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The Cost Effectiveness of Stratified Care in the Management of Migraine

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Abstract

Objective: To examine the cost effectivess of a stratified-care regimen for patients with migraine – in which patients are stratified by severity of illness, and then prescribed differing treatments according to level of severity – compared with a conventional stepped-care approach.

Design and methods: A decision analytic model was constructed to simulate a controlled clinical trial in which patients with migraine receiving primary medical care were randomly assigned to treatment under a stepped-care or a stratified-care regimen. A health service payer perspective was adopted and the time horizon was 1 year. Data inputs were: (i) the frequency and disability of migraine, derived from population-based studies; (ii) disability level-specific treatment response rates for over-the-counter analgesics,aspirin/metoclopramide and zolmitriptan as the representative of high-end therapy obtained from an international consensus opinion enquiry; and (iii) unit costs of healthcare obtained from UK health service sources.

Main outcome measures and results: The estimated 1-year direct healthcare costs per primary care patient with migraine were pound sterling (£) 156.82 for stepped care and £151.57 for stratified care. Estimates of treatment response rates were 40 and 71% for stepped and stratified care, respectively. The cost per successfully treated attack was £23.43 for stepped care and £12.60 for stratified care.

Stratified care remained cost effective when tested in a wide range of one-way sensitivity analyses, and probabilistic sensitivity analysis showed the cost effectiveness of stratified care to be significant at the 3% level. Conditional confidence analysis showed that the level of confidence in the cost effectiveness of stratified care varied positively with the case mix, i.e. in populations where the proportion of moderate and severely disabled patients with migraine was greater than 25%, the cost effectiveness of stratified care remained statistically significant.

Conclusion: A stratified-care treatment strategy (including zolmitriptan as the representative of high-end therapy) is a highly cost-effective method of managing migraine in the primary care setting compared with stepped care, delivering improved clinical outcomes at no additional cost.

Migraine is a common neurological disorder that affects 8 to 12% of the general population.[1,2] Onset of migraine peaks in childhood and adolescence[3] and prevalence peaks between the ages of 25 and 55 years, during the time of maximal work and family commitments.[1,2] Prevalence is higher in women than in men,[4] and in Caucasian than in non-Caucasian races.[2]

Migraine exerts a significant burden on the individual in terms of pain, disability and reduced quality of life.[5] This is compounded by the heterogeneity of migraine. The frequency, duration, symptomatology and resulting disability vary both among and between individual patients, from attack to attack and over time.[6]

Migraine also exerts a societal burden in terms of direct and indirect costs of illness. Direct costs comprise the cost of medical care. Indirect costs are caused by absence from work, reduced productivity at work and disability in other roles. Most individuals with migraine have consulted a physician at some time and take medications for the condition. Annual direct costs (adjusted to 1993 $US values) range from $US12.5 million in Sweden to $US1 billion in the US.[7,8] These figures probably underestimate present values, as they do not include the cost of recently introduced migraine therapies, such as the selective serotonin receptor agonists ('triptans').

The indirect costs of migraine are substantial, and are much higher than the direct costs. Work losses related to reduced productivity are higher than those related to work absence. Some of the estimated annual costs (adjusted to 1993 $US values) are $US220 million in Australia, $US732 million in Canada, $US1.1 billion in Spain and the UK, $US1.2 billion in The Netherlands and $US13 billion in the US.[7,8] The results of these studies show that the burden of migraine falls disproportionately on patients and their employers, while third-party payers shoulder less than 10% of migraine-related economic costs. The overall cost of migraine to society is comparable with that reported for diabetes mellitus[9] and higher than that reported for asthma.[10]

Optimal management of migraine requires a systematic evaluation of each patient and the development of an individualised management plan. However, currently recommended treatment guidelines for migraine typically involve a type of stepped care, applied across or within attacks, where patients move through a series of medications from nonspecific to specific therapies.[11] In stepped care across attacks, patients initiate treatment with 1 medication for a series of attacks. If this nonspecific treatment fails, physicians can step the patient up to alternative, specific therapies for subsequent attacks. In stepped care within attacks, patients initiate treatment with 1 medication for each attack. If this treatment fails, they can step up their treatment during their attack using escape medication.

Although stepped care may be an effective strategy for patients with mild migraine, those with greater treatment needs often find that initially prescribed medications fail to relieve their symptoms and they may lapse from medical care. Stratified care is an alternative strategy for managing migraine. It is designed to match treatment to the medical needs of each patient.[12,13] Patients can be stratified according to their illness severity, assessed as headache-related disability, for example using the Migraine Disability Assessment (MIDAS) Questionnaire,[14,15] a simple, widely available,[15] 5-item self-report questionnaire that can be completed easily and quickly by the patient. Treatment is then prescribed to match the severity of illness. In this way, patients who need specific therapies receive them at their initial consultation, not after a series of failed therapeutic efforts.

Stratified care for migraine (using the MIDAS Questionnaire to grade patients' illness severity) was compared with stepped care across and within attacks in a clinical trial, the Disability in Strategies for Care (DISC) study.[16] The study showed that stratified care, in which patients received zolmitriptan 2.5mg or aspirin (acetylsalicylic acid) and metoclopramide according to MIDAS grade, was clinically and statistically significantly superior to the 2 stepped-care approaches, i.e. the across and within attacks approaches. Significantly more

patients responded and became pain-free, and disability was significantly lower in the stratified care group. The results showed that stratified care optimised patients' responses from the start of treatment, whilst treatment benefits were delayed in the stepped-care groups.

Stratified care, however, clearly means that relatively more specific treatments will be prescribed, as the more severely disabled patients receive these treatments earlier than with stepped care, and specific treatments are more expensive. Can the increased effectiveness of stratified care be obtained without an additional burden on healthcare costs? Is stratified care cost effective, compared with stepped care? This is the focus of the study reported in this paper.

Methods and Data

General Approach

The approach taken was to construct a decision analytic model to simulate a controlled clinical trial in which primary medical care patients with a diagnosis of migraine would be randomly assigned to treatment under a stepped-care regimen across attacks or a stratified-care regimen. A health service payer perspective was adopted and the time horizon was 1 year (no discounting was therefore necessary).

The measure of effectiveness was the proportion of migraine attacks expected to respond to treatment during the notional year. The measure of cost was the total of expected primary care consultation costs, expected specialist referral and consultation costs, and expected drug acquisition costs, over the notional year. Inpatient costs were not included, as the likelihood of admission for treatment of a migraine attack is very low, especially in the context of the UK National Health Service (NHS), which was used to provide the cost base for this study (any bias introduced by the exclusion of inpatient costs can be presumed to act against stratified care, given its greater effectiveness). The cost of performing the MIDAS Questionnaire was considered to be negligible. Indirect costs were not included.

The cost-effectiveness measure was the total direct costs (as defined above, and including the costs incurred by treatment failures) expected to be incurred, divided by the expected number of effectively treated migraine attacks, over the notional year. Average cost-effectiveness ratios (for stepped and stratified care, respectively) and the incremental cost-effectiveness ratio (for stratified care compared with stepped care) were calculated as appropriate.

Structure of the Model

Three therapy levels were included in the model: over-the-counter (OTC) analgesics, aspirin and metoclopramide, and high-end therapy as represented by zolmitriptan. While an OTC arm was not included in the DISC trial we felt it appropriate to include this treatment here. Analgesics of this kind are widely used, and indeed recommended as the starting point, for example, by PRODIGY, the UK NHS computerised decision support system for general practitioners.[17]

Stepped Care

Figure 1 shows the structure of the stepped-care regimen as represented in the model. A patient consults a primary care physician and migraine is diagnosed. OTC medication is advised, and the patient is told to return after treating a further 3 attacks. At the second consultation, a judgement is made as to whether the treatment has provided relief in 2 or more of the 3 intervening attacks (the response criterion used in the DISC trial). If so, the patient continues on OTC medication and seeks care at a less frequent rate (i.e. there is a greater number of attacks between consultations; in the base case, it was assumed, based on experience, that the consultation rate would drop to 1 per 8 attacks). If not, the patient 'steps up' to aspirin and metoclopramide, and returns after treating a further 3 attacks.

At the third consultation, the physician again makes a judgement as to whether the treatment has provided relief on 2 or more of the 3 intervening attacks. If so, the patient continues on aspirin and metoclopramide and consults at a less frequent rate. If not, the patient 'steps up' to high-end therapy

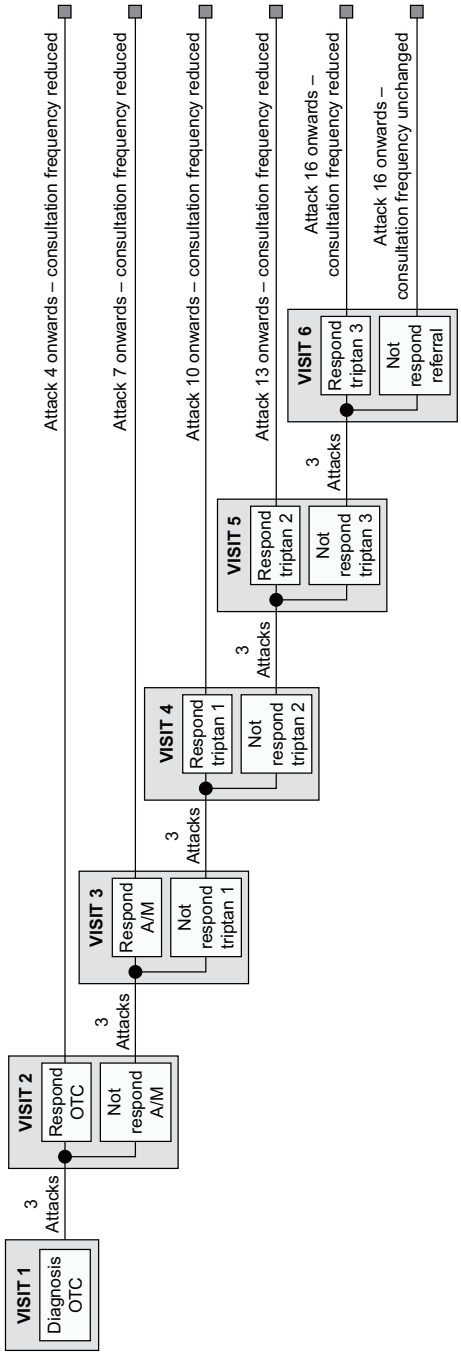

Fig. 1. Structure of the stepped-care decision tree. **A** = aspirin (acetylsalicylic acid); **M** = metoclopramide; **OTC** = over-the-counter.

(triptans) and returns after a further 3 attacks. The same logic, using the same response criterion, is followed at subsequent consultations, with patients whose migraines have not responded working their way through 3 different selective serotonin receptors agonists and ultimately being referred for specialist consultation (which, in the model, could only occur at this time).

The 6 end-states, once reached, were assumed to be absorbing (i.e. contain all patients) for the remainder of the notional year, and patients were assumed not to be lost to follow-up. For each end-state, the model calculated the expected number of attacks responsive to treatment, the expected number of primary care physician consultations, the expected number of attacks treated with a triptan, and the expected likelihood of specialist referral/consultation. These were multiplied by the calculated end-state probabilities to provide the expected costs and effectiveness for stepped care.

Stratified Care

Figure 2 shows the structure of the stratified-care regimen as represented in the model. A patient consults a primary care physician, migraine is diagnosed, and a disability assessment is carried out using the MIDAS Questionnaire. Patients in MIDAS grade I ('minimal or infrequent disability') follow the stepped-care approach, i.e. they may progress, according to clinical response, from OTC analgesics through aspirin and metoclopramide to a triptan and ultimately to specialist consultation. Patients in MIDAS grade II ('mild or infrequent disability') enter this process at the aspirin and metoclopramide stage, while patients in MIDAS grades III ('moderate disability') and IV ('severe disability') enter directly at the high-end therapy stage. The criteria for when next to consult, and for progressing through the treatments, were the same in both the stratified- and stepped-care decision trees.

There were 15 end-states (6 for MIDAS grade I, 5 for MIDAS grade II, and 4 for MIDAS grades III/IV). Once again, these end-states were assumed to be absorbing and patients were assumed not to be lost to follow-up. For each end-state, the model

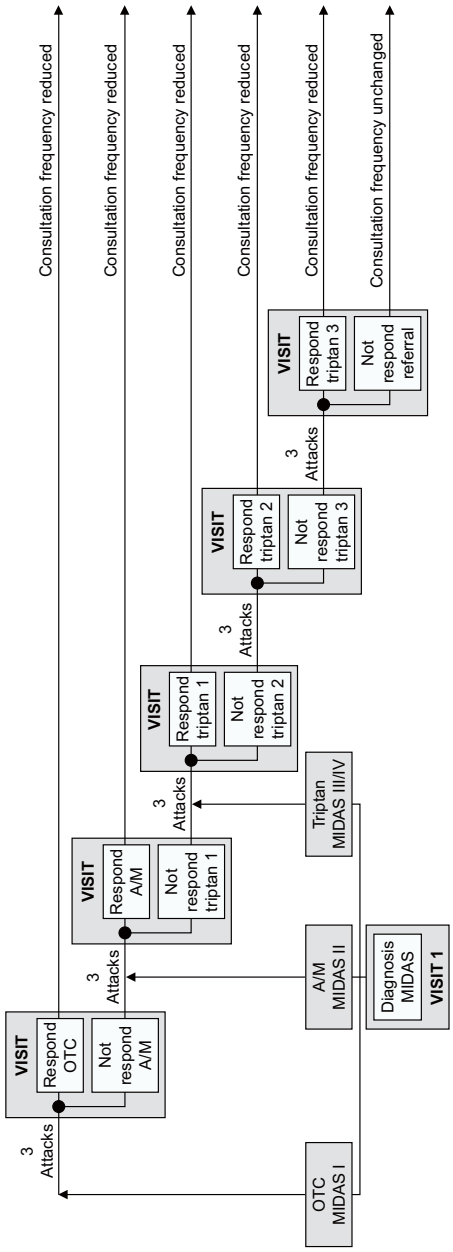

Fig. 2. Structure of the stratified-care decision tree. **A** = aspirin (acetylsalicylic acid); **M** = metoclopramide; **MIDAS** = Migraine Disability Assessment Questionnaire grade; **OTC** = over-the-counter.

calculated the expected costs and effectiveness for stratified care as for stepped care.

Variables in the Model

Distribution of MIDAS Grades in the Consulting Population (Case Mix)

Based on discussions with those who have clinical experience with the MIDAS Questionnaire in a UK general practice setting, it was assumed for the base case that 5% of patients with migraine seen in a primary medical care setting would fall into MIDAS grade I, 25% into grade II and 70% into grades III/IV. Because of the lack of actual data on this crucial variable, we explored case mix in some detail in the sensitivity analysis – see below.

Number of Migraine Attacks Per Year, by MIDAS Grade

Stewart et al.[18] carried out a validity study of the MIDAS Questionnaire in which they used headache diaries to assess the frequency of migraine attacks over a 90-day period. The MIDAS Grade-specific headache frequencies shown in table I were extracted from these data and provided to the present authors by Dr. Kenneth Kolodner (personal communication). These were scaled to provide figures applicable to 1 year (MIDAS grades III and IV were grouped together, see table I).

Response Rates Specific to Each MIDAS Grade for Each Level of Treatment

These were based on consensus expert opinion, collected by means of a 2-round consensus opinion (Delphi) enquiry designed to take account of Evans'[19] recommendations on the use of consensus methods and expert panels in pharmacoeconomic studies. The participants were an international group of 20 neurologists and headache specialists, selected on the basis of their previous involvement in the development and early use of the MIDAS Questionnaire. Respondents were asked to make judgements of clinical response based on their knowledge and experience of providing treatment at all 3 levels in the regimen, but were provided with no specific data on which to base their judgements. Estimates of attack response rate (table II)

Table I. Number of headaches per year, by MIDAS grade (from analyses carried out on data collected by Stewart et al.[18])

MIDAS grade	Number of migraine attacks in a 90-day period (mean ± SD)	Calculated annual number of migraine attacks used in the model (mean ± SD)
I	1.85 ± 2.52	7.49 ± 10.22
II	1.98 ± 2.62	8.02 ± 10.61
III	3.01 ± 2.65	12.22 ± 10.74
IV	6.66 ± 5.32	27.01 ± 21.59
III/IV combined	5.11 ± 4.36	20.74 ± 17.70

MIDAS = Migraine Disability Assessment Questionnaire; **SD** = standard deviation.

were used to calculate the likelihood of patients responding in at least 2 of 3 attacks, for use in the base case model. If the probability of responding in 1 migraine attack is p, then the probability of responding in at least 2 out of 3 attacks – assuming independence between attacks – is $p^3 + 3(p^2[1–p]) = 3p^2 – 2p^3$. (MIDAS grades III and IV were again grouped together). The interquartile ranges (table II) were used to represent the extent of uncertainty in the sensitivity analyses (as suggested by Rowe et al.[20]).

Unit Costs of Health Service Consumption

The UK NHS costs were used. For the base case, the cost of a primary care consultation and specialist referral/consultation were set at pounds sterling (£) 16 and £93, respectively.[21] The cost of treating a migraine attack with a selective serotonin receptor agonist was £6 for the base case (the cost of 1.5 tablets of zolmitriptan 2.5mg); OTC analgesics and aspirin and metoclopramide were considered to be of negligible cost and therefore were not included in the analysis.

Statistical Analysis

Estimates for cost indices, effectiveness indices and cost-effectiveness ratios were first estimated for the base case, following which extensive sensitivity analysis was undertaken.

Sensitivity Analysis

A set of 16 one-way sensitivity analyses was carried out to explore the impact of changes in each of the input variables on modelled cost, effectiveness, and cost-effectiveness ratios. Then, a Monte Carlo model was built to carry out a probabilistic sensitivity analysis, i.e. a 17-way sensitivity analysis (the 16 input variables examined in the one-way analyses, plus the effect of case mix) to assess the impact on the cost effectiveness of stratified care of changing all the input variables simultaneously. As part of this approach, conditional confidence analysis[22] was used to explore in more detail the impact of the level of disability (the case mix) on the cost effectiveness of stratified care in the consulting population.

The input variables were modelled as follows:

Per-Grade Mean Number of Migraine Attacks Per Year

The means and standard deviations calculated by Dr Kenneth Kolodner (personal communication) on the basis of the Stewart et al.[18] data transformed to be appropriate for 1-year rather than 90-day data (table I) were used as parameters to define γ distributions (the γ distribution was selected because of its appropriateness for right-skewed data

Table II. Estimates of response rates specific to each MIDAS grade for each level of treatment: medians and interquartile ranges from the second (final) round of the consensus opinion enquiry

Midas grade	Treatment	Response rates (%)	
		median	interquartile range
I	OTC analgesics	47	33–57
	Aspirin/metoclopramide	57	46–65
	Zolmitriptan	69	62–76
II	OTC analgesics	34	24–47
	Aspirin/metoclopramide	46	37–45
	Zolmitriptan	69	62–75
III	OTC analgesics	21	15–28
	Aspirin/metoclopramide	34	27–47
	Zolmitriptan	66	59–73
IV	OTC analgesics	15	7–21
	Aspirin/metoclopramide	24	18–32
	Zolmitriptan	61	53–69
III/IV combined	OTC analgesics	18	11–25
	Aspirin/metoclopramide	29	21–41
	Zolmitriptan	64	56–71

OTC = over-the-counter; **MIDAS** = Migraine Disability Assessment Questionnaire.

Table III. Expected units and costs of health service consumption, per patient per year, as estimated by the base-case model

Parameter	Stepped care	Stratified care	Difference (stratified care – stepped care)
Number of consultations with primary care physician	4.90	3.65	–1.25
Cost of consultations with primary care physician	£78.44	£58.34	–£20.10
Number of specialist referrals/consultations	0.23	0.02	–0.21
Cost of specialist referrals/consultations	£21.32	£1.68	–£19.64
Number of attacks treated with selective serotonin receptor agonists	9.51	15.26	5.75
Cost of selective serotonin receptor agonists	£57.06	£91.55	+£34.49
Total health service costs	**£156.82**	**£151.57**	**–£5.24**

£ = pounds sterling.

without negative values). The distributions were sampled randomly in each iteration of the model using the algorithm given by Morgan and Henrion.[23]

Per-Grade Treatment Response Rates

In each iteration of the model, values were sampled randomly from a uniform distribution between the twenty fifth and seventy fifth percentiles obtained from the consensus opinion enquiry study (table II). This approach was adopted rather than an algorithm making use of the central tendency – e.g. sampling from a triangular distribution – as this provided a more robust test of the cost effectiveness of stratified care.

Unit Costs of Health Service Consumption

In each iteration of the model, values were sampled randomly from a uniform distribution between the extremes of ±50% of the base case value.

Post-Recovery Consultation Rate

In each iteration of the model, values were sampled randomly from a uniform distribution between the extremes of the preconsultation rate (1 consultation per 3 attacks) and 1 consultation per year (1 consultation per 16.89 attacks).

Case mix

In each iteration of the model, the proportions of patients in each MIDAS grade were sampled randomly from uniform distributions between 0 and 1, subject to the constraint that the total of the 3 proportions (for Grades I, II, III/IV) should sum to 1.

Results

The Base Case

Table III shows the expected units and costs of health service consumption, per patient per year, as estimated by the model. In the base case – i.e. with input values as given in the previous section – the stratified-care regimen resulted in fewer primary care consultations and fewer specialist consultations than the stepped-care regimen, resulting in an expected saving to the health service (in 1 year per patient) of £20.10 and £19.64, respectively. These savings were partially offset by the greater number of attacks treated with a selective serotonin receptor agonist under stratified care, which incurred a correspondingly greater drug treatment cost. Even so, with base case input values the total health service cost was £5.24 per patient per year lower under a stratified-care regimen than under a stepped-care regimen (table III). These estimates for cost saving are likely to be underestimates, as it might be expected that the enhanced efficacy due to stratified care would result in reduced healthcare expenditure on comorbid conditions.

Table IV shows the mean number of migraine attacks per year (the mean of the values in table I weighted by the frequencies of the MIDAS grades assumed for the base case model, as described earlier). Under stepped care, the model estimated 6.69 attacks to be responsive to treatment (a 40% attack response rate), whereas under stratified care, the estimated number of treatment-responsive attacks was 12.02, or 71% of attacks over the notional year.

For stepped care, the model estimated that a health service expenditure of £23.43 was required to deliver 1 successfully treated migraine attack [£156.82 (table III) divided by 6.69 (table IV)]. For stratified care, however, an expenditure of only £12.60 was required to deliver the same outcome [£151.57 (table III) divided by 12.02 (table IV)].

The reciprocal of the cost-effectiveness ratios represents the number of successful outcomes that can be 'purchased' for a given health service expenditure. Table IV shows that, for stepped care, 4.27 successfully treated migraine attacks were 'purchased' for £100 of health service expenditure [6.69 (table IV) divided by £156.82 (table III) × 100]. For stratified care by comparison, the same expenditure purchased 7.93 successful outcomes [12.02 (table IV) divided by £151.57 (table III) × 100], an increase of 80%.

Calculating an incremental cost-effectiveness ratio for stratified care was unnecessary as stratified care was both less costly and more effective than stepped care (with base case input values).

Sensitivity Analyses

16 one-way sensitivity analyses were carried out. Stratified care remained dominant over stepped care in 10, while in the other 6, stratified care was cost effective, i.e. the incremental cost-effectiveness ratio was lower than the cost-effectiveness ratio for stepped care. Details of these one-way sensitivity analyses are available on request from the first author.

Table V shows the exact probabilities resulting from a run of 10 000 iterations of the Monte Carlo model of 17-way analysis, as outlined in the Methods section. Following Critchfield and Willard,[22] these exact probabilities can be interpreted as levels of confidence in the result. Therefore, within the confines of the model structure and the ranges of input values tested in the analysis, we can be:

- 33.6% confident that stratified care will be cost saving compared with stepped care
- 99.5% confident that stratified care will be more effective than stepped care
- 96.4% confident that stratified care will be cost effective, compared with stepped care: that is, the cost effectiveness of stratified care can be considered significant at the $p = 0.036$ level.

In the Monte Carlo analysis described in the Methods section, the case mix was allowed to vary widely (the probability of each of the grades was allowed to range between 0 and 1, subject only to the constraint that they should sum to 1). Even though the impact of case mix on the cost effectiveness of stratified care has been examined in this way, it is appropriate to examine this in more detail to discover the relevance of the stratified care approach in differing clinical populations (especially as the case mix in the model base case was based on assumption rather than data).

To do this, we used conditional confidence analysis, a technique in which the variable of interest is held constant, while the values of all the other input variables are allowed to vary in the Monte Carlo model. It is thus analogous to the 'step down' approach to examining the impact of a predictor variable in a multiple regression analysis. We used

Table IV. Effectiveness of, and cost-effectiveness ratios for, stepped and stratified care, as estimated by the base-case model

Parameter	Stepped care	Stratified care	Difference (stratified care – stepped care)
Number of migraine attacks per year[a]	16.89	16.89	
Number of migraine attacks per year responding to treatment	6.69	12.02	+5.33
Attack response rate (%)	40	71	31
Health service costs per successfully treated attack	£23.43	£12.60	Stratified care dominant
Number of successfully treated attacks that can be 'purchased' with £100 of health service expenditure	4.27	7.93	Stratified care dominant

a The figures in this row are an input to, rather than an output from, the model.

£ = pounds sterling.

Table V. Exact probabilities resulting from 10 000 iterations of the Monte Carlo model

Cost	Probability that health service costs are less with stratified care than with stepped care	0.336	
Effectiveness	Probability that effectiveness is greater with stratified care than with stepped care	0.995	
Cost-effectiveness ratio	Probability that stratified care is dominant over stepped care	0.335	Stratified care cost effective 0.964
	Probability that stratified care, while not dominant, is cost effective compared with stepped care[a]	0.629	
	Probability that stepped care, while not dominant, is cost effective compared with stratified care[b]	0.036	Stratified care not cost effective 0.036
	Probability that stepped care is dominant over stratified care	0	

a The incremental cost-effectiveness ratio for stratified care is less than that for stepped care.

b The cost-effectiveness ratio for stepped care is less than the incremental cost-effectiveness ratio for stratified care.

the probability of MIDAS grades III/IV as our index of case mix (i.e. the expected level of disability increases as this probability increases), and we carried out 9 runs of the model (1 for each probability decile) of 5000 iterations each.

Figure 3 shows that, as might be expected, the level of confidence in the cost effectiveness of stratified care (as compared with stepped care) increased as the expected level of disability increased. Even at the lowest disability level, however, the confidence in the cost effectiveness of stratified care was greater than 90%. If the usual 95/5% level is taken as the threshold of acceptability/significance, then stratified care can be considered significantly cost effective in populations where the probability of MIDAS grades III/IV is greater than 25%.

Discussion

Within the limitations of the study, stratified care was shown to be a cost-effective approach to the management of migraine in the primary care setting, compared with the usual stepped-care approach. Indeed, in the base case, stratified care was cost saving (albeit of a relatively small sum) with resources spent producing some 80% more benefit than the same resource spent in a stepped-care setting.

All modelling studies have limitations – those imposed by the structure of the model and the inherent assumptions, as well as those imposed by the data. As in all modelling studies, we attempted to keep these limitations to a minimum.

The imposition of a clinical trial structure does itself impose limitations on the interpretation of the results. For instance, in clinical practice, some patients in MIDAS grade I may already have tried OTC analgesics (and would thus step up immediately), while some patients in MIDAS grade IV may require particular care programmes tailored to their high disability level.

The data used in the model were, where possible, derived from published sources. There were 3 principal data limitations. First, there are no available data on attack response rates for each of the 3 treatment levels (low, intermediate and high-end) specific for MIDAS grades, so these were based on expert opinion collected by means of a 2-round consensus opinion enquiry (in which high-end treatment was represented by zolmitriptan). In accordance with published recommendations for such studies,[18] the participants were acknowledged experts in their field, and steps were taken to avoid attrition between the rounds (in fact, there was no attrition at all). The material provided to the experts was standardised and contained no anchoring information, and the feedback comprised both individual responses (anonymised except for the recipients' own) and group responses. Although there are no data with which the results of the consensus opinion enquiry can be compared directly (if there were, the enquiry would not have been necessary), we would expect a reasonable

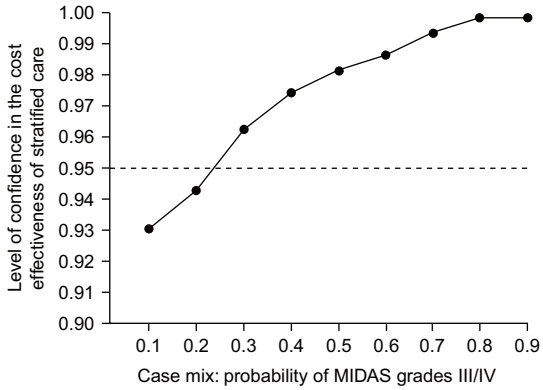

Fig. 3. The relationship between case mix (as measured by the probability of MIDAS grades III/IV) and level of confidence in the cost effectiveness of stratified care. **MIDAS** = Migraine Disability Assessment Questionnaire.

correspondence between the experts' estimates for MIDAS grades III/IV and results from migraine clinical trials, given that many migraine clinical trials are conducted at headache speciality centres and tend to enrol patients with more severe migraine. In the 5 clinical trials of zolmitriptan 2.5 to 5mg reported in the product labelling information, the response rate (defined in the same way as in the consensus opinion enquiry) ranged from 59 to 67%.[24] Table II shows that the interquartile range for the relevant rates from consensus opinion was 56 to 71%, a very satisfactory level of correspondence which provides a degree of convergent validity.

The second principal data limitation is the absence of survey information on the relative frequency of the MIDAS grades in patients with migraine receiving primary care. We made an assumption based on clinical experience of treating migraine in general practice (70% of patients seeking treatment would fall into MIDAS grades III/IV), but even so, we paid special attention to this case mix variable in the sensitivity analysis.

The third data limitation is the assumption that no patients were lost to follow-up. Once again, as far as we are aware, there are no data that address this point. It would be reasonable to assume, however, that effectiveness and compliance with follow-up are related – i.e. patients who find their treatment to be effective are more likely to remain in treatment. This being so, we believe it reasonable to assume that the insensitivity of the principal result to variation in treatment response rates (both in the one-way and 17-way sensitivity analyses) is a proxy for robustness of the result to reduced compliance with follow-up.

Given these limitations, the results of the sensitivity analyses are especially important. The cost effectiveness of stratified care was robust when examined in a set of 16 one-way sensitivity analyses (not including the relative frequency of MIDAS grades). Stratified care remained dominant in 10 of these, and was cost effective in the remaining 6 analyses, with the incremental cost-effectiveness ratio well below the average cost-effectiveness ratio for stepped care. In the probabilistic sensitivity analysis, all input variables (including the relative frequency of MIDAS grades) were allowed to vary simultaneously. Conservative assumptions were made in the design of the Monte Carlo model – for example, uniform distributions were used to model the treatment response rates, and the case mix was allowed to vary without constraint (except that the frequencies of the MIDAS categories were required to sum to 1). This latter assumption meant that, in this analysis, the expected proportion of MIDAS grades III/IV was 33% (each of the 3 grades had an equal probability of selection). On this basis, therefore, the cost effectiveness of stratified care was statistically significant even when assessed on a population considerably less severe than that expected in a general practice setting – i.e. the significance level $p = 0.036$ is a conservative estimate. This was confirmed and extended in the conditional confidence analysis, where the level of confidence (in the economic superiority of stratified care) was shown to vary positively with case mix, and to conform with the conventionally accepted level of significance in populations where the proportion of MIDAS grades III/IV was greater than 25%.

The results of any modelling study are immensely strengthened if they can be confirmed in the real world. While the DISC study[16] showed the clinical superiority of stratified care compared

with stepped care, it was not suitable for examining direct costs as these were largely protocol driven.

Conclusions

Using a decision analytic model designed to simulate a controlled clinical trial, stratified care (which included zolmitriptan as the representative of high-end therapy) was shown to be a highly cost-effective method of managing migraine in the primary care setting compared with stepped care, delivering improved clinical outcomes at no additional cost.

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