assessed for 6 weeks and the YMRS criterion for a switch was a score of 11 as opposed to the 14 used here. Nonetheless, the switch rates for venlafaxine (13.3%) *v.* paroxetine (3.0%) in that study were of a similar magnitude to the switch rates in this study for venlafaxine (15.4%) *v.* sertraline (6.9%).

These findings could also be consistent with the higher switch rates for the tricyclic antidepressants (Gijsman *et al*, 2004) which represent largely combined serotonin and noradrenaline reuptake inhibitors, or noradrenaline selective ones (e.g. nortriptyline and desipramine). Sachs *et al* (1994) and Guille *et al* (1999) also found a higher switch rate for desipramine than for bupropion.

Interestingly, in our study the greater switch rates on venlafaxine compared with the other drugs were largely accounted for by the increased switch risk in the rapid-cycling group, and those without rapid-cycling disorder did not show this

differential risk. It is especially noteworthy that those with rapid-cycling disorder did not appear more switch-prone when exposed to bupropion or sertraline than those with the non-rapid-cycling form on these drugs, as many might have predicted (log rank $\chi^2=0.321$, d.f.=1, $P=0.571$).

Methodological limitations

This study has several methodological limitations, including the combination of data for the first 27 open randomised patients with the next 147 studied in a double-blind fashion. However, this did not have a major impact on the observed rates of response, remission or switching. Generally similar findings were observed when only the 147 masked patients were included (further information available in the data supplement to the online version of this paper).

A problem not addressed by our study is the rate of response or switching related to antidepressant agents over that which might occur naturally through course of illness variation. It was decided not to include a placebo arm in this study to make it most similar to naturalistic treatment in the community and to focus on comparison of switch rates among the three agents. This was also intended to enhance participant recruitment in an out-patient setting in which a high percentage of patients were working full-time or part-time and generally wished to be treated with active agents as rapidly as possible. Thus, we do not know with any degree of certainty whether any of the antidepressants was efficacious, i.e. significantly more effective than placebo. This concern is also heightened by the finding of Nemeroff *et al* (2001) that the effectiveness of paroxetine did not exceed that of placebo when used as an adjunct to lithium (unless lithium levels were low). However, given that venlafaxine was more likely to be associated with hypomania or mania than two other active drugs (bupropion or sertraline), it would appear that venlafaxine carries an increased risk of switching compared with two other widely used antidepressants, especially in the treatment of patients with rapid-cycling bipolar illness. This differential liability of venlafaxine compared with two other active comparators to some extent obviates the need for a placebo comparison group, at least in relation to the rate of switching on venlafaxine.

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The study also did not address the optimal duration of antidepressant treatment, even though participants whose condition responded to therapy were offered continuation treatment on a masked basis (Post *et al*, 2001a, 2003b). However, based on data in three recent naturalistic studies (Altschuler *et al*, 2001, 2003; Joffe *et al*, 2005), it has been suggested that for the small minority of people with bipolar disorder who both respond to acute antidepressant treatment and remain well for at least 6 weeks, continuation of the antidepressant medication over the following year may be superior to its discontinuation because it is associated with a reduction in the occurrence of new depressive episodes without any increase in switch rates into mania. However, interim results of a 5-year study of 33 patients (Ghaemi *et al*, 2005) indicate that discontinuation of antidepressant may be either non-inferior or perhaps slightly superior to antidepressant continuation, which appeared to increase affective morbidity in non-rapid-cycling bipolar disorder.

Other limitations of this study include the flexible dosage titration, such that the rate of dosage increase and final levels achieved could have affected either response rates or switch vulnerability. However, the relatively low maximum dosage of venlafaxine compared with the other two drugs suggests that the high switch rate on venlafaxine was not related to an overly aggressive dose titration of this drug compared with the others.

Strengths of this study include its double-blind evaluation of 147 patients; that the study was relatively large

compared with many previous studies of bipolar depression; that the 174 patients randomised to one of the three second-generation antidepressants with different mechanisms of action were sufficient to discern a significant difference in switching into hypomania or mania on venlafaxine compared with bupropion and sertraline; and that the sample was representative of people receiving out-patient treatment, including those with a history of rapid-cycling disorder (Kupka *et al*, 2005).

Clinical and research implications

Other study designs, such as that used by Young *et al* (2000) in patients with non-rapid-cycling disorder, are now necessary to put these results in perspective, by examining the use of antidepressants with a low risk of switch (i.e. bupropion, sertraline or a related SSRI) compared with a second mood stabiliser (especially lamotrigine) or an atypical antipsychotic, in order to begin to develop an evidence-based algorithm for the best approach to the treatment of breakthrough bipolar depression in both rapid-cycling and non-rapid-cycling disorder. Since time depressed exceeds that of time manic by a factor of three in naturalistically treated out-patients (Judd *et al*, 2002; Post *et al*, 2003a,b,c; Nolen *et al*, 2004; Kupka *et al*, 2005), such direct comparisons for effectiveness, tolerability and switch risk would be timely and potentially highly informative for clinical practice.

The results of this study reveal non-significantly different acute antidepressant response and remission rates among the

three mechanistically different second-generation antidepressants used adjunctively in the acute treatment of bipolar depression. However, there was a significantly increased risk of switching into hypomania or mania on several measures during acute treatment with venlafaxine compared with bupropion or sertraline. This was largely accounted for by the increased switch rate in the rapid-cycling group taking venlafaxine. When daily NIMH-LCM ratings were used, venlafaxine also had a three times higher ratio than bupropion of full duration/severity switches compared with brief hypomanias in the 1-year continuation phase of the study, further suggesting that the increased risk of a full switch on venlafaxine does not dissipate after the end of the 10-week acute trial, as it tended to do for both bupropion and sertraline (Leverich *et al*, 2006). Clinicians should be aware of the risk of hypomania or mania for those prescribed venlafaxine (especially those with a history of four or more episodes in the prior year) when considering the choice of antidepressant for the common problem of bipolar depression breaking through ongoing treatment with one or more mood stabilisers.

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