Patterns of care, outcomes, and direct health plan costs of antiepileptic therapy: a pharmacoeconomic analysis of the available carbamazepine formulations

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined several formulations of carbamazepine (CBZ) used for the treatment of epilepsy. Specifically, immediate-release CBZ (IR-CBZ) generic and branded tablets, Carbatrol extended-release CBZ (ER-CBZ) capsules, and Tegretol-XR ER-CBZ tablets. The dosages used were not reported.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with a diagnosis of epilepsy and who had newly started on one of the study drugs. Patients who had a pre-existing adverse event or condition of aplastic anaemia, agranulocytosis, Lyell's or Stevens-Johnson syndrome, psychotic conditions, brain cancer, visual disturbances, ataxia, confusion, diplopia, or vertigo were excluded.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from July 1999 to June 2001. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations, if performed, were not reported. Of the 108,822 unique cases with epilepsy, a sample of 1,737 eligible patients was identified from a database (i.e. PharMetrics) containing claim data for almost 36 million patients from 61 US health plans. There were 230 patients (65.7% women) in the Carbatrol ER-CBZ group, 527 (61.9% women) in the Tegretol-XR-CBZ group, 275 (58.9% women) in the branded IR-CBZ group, and 705 (60.0% women) in the generic IR-CBZ group. The mean age was 37.6 (+/- 0.9) years (age range: 18 - 81) in the Carbatrol ER-CBZ.
group, 40.1 (+/- 0.6) years (age range: 18 - 87) in the Tegretol-XR-CBZ group, 40.6 (+/- 0.8) years (age range: 18 - 83) in the branded IR-CBZ group, and 43.5 (+/- 0.6) years (age range: 18 - 90) in the generic IR-CBZ group. Only patients with complete data records were selected. A detailed list of reasons why some patients were excluded was reported.

Study design
This was a retrospective cohort study that was carried out at several centres across the USA. The allocation of the patients to the study groups was based on the treatment each patient had received. The length of follow-up was not stated. No patient was lost to the follow-up assessment. Blinding was not performed.

Analysis of effectiveness
All patients included in the initial study sample were considered in the analysis of effectiveness. In effect, as expected, only patients with complete data records were considered. The outcome measures used were:

- the proportion of patients who added a different CBZ formulation to existing CBZ therapy, and the time to first therapy change;
- the proportion of patients who switched therapy, and the time to first change;
- the proportion of patients discontinuing their medication, and the time to first discontinuation; and
- adverse events.

No statistical test was applied to assess significant differences, but Cox proportional hazard models were used for selected clinical outcomes controlling for pre-treatment or demographic differences. The branded IR-CBZ group was not comparable at baseline with the other groups of patients, so it was excluded from the hazard regression analysis.

Effectiveness results
The proportion of patients who added a different CBZ formulation was 3% in the Carbatrol ER-CBZ group, 3.8% in the Tegretol-XR-CBZ group, 2.9% in the branded IR-CBZ group, and 2.3% in the generic IR-CBZ group. The time to first therapy change was 81 (+/- 42.8) days in the Carbatrol ER-CBZ group, 100 (+/- 24) days in the Tegretol-XR-CBZ group, 132 (+/- 37.7) days in the branded IR-CBZ group, and 47 (+/- 20.9) days in the generic IR-CBZ group.

The proportion of patients who switched therapy was 5.2% in the Carbatrol ER-CBZ group, 5.7% in the Tegretol-XR-CBZ group, 16.7% in the branded IR-CBZ group, and 13.0% in the generic IR-CBZ group. The time to first change was 123 (+/- 34) days in the Carbatrol ER-CBZ group, 155 (+/- 21) days in the Tegretol-XR-CBZ group, 150 (+/- 18) days in the branded IR-CBZ group, and 87 (+/- 8) days in the generic IR-CBZ group.

The proportion of patients who discontinued CBZ therapy was 63.9% with Carbatrol ER-CBZ, 63.8% with Tegretol-XR-CBZ, 57.1% with branded IR-CBZ, and 66.5% with generic IR-CBZ. The mean time to first discontinuation of CBZ was 98 (+/- 7) days in the Carbatrol ER-CBZ group, 93 (+/- 5) days in the Tegretol-XR group, and 74 (+/- 4) days on generic IR-CBZ.

The hazard ratio for time to discontinuation (using Carbatrol ER-CBZ as the reference group) was 1.04 (95% confidence interval, CI: 0.87 - 1.26; p=0.66) with Tegretol-XR-CBZ and 1.37 (95% CI: 1.14 - 1.63; p<0.001) with generic IR-CBZ.

The hazard ratio for central nervous system (CNS) adverse events (using Carbatrol ER-CBZ as the reference group) was 1.67 (95% CI: 1.02 - 2.73; p=0.043) with Tegretol-XR-CBZ and 1.55 (95% CI: 0.93 - 2.60; p=0.095) with generic IR-CBZ.

The hazard ratio for serious adverse events (using Carbatrol ER-CBZ as the reference group) was 0.97 (95% CI: 0.61 - 1.54; p=0.90) with Tegretol-XR-CBZ and 1.15 (95% CI: 0.75 - 1.79; p=0.52) with generic IR-CBZ.
Clinical conclusions
The effectiveness analysis showed that patients receiving ER-CBZ formulations were significantly less likely to discontinue therapy or to switch their CBZ medications than those receiving generic IR-CBZ. However, patients using Tegretol-XR were likely to experience higher peak plasma CBZ-E concentrations, leading to CNS side effects.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was carried out.

Direct costs
The perspective adopted in the study was not explicitly stated, but it might have been that of the health plan. A breakdown of the cost items was not provided, but the costs were grouped as ancillary (laboratory tests or imaging procedures), facility (hospitals, ambulatory care centres, or nursing homes), management visits (physician office visits), pharmacy, and surgical services. The unit costs were not presented separately from the quantities of resources used. Both the costs and resource use were estimated from the same claim database that was used in the effectiveness study. The costs reflected health plan payments. Discounting does not appear to have been relevant as the costs were incurred during less than 2 years. The price year was 2002.

Statistical analysis of costs
The costs between groups were compared using a generalised linear model that controlled for differences in demographic and clinical characteristics, as well as the use of medication in the pre-treatment phase.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total annual costs in 2002 prices were $2,414 in the Carbatrol ER-CBZ group, $2,914 in the Tegretol-XR-CBZ group, $2,586 in the branded IR-CBZ group, and $3,150 in the generic IR-CBZ group. The difference in costs did not reach statistical significance.

The largest difference in individual epilepsy-related care costs among the treatment groups was facility costs related to any claim submitted by institutions (e.g. hospitals, ambulatory care centres): $561 for Carbatrol-ER-CBZ, $808 for branded IR-CBZ, $676 for Tegretol-XR CBZ, and $1,368 for generic IR-CBZ.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was carried out.
Authors' conclusions
Carbatrol was associated with a lower incidence of central nervous system (CNS) adverse events relative to Tegretol-XR and generic or branded immediate-release carbamazepine (IR-CBZ) in epileptic patients. The rate of therapy discontinuation was significantly lower for extended-release formulations (Tegretol-XR and Carbatrol). Further, patients switched off extended-release carbamazepine (ER-CBZ) at a lower rate relative to generic IR-CBZ. No statistically significant difference in the costs was observed.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as all available formulations of CBZ were considered in the analysis. However, the dosages used were not clear. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness came from a cohort study. The retrospective nature of the study and the lack of random allocation of the patients to the study groups represent two important limitations of the validity of the analysis. Consequently, the potential impact of selection bias and confounding factors cannot be ruled out. The study groups were not well matched at baseline, but statistical analyses were used to control for baseline differences. The evidence came from several centres, thus the study sample should be representative of the patient population. No formal justification for the size of the sample was provided, and power calculations were not reported. However, a quite large sample of patients was included. Details of the follow-up were not clearly provided. These issues tend to limit the internal validity of the analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The perspective adopted in the analysis of the costs was not stated. The costs were estimated using health plan payments, suggesting that the cost/resource boundary of the health plan might have been used. The costs were presented as macro-categories and details of resource consumption were not provided. This limits the possibility of replicating the cost analysis in other settings. The cost estimates were specific to the study setting, but statistical analyses were carried out to test for cost-differences. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Sensitivity analyses were not carried out, which limits the external validity of the study. The authors noted that the study referred to an adult population, thus the conclusions of the analysis should not be extrapolated to paediatric patients. Moreover, dosage and titration methods were unobtainable from the database, thus the effect of more aggressive therapies could not be assessed.

Implications of the study
The study results suggested that extended-release formulations of CBZ lead to lower discontinuation and switch rates of initial therapy. Carbatrol is associated with the lowest rate of CNS adverse events. The authors stated that future studies should further explore the reasons why patients are more likely to continue taking ER-CBZ relative to immediate-release formulations.

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