Effect of splitting simvastatin tablets for control of low-density lipoprotein cholesterol
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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 therapeutic substitution of split tablets for whole tablets of the same dose of simvastatin was examined. The intervention was applied only to patients receiving a dose of simvastatin that could be achieved by splitting a larger dose in half (i.e. 5, 10, 20 or 40 mg).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients requiring simvastatin therapy.

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 in 1999. The price year appears also to have been 1999.

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 clinical study.

Study sample
The patients were identified using the VA system. A group of 3,787 patients who met the following criteria was identified:

- remained on a consistent daily dose of simvastatin between January 1 and December 31, 1999;
- used a dose of simvastatin that could be achieved by splitting a larger dose in half (i.e. 5, 10, 20 or 40 mg); and
- had at least one LDL cholesterol result before and after the switch to a split tablet, or at least two LDL cholesterol results for patients who did not split tablets.
Patients were then removed from the analysis if the time between the first LDL cholesterol measurement, or switch date, and the final LDL cholesterol measurement was less than 45 days. This left 1,331 patients who were converted to split tablets and 2,099 patients who were not. Patients in each group were then stratified by the following baseline LDL cholesterol groups: 75 to 100 mg/dL, 101 to 130 mg/dL, 131 to 160 mg/dL, or 160 to 225 mg/dL. Since an equal number of patients within each baseline LDL cholesterol group were randomly selected for each simvastatin dose per day, there were 1,098 patients in each group for analysis. Patient demographics were not reported. Power calculations showed that the sample of 2,196 patients allowed the detection of a clinically significant difference in LDL cholesterol of at least 5 mg/dL between groups, with a power of 80% and an alpha value of 0.05.

Study design
This was a retrospective cohort study in which some patients were randomised to different simvastatin doses per day. The study was carried out at six VA medical centres and their associated outpatient clinics that serviced Florida, Puerto Rico and southern Georgia. The length of follow-up was approximately one year. No loss to follow-up appears to have occurred.

Analysis of effectiveness
All of the patients included in the initial study sample were accounted for in the analysis of effectiveness. The primary outcome measures used in the clinical study were the average final LDL cholesterol values and the average change from baseline between the split group and the whole tablet group. The secondary outcome measures were incidence of transaminase increases of more than 2 to 3 times the upper limit of normal, and assessment of compliance. For patients who split tablets, the most recent LDL cholesterol value before the conversion date served as the baseline LDL cholesterol value, while the LDL cholesterol value closest to December 31, 1999 served as the final LDL cholesterol value. For patients in the unsplit group, the LDL cholesterol value closest to January 1, 1999 served as the baseline LDL cholesterol value, while the LDL cholesterol value closest to December 31, 1999 served as the final LDL cholesterol value. If the 95% confidence level of the difference between groups was less than 5 mg/dL, then tablet splitting was judged to be not inferior to the use of whole tablets. The baseline comparability of the study groups was not reported.

Effectiveness results
The mean baseline LDL cholesterol level was 119 (+/- 29) mg/dL in the split group compared with 120 (+/- 30) mg/dL in the whole tablet group, (p=0.728).

The final LDL cholesterol level was 111 (+/- 30) mg/dL after tablet splitting compared with 112 (+/- 32) mg/dL in the group that did not split tablets, (p=0.304).

The mean changes in LDL cholesterol levels from baseline were -9 (+/- 32) mg/dL for the split group versus -8 (+/- 33) mg/dL for the whole tablet group, (p=0.503).

The lower and upper boundaries of the 95% confidence interval for the mean difference in LDL levels between groups were -3.5 and 0.8 mg/dL, indicating that tablet splitting was not inferior to the use of whole tablets.

The incidence of alanine aminotransferase increases more than 2 to 3 times the upper limit of normal was similar between groups (0.53% for the split group and 0.61% for the whole tablet group). The difference was not statistically different.

The incidence of aspartate aminotransferase elevations was 0.13% for the split group and 0.28% for the whole tablet group, (p=0.32).

No significant difference in patient compliance was observed.

Clinical conclusions
The effectiveness analysis showed that the use of split tablets was equivalent to the use of whole tablets for patients taking simvastatin.
Measure of benefits used in the economic analysis
No summary benefit measure was used in the analysis since no statistically significant differences between the groups were observed in any of the outcome measures. In effect, a cost-minimisation analysis was performed.

Direct costs
The cost analysis was carried out from the perspective of the VA system. Thus, only the costs of simvastatin prescriptions and tablet splitters were considered in the analysis. The monthly costs were presented separately from the quantities of resources used. Resource use was estimated from the actual doses of simvastatin used in the sample of patients included in the effectiveness study. The costs came from the average acquisition cost of a 30-day supply of split simvastatin tablets and unsplit tablets derived from the VISN 8 Pharmacy Benefits Management Database. Discounting was not relevant since the costs were incurred during one year. The costs were assessed in the fiscal year 1999.

Statistical analysis of costs
Student's t-test was used to test the statistical significance of differences in total costs between the groups.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

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

Cost results
The total yearly cost of simvastatin (including the cost of tablet splitters) was $211,738 for the 1,098 patients in the split group and $339,018 for the 1,098 patients in the whole tablet group. This represented a cost avoidance of $126,127, (p<0.0001).

Considering the 44,522 patients on simvastatin that were included in the VA system in 1999, the widespread implementation of this therapeutic initiative would result in a cost avoidance of $5.83 million for that year.

Across the VA system in fiscal year 2003, more than $46.5 million was saved by the splitting of simvastatin tablets.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-minimisation analysis was carried out.

Authors' conclusions
The widespread therapeutic substitution of split tablets for whole tablets of the same dose of simvastatin was effective, safe and cost-saving from the perspective the VA system.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. The recently proposed therapeutic option was compared with the standard of care (whole tablet option). You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from a cohort study. The retrospective nature of the study is usually associated with a weak design. The allocation of patients to the study groups was not randomised, although some random selection of patients was used in the sub-group classification. The baseline comparability of the study groups was not discussed. Thus, the impact of confounding factors and selection bias cannot be ruled out. The assessment of the outcomes was not blinded. Some of the strengths of the study were the multi-centre design and the use of power calculations. The study sample consisted of patients identified over a fiscal year using wide selection criteria, which made the study sample quite representative of the patient population.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-minimisation 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 costs included were consistent with the perspective adopted in the study, although only simvastatin costs were considered. The impact of the intervention on other resources, such as those related to physician visits and hospital services, was not investigated. The source of the costs was reported. Resource use came from a large sample of patients and the treatment patterns are likely to reflect those of the VA system. The unit costs were presented separately from the quantities of resources used, thus enhancing the possibility of replicating the cost analysis in other settings. Some statistical analyses of the costs were performed to assess the significance of differences observed between the groups. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies, but stated that their findings confirmed those from other published economic evaluations that had suggested the potential cost-savings associated with splitting tablets. The issue of the generalisability of the study results was not explicitly addressed and sensitivity analyses were not performed. Thus, the external validity of the study was limited. The study referred to patients taking simvastatin and this was reflected in the authors’ conclusions.

Implications of the study
The study results supported the therapeutic substitution of split tablets for whole tablets of the same dose of simvastatin. The authors stated that future studies should “evaluate this intervention with other medications that also possess favorable dose-response relations and therapeutic windows and to evaluate patient and provider acceptability and patient adherence to tablet splitting”.

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