

Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes

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Background

Combinations of olanzapine and carbamazepine are often used in clinical practice in the management of mania.

Aims

To assess the efficacy and safety of olanzapine plus carbamazepine in mixed and manic bipolar episodes.

Method

Randomised, double-blind, 6-week trial of olanzapine (10–30 mg/day) plus carbamazepine (400–1200 mg/day; $n=58$) v. placebo plus carbamazepine ($n=60$) followed by open-label, 20-week olanzapine (10–30 mg/day) plus carbamazepine (400–1200 mg/day, $n=86$), with change in manic symptoms as main outcome measure. Safety and pharmacokinetics were also evaluated.

Results

There were no significant differences (baseline to endpoint) in efficacy measures between treatment groups, but at 6

weeks triglyceride levels were significantly higher ($P=0.008$) and potentially clinically significant weight gain ($\geq 7\%$) occurred more frequently (24.6% v. 3.4%, $P=0.002$) in the combined olanzapine and carbamazepine group. Carbamazepine reduced olanzapine concentrations but olanzapine had no effect on carbamazepine concentrations.

Conclusions

The combination of olanzapine and carbamazepine did not have superior efficacy to carbamazepine alone. The increases in weight and triglycerides observed during combination treatment are a matter of concern.

Declaration of interest

Study sponsor: Eli Lilly & Company (employees: M.T., R.B., T.Q., O.O., W.W., F.M. and L.K.). Full declaration in Acknowledgements.

Olanzapine and carbamazepine (including extended release) each have proven efficacy when administered as monotherapy in treating people with acute mania and mixed episodes of bipolar disorder.^{1–5} None the less, people with bipolar disorder often require combinations of medications for symptom control. Therapeutic guidelines recommend carbamazepine as a second-line choice for maintenance treatment of bipolar disorder;^{6–8} thus, concomitant use of carbamazepine and olanzapine occurs in clinical practice. Because carbamazepine substantially induces the cytochrome P450 1A2 metabolism of olanzapine,⁹ an increase in the dose of olanzapine may be needed in such combinations. The objectives of this multicentre, randomised, two-arm, active-control, parallel, double-blind 6-week study with a follow-on 20-week open-label treatment phase were to assess the efficacy and safety of concomitant use of olanzapine (≤ 30 mg/day) and carbamazepine (400–1200 mg/day) for the treatment of individuals with bipolar disorder during manic or mixed episodes.

Method

Study design

The study (NCT00190892; Lilly study code: F1D-MC-HGKR) was composed of three phases: 1-week screening/washout phase, followed by a 6-week double-blind treatment phase, which was followed by a 20-week open-label phase. The screening/washout phase enabled individuals to taper off and discontinue medications not allowed during the study. Participants were randomly assigned after the screening/washout phase at a ratio of 1:1 to receive olanzapine plus carbamazepine or placebo plus carbamazepine (carbamazepine monotherapy). A computer-generated random sequence randomly assigned individuals to treatment groups within each study site.

The 6-week double-blind treatment phase evaluated the efficacy and safety of olanzapine (10–30 mg/day) plus carbamazepine (400–1200 mg/day) compared with carbamazepine monotherapy (400–1200 mg/day plus a placebo identical to olanzapine) in the treatment of mania associated with bipolar I disorder. The 26-week open-label phase focused on safety measures. During the open-label phase all participants received olanzapine (10–30 mg/day) plus carbamazepine (400–1200 mg/day). The study was conducted following the principles of the Declaration of Helsinki. All participants gave written informed consent after the procedures had been fully explained.

Participants

Participants were men or women, aged 18–65 years, with a diagnosis of DSM-IV¹⁰ bipolar manic or mixed episode (with or without psychotic features), based on clinical assessment and confirmed by the Structured Clinical Interview for the DSM-IV, Axis I Disorders (SCID-I: Clinical Version).¹¹ Individuals were required to have had a Young Mania Rating Scale (YMRS)¹² total score of ≥ 20 at screening (visit 1, week -1) and at randomisation (visit 2, week 0).

All participants completing the double-blind phase were eligible to enter the open-label phase. Those who had a history of allergic or adverse reaction, had treatment resistance, or who showed lack of response to either olanzapine or carbamazepine were excluded, as were those who had acute, serious or unstable medical conditions.

Treatments

All patients began the double-blind phase with carbamazepine 400 mg/day, administered in divided doses. The dose was

increased by increments of 200 mg approximately every 3 days, as tolerated by the individual, reaching a maximum of 1200 mg/day by week 2. The dose could be decreased at any time if an adverse event occurred. Participants unable to tolerate the minimum dosage of carbamazepine (400 mg/day) were asked to withdraw from the study.

In addition to the carbamazepine, participants received either placebo or up to 30 mg/day of olanzapine. Olanzapine therapy began at 10 mg/day and the daily dose was titrated up according to the following titration scheme: 15 mg/day at week 1, 20 mg/day at week 2 and 30 mg/day at week 3. Once reaching 30 mg/day, the olanzapine dosage remained fixed for the duration of the double-blind treatment phase. Individuals unable to reach the fixed dosage of olanzapine at 30 mg/day were asked to withdraw. However, if 30 mg/day was reached but not tolerated, the investigator could decrease the dosage to 20 mg/day. If 20 mg/day was not tolerated, the participant was withdrawn from the study.

Participants randomly assigned to the carbamazepine monotherapy treatment in the double-blind phase began the open-label treatment phase with olanzapine at a dosage of 10 mg/day and carbamazepine at the last dose tolerated during the double-blind phase. Individuals randomly assigned to the olanzapine plus carbamazepine group in the double-blind phase continued taking the last tolerated dose in the open-label phase. Dose adjustments occurred as judged by the investigator, based on perceived therapeutic need/benefit and as tolerated by the individual.

Participants were permitted use of a limited dose of benzodiazepines (lorazepam ≤ 2 mg/day or equivalents), anticholinergics (benzotropine mesilate or biperiden ≤ 6 mg/day), and chronic thyroid supplement therapy if they were on a stable dose of the medication for at least 60 days before randomisation.

Investigators assessed adherence to the study drug regimen at each visit, by direct questioning and by counting returned study drug.

Outcome measures

Efficacy: double-blind phase

The severity of manic symptoms was assessed with the YMRS¹² (primary efficacy variable), the severity of depressive mood symptoms was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS),¹³ and the severity of illness was measured with the Clinical Global Impressions – Bipolar Version Severity of Illness Scale (CGI-BP).¹⁴ Both the MADRS and the CGI-BP were used as secondary efficacy measures. Additional secondary measures were the rate of response, remission and switch to depression. A symptomatic responder was defined as any person who demonstrated an improvement of $\geq 50\%$ in the YMRS total score from baseline to the last measurement value. A symptomatic remitter was defined as any person who achieved a total score ≤ 12 on the YMRS at the last measurement value. Switch to depression was defined as a baseline MADRS total score ≤ 12 , followed by either a post-baseline MADRS total score ≥ 16 during the 6 weeks of the double-blind treatment phase or hospitalisation due to deterioration in clinical symptoms of depression.

Efficacy: open-label phase

The maintenance of treatment effect (primary efficacy measure) was analysed using the YMRS total score change from baseline (week 6) to endpoint of the open-label treatment phase. Secondary efficacy measures included relapse into mania (defined as a person reaching remission of mania, as defined by a YMRS score ≤ 12 , by the endpoint of the double-blind phase and subsequently

having a YMRS score ≥ 15 at any time and/or becoming hospitalised due to deterioration in clinical symptoms of mania) and relapse into depression (defined as a baseline MADRS total score ≤ 12 , followed by either a post-baseline MADRS total score ≥ 16 or hospitalisation due to deterioration in clinical symptoms of depression).

Pharmacokinetics

A venous blood sample was collected only during the double-blind phase (at weeks 4 and 6) to determine the plasma concentrations of olanzapine, carbamazepine and carbamazepine-10,11-epoxide. The steady-state plasma concentrations of olanzapine were measured in individuals treated with olanzapine plus carbamazepine. Participants took their dose of olanzapine and carbamazepine on the evening before the visit.

Safety

For both study phases, safety was monitored by assessing adverse events, laboratory values, electrocardiograms (ECGs), vital signs and extrapyramidal symptoms. The latter were measured with the Simpson–Angus Scale,¹⁵ the Barnes Akathisia Scale,¹⁶ and the Abnormal Involuntary Movement Scale.¹⁷ Clinical analysis of blood and urine samples was carried out by Covance Central Laboratory Services, Inc., using Covance reference ranges adjusted for gender and age. The criteria for clinically significant treatment-emergent changes in lipids and glucose were based on guidelines from the National Cholesterol Education Program¹⁸ and American Diabetes Association.¹⁹ Long-term metabolic data were obtained by evaluating participants who had received olanzapine plus carbamazepine for 26 weeks.

Statistical analyses

Data were analysed on an intent-to-treat basis. Approximately 120 adults were to be randomly assigned to the treatment groups in a 1:1 ratio. Sample size was estimated to provide more than 80% power to detect a difference of 5.6 in YMRS total reduction with a pooled s.d. of 10.

For the double-blind phase, an analysis-of-covariance (ANCOVA) model was used to evaluate the difference in continuous efficacy and tolerability measures (outcome) between the two treatment arms. The ANCOVA model included terms for investigator site, therapy and baseline measures of the specific outcome. A mixed-model repeated measures ANCOVA was used to analyse the change from baseline to each post-baseline visit in the YMRS and MADRS total scores, and included the terms for baseline measures of the YMRS/MADRS total score, visit, investigator site, therapy and therapy by visit in the model. The last-observation-carried-forward (LOCF) method was used to analyse mean changes from baseline to endpoint. The Cochran–Mantel–Haenszel² χ^2 -test adjusted for investigator site was used to test the proportion differences in the two treatment arms.

A *post hoc* subgroup analysis (ANCOVA) of the change from baseline to endpoint (LOCF) for the YMRS total score was performed comparing the responders and non-responders of the double-blind phase. In addition, the long-term metabolic analyses were completed *post hoc*.

A potentially clinically significant change was defined as a value that did not meet the criteria at baseline but met the criteria any time after baseline. For mean change analyses in efficacy and safety measures, as well as potentially clinically significant categorical changes in vital-sign measurements and ECG findings, baseline was defined as the last observation before the start of the study period (for the double-blind phase, screening and randomisation,

Results

Patient characteristics

i.e. visits 1 and 2, weeks -1 and 0; for the open-label phase, the end of double-blind phase, i.e. LOCF visit 7, week 6). For treatment-emergent categorical analyses with regard to treatment-emergent adverse events, laboratory abnormalities and scale-based abnormalities in extrapyramidal symptoms and for potentially clinically significant changes in laboratory values, baseline was visits 1 and 2 for the double-blind phase and for the open-label phase it was the LOCF endpoint of the double-blind phase. Categorical outcomes that first occurred within the study period, as well as adverse events that worsened from baseline, were considered treatment emergent.

Analyses were tested using a two-sided alpha level of 0.05. Throughout, demographic and safety data are described with mean (s.d.), and efficacy data are described with least squares means.

An analysis-of-variance (ANOVA) statistical evaluation was used to compare the carbamazepine and carbamazepine-10,11-epoxide steady-state plasma concentrations between treatments.

All statistical analyses were conducted using SAS version 8.2 (SAS Institute, Cary, North Carolina, USA) on a mainframe computer.

The study was conducted in Australia, Greece, Hungary and Russia from 17 September 2004 to 28 June 2006 (study settings: psychiatric or mental health clinics, hospital units, or health research institutes). A total of 134 adults entered the study and 118 eligible adults were randomly assigned in 1:1 ratio to olanzapine plus carbamazepine ($n=58$) and carbamazepine monotherapy ($n=60$). The double-blind phase was completed by 72.0% (85/118) of participants. Of the 86 individuals who entered the open-label phase, 62 (72.1%) completed the study. The progress of participants through the trial is illustrated in Fig. 1. There were no statistically significant differences in the proportions of participants in the olanzapine plus carbamazepine group and the carbamazepine monotherapy group who had to withdraw for any particular reason.

The 118 individuals who participated in the double-blind phase had a mean age of 40.7 years, 99.2% were White and

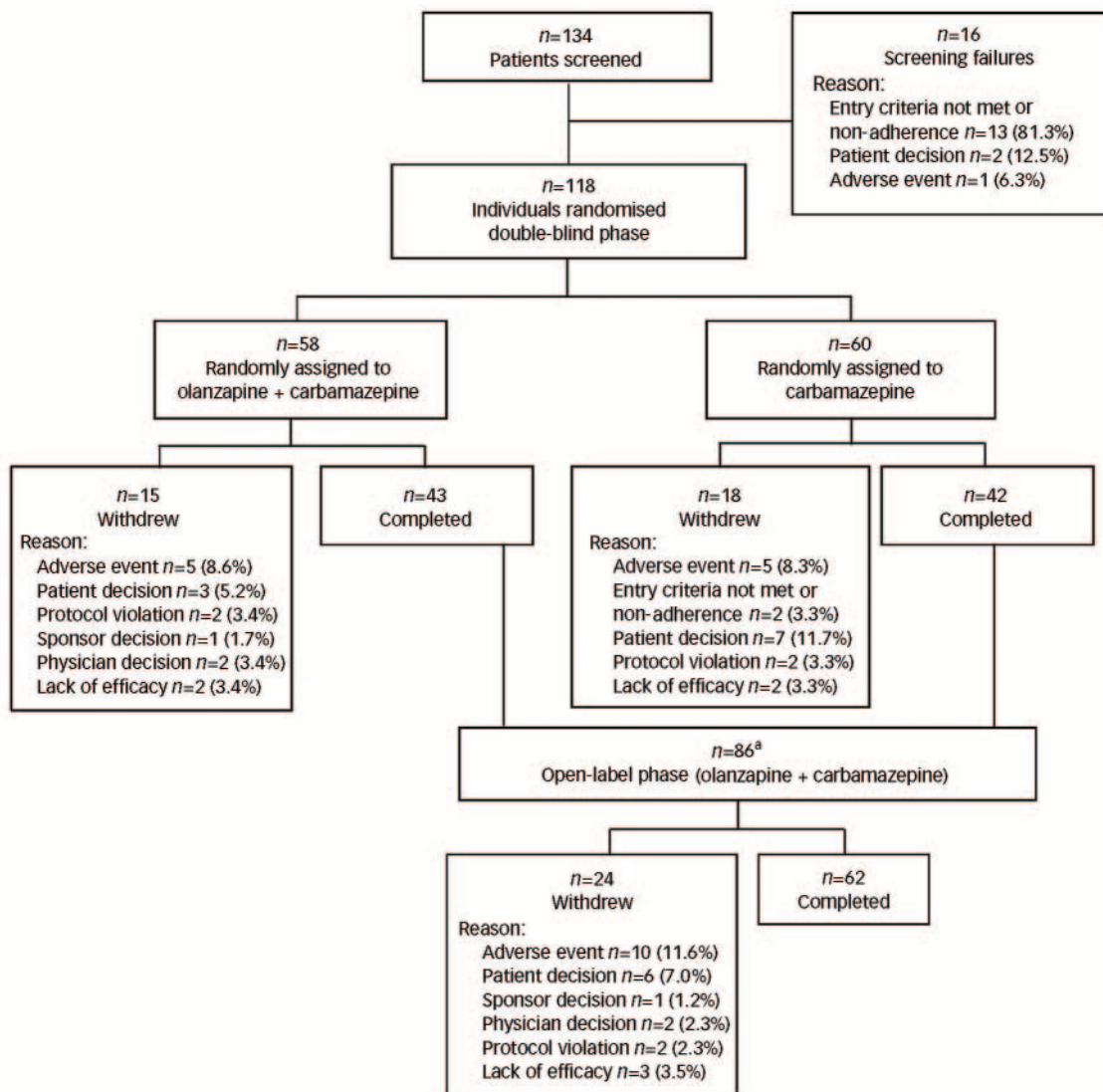


Fig. 1 Diagram showing progress of the participants through the trial.

a. One participant withdrew from the double-blind phase owing to an adverse event (elevated liver enzyme) but was dispensed the open-label treatment, so the individual was considered to have entered the open-label phase. The participant decided to withdraw from the open-label phase. Hence the number of individuals completing the double-blind phase does not directly correspond with the number of people entering the open-label phase.

57.6% were women (see online Table DS1). Most people (98.3%) had bipolar mania with a moderate to severe episode. In general, the treatment groups were comparable at baseline with respect to physical and illness characteristics, severity of illness, previous drug therapy for manic or mixed episodes, concomitant medication use and were similar in adherence to the study treatment. The treatment groups did not significantly differ in the percentage of participants who received one or more doses of benzodiazepine medications. Significantly more people in the carbamazepine monotherapy group took anticholinergics: 6.7% (4/60) *v.* 0%, $P=0.044$.

Efficacy

Double-blind phase

The change from baseline to endpoint (LOCF) in the YMRS total score was not significantly different between the olanzapine plus carbamazepine and the carbamazepine monotherapy treatment groups (Table 1). Likewise, the changes in YMRS total score from baseline to each weekly assessment (LOCF) were not statistically significantly different between treatment groups (Table 1). Clinical response was reported in 63.8% (37/58) of the olanzapine plus carbamazepine-treated participants and 66.1% (39/59) of the carbamazepine monotherapy-treated participants, a statistically nonsignificant difference. Similarly, the treatment groups did not significantly differ in the proportion of individuals who reached remission at endpoint (LOCF: olanzapine plus carbamazepine 55.2% (32/58); carbamazepine monotherapy 59.3% (35/59)) or switched to depression (olanzapine plus carbamazepine 10.2% (5/49); carbamazepine monotherapy 14.0% (7/50)). In addition, the groups did not significantly differ in baseline-to-endpoint changes in CGI-BP or MADRS total scores (Table 1).

The mean dosage of carbamazepine was 617.52 mg/day for the olanzapine plus carbamazepine group and 717.33 mg/day for the monotherapy group ($P=0.015$, *d.f.*=1,104, $F=6.14$). Adjusting for mean carbamazepine dose, the treatment groups did not significantly differ in mean changes in their YMRS total score from baseline to endpoint (LOCF; olanzapine plus carbamazepine -15.97 ; carbamazepine monotherapy -14.99 ; $P=0.513$, *d.f.*=1,101, $F=0.43$).

Open-label phase

Among the individuals with both baseline and post-baseline visits ($n=85$), there was a statistically significant mean decrease from baseline (week 6) to endpoint (LOCF) for YMRS total score (baseline mean 9.56, *s.d.*=8.36; change -5.94 , *s.d.*=8.09, $P<0.001$, *d.f.*=84, $t=-6.77$). In total, 66 responders and 19 non-responders entered the open-label phase. During this phase, no statistically significant difference between responders and non-responders ($P=0.298$, *d.f.*=1,82, $F=1.10$) was observed for the change from baseline to endpoint (LOCF) in the YMRS total score. However, statistically significant within-group improvements were noted from baseline for both responders and non-responders ($P<0.001$ for each group, *d.f.*=82, $t=-6.01$ for responders, $t=-3.88$ for non-responders). Also during the open-label phase, 9.1% (7/77) of participants relapsed into depression and 3.4% (2/59) relapsed into mania.

Pharmacokinetics (double-blind phase only)

The majority of individuals (69.0%) were titrated to a mean daily dose of 30 mg olanzapine. Participants ($n=43$ providing $n=81$ concentration measurements) who received an olanzapine dose of 20 mg ($n=5$) or 30 mg ($n=76$) had a median olanzapine plasma

Table 1 Efficacy outcomes during the 6-week double-blind phase (last observation carried forward)^a

	Olanzapine + carbamazepine ($n=58$) ^b	Carbamazepine ($n=59$) ^b
	Least squares mean (s.e.)	Least squares mean (s.e.)
Change from baseline to endpoint in efficacy scores		
YMRS total ^c	-15.49 (1.07)	-15.25 (1.09)
CGI-BP overall	-1.29 (0.16)	-1.35 (0.16)
CGI-BP mania	-2.05 (0.16)	-2.07 (0.16)
CGI-BP depression	0.05 (0.12)	0.09 (0.12)
MADRS total	-1.22 (0.96)	-1.00 (0.96)
Visitwise change from baseline in YMRS total score		
Week 1	-5.77 (0.69)	-5.55 (0.71)
Week 2	-9.78 (0.91)	-11.14 (0.96)
Week 3	-11.75 (0.92)	-12.19 (0.94)
Week 4	-14.04 (1.04)	-13.52 (1.06)
Week 6	-15.49 (1.07)	-15.25 (1.09)

CGI-BP, Clinical Global Impressions – Bipolar Version Severity of Illness; MADRS, Montgomery-Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale.
a. There were no significant differences between the groups.
b. *N*=individuals having both baseline and post-baseline measures.
c. $P=0.869$, *d.f.*=1,102, $F=0.027$.

concentration of 32.8 ng/ml (minimum 2.6 ng/ml, maximum 85.7 ng/ml; see also Table 2).

Olanzapine did not affect the pharmacokinetics of carbamazepine. The carbamazepine and carbamazepine-10,11-epoxide steady-state concentrations were not significantly different between the treatments. The distribution (*n*, 10th to 90th percentile) of carbamazepine concentrations for carbamazepine plus olanzapine treatment ($n=83$; 4.3–9.5 µg/ml) *v.* carbamazepine monotherapy ($n=88$; 3.8–9.6 µg/ml) showed the lack of difference (Fig. 2). Furthermore, for both treatments most (89%) carbamazepine plasma concentrations were within the therapeutic concentration window of 4–12 µg/ml.²² An evaluation of the change from baseline for YMRS total score *v.* plasma concentrations of olanzapine or carbamazepine did not reveal a meaningful relationship.

Safety: double-blind phase

Adverse events

A total of 8.6% (5/58) olanzapine plus carbamazepine-treated individuals and 8.3% (5/60) carbamazepine monotherapy-treated individuals withdrew from the study because of adverse events. Specifically, participants in the olanzapine plus carbamazepine group withdrew because of depressive symptoms, increased gamma-glutamyltransferase, headache, vertebrobasilar insufficiency and increased weight. Participants in the carbamazepine monotherapy group withdrew because of adenovirus infection, increased blood triglycerides, constipation, depression and non-insulin-dependent diabetes mellitus. None of the adverse events contributed to withdrawals for more than one person within each treatment group. Two individuals in the olanzapine plus carbamazepine treatment group (3.4%, 2/58) experienced serious adverse events (depression $n=1$; nephrolithiasis $n=1$) and one person in the carbamazepine monotherapy group (1.7%, 1/60) reported a serious adverse event (adenovirus infection).

Although the individuals with depression and adenovirus infection withdrew from the study, the person with nephrolithiasis continued with the study. None of the serious events were considered by the investigator to be possibly related to study drugs. No deaths were reported.

Table 2 Olanzapine plasma concentration summary after multiple doses of olanzapine administered with carbamazepine (6-week double-blind phase)

Olanzapine dose, mg	Olanzapine plasma concentration, ng/ml			Comparative data for 15 mg ^b
	20	30	20 + 30 ^a	
<i>n</i>	5	76	81	674
Geometric mean	22.8	32.0	31.8	29.5
Geometric coefficient of variation, %	51.7	61.8	61.0	57.2
Minimum	15.6	2.59	2.59	0.78
Median	26.4	33.5	32.8	29.7
Maximum	59.8	85.7	85.7	91.2
10th percentile	15.6	16.5	16.3	16.3
90th percentile	59.8	64.0	63.0	56.4

a. Based upon these data, the median calculated concentration/dose ratio for olanzapine is 3.8 nmol/l/mg for this study, which is 39% lower than the published historical median concentration/dose ratio values from a naturalistic study of olanzapine concentrations that reported a median concentration/dose ratio value of 6.2 nmol/l/mg (*n*=194).^{20,21}
b. Comparative plasma concentrations of olanzapine data for participants in clinical trials taking a dose of 15 mg olanzapine once daily.

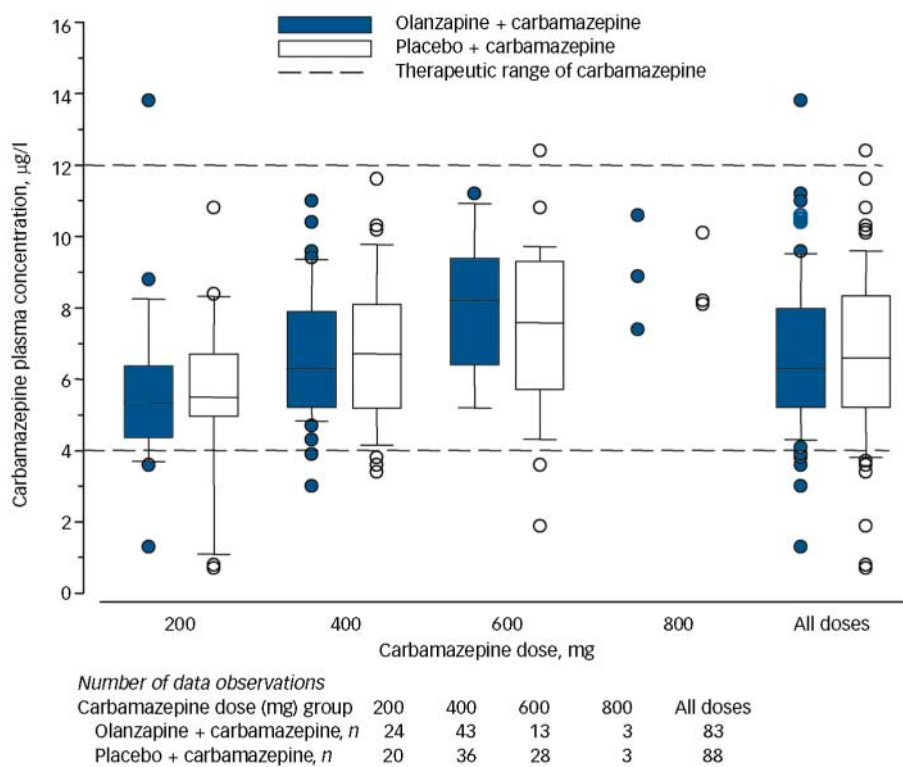
Treatment-emergent adverse events occurring in $\geq 5\%$ of the population are listed in Table 3. The only statistically significant between-group differences in the incidence of treatment-emergent adverse events were for alanine aminotransferase and constipation (alanine aminotransferase $P=0.05$, d.f.=1, $\chi^2=3.85$ more often in individuals treated with combination therapy; constipation $P=0.005$, d.f.=1, $\chi^2=7.81$ more often in individuals treated with monotherapy; Table 3).

Clinical laboratory evaluation

Statistically significant differences in mean changes at endpoint were observed between treatment groups for several laboratory measures (see online Table DS2). Both treatment groups had a mean increase from baseline to endpoint in total cholesterol

(olanzapine plus carbamazepine 0.81 mmol/l, s.d.=0.88; carbamazepine 0.62 mmol/l, s.d.=1.02), but this difference was not statistically significant ($P=0.226$, d.f.=1,99, $F=1.49$).

The incidences of treatment-emergent clinically significant changes in fasting glucose levels (normal to high) were not statistically significantly different between the groups (olanzapine plus carbamazepine 7.7% (4/52); carbamazepine monotherapy 2.3% (1/44); $P=0.352$, d.f.=1, $\chi^2=0.87$; see online Table DS3). The groups did significantly differ in the incidence of treatment-emergent changes from normal to high triglycerides (olanzapine plus carbamazepine 20.6% (7/34); carbamazepine monotherapy 3.2% (1/31); $P=0.049$, d.f.=1, $\chi^2=3.86$). Also, there was a three times greater, but not a statistically significant, difference ($P=0.117$, d.f.=1, $\chi^2=2.46$) in the incidence of treatment-emergent

**Fig. 2** Carbamazepine plasma concentration when administered with placebo or olanzapine.

The middle line in each box represents the median; the top and bottom margins of each box represent the 75th and 25th percentiles. The whiskers extend to the 90th and the 10th percentiles; data points beyond the whiskers represent individual data in the tails of the distribution. *n*, total number of observations; all quantifiable concentrations were included.

Table 3 Summary of treatment-emergent adverse events occurring in $\geq 5\%$ of participants in either treatment group during the 6-week double-blind phase

	Olanzapine + carbamazepine (n=58) n (%)	Carbamazepine (n=60) n (%)	Total (n=118) n (%)
Somnolence	9 (15.5)	8 (13.3)	17 (14.4)
Dry mouth	5 (8.6)	1 (1.7)	6 (5.1)
Headache	5 (8.6)	5 (8.3)	10 (8.5)
Alanine aminotransferase increased	4 (6.9)*	0 (0.0)	4 (3.4)
Vision blurred	4 (6.9)	1 (1.7)	5 (4.2)
Dizziness	3 (5.2)	2 (3.3)	5 (4.2)
Rash	3 (5.2)	0 (0.0)	3 (2.5)
Sedation	3 (5.2)	1 (1.7)	4 (3.4)
Nausea	1 (1.7)	4 (6.7)	5 (4.2)
Weight increased	1 (1.7)	3 (5.0)	4 (3.4)
Constipation	0 (0.0)**	6 (10.0)	6 (5.1)

* $P=0.05$ (d.f.=1, $\chi^2=3.85$); ** $P=0.005$ (d.f.=1, $\chi^2=7.81$).

changes from normal to high total cholesterol (olanzapine plus carbamazepine 25.0% (6/24); carbamazepine monotherapy 8.0% (2/25)).

Vital signs, ECGs, extrapyramidal symptoms and weight

Although there were no statistically significant differences between groups on several measures of vital signs (namely orthostatic pulse, standing pulse and temperature; see online Table DS2), the incidences of potentially clinically significant changes in vital signs were all $< 8\%$. Carbamazepine monotherapy-treated participants had a statistically significantly greater mean decrease in heart rate than olanzapine plus carbamazepine-treated participants (-5.51 beats per minute, s.d.=13.87 *v.* 0.87, s.d.=12.81 respectively; $P=0.021$, d.f.=1,95, $F=5.54$). Also, the groups statistically significantly differed in the mean changes in uncorrected QT intervals, with carbamazepine monotherapy-treated participants experiencing an increase (8.11 ms, s.d.=25.11) and olanzapine plus carbamazepine-treated participants having a decrease (-7.79 ms, s.d.=27.07; $P=0.023$, d.f.=1, 96, $F=5.37$). However, none of these changes were deemed clinically significant.

Extrapyramidal symptom scores during the double-blind phase were not statistically significantly different between the groups on any scale measurement.

From baseline to endpoint, olanzapine plus carbamazepine-treated individuals had a statistically significantly greater mean weight gain than carbamazepine-treated individuals (see online Table DS2). In addition, potentially clinically significant weight gain ($\geq 7\%$ from baseline) at any time was significantly more common in the olanzapine plus carbamazepine treatment group (olanzapine plus carbamazepine 24.6% (14/57); carbamazepine 3.4% (2/59); $P=0.002$, d.f.=1, $\chi^2=9.57$).

Safety: open-label phase

Adverse events

A total of 11.6% (10/86) of the olanzapine plus carbamazepine-treated individuals withdrew from the open-label study because of adverse events, specifically: increased alanine aminotransferase, depression, hypersensitivity, major depression, oligomenorrhoea, renal colic, sedation and suicide attempt. Depression was the only adverse event that resulted in the withdrawal of more than one person ($n=3$). A total of 4 people experienced serious adverse events ($n=1$ nephrolithiasis and renal colic; $n=1$ adenovirus infection; $n=1$ anxiety, insomnia and suicide attempt; $n=1$

hypersensitivity reaction). Only the hypersensitivity reaction was considered possibly related to the study drugs. No deaths were reported.

Weight gain was the only treatment-emergent adverse event that occurred in $\geq 5\%$ of participants and was reported by 5.8% (5/86) of the open-label sample. At least one treatment-emergent adverse event was reported in 38.4% (33/86) of the patients during the 20-week open-label period.

Clinical laboratory evaluation

In the open-label phase, statistically significant differences in mean changes at endpoint were observed for several laboratory measures (see online Table DS2). There was a statistically significant decline in platelet count at the end of the open-label phase ($P=0.004$, d.f.=84, $t=-2.99$). Mean levels of alanine aminotransferase or aspartate aminotransferase did not significantly change from baseline; however, the measures did decrease by endpoint (alanine aminotransferase -2.75 U/l, s.d.=20.20; aspartate aminotransferase -1.27 U/l, s.d.=10.48). High levels of fasting glucose were reported by 4.2% (3/71) of the sample and high levels of gamma-glutamyl transferase were reported by 2.5% (2/80) of the sample.

Similar to the double-blind phase, at the end of the open-label phase, 9.9% (7/71) of participants had treatment-emergent clinically significant changes in fasting glucose levels (from normal to high; see online Table DS3). Most cholesterol and triglycerides categories, except for high-density lipoprotein cholesterol, showed increases from normal to borderline, normal to high, or borderline to high (see online Table DS3).

Vital signs, ECGs, extrapyramidal symptoms and weight

No statistically significant changes in vital signs, ECG, or extrapyramidal symptoms were observed during the open-label phase.

Individuals had a statistically and clinically significant mean weight increase at study end (see online Table DS2). Approximately 15.0% (13/85) of participants had a potentially clinically significant weight gain ($\geq 7\%$ from baseline) at any time during the open-label phase. Figure 3 presents the weight change by randomisation groups during the entire course of the study. The carbamazepine monotherapy-treated individuals did not demonstrate weight increase during the double-blind phase (mean change from randomisation to week 6: 0.60 kg, s.d.=2.56); however, their weight increased during the open-label phase when they

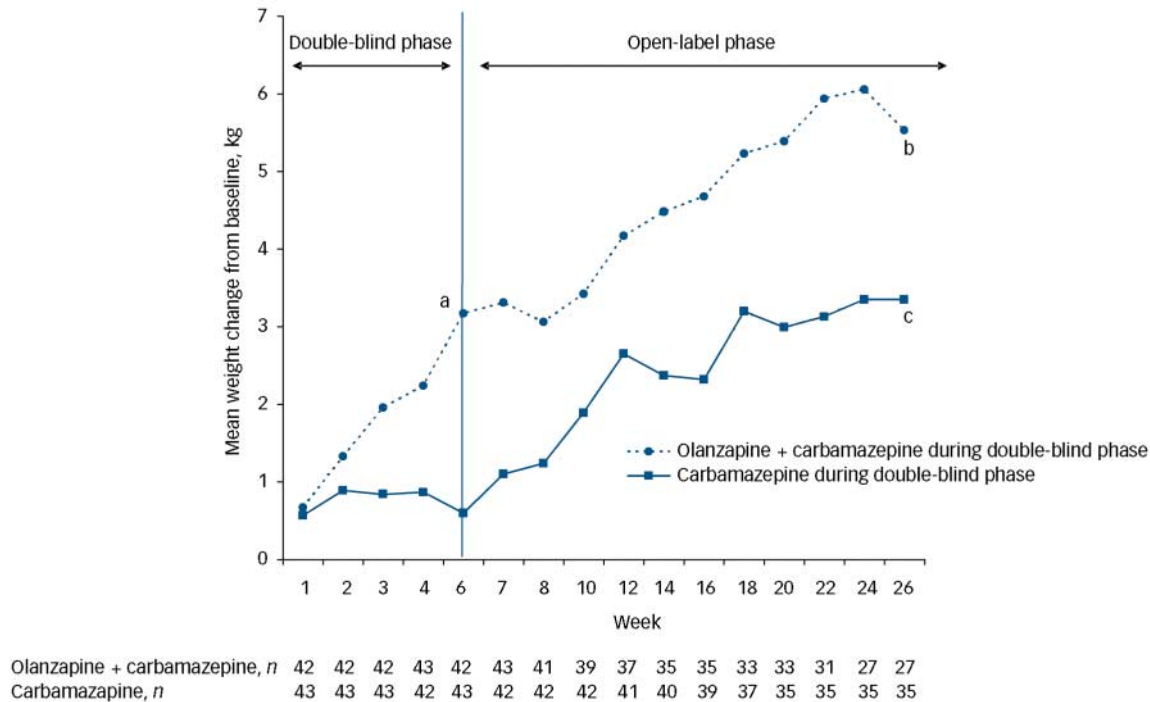


Fig. 3 Visit-wise mean weight changes from randomisation for participants who entered the open-label phase.

All participants were exposed to olanzapine plus carbamazepine in the open-label phase. *n*, total number of observations at each weekly visit.
 a. Olanzapine plus carbamazepine *v.* carbamazepine monotherapy at the end of the 6-week double-blind phase, $P < 0.001$ (d.f.=1,101, $F=24.41$).
 b. Change from randomisation to endpoint (week 26), $P < 0.001$ (d.f.=56, $t=5.51$).
 c. Change from baseline (week 6) to endpoint (week 26), $P < 0.001$ (d.f.=41, $t=4.60$).

were exposed to olanzapine plus carbamazepine treatment (mean change from randomisation to study end: 3.35 kg, s.d.=4.26 – an additional mean gain of 2.75 kg). Participants randomly assigned to the olanzapine plus carbamazepine group had a continuous weight gain (mean change from randomisation to study end: 5.53 kg, s.d.=4.90).

Forty-three of the 58 individuals who were randomly assigned to olanzapine plus carbamazepine treatment during the double-blind phase entered the open-label phase. Their metabolic laboratory results are shown in the online Tables DS2 and DS3. In addition we observed that of the 52 participants with low or normal cholesterol at baseline, 23 (44.2%) had an increase in cholesterol higher than the upper limit of the Covance reference range during the 26-week treatment period. Also, participants with normal or low measures at baseline reached laboratory values higher than the upper limit of the Covance reference range for fasting glucose (19.6% (9/46)), high-density lipoprotein (19.6% (11/56)), low-density lipoprotein (34.6% (18/52)) and triglycerides (46.0% (23/50)). Long-term treatment with olanzapine plus carbamazepine resulted in a 3.70 kg mean weight gain from randomisation to endpoint.

Discussion

Importance of publishing negative studies

In an attempt to prevent publication bias and to meet an ethical obligation to study participants, this paper reports results of a negative study (i.e. one that demonstrates no statistically significant difference in the primary outcome for two groups treated with pharmacologically active drugs). Specifically, the combination of olanzapine and carbamazepine did not appear to provide

any therapeutic benefits beyond carbamazepine monotherapy. Although the efficacy results were not synergistic, the safety findings are of clinical interest.

Study safety findings

Weight gain observed during treatment with both carbamazepine and olanzapine has been previously reported in people with bipolar disorder.^{1–3,23–25} In the present study, individuals in both treatment groups (olanzapine plus carbamazepine and carbamazepine monotherapy) had a mean increase in weight from randomisation. Individuals treated with olanzapine plus carbamazepine, however, had a statistically significantly greater weight gain than those treated with carbamazepine monotherapy (see Fig. 2 and online Table DS2). In addition, a potentially clinically significant weight gain ($\geq 7\%$ from baseline) during the 6-week double-blind phase occurred in 24.6% (14/57) of the olanzapine plus carbamazepine-treated participants and 3.4% (2/59) of the carbamazepine-treated participants, and during the 20-week open-label phase in 15.3% (13/85) of the olanzapine plus carbamazepine-treated participants. Those treated with olanzapine plus carbamazepine long term (26 weeks) had a 3.70 kg mean weight gain from randomisation to endpoint, which is comparable with a 3.41 kg weight gain at 30 weeks in a previously published double-blind study of olanzapine.²⁴

Hyperlipidemia has been reported during olanzapine and carbamazepine monotherapies. Several clinical trial publications report an increase in total cholesterol and triglycerides during treatment with olanzapine.^{23,24,26} Likewise, several clinical trials report an increase in total cholesterol, low-density lipoprotein, cholesterol and triglycerides with carbamazepine use.^{3,4,25,27} From

baseline to endpoint of the double-blind phase of the present study, participants treated with olanzapine plus carbamazepine had statistically significantly higher increases in mean triglyceride levels than individuals treated with carbamazepine alone ($P < 0.008$; see online Table DS2). A limitation of the study is that the carbamazepine monotherapy arm was not continued into the open-label phase and there was no olanzapine monotherapy arm. Thus, it would be speculative to draw conclusions on whether this increase was driven by olanzapine or by the synergism of the combination. In addition, individuals in both the olanzapine plus carbamazepine and carbamazepine monotherapy groups showed a mean increase in total cholesterol, which was not statistically significantly different between the groups. Long term (26 weeks), individuals treated with olanzapine plus carbamazepine had a 0.84 mmol/l (s.d.=1.11) mean increase in cholesterol from randomisation to endpoint, which is higher than the 0.24 mmol/l (s.d.=1.15) mean change during 47 weeks in individuals treated with olanzapine monotherapy.²⁴ Further, 44.2% of the individuals receiving long-term treatment had an increase in cholesterol beyond the upper limit of the Covance reference range compared with a previous report of 14.0% of individuals treated with olanzapine monotherapy for 47 weeks²⁴ (for the purposes of this comparison, the percentage reported in this article – 12.2% – was converted to 14.0% using the Covance reference range). Thus, there is a suggestion of an additive effect on cholesterol, which is attributed to the combination.

Pharmacokinetic considerations

Any time two drugs are taken concomitantly, there is the potential for drug–drug interactions. Concomitant administration of carbamazepine has been shown to increase the clearance of olanzapine by 40–50%, most likely owing to the induction of cytochrome P450 1A2 and glucuronidation pathways.⁹ In a naturalistic clinical setting, substantially lower concentrations of olanzapine were consistently observed during treatment with olanzapine plus carbamazepine.²¹ Likewise, in the present study, carbamazepine induced the metabolism of olanzapine and lowered the exposure of olanzapine by approximately 50%. In anticipation of this clinically meaningful decrease in olanzapine concentration, the present study used a fixed olanzapine dosage of 30 mg/day, even though any dosage greater than 20 mg/day is outside the currently recommended dose range for olanzapine (5–20 mg/day).²⁸ Indeed, the higher dose was needed to compensate for the cytochrome P450 enzyme induction attributed to carbamazepine – the systemic olanzapine exposure was similar to that achieved after administering 15 mg/day to an individual not taking an enzyme inducer.

It is conceivable that the known metabolic induction of carbamazepine that affects olanzapine pharmacokinetics may have driven olanzapine concentrations to potentially subtherapeutic levels, even after the olanzapine dose was increased to 30 mg/day. This induction could explain the failure of the combination therapy to demonstrate superior efficacy over carbamazepine monotherapy. However, this theory appears unlikely given that the concentrations of olanzapine were within a range that is typically associated with therapeutic effectiveness.

The wide carbamazepine dosage range of 400–1200 mg/day used in this study is consistent with the dosage recommendations for carbamazepine treatment²² and is needed to individualise the dosage that will achieve therapeutic concentrations of carbamazepine. None the less, the steady-state concentrations of carbamazepine and its metabolite were not affected by olanzapine. The carbamazepine plasma concentrations were maintained in the therapeutic range when administered with placebo or olanzapine. These results

suggest that olanzapine does not affect the pharmacokinetics of carbamazepine.

Given the complexity of pharmacokinetic/pharmacodynamic relationships for neuropsychiatry drugs and limited number of measurements of the concentrations of olanzapine and carbamazepine, an analysis of the data from this study did not reveal a predictive, clinically meaningful or simple relationship between the concentrations of these drugs and the clinical response.

Summary

Other studies have been published with negative outcomes on the primary efficacy variable. For example, Bowden *et al*²⁹ reported that divalproex and lithium were not significantly different from placebo in preventing mania or depression in a 1-year, randomised double-blind study. In addition, Yatham *et al*³⁰ reported that quetiapine plus lithium/divalproex failed to differentiate from placebo plus lithium/divalproex treatment on the primary efficacy variable in a randomised double-blind study. These negative findings are not unique. One out of four placebo-controlled trials of atypical antipsychotics in acute mania and 40% of unpublished trials in mania fail to differentiate statistically between placebo and treatment effects on the primary outcome variable.³¹ The greater response to placebo has been attributed to low symptomatic severity, concomitant or rescue medications, high number of active treatment groups, mixed episode and absence of psychotic symptoms.³¹ Therefore, reasons other than pharmacokinetics may explain the negative outcome in this study. Further, a recent review found that add-on designs are more likely to have negative results (further details available from the author on request). For example, another add-on trial that used carbamazepine was also negative.³²

To summarise, olanzapine (up to 30 mg/day) plus carbamazepine (400–1200 mg/day) did not have superior efficacy to carbamazepine monotherapy (400–1200 mg/day) in treating bipolar mania. The types of adverse events reported for olanzapine plus carbamazepine treatment were consistent with the known olanzapine and carbamazepine safety profiles. The combination was associated with a potential additive increase in weight, total cholesterol and triglycerides. Weight, total cholesterol and triglycerides should be monitored when combining carbamazepine with olanzapine treatment.

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