Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials
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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 use of co-prescribed heroin (i.e. heroin plus methadone) for heroin addicts. Heroin (inhaler or injection) was given at a maximum of 1000 mg/day and methadone at a maximum of 150 mg/day.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised heroin addicts who had received methadone maintenance treatment.

Setting
The setting was the community. The economic study was carried out in the Netherlands.

Dates to which data relate
The effectiveness and resource use data were gathered from July 1998 to October 2000. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out on the same sample of patients as that included in the effectiveness analysis.

Study sample
Power calculations were not reported. The participants were recruited from existing methadone maintenance programmes implemented in six cities in the Netherlands. Of the 549 heroin addicts who participated in the trials, the current analysis focused on 430 patients who were intended to receive the experimental or control treatment for a full year. There were 193 patients in the co-prescribed heroin group and 237 patients in the methadone alone group. When the whole group was considered, the mean age was 39.3 (+/- 5.7) years. Most of the patients were men (80%), of Dutch nationality (92%), of low education (74%), living independently or with relatives and friends (84%), and unemployed or disabled (82%).
Study design
The studies were two randomised clinical trials, which were pooled as if they were a single trial. Patients were identified at several centres. The participants were allowed to visit the treatment units three times a day, 7 days a week. The patients in the experimental group could receive a maximum of 400 mg heroin per visit and 1,000 mg/day. The length of follow-up was one year. After randomisation, 13 participants in the co-prescribed heroin group and one in the methadone alone group rejected treatment. Moreover, during the study period, 45 patients in the co-prescribed heroin group and 32 in the methadone alone group discontinued treatment for various reasons. Thus, 135 (70%) in the co-prescribed heroin group and 204 (86%) in the methadone alone group completed the full year of treatment. Missing values were imputed.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary outcome measure was quality of life, which was assessed using the EuroQol EQ-5D questionnaire. Each participant completed the EQ-5D at baseline and at months 6, 10 and 12 during treatment. Patients who responded to treatment, and the numbers of deaths and illegal activities (that were assessed at the same time as the EQ-5D) were also reported. The study groups were comparable at baseline.

Effectiveness results
The mean (median; interquartile range, IQR) quality of life scores for the intervention versus the control group, respectively, were:

- Baseline: 0.740 (0.796; IQR: 0.689 - 1) and 0.731 (0.796; IQR: 0.689 - 0.883)
- Month 2: 0.762 (0.796; IQR: 0.691 - 1) and 0.718 (0.796; IQR: 0.656 - 0.883)
- Month 6: 0.771 (0.815; IQR: 0.709 - 1) and 0.729 (0.796; IQR: 0.656 - 0.942)
- Month 10: 0.805 (0.848; IQR: 0.725 - 1) and 0.729 (0.796; IQR: 0.638 - 1)
- Month 12: 0.813 (0.848; IQR: 0.725 - 1) and 0.742 (0.796; IQR: 0.673 - 1)

One hundred (51.8%) participants in the experimental group responded to treatment compared with 68 (28.7%) in the control group. Two deaths occurred, one in each group, but both were unrelated to treatment.

In the co-prescribed heroin group versus methadone alone group:
- The number of days with crime against property were 10.3 (+/- 34.8) and 37.5 (+/- 78.6), respectively.
- The total arrests were 208 (+/- 465) and 276 (+/- 682), respectively.
- The convictions for possession or traffic of illegal drugs, crime against property, and acts of violence were 25 (+/- 96) and 54 (+/- 204), respectively.
- The days of imprisonment were 1,165 (+/- 4,077) and 1,247 (+/- 3,967), respectively.
- The contacts with the probation officer were 4 (+/- 44) and 19 (+/- 116), respectively.

After the exclusion of patients with missing data or with more than 200 illegal activities a month (n=47 remaining), the mean number of crimes against property per day of illegal activity with possible damage to third parties amounted to 3.4, with 2.5 (74%) crimes against companies and 0.9 (26%) against civilians.

Clinical conclusions
The effectiveness analysis showed that patients who received co-prescribed heroin had higher quality of life scores and
engaged in criminal activities less often than patients who received methadone alone.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated from the effectiveness analysis. The utility values were elicited from the UK population using the time trade-off approach. No discounting was performed.

Direct costs
The analysis of the costs was undertaken from a societal perspective. The categories of costs included in the economic evaluation were health care resources (including methadone, heroin, consultations, and inpatient stay), travel related to the programme, and expenses associated with illegal activities (including law enforcement and damage to victims). The unit costs and the quantities of resources used were presented separately. Resource use was estimated alongside the clinical trials using the European version of the Addiction Severity Index (EuropASI), which was completed by study participants at baseline and at months 6, 10 and 12 during treatment. Standardised distances to relevant locations were used to derive the travel costs. A sub-study was performed during February and March 2004 in 51 new patients to derive data on the number, type and victims of illegal activities needed to estimate the potential damage to civilians or companies, since such data were not available using the EuropASI. The costs were estimated from several sources, including official national tariffs, market prices and the Dutch Ministry of Justice. Discounting was not relevant as the costs were incurred during one year. The costs were presented as 2001 values using a general price index of 2% a year.

Statistical analysis of costs
Statistical analyses were performed because of the skewed distribution of the costs. Thus differences were estimated by calculating 95% confidence intervals (CIs) after correction for bias and using non-parametric bootstrapping (25,000 samples).

Indirect Costs
The indirect costs were not included because unemployment or disability rates in the target population were expected to be high.

Currency
Euros (Euro).

Sensitivity analysis
Multi-way sensitivity analyses were carried out to investigate the robustness of the cost acceptability of co-prescribed heroin (for willingness to pay values up to Euro 50,000) to plausible changes in key unit costs and to a Dutch time trade-off-based health utility algorithm. A sub-group analysis was also performed for patients who did or did not participate in abstinence-oriented treatment before baseline. A further sub-group analysis was performed for patients who did or did not complete the 12-month treatment schedule. The ranges for the sensitivity analyses were based on authors’ assumptions and plausible changes were considered for key parameters.

Estimated benefits used in the economic analysis
The estimated mean (median) QALYs over a 12-month period were 0.788 (0.837; IQR: 0.708 - 0.949) in the co-prescribed heroin group and 0.730 (0.771; IQR: 0.620 - 0.903) in the methadone alone group. The mean difference in QALYs was 0.058 (95% CI: 0.016 - 0.099; p=0.01).

Cost results
The estimated mean (median) costs over the 12-month period were Euro 37,767 (26,104; IQR: 18,544 - 39,554) in the
co-prescribed heroin group and Euro 50,560 (11,847; IQR: 1,987 - 51,530) in the methadone alone group.

The mean difference in costs was Euro 12,793 (95% CI: 25,229 - 1,083; p=0.032). In particular, the extra medical costs for the co-prescribed group was more than compensated for by the cost-savings to the society arising from less damage to victims of criminal acts.

**Synthesis of costs and benefits**

In principle, an incremental cost-utility ratio (i.e. the cost per QALY) should have been calculated to combine the costs and QALYs. However, co-prescribed heroin was more effective and less costly than methadone alone, which was dominated, thus no ratio was calculated.

The sensitivity analysis showed that the dominance of the experimental treatment persisted when Dutch time trade-off-based health utility values were used rather than UK values. The exclusion of initial implementation costs in the co-prescribed heroin group strengthened the conclusions of the analysis. Participation in any abstinence-oriented treatment in the past did not substantially influence the effectiveness of the experimental treatment. Completion of treatment strongly influenced the programme's efficiency. The cost acceptability of co-prescribed heroin for willingness-to-pay values of up to Euro 50,000 did not exceed 32% in the case of non-completers, while for treatment completers the cost acceptability was higher than 99% for willingness-to-pay values of at least Euro 5,000.

**Authors' conclusions**

The co-prescription of heroin was cost-effective in comparison with treatment with methadone alone for chronic, treatment-resistant heroin addicts. It resulted in more quality-adjusted life-years (QALYs) to the patients and less costs to society.

**CRD COMMENTARY - Selection of comparators**

The selection of methadone alone as the basic comparator was appropriate since it represented standard care in the authors' context. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data came from two pooled clinical trials, which were appropriate for the study question. Limited information on the design and other characteristics of the trials was provided as they had been published already. However, clinical trials are usually associated with a high internal validity. The robustness of the data was ensured by several factors. More specifically, the intention to treat basis for the analysis of the clinical outcomes, the baseline comparability of the study groups, and the multi-centre design. However, the authors noted that the robustness of the EQ-5D in drug addicts had not been validated.

**Validity of estimate of measure of benefit**

QALYs were the most appropriate benefit measure because they capture the impact of the intervention on quality of care, which is the most relevant dimension of care. Utility was derived from a sample of UK patients and then applied to Dutch participants. The instrument used to assess the utility values was reported. An alternative set of utility weights was used in the sensitivity analysis. The use of QALYs permits comparisons with the benefits of other health care interventions.

**Validity of estimate of costs**

The use of a societal perspective was appropriate as the authors noted that the economic consequences of treating heroin addicts extend beyond the domain of health care. Some categories of costs, namely indirect costs, costs associated with changes in patients' housing arrangements in the community, or the intangible costs of victims of crime and changes in the public's perception of safety, were not included in the economic evaluation. The authors justified their exclusion of such costs. Extensive information on the unit costs, quantities of resources used and source of the
data was provided. This enhances the possibility of replicating the analysis in other settings. Statistical analyses of the costs were performed because of the expected skewed distribution of the cost data. The impact of alternative cost assumptions was also tested in the sensitivity analysis. The price year was reported, which makes reflation exercises in other timeframes possible.

Other issues
The authors stated that their results were consistent with those from other economic evaluations. Regarding generalisability, the authors pointed out that as the study participants were chronic, treatment resistant heroin addicts, the results should not be generalised to heroin addicts who have not received methadone maintenance treatment before. Some sensitivity analyses were carried out on key estimates. The authors noted that the use of an appropriate time horizon (12 months) and the adoption of a societal perspective represent two strengths of the analysis. The study results were presented extensively.

Implications of the study
The study results supported the use of co-prescribed heroin for the treatment of heroin addict in the Netherlands. Since most patients need lifetime monitoring, a long-term evaluation of the cost-effectiveness of co-prescribed heroin should be performed.

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