Treating Helicobacter pylori infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment - Helicobacter pylori positive (CADET-Hp) randomised controlled trial


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 "test and treat" strategy for the management of patients with uninvestigated dyspepsia. Patients underwent the Helisal rapid blood test and the 13C-urea breath test. Those testing positive with both tests received a course of treatment. The treatment consisted of omeprazole 20 mg, metronidazole 500 mg, and clarithromycin 250 mg twice daily for 7 days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with uninvestigated symptoms of dyspepsia for at least 3 months beforehand. Dyspepsia was defined as a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, and including any of the following additional symptoms: heartburn, acid regurgitation, excessive burping or belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety.

Patients with only heartburn and/or regurgitation were excluded. Also excluded were patients investigated by upper gastrointestinal endoscopy and/or barium study less than 6 months before inclusion in the study, or on more than two separate occasions within the preceding 10 years. Other exclusion criteria were patients given eradication therapy for H. pylori less than 6 months before study inclusion, prior gastric surgery, prior documented ulcer disease or endoscopic oesophagitis, irritable bowel syndrome, clinically significant laboratory abnormalities, and pregnancy.

The patients were required not to have received a course of treatment within 30 days before randomisation, or during the treatment period, with a non-steroidal anti-inflammatory drug, aspirin, antibiotic, H2-receptor antagonist, proton-pump inhibitor, misoprostol, sucralfate, prokinetic agent, or bismuth compound.

Setting
The setting was primary care. The economic study was conducted in Canada.

Dates to which data relate
The effectiveness and resource use were data gathered from September 1997 to April 1999. The price year was not reported.
Source of effectiveness data
The effectiveness evidence was derived from a single study.

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

Study sample
Power calculations were based on the assumed difference in treatment success between the groups. It was estimated that 150 patients in each group were needed to achieve a significance level of 0.05 and a power of 90%, when considering dropouts. Of the initial sample of 489 patients with a positive Helisal blood test who were assessed for eligibility, the urea breath test was not available in 24 and was negative in 152. A further 19 patients did not participate (14 withdrew consent, 4 had no study drug available, and 1 had an aortic aneurysm repair). Therefore, the final sample comprised 294 patients. Of these, 145 were in the intervention group and 149 were in the control group. The participants in the intervention group had a mean age of 50 years (age range: 18 - 82), 48% were men and 88% were white. The participants in the control group had a mean age of 49 years (age range: 19 - 81), 53% were men and 93% were white.

Study design
This was a prospective, double-blind, randomised, placebo-controlled clinical trial that was conducted in 36 family practitioner centres across Canada. Block randomisation was computer-generated and the randomisation code was broken only at the end of the study. The length of follow-up was 12 months. The patients were managed by their family practitioners, according to their usual clinical practice. Monthly follow-up assessments were conducted. At the end of the study, 127 patients in the intervention group and 128 in the control group completed the 12-month follow-up. There were 133 evaluable patients in the intervention group and 134 in the control group. Evaluable patients were those who had valid symptom data at the 6 month assessment, or who were later carried forward to replace missing 12-month data. Neither the patients nor the investigators were aware of the treatment allocation.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. A secondary analysis considered all evaluable patients. The primary outcome measure used was treatment success. This was defined as the proportion of patients with a global overall symptom (GOS) score, measured on the 7-point Likert-type scale, of 1 (no symptoms) or 2 (minimal symptoms) at final visit. The secondary outcome measures were:

- the proportion of patients becoming completely asymptomatic;
- treatment success according to H. pylori status;
- quality of life assessment, based on the self-administered quality of life in reflux and dyspepsia tool; and adverse events.

A sub-group analysis was also conducted. This compared patients with reflux predominant symptoms with those for whom the reflux symptoms were not predominant. The study groups were fairly comparable at baseline in terms of their age, gender, race, smoker status, alcohol consumption, previous use of eradication treatment, overall symptoms, years since first onset of dyspepsia, and adherence to drugs. Multiple regression analysis was conducted to assess the impact of baseline factors on the estimated treatment success.

Effectiveness results
No patient withdrew as a result of poor adherence.

The treatment success rate was 50% (95% confidence interval, CI: 42 - 58) in the intervention group and 36% (95% CI: 28 - 44) in the control group. The difference was 14% (95% CI: 2 - 25; p=0.02). Similar results were obtained in the
sample of all evaluable patients.

The proportion of patients becoming completely asymptomatic was 28% (95% CI: 21 - 36) in the intervention group and 15% (95% CI: 9 - 20) in the control group. The difference was 13% (95% CI: 4 - 24; p=0.008).

In the sub-group of patients with reflux predominant dyspepsia symptoms, the treatment success rate was 43% (95% CI: 29 - 56) in the intervention group and 32% (95% CI: 20 - 45) in the control group. The difference of 11% was not tested statistically.

In the sub-group of patients with non-reflux predominant dyspepsia symptoms, the treatment success rate was 54% (95% CI: 44 - 64) in the intervention group and 39% (95% CI: 29 - 48) in the control group. The difference of 15% was not tested statistically.

The multiregression analysis showed that only eradication therapy was significantly associated with treatment success. H. pylori was eradicated in 75% of the intervention group and 14% of the control group.

Three quality of life dimensions were significantly improved in the intervention group relative to the control group. These were emotional distress (mean difference 0.34, range: 0.04 - 0.65; p=0.03), physical and social functioning (mean difference 0.25, range: 0.01 - 0.48; p=0.04), and vitality (mean difference 0.39, range: 0.08 - 0.70; p=0.02).

Adverse events were comparable in the two groups (42%).

**Clinical conclusions**
The effectiveness study showed that the test-and-treat strategy was more effective than placebo in improving success rate and some dimensions of quality of life.

**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 conducted.

**Direct costs**
Discounting was not relevant since the costs were incurred during one year. The unit costs were reported separately from the quantities of resources for all items. The health services included in the economic evaluation were visits to the physician (specialist, family physician) and other health care professionals, drugs (prescriptions, over the counter), and investigations (laboratory tests, radiography, endoscopy). The cost/resource boundary of the study was that of the third-party payer. The costs came from several sources but all reflected the perspective of the Ontario Ministry of Health. Resource use was estimated on the basis of prospectively collected, patient-level data, which were derived from the effectiveness study. The price year was not reported.

**Statistical analysis of costs**
The corrected alpha percentile bootstrap method was used to measure the costs per patient, as they were not normally distributed.

**Indirect Costs**
The indirect costs were included as a societal perspective was also adopted. The unit costs and the quantities of resources used were provided separately. The indirect costs were derived from Canadian statistics. Days of missed work were derived from the sample of patients who were included in the effectiveness study. The price year was not reported. Discounting was not relevant because of the short time horizon of the study.

**Currency**
Canadian dollars (Can$). The exchange rate between Can$, US dollars ($) and UK pounds sterling () was Can$1 = $0.60 = 0.43.

**Sensitivity analysis**
Sensitivity analyses were not conducted.

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

**Cost results**
The average societal costs per patient were Can$477 (range: 27 - 3,069) in the intervention group and Can$530 (range: 31 - 3,315) in the control group. The cost-difference was Can$53 (95% CI: -86 - 180).

The average third-party payer costs per patient were Can$136 (range: 0 - 1,066) in the intervention group and Can$181 (range: 0 - 1,860) in the control group. The cost-difference was Can$45 (95% CI: -20 - $114).

Therefore, there was no statistically significant difference in costs between the groups.

**Synthesis of costs and benefits**
A synthesis of the costs and benefits was not relevant since a cost-consequence analysis was, in effect, conducted.

**Authors' conclusions**
Compared with placebo, the test-and-treat strategy in patients with uninvestigated dyspepsia led to long-term relief from symptoms. A trend towards a reduction in costs was also observed.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator (no intervention) appears to have been appropriate as it represented the standard approach for patients with uninvestigated dyspepsia. You should decide whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness was based on a well-conducted clinical trial, which was appropriate for the study question. The internal validity of the analysis was high for several reasons. First, the use of power calculations to ensure the appropriate sample size. Second, the long-term follow-up. Third, the double-blind design. Fourth, the use of block randomisation. Fifth, the analysis of the clinical study was conducted on an intention to treat basis. Sixth, the baseline comparability of the study groups. Seventh, the use of multiregression analysis to assess the potential impact of confounding factors. Finally, the use of appropriate outcome measures and sub-group analysis. The study sample was selected from several centres and it appears to have been representative of the study population.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted.

**Validity of estimate of costs**
The authors analysed the economic impact of the study intervention from two distinct perspectives. Both were appropriate as they mirrored the societal and payer boundaries. Detailed information on the unit costs and resources used was provided for all items, which enhances the possibility of replicating the study in other settings. The costs were
not normally distributed and appropriate statistical tests were used to measure the mean costs. The source of the data was reported. The price year was not provided, which makes reflation exercises in other settings difficult. However, the costs were estimated alongside the clinical trials, the dates of which were reported. The cost estimates were specific to the study setting and no sensitivity analyses were conducted. The authors noted that the study was not powered to detect statistically significant differences in the costs.

Other issues
The authors made only limited comparisons of their findings with those from other studies. They stated that their results were quite generalisable to primary care. However, sensitivity analyses were not conducted. The study involved patients with uninvestigated dyspepsia and this was reflected in the authors’ conclusions.

Implications of the study
The authors suggested that the 13C-urea breath test should replace blood tests for the detection of H. pylori, owing to its higher reliability.

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Other publications of related interest


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