ABSTRACT

Introduction: The safety of a treatment regimen is an important consideration when considering pharmacotherapy. Given the frequency of polypharmacy in patients with bipolar disorder and the myriad of adverse events that can occur with various agents, safety is paramount in this population. Accordingly, this retrospective analysis was performed to evaluate the safety of carbamazepine extended-release capsules (CBZ-ERC) (Shire, Wayne, Pa) used in polypharmacy of those patients with bipolar disorder in a private practice setting.

Methods: Data were obtained from the charts of 300 patients aged 18 to 70 years who met *DSM-IV* criteria for bipolar disorder. Polypharmacy with CBZ-ERC combined with other psychotropic agents was investigated. Safety was analyzed by comparing the adverse event profiles of patients on CBZ-ERC monotherapy with the profiles of patients on polypharmacy (therapeutic agents were analyzed separately).

Results: When compared to those patients on CBZ-ERC monotherapy, patients taking CBZ-ERC together with other psychiatric agents (antipsychotics, antiepileptics, selective serotonin reuptake inhibitors, other antidepressants, anxiolytics, lithium, and attention-deficit/hyperactivity disorder medications) were no more likely to report gastrointestinal, nervous system, or dermatological adverse events.

Conclusions: These real-world data suggest that CBZ-ERC is safe in the treatment of patients with bipolar disorder, both as monotherapy and as polytherapy combined with other psychiatric agents.

SAFETY OF EXTENDED-RELEASE CARBAMAZEPINE IN BIPOLAR DISORDER: IMPLICATIONS OF POLYPHARMACY

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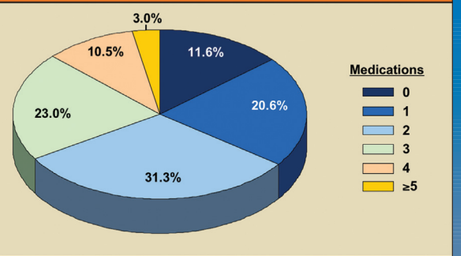
INTRODUCTION

- Currently there are increasing numbers of pharmacologic therapies to treat patients with bipolar disorder
  - Unfortunately, monotherapy with any one of these agents often fails
  - This result leads the clinician to utilize polypharmacy as a way of improving treatment outcome[1]
- Although the efficacy of therapeutic polypharmacy is largely unknown because of the lack of controlled studies, data from the United States and Europe indicate polypharmacy is the rule rather than the exception[2]
- A study by Kupfer and colleagues examined the percentages of polypharmacy with multiple medications among patients in a bipolar disorder case registry[3] **(1):**
  - 20.6% were on 1 medication
  - 31.3% were on 2 medications
  - 23.0% were on 3 medications
  - 10.5% were on 4 medications
  - 3.0% were on ≥5 medications
- Combining agents used in the treatment of bipolar disorder with carbamazepine (CBZ) is sometimes seen as problematic due to the perception of drug interactions and adverse event occurrence
- The intent of this retrospective review of the charts of 300 patients was to analyze the safety of CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, Pa) when given in combination with other psychotropic agents for the treatment of bipolar disorder

METHODS

- Data were obtained from the charts of 300 patients aged 18 to 70 years who met *DSM-IV* criteria for bipolar disorder
- These patients represent all those who had taken CBZ-ERC at a private practice setting (Red Oak Psychiatry Associates, Houston, Tex) between October 1998 and November 2003
- The safety of polypharmacy with CBZ-ERC combined with other psychotropic agents was investigated
  - Safety was analyzed by comparing the adverse event profiles of patients on CBZ-ERC monotherapy with the profiles of patients on polypharmacy (therapeutic agents were analyzed separately)
  - Safety took into account gastrointestinal disturbances (nausea, vomiting), central nervous system disturbances (dizziness, somnolence), skin disorders (rash), and headache
- Clinical Global Impression–Improvement (CGI-I) scores of patients were also analyzed to assess treatment response between monotherapy and polypharmacy groups
  - Scores ≤3 signified a clinical response to CBZ-ERC therapy

1. Polypharmacy in Bipolar Disorder



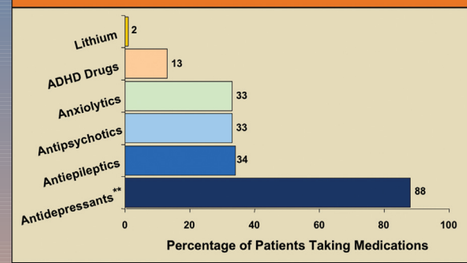
Source: Kupfer DJ, et al. *J Clin Psychiatry.* 2002;63:120-125.

2. Patient Demographics

	CBZ-ERC Monotherapy	Polypharmacy	*P* Value
Participants (n)	57	243	NS
Percentage female	63	72	NS
Age (y) (mean ± SD)	32.6 ± 10.0	35.6 ± 11.5	.07
Age range (y)	19-66	18-70	NS
Bipolar I manic/mixed	27	110	.89
Bipolar I depressed	10	57	.43
Bipolar II	11	34	.42
Bipolar NOS	9	42	.94

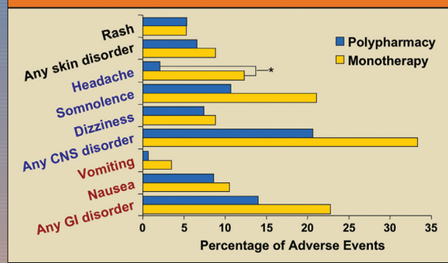
CBZ-ERC = carbamazepine extended-release capsules; NOS = not otherwise specified; NS = not significant.

3. Concomitant Medications*



*For those patients in the polypharmacy group (n = 243).
**Includes tricyclics and selective serotonin reuptake inhibitors.
ADHD = attention-deficit/hyperactivity disorder.

4. Adverse Event Occurrence



*P = .002.
GI = gastrointestinal; CNS = central nervous system.

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1. Solomon DA, Keitner GI, Ryan CE, Miller IW. Polypharmacy in bipolar I disorder. *Psychopharmacol Bull.* 1996;32:579-587.
2. Zarate CA Jr, Quiroz JA. Combination treatment in bipolar disorder: a review of controlled trials. *Bipolar Disord.* 2003;5:217-225.
3. Kupfer DJ, Frank E, Grochocinski VJ, et al. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. *J Clin Psychiatry.* 2002;63:120-125.

RESULTS

- Data from the medical records of 300 patients taking CBZ-ERC indicated that 243 were taking another psychotropic drug, while 57 patients were receiving CBZ-ERC monotherapy **(2)**
- A significant portion of the study population was female, and the mean ages in the 2 groups ranged from 32.6 years to 35.6 years **(2)**
- Concomitant medications taken by polypharmacy patients included: antidepressants (n = 215), antiepileptic drugs (n = 83), antipsychotics (n = 81), anxiolytics (n = 79), attention-deficit/hyperactivity disorder drugs (n = 32), and lithium (n = 5) **(3)**
- The percentage of responders based on a CGI-I score of no greater than 3 was significantly greater in the polypharmacy than in the monotherapy group (78% vs 53%, respectively)
- In general, the incidences of various adverse events were not statistically significant between patients who were taking CBZ-ERC as monotherapy and those patients who were taking more than 1 medication **(4)**
  - Incidence of headache was the only adverse event variable that showed a statistically significant difference between the monotherapy and polypharmacy groups (P = .002)
- Although not statistically significant, other adverse event variables showed trends toward higher incidence in the monotherapy group
  - This result may reflect higher dosing of CBZ-ERC undertaken without the addition of other mood-stabilizing agents

CONCLUSIONS

- The pharmacokinetic properties of CBZ can present a challenge in its use with other medications
- The most common problems associated with a polypharmacy regimen including CBZ relate to the induction of liver enzymes, which can thereby increase the metabolism of concomitant drugs, reducing their efficacy
  - CBZ metabolism can also be inhibited by other drugs, leading to CBZ toxicity. This study indicates, however, that the incidence of adverse events was not significantly different in patients on CBZ-ERC polypharmacy vs monotherapy
  - This result suggests that CBZ-ERC may be used safely as part of a polypharmacy regimen with a variety of pharmacologic agents
  - More rigorous, controlled studies are warranted, however, to justify this conclusion

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