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The Costs of Managing Severe Cancer Pain and Potential Savings from Transdermal Administration

K. Bloor, B. Leese and A. Maynard

The economic evaluation of any new or existing therapy should include a comprehensive appraisal of costs. When evaluating pharmaceutical interventions, it is inappropriate to identify the purchase price alone. Other relevant costs include the costs of time of doctors, nurses and other personnel in administering and monitoring the effects of the therapy, and the costs of treating any side-effects. This study estimates direct National Health Service (NHS) costs in the U.K. of current medical practice in managing severe cancer pain, using a review of the published literature and constructing a cost analysis for four 'typical' patients. Costs are estimated for patients with severe cancer pain in a hospital and an ambulatory setting, with oral and subcutaneous routes of drug administration. The study includes costs of drugs, supplies, equipment and personnel time. The results demonstrate the importance of personnel time costs, and potential cost savings which could result from the use of transdermally administered opioid analgesics.

Key words: costs and cost analysis, opioid analgesics, pain management, transdermal administration
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INTRODUCTION

WORLDWIDE INFLATION in health care budgets has led to the emphasis of the need to investigate the costs of existing therapy, and to demonstrate the cost-effectiveness of any new therapies. In economic evaluation, drug therapy should not be considered in isolation but in the context of all other costs of patient care [1], for example, the costs of treating side-effects and the value of time savings in an industry where personnel costs exceed 70% of total expenditure.

In this study, estimates were made of the direct National

Health Service (NHS) costs in the U.K. of current medical practice in managing severe cancer pain. Firstly, some of the published literature on the management of severe cancer pain is reviewed. Then a cost analysis of four 'typical' patients is described. The four scenarios cover patients in both hospital and ambulatory settings treated with the two most frequently used routes of administration of pain control therapy, the oral and subcutaneous routes. The costs of treating each of these were estimated using published cost data and estimates of staff time. The potential cost savings from the use of transdermally administered opioid analgesics (fentanyl) are then considered.

General background

Pain is the most common complaint in patients seeking medical care, and the major symptom anticipated by patients when cancer care is diagnosed [2]. Advances in knowledge of the mechanisms of pain and the actions of potent analgesics have resulted in much more effective control of severe cancer pain in recent years.

In this study, recent literature on the management of severe cancer pain is examined, concentrating on the resource implications of therapy. Many of the analgesic therapies examined are relevant not only to people with cancer, but also to others in severe pain, for example, post operative patients and those with arthritis.

Routes of administration of analgesics

It is generally considered preferable to administer analgesics orally, either as controlled release (CR) tablets or immediate release (IR) solutions. Oral administration has a number of benefits over parenteral routes, including avoidance of the discomfort and psychological complications of repeated injections, allowing greater activity, and giving a greater sense of independence and control to the patient. It also reduces the possibility of infection. In addition, the cost of oral administration is lower due to less equipment being needed, and administration is faster, which results in lower staff time costs [3]. Acquisition costs of CR tablets are higher than traditional morphine sulphate solutions, but when the costs of staff time are taken into account, the total costs of CR administration appear to be lower than oral morphine sulphate solutions [3,4]. This is largely due to the time costs of filling in the register of controlled drugs and making up solutions, which are all greatly reduced by less frequent administration.

Although oral administration of analgesics is standard clinical practice, a significant proportion of patients cannot be treated in this way. It has been estimated that more than 50% of patients with advanced cancer will eventually be unable to tolerate oral morphine [5] because of problems with swallowing, persistent nausea and vomiting, bowel obstruction, intolerance to oral opioids, incident pain or poor compliance to an oral regimen [6]. As a consequence, these patients will require alternative routes of administration.

There are five alternatives to the oral route of administration: rectal, parenteral, spinal, intraventricular and transdermal. The route chosen has important consequences for the patient and for resource use [5].

Parenteral administration of morphine and other analgesics is the most frequent alternative to oral therapy [7]. Injections of morphine provide rapid pain relief, and are often used in conjunction with oral analgesics to treat 'breakthrough pain'. For more continuous pain relief in patients unable to tolerate oral therapy, subcutaneous infusions of morphine or morphine substitutes can be used [8–10]. Infusion pumps enable patients to be treated at home rather than in hospital. Home treatment, as a replacement for inpatient hospital stay, may result in cost savings to the health service and benefits to the patient [9].

Parenteral administration of analgesics does, however, have a number of disadvantages. It can cause discomfort to patients, and in some cases it can result in infections or tissue irritation. Moreover, the resource costs of this method of administration are quite high—drugs, supplies and equipment costs are higher than for oral analgesics, and staff time costs are also much higher. Even for outpatients, doctors and district nurses may check infusions to monitor pain control and minimise the risk of infection [11].

The newest route of administration of opioid analgesics is transdermal administration via an adhesive patch known as a 'transdermal therapeutic system' (TTS). The strong opioid, fentanyl, can be absorbed through the skin using a TTS patch, and has been demonstrated to control pain successfully in both postoperative patients [12,13] and in cancer patients [14–16]. The TTS releases fentanyl into the skin beneath the patch, forming a reservoir in the upper skin layers. This gives pain relief for approximately 3 days, and the patch is then disposed of and replaced. Disposal of the patches may involve additional costs due to the possibility of residual opioids in the used patch, depending on the instructions given in the specific country involved. Experience with this product so far indicates that it is effective in the long-term management of cancer-related pain. However, it is relatively new to the market and is currently undergoing further study.

There are a number of potential benefits to this innovation. It is much more convenient for the patient than parenteral, rectal or spinal routes, and the resource costs are thought to be much lower [3]. It could perhaps be used in patients who are unable to tolerate oral morphine, and are too sick or confused to be taught how to use a patient-controlled infusion pump. When compared with oral administration, it is also potentially beneficial, largely due to the 3-day dose. This reduces staff time in administering the drug (e.g. noting doses in the register of controlled drugs) and may also improve patient compliance. It may, therefore, be suitable for use in patients who can tolerate oral opioids, and appears potentially to be a highly beneficial alternative for those who cannot. Possible disadvantages of transdermal administration include the slow onset of action and the continued absorption from a subcutaneous depot after the patch is removed. During a dose titration and stabilisation period, patients may require other opioid analgesics, and these may also be required for breakthrough pain once patients are stabilised. It appears that transdermal administration is most applicable to patients who have relatively stable levels of pain.

Treatment settings

There are three main locations in which cancer patients with severe pain receive treatment: hospitals, hospices and at home. The resource consequences of treatment vary in each setting. In most cases, the direct health service costs of treating patients with cancer pain are lower if the patient is able to be discharged home. Subcutaneous infusions and spinal analgesic delivery pumps can be used out of the hospital setting, and have been

Correspondence to K. Bloor.
The authors are at the Centre for Health Economics, University of York, Heslington, York YO1 5DD, U.K.
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shown to be cost-effective compared with inpatient treatment [11]. It is, however, important to remember that they require regular and careful monitoring by community nurses and general practitioners (GPs). These costs must be included in economic studies. Patients receiving oral analgesics also require regular GP visits, and the attitude of GPs can be an important factor in determining where cancer patients receive their treatment [17].

It is clear that the location of the patient will influence the choice of analgesic. In the majority of cases, oral opioids are still the first choice agent. Where the patient is no longer able to tolerate oral administration, a number of factors must be considered. Resource use is one such factor which should not be neglected.

Resource use issues

There are four main aspects to the costs of administering different formulations of opioid analgesics: costs of drug acquisition, costs of drug administration supplies, costs of initial equipment (infusion pumps etc.) and the costs of personnel time in administering the drugs (primarily nursing time in administering the drugs and completing drug records). The relative capital costs (equipment) and variable costs (drugs, supplies and personnel time) of providing analgesic therapy by major alternative routes were summarised by Goughnour [3] (Table 1).

In a study of Canadian hospitals, Goughnour [3] used this framework to compare the total costs of administration of equivalent daily doses of CR morphine tablets and IR morphine solution. Using a work sampling methodology, researchers observed the time required to administer analgesics, including time spent by pharmacy staff and nurses. The cost of staff time was determined by multiplying the mean time required to perform the task by the median of the relevant wage scale. Labour costs were then added to drug and supplies acquisition costs to give a total daily administration cost, assuming that CR tablets were administered every 12 hours and morphine sulphate solution every 4 hours.

This study illustrates the importance of including all relevant costs in economic evaluations. IR morphine sulphate solution has a lower acquisition cost than CR tablets, but when labour costs of administration are included, it becomes apparent that the frequency of administration is an important factor in overall cost. CR tablets may, therefore, be less costly in total than IR solutions.

Table 1. Relative start-up and on-going costs of providing analgesic therapy by alternative routes.

	Drug costs	Supplies costs	Initial equipment	Personnel time
Oral				
Controlled response tablets	++	+	−	+
Immediate release solution	+	++	−	+++
Rectal	+++	+	−	++++
Parenteral				
Intramuscular	+++	++	−	+++++
Subcutaneous infusion	+++	+++	++	++
Intravenous infusion	+++	+++	+++	+−
Spinal	+++++++++		+++	+++
Transdermal	?	−	−	+

Adapted from Goughnour [3]. +, relative cost; −, no cost.

The resource consequences of managing severe cancer pain have been relatively neglected in the research literature. Whilst numerous studies have examined the clinical aspects of various different therapies and routes of administration of therapy (reviewed in [5]), economic aspects are rarely included. Those studies which have examined the costs of therapy illustrate the importance of including a wide range of different costs—particularly costs of personnel time, as well as the acquisition costs of drugs. Ferris and colleagues [11] also showed the significance of different treatment settings in influencing resource use.

A cost study of treatment strategies in the management of severe cancer pain should, therefore, incorporate a wide range of costs rather than concentrating solely on the acquisition costs of drugs. It should also consider the influence of the treatment setting, given that costs differ in ambulatory and hospital settings.

METHODS

This cost study used a cost analysis in four different scenarios to estimate the direct costs of current medical practice in managing severe cancer pain. It concentrated on oral and subcutaneous infusion therapy, and examined a 'typical' patient in both hospital and ambulatory settings. Direct costs were estimated separately for the following types of patient: (1) patient in hospital setting given oral drug therapy; (2) patient in hospital setting given subcutaneous drug therapy; (3) patient in ambulatory setting given oral drug therapy; (4) patient in ambulatory setting given subcutaneous drug therapy.

Information was collected on each of the main sources of direct costs of therapy: acquisition costs of drugs, supplies and equipment, and costs of personnel time in administering and monitoring therapy. While acquisition costs were relatively straightforward to obtain, it was more difficult to estimate the costs of personnel time in administering and monitoring therapy. In an attempt to elicit information on the time taken to administer and monitor analgesics for severe cancer pain, a number of hospital consultants, nurse managers and hospice clinicians were consulted. Their responses were somewhat variable, and the sample was small. The following analysis uses both the average of these seven responses and the estimates of Goughnour [3], applying the mean time taken by the median salary scale of equivalent U.K. personnel. These results were combined with published data to estimate the overall costs of pain control therapy.

Following the cost estimation, potential cost savings from the use of transdermally administered opioid analgesics (Fentanyl TTS) were considered. Clinical trials indicated that transdermally administered fentanyl successfully controls cancer pain [14], and may result in cost savings due to the single 3-day dose.

RESULTS

Cost of drugs

Consultation with a small sample of clinicians suggested that the most frequently used dose of oral morphine for patients with severe cancer pain is 60 mg of CR morphine (MST Continus) twice daily. The total cost is £1.20 per day [18]. This cost is, therefore, assumed to apply to patients in hospital or ambulatory settings on oral morphine therapy. This does not take account of discounts for bulk purchase which are frequently obtained by hospital pharmacies and, therefore, real costs of drugs in hospital may be slightly overestimated.

Subcutaneous infusions of opioid analgesics are highly vari-

able. Cost calculations are based on a daily dose of 60 mg of diamorphine, assumed to cost £3.20 per day.

Drugs prescribed to ameliorate side-effects of opioid analgesics (constipation, nausea, etc.) are the same for all four scenarios, and as side-effects are unlikely to be affected significantly by transdermal administration, the costs are disregarded in the following analysis. Transdermal administration may reduce the incidence of constipation among patients, as suggested by Zech and colleagues [19]. This may reduce costs of treating side-effects, but it may be that patients still receive prophylactic laxatives, as is currently the case with parenteral and oral administration.

Cost of supplies

The cost of supplies for oral morphine is negligible in both the ambulatory and hospital setting and is, therefore, disregarded. Supplies (e.g. disposable syringes and tubing) are, however, necessary for subcutaneous administration of drugs. For infusion pumps it is necessary to change syringes daily and cannulae every week. Supplies for the Graseby infusion pump cost £0.20 per day for syringes and £1.00 per week (14p per day) for cannulae. Total supplies cost for subcutaneous administration in both ambulatory and hospital settings was, therefore, £0.34 per day.

Cost of equipment

Again, this is relevant only to subcutaneous administration of opioids. The study used the purchase costs of Graseby infusion pumps. A portable infusion pump costs approximately £500 and a hospital model costs £2600. Assuming both have a 10-year lifespan, and taking an annual equivalent cost based on a discount rate of 6%, this means that the equipment cost is £0.19 per day in an ambulatory setting and £0.97 per day in a hospital setting. This assumes that infusion pumps purchased have 100% utilisation, and it does not account for any breakdown of the equipment.

Costs of personnel time

As discussed by Goughnour [3], the amount of time spent by pharmacists, nurses and clinicians in administering analgesics can significantly influence the overall cost of therapy. For this reason, an attempt was made to elicit views of staff regarding time taken in preparing, administering and monitoring each dose of opioid analgesics. This required information on hospital staff and also on out-patient services, such as GP and community nurse visits. Mean results of responses from the sample clinicians, with costs consisting of the median of relevant salary scales are shown below. In addition, 20% has been added to salary levels for employers costs (national insurance, superannuation, costs of administering salaries, etc).

Median salary scales used (1992 levels) were as follows: pharmacists: £25 186, nurses: £11 913, consultant clinicians: £43 425.

In-hospital, subcutaneous infusion therapy. Pharmacists' time—mean 11.6 (median 7) min per dose = £5.57 (£3.36) per day. Clinicians' time—mean 11 (median 10) min per dose = £9.24 (£8.40) per day. Nurses' time—mean 12 (median 11.3) min per dose = £2.88 (£2.71) per day. Total cost of personnel time = £17.69 (£14.47) per day.

In-hospital, oral therapy. Pharmacists' time—mean 11.6 (median 7) min per dose = £5.57 (£3.36) per day. Clinicians' time—mean 7 (median 6) min per dose = £5.88 (£5.04) per day. Nurses' time—mean 9.5 (median 5) min per dose = £2.28 (£1.20) per day. Total cost of personnel time = £13.73 (£9.60) per day.

Ambulatory care, oral therapy. Consultation with a small sample of clinicians suggested that cancer patients in an ambulatory setting receiving oral opioid analgesics are visited on average by their GP once a month, and by a community or hospice home care nurse approximately six times per month. At an estimated cost of £19.58 per GP home visit (this figure was calculated at 1992 prices from a variety of sources, including OHE Compendium of Health Statistics 1989; GP Workload Study—report prepared for the Doctors and Dentists Review Body 1985/86 and HCHS pay and prices indices. D Coyle, personal communication) and £8.04 per community nurse visit (this was again at 1992 prices, from DoH Patient Care in the Community—District Nurses, Summary; Information from Form KC56, 1988-89 and HCHS pay and prices indices. D. Coyle, personal communication) this represented a total daily cost of £2.26. As hospital clinicians were consulted regarding this issue, the estimate of GP visits may not be realistic and, therefore, it is appropriate to carry out some sensitivity analysis.

Ambulatory care, subcutaneous infusion therapy. Results from the sample of clinicians suggested that cancer patients in an ambulatory setting receiving subcutaneous opioids are visited twice a month by their GP and daily by a community or hospice home care nurse. This represented a total daily cost of £9.35.

Total baseline average costs of each of the four types of patient, using mean staff time estimates, are summarised in Table 2.

Sensitivity analysis

The estimates of staff time spent in preparing and administering doses for inpatients from this English questionnaire survey were considerably higher than those in the Canadian study [3]. Median estimates tended to be lower than the mean estimates, but were still considerably higher than those estimated by Goughnour [3]. It is possible that respondents overestimated the time spent on these tasks and it was, therefore, felt that sensitivity analysis should be carried out. In addition, as estimates of GP and community visits were given by hospital and hospice clinicians, sensitivity analysis for the cost estimates for ambulatory patients was also thought to be important.

Using estimates of time spent preparing and administering doses from Goughnour [3], with appropriate U.K. salary scales, costs of personnel time were significantly different from the estimates suggested by the English survey. This study did not include any clinician time, and time spent by pharmacists and nurses was much lower than our estimates suggest. Preparing and administering oral morphine tablets was thought to take 0.53 min of pharmacists time and 4.45 min of nursing time per dose. Applying U.K. salary scales to these estimates suggested a daily personnel cost for oral morphine in hospital of £1.33, a much lower figure than that shown in Table 2. The corresponding figure for subcutaneous administration was £9.26, again much lower than the earlier estimate. This suggested total costs of only £2.53 per day for patients treated orally in hospital and £13.77 for patients in hospital treated by subcutaneous infusion, compared with the earlier estimates of £14.93 and £22.20, respectively.

For ambulatory patients on oral therapy, it is appropriate to

Table 2. Summary: daily costs of managing severe cancer pain

	Oral therapy in hospital	Parenteral therapy in hospital	Oral therapy ambulant	Parenteral therapy ambulant
Drug costs	1.20	3.20	1.20	3.20
Supplies costs	—	0.34	—	0.34
Equipment costs	—	0.97	—	0.19
Total materials	1.20	4.51	1.20	3.73
Pharmacist time	5.57	5.57	—	—
Nurse time	2.28	2.88	—	—
Clinician time	5.88	9.24	—	—
GP time	—	—	0.65	1.31
District nurse time	—	—	1.61	8.04
Total personnel	13.73	17.69	2.26	9.35
Total	14.93	22.20	3.46	13.08

consider a range of possible costs. If a patient visits the GP surgery once a month instead of having a home visit, together with six community nurse visits, with an average cost per GP surgery consultation of £8.00 [20], the total daily cost will be approximately £1.85. If patients are visited by their GP more often than baseline estimates suggest, for example weekly, and twice weekly by a community nurse, this gives a total daily cost of approximately £5.08. The cost will vary with the severity of illness of the patient and the level of their pain control.

Patients receiving subcutaneous opioids are likely to require relatively frequent visits. If they are visited twice weekly by a GP and daily by a community nurse, the cost increases to approximately £13.61 per day. Again the true cost will vary greatly with the severity of illness.

Transdermal administration

Transdermal administration of opioid analgesics (Fentanyl TTS) may avert a number of costs. When compared with subcutaneous administration, costs of supplies and equipment will be completely averted, and personnel time costs greatly reduced due to the single 3-day dose. This is true for patients in both hospital and ambulatory settings, as patients in ambulatory settings with portable infusion pumps are visited very frequently by GPs and/or community nurses. Cost savings in comparison with oral morphine were less clear, and to some extent depend on the true cost of personnel time involved in administering doses. It is evident that personnel time is a significant part of the total cost of pain control therapy. The single 3-day dose of Fentanyl TTS should, therefore, reduce both inpatient and outpatient personnel time costs.

Using the estimates of inpatient staff time per dose of oral morphine (Table 2), an estimate of the potential costs averted using transdermally administered fentanyl can be made. The following assumptions were used:

1. Pharmacist time in making up and packaging doses, and entering transactions in the register will be reduced to one sixth of that for oral morphine, because of the single 3-day dose.
2. Clinician and nurse time spent administering drugs and entering transactions in the register of controlled drugs will also be reduced to one sixth of that for oral morphine, but time spent monitoring the patient's response to therapy will be maintained.

With these assumptions, staff time costs could be reduced to £0.93 per day for pharmacist time, £1.36 per day for nurse time and £5.88 per day for clinician time, giving a total daily cost of £8.17 compared with estimated costs of £13.73 per day for oral morphine and £17.69 per day for subcutaneous therapy. These estimates should, however, be handled with care, given the uncertainty regarding the order of magnitude of time costs illustrated by the sensitivity analysis. These estimates are also relevant only to patients who are stabilised on transdermally delivered opioids. Initial use of a patch would have to be covered with another form of rapidly acting analgesic, as a period of 12 to 24 h is required before full pain relief can be achieved from a dose. The above estimate does not include this period of dose titration, when patients would require more staff time in monitoring pain control and administering additional analgesia.

For patients in ambulatory care with parentally administered analgesics, cost savings may also be made from the use of transdermally administered fentanyl. Currently, patients with portable infusion pumps are visited twice daily by a community nurse and twice a month by their GP. Transdermal therapy may reduce the necessity of these frequent visits, perhaps to the level of those carried out for ambulatory patients receiving oral morphine, i.e. approximately six visits per month from a community nurse and one per month from a GP. Costs would in this case be reduced from £9.35 per day to £2.26 per day. This again assumes that patients are stabilised on this form of delivery.

Finally, it is likely that home care will be possible for more patients with the use of transdermal administration as this is much more convenient than subcutaneous administration. Transdermal administration may make hospitalisation of cancer patients solely for pain control unnecessary, or, when necessary, it may reduce the length of stay. More research is needed to estimate accurately these potential cost savings.

DISCUSSION AND CONCLUSIONS

The results of this cost analysis reinforce the intuitive view that it is less costly to administer morphine orally than parenterally. This is, however, frequently impossible, for example when cancer patients suffer from gastrointestinal problems. Patients in this situation currently have to be treated by costly and uncomfortable parenteral routes. Transdermal delivery is a more convenient route of administration for patients and for medical and nursing staff, as it avoids the use of injections and,

once patients are stabilised, it is likely to require less monitoring by medical staff in hospital or in the community.

The foregoing analysis has a number of limitations. The estimates of staff time spent on different tasks result from questioning a small number of hospital and hospice staff, and resource use in the community requires further study. A more accurate impression of staff time in hospitals may be achieved by using a work sampling methodology, as in Goughnour [4], and a subsequent economic evaluation could perhaps incorporate this approach. In addition, the resources used by patients with severe cancer pain could be measured prospectively for individuals randomised to transdermal and traditional delivery, to investigate potential resource differences between the alternative methods of administration.

Economic issues in the management of severe pain in cancer patients are relatively neglected in published literature. Where costs are taken into account, the influence of staff time costs is constantly shown to be an important issue. This cost analysis confirms this. Transdermally administered fentanyl, with its single 3-day dose, may significantly reduce both the material costs (supplies and equipment) and staff time costs associated with management of severe pain. The cost effectiveness of this new form of pain control should be measured in a prospective trial which incorporates an appropriate economic component. As in many areas of evaluation of cancer interventions, the absence of such economic appraisal ensures that clinical and other decision makers are poorly informed.

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