Compliance with drug therapies for the treatment and prevention of osteoporosis
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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 looked at health technologies for the prevention and treatment of osteoporosis. In particular, oestrogens only, oestrogen plus progestin, raloxifene or bisphosphonate.

Type of intervention
Treatment

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with a diagnosis of osteoporosis meeting various qualification criteria required by the insurer. The unit of observation was the initial observed treatment episode for any of the following osteoporosis drug therapies:

for single HRT, estradiol, conjugated oestrogens, conjugated synthetic oestrogens, esterified oestrogens, estropipate, medroxyprogesterone acetate, norethindrone or norethindrone acetate;

for two HRTs, oestrogen plus medroxyprogesterone acetate, norethindrone, norethindrone acetate or oestrogen;

for bisphosphonate, alendronate sodium, etidronate disodium or risedronate sodium; or raloxifene.

Given the common use of HRT therapies to treat the symptoms of the menopause, female patients had to be over the age of 55 to be included.

Setting
The study setting was secondary care. The insurer was based in California, USA.

Dates to which data relate
Data for this analysis were derived from the historical paid claims files for a large health insurance company located in California, USA. Paid claims from the period 1 January 1998 to 30 August 2001 were available for inclusion in the analysis.

Source of effectiveness data
The effectiveness data were derived from a single study.
Link between effectiveness and cost data
The effectiveness and cost data were collected from the same database and group of patients. The costing was carried out retrospectively.

Study sample
The total sample size was 58,109 patients (single HRT 46,109; two HRT 6,766; bisphosphonate 3,720, raloxifene 1,514). No power calculations were conducted before the study. All registries in the database that met the inclusion criteria were incorporated in the analysis.

Study design
This was a non-experimental study, a retrospective cohort study. The authors did not report whether it was conducted in one or more centres but, as the data were obtained from a health insurance company dataset, it was likely to have used data from more than one centre. The follow-up period appears to have been one year since the results were presented for that amount of time. No patient was lost to follow-up as this was a retrospective study. No method of blinding was reported.

Analysis of effectiveness
The analysis of the clinical data was based on all available data (in effect treatment completers). The primary health outcomes used were fractures in first post-treatment year (vertebral, hip, Colles or other), as well as the duration of therapy. The authors used the following variables to control for baseline characteristic of the study population to avoid possible bias:

- patient age and gender;
- type of health insurance coverage (Fee For Service, Health Maintenance Organisation, point-of-service, Preferred Provider Options);
- use of health care services (cost) by type of service in the 6 months prior to initiation of the drug therapy episode;
- diagnostic profile, as determined by the ICD-9 codes recorded on paid claims during the prior 6 months and the month in which treatment was initiated;
- prior fractures (vertebral, hip, Colles, all others); and
- prior use of the following classes of prescription drugs, non-steroidal anti-inflammatory drugs, arthritis medications, drugs to treat diabetes, vitamin D therapy, anticoagulation therapy, antidepressants and steroids.

Effectiveness results
The study found that bisphosphonate patients were 6.9% more likely to break therapy, (p<0.05) and used 17.7 fewer days of total drug therapy over 1 year, (p<0.0001) than patients treated initially with a single HRT. Bisphosphonate patients were also four times more likely to change therapies than single HRT patients, (p<0.0001).

In comparison, raloxifene patients were uniformly less compliant and more likely to change therapies than single HRT patients, (p<0.0001). Moreover, older patients were more compliant and more likely to change therapies than patients under 55 years of age, (p<0.0001).

The results for fractures indicated that patients treated with bisphosphonates were twice as likely as single HRT patients to experience a vertebral fracture (odds ratio, OR=2.364, p<0.0001), Colles fracture (OR=2.080, p<0.01) or other fracture (OR=2.073, p<0.0001) in the first post-treatment year.

The risk of fracture was not found to differ between HRT and raloxifene patients. While compliance with therapy for 1 year was found to reduce the likelihood of all types of fractures (OR<1.00), the estimated impact was only statistically
significant for hip fractures (OR=0.382, p<0.01) and vertebral fractures (OR=0.601, p<0.05).

Switching therapies during the year was associated with an increased risk of all types of fractures except hip fractures.

Clinical conclusions
Patients who achieved 1 year of uninterrupted drug therapy for osteoporosis achieved better patient outcomes than patients who terminated or interrupted therapy during the first year. Compliance with drug therapies for osteoporosis was poor, leaving patients at risk for fractures.

Modelling
Multivariate statistical models were used to take baseline differences between the populations being compared into consideration. Several different multivariate models were developed. For example, simple dichotomous patient outcome measures, such as whether or not a patient completed a year of uninterrupted therapy, switched drugs, or experienced a fracture, were analysed using logistic regression models. Outcome measures based on the time to these events were analysed using Cox proportional hazards models. Continuous outcome measures, such as health care costs over the first year, were analysed using ordinary least-squares (OLS) regression models. For hospital costs that may have a large number of patients with zero values, the two-step approach was used.

Measure of benefits used in the economic analysis
No summary measure of health benefit was used in the economic analysis. The clinical outcomes were left disaggregated. Hence, in effect, a cost-consequences analysis was performed.

Direct costs
The costs associated with treating osteoporosis patients were investigated using the total cost of treating patients over the first year. The total costs were also broken down into the individual components of cost. Such components were drug costs, ambulatory care (physician services), hospital outpatient care, laboratory tests and hospital services. Three alternative models of health care cost were investigated. The first model for drug use patterns used dichotomous variables indicating whether or not the patient achieved 360 days of continuous therapy or switched therapies during the first treatment year. The second model for drug use patterns used the count of days of therapy as its measure of compliance. The third cost model used independent variables for the initial therapy used by the patient with single HRT patients as the comparison group. Simple OLS models were used for all costs, except hospital costs for which a two-part model was estimated. These estimations were based on actual data. Discounting was not carried out, but it was not relevant as the follow-up period was 1 year. The price year was not reported.

Statistical analysis of costs
The costs were treated stochastically. P-values were reported for regression coefficients (type of test not reported but likely to be t-test for OLS) and R-squared for goodness of regression fit.

Indirect Costs
The indirect costs were not reported.

Currency
US dollars ($).

Sensitivity analysis
In an effort to document the extent to which bias might have been introduced by the inclusion of patients using HRT to treat menopause, sensitivity analyses were conducted to investigate if the impact of raloxifene and bisphosphonates
relative to HRT varied with age. Cost data are often highly skewed, thus violating the normality assumptions of OLS regressions. Sensitivity analyses were also conducted using log-transform cost models to investigate the robustness of the OLS cost results.

**Estimated benefits used in the economic analysis**
The authors did not determine a summary measure of health benefits. See the 'Effectiveness Results' section.

**Cost results**
The uninterrupted use of one or more medications for osteoporosis was not associated with lower total health care costs, inclusive of patient co-payments, in the year following the initiation of drug therapy. This result for total cost reflects the offsetting effects of a significant increase in drug costs of +$266, (p<0.0001) associated with continuous therapy against significant reductions in physician services (-$56, p<0.0001), hospital outpatient services (-$38, p<0.05), laboratory tests (-$9, p<0.01) and hospital costs (-$155, p<0.01).

Patients treated with raloxifene experienced a reduction in total costs in the year following treatment (-$280), but this estimated effect was not statistically significant. However, raloxifene use was correlated with significantly lower costs for physicians' services (-$92, p<0.01) and laboratory tests (-$21, p<0.05), and a reduction of 38% in the likelihood of a hospital admission (OR=0.622, p<0.0001).

Conversely, patients treated with a bisphosphonate medication experienced significantly higher total costs than single HRT patients (+$420, p<0.01), owing to higher drug costs (+$188, p<0.0001) and hospital costs per patient (+$266, p<0.01). The latter was due to a significant increase in the cost per hospitalised patient ($2,917, p<0.05).

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors' conclusions**
Compliance with drug therapies for osteoporosis over 1 year is poor, leaving patients at risk for fractures and higher health care costs.

**CRD COMMENTARY - Selection of comparators**
The authors did not state a definite reason for the comparators used. However, the comparators appear to have been the drugs used to treat osteoporosis that were present in their database. You should decide if these drugs are relevant to osteoporosis treatment in your own setting.

**Validity of estimate of measure of effectiveness**
The authors were studying the impact of different treatments on osteoporosis patients. In this sense, the study design was not entirely appropriate to address the study question. As the authors stated, the study groups were not comparable at baseline. Therefore, they controlled for several of the characteristics that were known to be statistically significantly different between the groups. A randomised controlled trial (RCT) might have been a more appropriate method to address the question in this study as, in an RCT, it is possible to control for not only those characteristics that are likely to differ, but also those that are not known to be different between study groups. The authors acknowledged this issue as a limitation of their study, stating "retrospective database research cannot establish causality primarily due to the fact that patients are not randomly assigned to the treatment alternatives under study". Of particular concern for them was the lack of data for height, weight and bone density, which are likely to be correlated with both patient outcomes and the selection of an initial therapy. It might have been worthwhile to have checked other methods used in the economic literature to adjust for selection bias.
Validity of estimate of measure of benefit
The authors did not derive a measure of health benefit. The analysis was therefore categorised as cost-consequences analysis and the comments in the 'Validity of estimate of measure of effectiveness' field (above) apply.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted seem to have been included in the analysis. The costs and the quantities were not presented separately. Hence, reproducing the results in other settings would be difficult. Appropriate statistical analyses were conducted and reported for cost coefficients. The analysis was performed over a period base on one year, so discounting or price adjustments were not relevant and were not undertaken.

Other issues
The authors did not compare their findings with those of other studies. The issue of generalisability to other settings was also not addressed. The authors do not appear to have presented their findings selectively and their conclusions reflected the scope of the analysis.

Implications of the study
Therapies to replace HRT for the long-term treatment of osteoporosis are needed. Much remains to be done to improve long-term patient compliance with bisphosphonate medications and raloxifene before the full benefit of these therapies can be achieved.

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