A pharmacoeconomic analysis of the impact of therapeutic drug monitoring in adult patients with generalized tonic-clonic epilepsy

Rane C T, Dalvi S S, Gogtay N J, Shah P U, Kshirsagar N A

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 use of therapeutic drug monitoring (TDM) in adult patients with generalised tonic-clonic (GTC) epilepsy. The intervention was intended to enhance the efficacy of anticonvulsant therapy by showing unrecognised under- or over-dosage, detecting failure of compliance, drug interactions, or indicating the lack of utility in treatment continuation. The samples were analysed by high-performance liquid chromatography.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population included patients who experienced onset of epilepsy between 18 and 35 years, had been epileptic for at least 4 years, were aged between 24 and 40 years at enrolment, had been taking anti-epileptic medication for at least 4 years, and had visited the epilepsy clinic twice a year for at least two years. Patients receiving TDM had a minimum of two TDMs per year. The exclusion criteria were secondary epilepsy, seizure type other than GTC, concomitant diseases or concomitant drug therapy.

Setting
The setting was tertiary care (tertiary referral centre). The economic study was carried out in India.

Dates to which data relate
Resource use data were collected during the period 1998 - 1999. The price year was not reported.

Source of effectiveness data
The effectiveness evidence came from a single study.

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

Study sample
Power calculations, if conducted, were not reported. Fifty patients in the TDM group were contacted from those attending the TDM clinic, and the first 25 consecutive eligible patients who responded were enrolled into the study. Patients in the control group were selected from those who had simultaneously attended the epilepsy clinic, but who had
not undergone TDM. The study groups were matched in terms of age, disease, duration of drug therapy, and duration of epilepsy clinic attendance. There were 16 men in both groups. The mean age at onset of epilepsy was 21.22 (+/- 3.26) years in the TDM group and 21 (+/- 3.7) years in the control group.

**Study design**
This was a retrospective cohort study, which was carried out at the Department of Clinical Pharmacology of the Seth GS Medical College and KEM Hospital in Mumbai, India. The patients were interviewed at the time of the study using a pre-designed questionnaire. They were then asked to report some clinical outcomes referring to the period before TDM (TDM group) and the year before interview (control group). No loss to follow-up was reported.

**Analysis of effectiveness**
All patients included in the initial study sample were taken into account when estimating the effectiveness. The health outcomes used in the analysis were seizure control, adverse events, proportion of patients earning, and marital status. Each outcome measure was compared twice, that is, between groups, and within the same group between pre-intervention and interview evaluation. The study groups were shown to have been comparable at baseline with respect to their demographics and disease characteristics (such as duration of treatment and age at epilepsy onset).

**Effectiveness results**
With respect to seizure control, in the TDM group (25 patients), 23 patients (92%) had uncontrolled epilepsy at the time of TDM referral. At interview, 4 patients (16%) still had uncontrolled epilepsy, 11 (44%) achieved complete seizure control, and 10 (40%) had 50% reduction in seizure frequency. In the control group (25 patients), 25 patients (100%) had uncontrolled epilepsy one year before interview. At interview, 12 patients (48%) still had uncontrolled epilepsy, 2 (8%) achieved complete seizure control, and 11 (44%) had greater than 50% reduction in seizure frequency. The difference in pre- and post-seizure control was statistically significant, (p<0.05), in both study groups.

In the TDM group, adverse events were observed in 28% in the period before TDM referral and in 8% of patients at interview. The corresponding rates in the control group were 0% (pre-interview) and 40% (at interview). Both differences in each study group were statistically significant, (p=0.004).

The proportion of patients earning in the intervention group was 0% before TDM and 76% at interview, (p<0.001). The corresponding percentages for the control group were 12% (one year before interview) and 48% (at interview), (p=0.012).

In terms of marital status, 0% of the patients in the TDM group were married with children before TDM referral, compared with 60% at interview. The corresponding rates in the control group were 0% (pre-interview) and 28% (at interview).

Between-group comparisons showed that the differences in seizure control and adverse effects at interview were statistically significant.

**Clinical conclusions**
The effectiveness analysis showed that patients in the TDM group improved their seizure control and reduced side effects in comparison with those who did not receive the intervention. The proportion of those earning and married was also greater in the intervention group.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the number of seizures prevented, which was derived from the effectiveness study.
Direct costs
Discounting was not relevant since the costs were incurred in less than two years. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic evaluation were equipment, depreciation, repairs and maintenance, interest on capital, and consumables and salaries of the staff. The cost/resource boundary adopted in the study was that of a large public non-profit hospital, but the costs to the patient (consumables) were also considered, although analysed separately. The resource use was estimated on the basis of retrospectively collected data derived from the same patient sample as that used in the effectiveness study. The unit costs represented charges used at the study institution. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included.

Currency
Indian rupees (Rs). The reported exchange rate from rupees into UK pounds sterling () was approximately Rs 75 = 1.

Sensitivity analysis
Sensitivity analyses were not conducted.

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

Cost results
The average cost of the TDM service per patient was Rs 147 from the perspective of the hospital, while each patient was charged only Rs 30 per sample. Thus, the TDM procedure cost the patient Rs 60 per year. The costs in the control group were not evaluated.

Synthesis of costs and benefits
An average cost-effectiveness ratio was calculated to combine the cost and benefit of the study intervention. An incremental analysis was not conducted. The cost of TDM to the hospital per seizure prevented was Rs 22.35, while the cost to the patient was Rs 4.50.

Authors' conclusions
Patients undergoing therapeutic drug monitoring (TDM) showed a significant reduction in the number of seizures and adverse events, and better earning status and marital status, when compared with patients who received standard care. The extra cost of the service was modest.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Standard care without drug monitoring was selected because it represented the routine procedure at the study institution. The authors stated that further monitoring approaches were available, but TDM was used due to its low costs. You should decide whether no monitoring represents a valid comparator in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness used a retrospective study, which relied on a questionnaire and records. The authors acknowledged that the retrospective nature of the study might have represented a limitation of the analysis. A further threat to the internal validity of the study was the small sample size and the lack of power calculations to determine the sample size required to detect statistically significant differences in the study outcomes. The strengths of the study were baseline comparability and the lack of loss to follow-up. The study sample was quite unselected and appears to have been representative of the study population.

Validity of estimate of measure of benefit
The benefit measure was derived from the effectiveness study.

Validity of estimate of costs
The perspective adopted in the study was reported, and the costs relevant to the hospital and the patient were included in the economic evaluation. The unit costs and the quantities of resources used were not reported separately, and the price year was not stated. Thus, the reproducibility of the study in other settings does not appear feasible. The costs were estimated prospectively on the basis of charges evaluated at the study hospital. The cost estimates were specific to the study setting and no sensitivity analyses were conducted. The costs were treated deterministically.

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. The overall external validity of the analysis was low. The study referred to adult patients with epilepsy and this was reflected in the conclusions of the analysis. The authors highlighted the main limitation of the study, which was the retrospective nature of the effectiveness analysis.

Implications of the study
The study suggests that a TDM service may be useful for adult patients with epilepsy. It was associated with modest costs and it resulted in better seizure control, fewer adverse events, and greater chance of readmission in comparison with a standard approach, which did not include TDM. However, caution is required when interpreting this conclusion, due to the methodological limitations of the analysis.

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