Patterns of Care, Outcomes, and Direct Health Plan Costs of Antiepileptic Therapy: A Pharmacoeconomic Analysis of the Available Carbamazepine Formulations

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ABSTRACT

Background: Although generic formulations of immediate-release carbamazepine (IR-CBZ) are available, extended-release delivery systems may offer important advantages, including the convenience of less-frequent administration and smaller peak-to-trough serum carbamazepine (CBZ) fluctuations.

Objective: The aim of this study was to compare the patterns of pharmacotherapy, rates of adverse events, and the utilization costs among patients treated with the available CBZ formulations (ie, generic and branded IR-CBZ, and extended-release CBZ (ER-CBZ) capsules [Carbatrol®, Shire US Inc., Wayne, Pennsylvania] and tablets [Tegretol®-XR, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey]).

Methods: Data were retrieved from the PharMetrics patient-centric database (which contains integrated claims data for almost 36 million unique patients from 61 US health plans) for patients who were diagnosed with epilepsy and initiated CBZ between July 1999 and June 2001. Patient demographic and clinical characteristics, adverse events, discontinuations, CBZ therapy switches, and utilization and costs for related care subsequent to treatment initiation were recorded. Annual rates of adverse events and discontinuations were calculated, and the risks of these events were compared across treatment groups.

Results: Data were gathered for 1737 patients. The branded CBZ group was demographically and clinically different than the other groups (ie, migraine and cerebral palsy prevalence) and therefore was excluded from event-risk analyses. Results of the proportional hazards regression analysis indicated that Tegretol-XR patients were more likely to experience common central nervous system (CNS)–related adverse events relative to Carbatrol (hazard ratio, 1.67; $P = 0.043$). A lower percentage of subjects switched off ER-CBZ relative to IR-CBZ (Carbatrol, 5.2%; Tegretol-XR, 5.7%; generic IR-CBZ, 13.0%; branded IR-CBZ, 16.7%). Differences in mean payments for epilepsy-related health care services at 1 year among Carbatrol, Tegretol-XR, and branded or generic CBZ did not reach statistical significance.

Conclusions: Among the available CBZ formulations, Carbatrol was associated with a lower incidence of common CNS adverse events. ER-CBZ formulations were also associated with reduced likelihood of therapy discontinuation or switching CBZ medications, relative to patients taking generic IR-CBZ, in this retrospective data analysis. (*Clin Ther.* 2005;27:1092–1103) Copyright © 2005 Excerpta Medica, Inc.

Key words: carbamazepine, pharmacoeconomics, epilepsy, generics.

INTRODUCTION

Carbamazepine (CBZ), a first-line therapy for the treatment of partial seizures and generalized tonic-clonic seizures, is available in several formulations: immediate-release CBZ (IR-CBZ) generic and branded* tablets, Carbatrol®† extended-release CBZ (ER-CBZ) capsules, and Tegretol®-XR‡ ER-CBZ tablets. The IR-CBZ formulations must be taken on a strict

*Trademark: Tegretol® (Novartis Pharmaceuticals Corporation, East Hanover, New Jersey).
†Trademark of Shire US Inc., Wayne, Pennsylvania.
‡Trademark of Novartis Pharmaceuticals Corporation.

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TID or QID basis to avoid significant peak-to-trough serum CBZ fluctuations. These fluctuations in CBZ levels can be as large as 2.5-fold[1] and may lead to peak-related neurotoxicity, such as tiredness, vertigo, dizziness, and diplopia,[2–5] as well as trough-related breakthrough seizures.[6]

ER delivery systems offer important advantages relative to IR-CBZ formulations, including smaller peak-to-trough serum CBZ fluctuations, which help maintain CBZ levels in the narrow therapeutic range and potentially yield less peak-related neurotoxicity and trough-related breakthrough seizures.[7,8] In addition, less-frequent administration can improve patient adherence.[9] Moreover, clinical studies of ER-CBZ in patients with epilepsy have found a reduction in the incidence of adverse events and an improvement in patient-perceived quality of life.[10,11] Carbatrol capsules are filled with 3 different types of beads—25% IR, 40% ER, and 35% enteric release—designed to extend the delivery of the drug to 12 hours. Tegretol-XR utilizes the OROS osmotic release delivery system (ALZA Corporation, Mountain View, California). In each Tegretol-XR tablet, drug is contained in an osmotic core surrounded by a semipermeable membrane. When water diffuses into the tablet through this membrane, drug solution is slowly released through an orifice in the tablet.[12]

Carbatrol and Tegretol-XR have been shown to have similar efficacy and tolerability profiles in studies in patients with epilepsy.[10,13] In addition, both formulations have comparable major pharmacokinetic parameters (ie, AUC and C_{max}).[14,15] However, delivery of CBZ may be more consistent in Carbatrol than Tegretol-XR.[15] In a study of healthy volunteers, each subject received either Carbatrol or Tegretol-XR for 5 days, followed by a washout period, and then switched to the other medication for 5 days.[15] The basic pharmacokinetic values (ie, AUC and C_{max}) were comparable, but there was greater variability in absorption with Tegretol-XR (ie, the error bars around the mean were wider). Fluctuations in CBZ concentrations may be more prominent with Carbatrol than Tegretol-XR, but fluctuations in CBZ-10,11-epoxide (CBZ-E), its active metabolite, may be more pronounced in Tegretol-XR than Carbatrol.[15] Nevertheless, plasma CBZ and CBZ-E peak-to-trough ratios for both formulations are <50%, suggesting minimal plasma drug fluctuations[15]; it should be noted that because the participants received medication for 5 days, they were at steady state, but the autoinduction feature of carbamazepine may not have taken effect.

The objective of the present study was to compare the patterns of pharmacotherapy (including discontinuations of therapy and switching among CBZ formulations), rates of serious and common central nervous system (CNS) adverse events, and the utilization and costs among patients treated with the available CBZ formulations: Carbatrol, Tegretol-XR, and branded and generic IR-CBZ.

PATIENTS AND METHODS

The PharMetrics patient-centric database, which at the time of this study contained integrated claims data for almost 36 million unique patients from 61 US health plans, includes information on both inpatient and outpatient diagnoses (in *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*][16] format) and procedures (in *ICD-9-CM; Current Procedural Terminology*, 4th edition[17]; and Healthcare Common Procedure Coding System[18] formats), and standard and mail order prescription records. Prescription records include days supplied and quantity dispensed. Furthermore, data elements on paid and charged amounts for all services and dates of service for all claims are recorded. Other variables include demographics, product type (eg, health maintenance organization, preferred-provider organization), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment. Due to the size of the database, its patient records are likely to be representative of the national managed care population in demographic measures. Typically, members have been enrolled in the health plan for ≥2 years. To ensure unbiased samples, only health plans that submit records for all members are included.

This study was exempt from informed-consent requirements. Subjects were not identified by name. Instead, each subject was given a study number that could not be linked to his or her name. Confidentiality was preserved at all times.

The PharMetrics patient-centric database was used to retrieve data for patients aged ≥18 years who were diagnosed with epilepsy (*ICD-9-CM* diagnoses 345.xx or 780.3x) and newly started on Carbatrol, Tegretol-XR, or IR-CBZ between July 1999 and June 2001. *Newly started* was defined on the basis of ≥1 prescription for