Clinical and economic impact of replacing divalproex sodium with valproic acid
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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
Divalproex sodium and valproic acid in the treatment of mentally retarded adults with epilepsy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Adults with a learning disability and epilepsy.

Setting
State-supported mental health facility setting. This study was carried out in the USA.

Dates to which data relate
The effectiveness data related to the periods extending 12 months before and 18 months after the change in therapy. The switch from divalproex to valproic acid took place between October 1993 and July 1994, and therefore records were reviewed over the period 1992-1996. The price year was 1995.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
82 patients receiving divalproex were initially considered for inclusion. 21 were not switched to valproic acid during the study period and 13 were lost to follow-up. Two patients were excluded because of resolution of their seizure disorder. Data for 46 patients were included in the analysis. No power calculations were reported. Patients were included if they had received divalproex for at least three months and if treatment was switched to valproic acid between October 1 1993 and June 30 1994. To minimise the effect of confounding variables, patients who were admitted to an outside hospital or another facility for people with learning disability during the observation period were excluded from the study if their institutionalisation lasted more than 7 days.
Study design
The study was a retrospective before-and-after study carried out at a single centre. Patients were followed up for 18 months after the change in therapy. 13 patients were lost to follow-up.

Analysis of effectiveness
The analysis of the clinical study was based on the intention to treat principle. The primary health outcomes used included effectiveness (use of valproic acid was considered to be effective if the patient continued taking the agent at the end of the valproic acid period, either with or without new drug therapy for GI disorders), number of seizures per month, number of patients requiring new drug therapy for a GI disorder, GI disorders, number of complete blood counts, stool guaiac tests, serum valproate concentration determinations, divalproex or valproic acid dosage changes, and prescribing patterns. No testing was undertaken to ascertain whether groups at analysis were comparable. The majority of the study group members were male, ambulatory, non-verbal and profoundly learning disabled. 19 patients had at least one confirmed prior GI diagnosis.

Effectiveness results
Replacement of divalproex with valproic acid was effective in 41 of the 46 patients. 13 patients in the divalproex group and 6 patients in the valproic acid group had GI disorders. 14 patients in the divalproex group and 8 patients in the valproic acid group required drug therapy for a GI disorder. 8 patients in the divalproex group and 3 patients in the valproic acid group who required treatment of a GI problem had a prior GI diagnosis. There was no significant difference in terms of the number of seizures per month, the number of patients who required new drug therapy for a GI disorder, number of complete blood counts, stool guaiac tests, serum valproate concentration determinations, divalproex or valproic acid dosage changes. There was a higher rate of valproic acid prescriptions during the early months of the study, followed by a plateau in the later months.

Clinical conclusions
Replacing divalproex with valproic acid was effective in the majority of patients studied. No significant change in either the seizure rate or the frequency of new therapy for GI disorders occurred.

Modelling
No modelling was undertaken.

Measure of benefits used in the economic analysis
The primary benefit measure was effectiveness. The use of valproic acid was considered to be effective if the patient continued taking the agent at the end of the valproic acid period, either with or without new drug therapy for GI disorders.

Direct costs
All costs were adjusted to 1995 dollars by using the Department of Labor Statistics Consumer Price Index for medical care and the first year of each fiscal year as the reference year. Quantities and costs were not reported separately. Direct costs were the acquisition cost of drugs and supplies, the cost of additional laboratory tests resulting from GI disorders associated with divalproex and valproic acid use, and the cost of pharmacy employee time for repackaging valproic acid products. The quantity/cost boundary adopted was that of the hospital. The estimation of quantities and costs was based on actual data. Data were obtained from the facility.

Statistical analysis of costs
Outcomes between groups were compared by using the Wilcoxon signed-ranks test for paired data and frequency distribution tables.
Indirect Costs
No indirect costs were explicitly included.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
Replacing divalproex with valproic acid was effective in 41 of the 46 patients.

Cost results
Total direct costs declined steadily over the study period: $139,000 in 1992-3, $99,193 in 1993-4, $68,746 in 1994-5 and $61,019 in 1995-6. This represented a cost reduction of -29%, -51% and -56% (p<0.05) for the years following 1992-3, respectively. The decrease was most directly associated with a change in the proportion of valproic acid use compared with divalproex use. Despite the decline in the overall use of divalproex, its cost continued to account for a majority of total drug costs in each year studied. The direct cost of new drug treatment required for GI symptoms had no significant effect on overall cost of care. Total cost savings were significant at a 5% level.

Synthesis of costs and benefits
Costs and benefits were not combined into a cost-effectiveness ratio.

Authors’ conclusions
Replacing divalproex sodium with valproic acid in a group of institutionalised learning disabled adults with epilepsy was clinically effective and economically advantageous.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear.

Validity of estimate of measure of benefit
The measure of benefit seems to be valid. No effort was made to measure quality of life, which is of course difficult to elicit in patients with a learning disability. All relevant effectiveness measures would appear to have been included.

Validity of estimate of costs
Only direct costs associated with treatment were included. No sensitivity analysis was carried out, which makes it difficult to assess the robustness of the results.

Other issues
No explicit justification for the nature of the null hypotheses was provided. No statistical analyses were conducted on the effectiveness results. The authors assessed the reliability of the data retrieved from patient charts. No attempt was made to assess the generalisability of the results. It is highly unlikely that these results also apply to other settings or countries since the study institution provides a higher level of care than many residential mental health facilities. The study suffered from a small sample size. The main limitation of the study is its retrospective, descriptive design which raises concerns regarding selection bias. The results might have been influenced by recent pressure to reduce drug
The lack of a standardised protocol for patient monitoring and reporting of outcomes during routine care may have also biased the results. The use of medical records for data extraction is likely to result in incomplete reporting of relevant information.

**Implications of the study**
These results should be validated by a prospective randomised controlled trial, set in a typical mental health facility.

**Source of funding**
None stated.

**Bibliographic details**

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**Other publications of related interest**


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