DRUG DISPOSITION & PHARMACOKINETICS

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Switching from Other Agents to Extended-Release Carbamazepine in Acute Mania

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ABSTRACT ~ **Background:** *There is a dearth of available knowledge relating to the efficacy of switching from one psychotropic agent to another in treating patients with acute mania.* **Methods:** *This is a post hoc analysis of data from two randomized, placebo-controlled trials of carbamazepine extended-release capsules (CBZ-ERC) in the treatment of mania, to evaluate the efficacy of CBZ-ERC in patients previously nonresponsive to lithium ($n = 40$), olanzapine ($n = 38$), or valproate (VPA, $n = 77$).* **Results:** *In patients previously on lithium, Young Mania Rating Scale (YMRS) scores improved significantly from baseline to end point (27.4 ± SD 3.5 vs. 15.8 ± 11.1; $P = .0002$). In patients previously on VPA or olanzapine, YMRS scores significantly improved in both CBZ-ERC- and placebo-treated groups (VPA: CBZ-ERC, $P < .0001$; placebo, $P = .0002$; olanzapine: CBZ-ERC, $P < .0001$; placebo, $P = .0054$). Improvement in YMRS was significantly greater in CBZ-ERC-treated patients versus placebo in subjects previously nonresponsive to lithium (CBZ-ERC 11.6 ± 10.3 vs. placebo 4.0 ± 11.2, $P = .03$), or VPA (CBZ-ERC 10.8 ± 11.9 vs. placebo 5.7 ± 9.2; $P = .04$), and trending to be greater for those previously nonresponsive to olanzapine (olanzapine 13.2 ± 9.3 vs. placebo 7.3 ± 9.7, $P = .06$).* **Conclusions:** *CBZ-ERC is an effective therapy for bipolar patients previously nonresponsive to lithium or valproate. Medication switch is*

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INTRODUCTION

Although a multitude of agents have been shown to be effective in the treatment of acute mania, the illness remains difficult to treat. Rates of nonresponse range from one third to one half of acutely ill manic patients[1,2] and polypharmacy is commonly required.[3] Additionally, nonadherance and partial adherence are common in bipolar illness,[4,5] frequently because of the adverse effects[6,7] and poor insight,[8,9] giving the impression of nonresponse. For these reasons, the need for switch of pharmacologic agent arises frequently in bipolar treatment (36.6%[10]). However, there is a dearth of data regarding the efficacy of switching agents, and most of the available studies examine switching neuroleptic agents in schizophrenia.[1,11]

This study analysis was undertaken to glean insights into the results of switching agents in acutely ill manic or mixed patients. Patients who were previously on lithium, valproate, or olanzapine, and who were still significantly symptomatic were switched to extended-release carbamazepine capsules (CBZ-ERC) or placebo and followed for 3 weeks. Primary response was measured with the Young Mania Rating Scale (YMRS). Secondary outcome measures included clinicians' global impression and the Hamilton Depression Rating Scale (HDRS).

METHODS

This is a post hoc analysis of pooled data from the two nearly identical pivotal trials of CBZ-ERC versus placebo in acutely manic or mixed patients. The methods have been presented elsewhere in detail,[12,13] but briefly, patients were recruited for a 3-week, multicenter, placebo-controlled trial of CBZ-ERC versus placebo. After a washout period of 2–5 days, CBZ-ERC was initiated at 200 mg twice daily and increased in 200 mg increments every subsequent day until efficacy, side effects, or a maximum dose of 1,600 mg/day. These subjects may have been receiving therapeutic doses of other agents at study entry. This post hoc analysis identified 40 subjects previously on lithium, 77 subjects previously on valproate, and 38 subjects previously on olanzapine. The defined primary outcome measure for this analysis was the change in the YMRS[14] from baseline to endpoint (last observation carried forward [LCOF]). Secondary outcome measures included change in the HDRS[15] and Clinical Global Impression-Severity (CGI-S) scale.[16] Paired data, comparing baseline and endpoint outcome, utilized paired *t*-test. Unpaired data, comparing placebo- versus carbamazepine-treated subjects, were analyzed by unpaired two-tailed *t*-test. Bonfronni's correction was

TABLE 1

DEMOGRAPHICS OF SUBJECTS STUDIED

	PREVIOUS TREATMENT					
	LITHIUM		VALPROATE		OLANZAPINE	
TREATMENT GROUP	CBZ-ERC	PLACEBO	CBZ-ERC	PLACEBO	CBZ-ERC	PLACEBO
Sample size	18	22	35	42	20	18
Gender (% female)	38.9	36.4	40.0	33.3	40.0	38.9
Age (years)	39.2	34.9	37.6	37.2	36.5	42.5
Diagnosis (% mixed)	27.8	31.8	40.0	23.8	35.0	44.4

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TABLE 2

BASELINE, ENDPOINT (LOCF), AND CHANGE MEAN VALUES (±SD) FOR THE YOUNG MANIA RATING SCALE (YMRS) IN CBZ-ERC AND PLACEBO-TREATED PATIENTS PREVIOUSLY UNRESPONSIVE TO LITHIUM, VALPROATE, OR OLANZAPINE

	PLACEBO				EXTENDED RELEASE CARBAMAZEPINE CAPSULES			
	BASELINE	ENDPOINT	CHANGE	P (POWER)	BASELINE	ENDPOINT	CHANGE	P (POWER)
Lithium	26.7 ± 4.5	22.7 ± 13.3	4.0 ± 11.2	0.11 (0.52)	27.4 ± 3.5	15.8 ± 11.1	11.6 ± 10.3	0.002 (>0.99)
Valproate	29.2 ± 6.2	23.5 ± 12.1	5.7 ± 9.2	0.002 (0.97)	28.7 ± 6.5	17.9 ± 14.2	10.8 ± 11.9	0.001 (>0.99)
Olanzapine	26.5 ± 19.2	19.2 ± 11.0	7.3 ± 9.7	0.05 (0.52)	28.5 ± 5.1	15.3 ± 8.6	13.2 ± 9.3	0.001 (>0.99)

Both CBZ-ERC and placebo-treated subjects significantly improved at endpoint when compared with baseline (with the exception of lithium-unresponsive subjects assigned to placebo).

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utilized for all the secondary outcome measures. Power analysis followed Cohen.[17]

RESULTS

The demographics of the subjects are presented in Table 1. There were no significant differences between any of the groups. Baseline and endpoint YMRS ratings for subjects who were previously on lithium, valproate, or olanzapine are presented in Table 2. There was significant improvement in all the groups with the exception of the subjects previously on lithium randomized to receive placebo (Table 2). The majority of these comparisons had reasonable power (see power values in Table 2).

Subjects receiving CBZ-ERC significantly improved when compared with subjects receiving placebo if they were previously on lithium or

valproate, and approached significance if they were previously on olanzapine. This can be explained by the power of the analysis. Calculated power for subjects previously on lithium is 0.74; for subjects previously on valproate is 0.77; but for subjects previously on olanzapine, it is only 0.26.

Secondary outcome measures regarding global function (CGI) and depressive symptoms (HDRS) showed a similar pattern in which most subjects improved as compared with their baseline scores, and a drug effect when compared with placebo (Table 3). Only subjects previously unresponsive to olanzapine showed improvement in CGI and HDRS (Table 3). The power for these analyses appears to predict which ones reach statistical significance (see power values in Table 3).

Responder analysis was only significant in subjects previously unresponsive to valproate, because the larger sample size in that group provided sufficient power.

DISCUSSION

Carbamazepine monotherapy treatment for acute mania or mixed mania was significantly effective in subjects who previously failed lithium and valproate treatment, and approached significance in subjects previously treated with olanzapine (Figure 1). These results expand on previous work showing that carbamazepine is effective in manic and mixed manic patients,[12,13] by showing that it may be effective even if the patients had failed to respond to another mood stabilizer. This suggests that switching patients who may not have responded to lithium or valproate to carbamazepine is a reasonable clinical strategy for the treatment of acute mania or mixed mania. This is especially true if there was no noted improvement, or if unacceptable adverse events were experienced, with their prior therapy, which would argue against an augmentation strategy.

The data also suggest that study entry also ameliorates manic symptoms. Whether subjects were randomized to carbamazepine or placebo, most improved (Table 2). The one exception is subjects previously on lithium and randomized to placebo. In other words, a significant improvement in target and "treatment resistant" symptoms may occur just as a consequence of study entry and associated factors such as hospital milieu, group therapy, family involvement, and structure, as well as office-based support following discharge. These results have important implications on studies of treatment-resistant patients, particularly in open studies. These findings increase the level of suspicion one may have while interpreting open studies of treatment-resistant patients, since without a control group, many such studies would appear positive. Critical reviews of the literature arrive at similar conclusions even if their intent is to argue against the use of placebo in psychiatric studies[18,19] and with antiepileptic agents.[2]

TABLE 3

Baseline, Endpoint (LOCF), and Change Mean Values (±SD) for the Clinical Global Impression (CGI) and Hamilton Depression Rating Scale (HDRS) in CBZ-ERC and Placebo-Treated Patients Previously Unresponsive to Lithium, Valproate, or Olanzapine

	PLACEBO				EXTENDED RELEASE CARBAMAZEPINE CAPSULES				ACTIVE VS. PLACEBO
	BASELINE	ENDPOINT	CHANGE	P (POWER)	BASELINE	ENDPOINT	CHANGE	P (POWER)	P (POWER)
CGI									
Lithium	4.6 ± 0.8	4.2 ± 1.6	0.4 ± 1.4	0.19 (0.32)	4.2 ± 0.9	3.3 ± 1.4	0.9 ± 1.2	0.007 (0.93)	0.26 (0.77)
Valproate	4.5 ± 0.9	4.1 ± 1.5	0.5 ± 1.4	0.031 (0.5)	4.5 ± 0.9	3.4 ± 1.7	1.1 ± 1.5	0.0003 (>.99)	0.08 (0.77)
Olanzapine	4.4 ± 0.6	3.9 ± 1.3	0.6 ± 1.1	0.046 (0.6)	4.7 ± 3.4	3.4 ± 1.3	1.3 ± 1.1	<0.0001 (.7)	0.04 (0.04)
HDRS									
Lithium	8.3 ± 5.5	7.4 ± 6.0	1.0 ± 5.3	0.41 (0.11)	10.2 ± 6.9	8.2 ± 4.7	2.0 ± 4.9	0.098 (0.32)	0.52 (0.11)
Valproate	12.3 ± 5.7	10.7 ± 6.3	1.6 ± 5.7	0.08 (0.4)	11.0 ± 5.9	8.3 ± 5.5	2.7 ± 6.7	0.023 (0.83)	0.43 (0.71)
Olanzapine	12.3 ± 6.7	12.0 ± 8.1	0.3 ± 6.8	0.87 (0.05)	14.5 ± 10.2	9.4 ± 9.3	5.1 ± 7.9	0.0091 (0.63)	0.05 (0.26)

Entry into the study is frequently associated with significant improvement. Although the effect is generally greater for patient treated with CBZ-ERC than placebo, the difference frequently does not reach statistical significance because of inadequate power.

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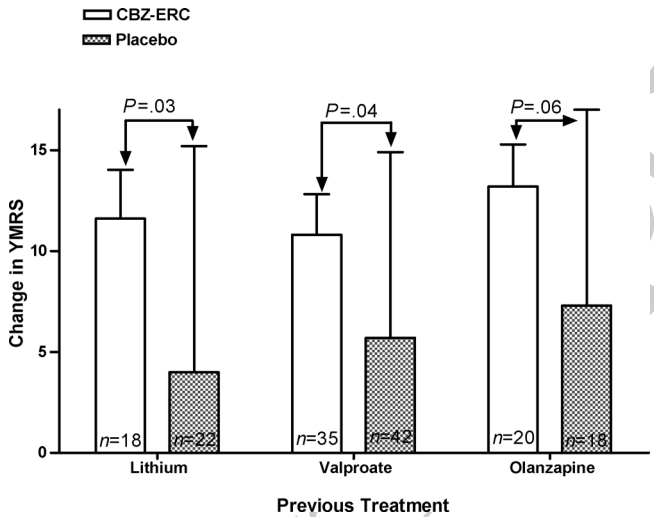
FIGURE 1

THE CHANGE IN YMRS IN PATIENTS TREATED WITH CBZ-ERC (OPEN BARS) AND THOSE TREATED WITH PLACEBO (SHADED BARS) WHO WERE PREVIOUSLY UNRESPONSIVE TO LITHIUM, VALPROATE, OR OLANZAPINE. CARBAMAZEPINE WAS SIGNIFICANTLY EFFECTIVE IN SUBJECTS WHO PREVIOUSLY FAILED LITHIUM AND VALPROATE TREATMENT, AND APPROACHED SIGNIFICANCE IN SUBJECTS PREVIOUSLY TREATED WITH OLANZAPINE



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The findings could also be used to argue for the continued need for placebo-controlled studies to determine the real impact of study medications. This is especially true, since the ethical argument against placebo is weakened with the observation that placebo-treated subjects improve significantly (Tables 2 and 3). However, some believe that the current United States Food and Drug Administration (FDA) standard of two positive placebo-controlled trials may be excessive. Such proponents reason that it may be more reasonable to demand one positive placebo-controlled study and one comparator study powered to capture a 25% difference between the new agent and the gold standard agent.

There are clear limitations to this report. This was a post hoc analysis of pivotal trials for CBZ-ERC, and the design was not intended to test antimanic response in treatment failure subjects. Second, the previous treatments (lithium, valproate, or olanzapine) may not have been optimized prior to study entry. In other words, these patients may not have failed more aggressive treatment with the original agent. Finally, it is clear from the power analyses (Tables 2 and 3) that many of the comparisons were underpowered. This limits the conclusions that can be drawn from the nonsignificant comparisons.

Despite these limitations, the study suggests that carbamazepine is an effective agent in treating manic and mixed manic patients who had previously not responded to treatment with lithium or valproate, and possibly olanzapine. Furthermore, the data also suggests that study entry is associated with improvement in manic symptoms and CGI. ✤

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