ORIGINAL RESEARCH ARTICLE

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Economic Evaluation of Oral Sumatriptan Compared with Oral Caffeine/Ergotamine for Migraine

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Summary

We conducted an economic comparison of oral sumatriptan with oral caffeine/ergotamine in the treatment of patients with migraine. Cost-effectiveness, cost-utility and cost-benefit analyses were conducted from societal and health-departmental perspectives. A decision tree was used. Utilities were assigned to health states using the Quality of Well-Being Scale. Simple and probabilistic sensitivity analyses were also carried out.

From a societal perspective, using sumatriptan instead of caffeine/ergotamine resulted in an incremental cost-effectiveness ratio of –25 Canadian dollars ($Can) per attack aborted, an incremental cost-utility ratio of –$Can7507 per quality-adjusted life-year (QALY), and a net economic benefit of $Can42 per patient per year (1995 values). From the perspective of the health department, the incremental cost-effectiveness ratio was $Can98 per attack aborted, the incremental cost-utility ratio was $Can29 366 per QALY; the grade of recommendation based on past decisions regarding health technology for adoption into health insurance plans was 'moderate'. Sensitivity analysis showed that the results were robust to relatively large changes in the input variables.

The incremental health benefits obtained from using oral sumatriptan rather than oral caffeine/ergotamine were achieved at moderately acceptable incremental costs, if past decisions on the adoption of other health technologies are used as a guide.

Migraine is very costly to society, both in terms of consumption of healthcare resources (direct costs) and lost productivity (indirect costs).[1-4] There are also intangible costs, such as pain, suffering and discomfort, which are difficult to quantify accurately. Cost-effective strategies for preventing and treating migraine are needed. In the early 1990s, sumatriptan, an antimigraine drug with a relatively high acquisition cost, was introduced in several countries.

Sumatriptan is a serotonin 5-HT_1 receptor agonist. Its primary mechanism of action is constriction of dilated and oedematous cranial blood vessels, which are present during a migraine attack, restoring them to a normal diameter. This leads to an inhibition of the firing of sensory neurons and thus alleviation of pain.[5] Sumatriptan also blocks plasma extravasation from blood vessels, which may also be a part of migraine pathogenesis.[6] Via these mechanisms, a full-blown migraine attack

Table I. Selected results of the multinational oral sumatriptan and caffeine/ergotamine comparative study[12]

Event	Absolute % risk difference (95% confidence interval)
Moderate or severe headache to mild or no headache at 2 hours	17.9 (9.1 to 26.8)
Moderate or severe headache to none at 2 hours	22.0 (14.4 to 29.6)
Relief of nausea at 2 hours	25.4 (16.9 to 34.0)
Relief of vomiting at 2 hours	11.5 (-0.5 to 23.6)
Relief of photophobia/phonophobia at 2 hours	21.5 (12.3 to 30.7)
Recurrence within 48 hours	10.9 (3.1 to 18.6)

may be averted. Patients who have had a successful response to oral sumatriptan 100mg may treat a later recurrence of headache with another 100mg tablet (a 50mg tablet is now available in Canada, and future studies should also consider this strength). The maximum total dose in 24 hours is 300mg.[7] The major disadvantages of sumatriptan are its acquisition cost [approximately 16 Canadian dollars ($Can) per 100mg tablet] and the short duration of its action. The latter property and the physiology of the particular receptors involved result in a substantial probability (32 to 40% according to clinical trials) of headache recurrence during a single attack.[8]

Another oral therapy used in patients with a migraine attack is the combination of caffeine 100mg and ergotamine 1mg [caffeine/ergotamine (known as Cafergot® in some countries)]. The dosage is 2 tablets at the first sign of a migraine, followed by 1 tablet every 30 minutes until the attack is aborted, or until 6 tablets have been taken.[9] Ergotamine is a 5-HT receptor agonist and α-adrenergic–receptor blocker. Its mechanism of action is similar to that of sumatriptan in that it causes cerebral vasoconstriction. The addition of caffeine to ergotamine enhances its absorption[10] and possibly its vasoconstrictive activity.[11]

This article presents an economic comparison of oral sumatriptan with oral caffeine/ergotamine in the treatment of migraine attacks. Cost-effectiveness, cost-utility and cost-benefit analyses were performed from the societal perspective and the perspective of any provincial health department.

Methods

Literature Search

A bibliographic database literature search, limited to English-language clinical studies was conducted using:

- MEDLINE (1966 to present)
- EMBASE (1974 to present)
- SCISEARCH (1974 to present)
- HealthPLAN (1975 to present)
- International Pharmaceutical Abstracts (1970 to present)
- TOXLINE (1965 to present)
- PsycINFO (1967 to present)
- IMSworld R&D Focus (1991 to present).

The following terms were searched for in the titles, abstracts and index terms of articles: (i) 'sumatriptan' or 'GR43175', 'migraine' and 'random' (textword); and (ii) 'ergot' (textword) or 'cafergot', 'migraine' and 'random' (textword).

Other information sources were also consulted, including the reference lists of relevant articles, technology assessment organisations [such as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA)], the manufacturer of sumatriptan (Glaxo Wellcome) and the manufacturer of Cafergot® (Sandoz).

Efficacy Measure

A migraine attack comprises many symptoms, however, pain is the most important symptom causing disability and distress. Therefore, the conversion of a moderate or severe headache to mild or no headache at 2 hours was chosen as the primary efficacy measure used in the economic analyses.

Only 1 randomised controlled trial comparing sumatriptan with caffeine/ergotamine was found.[12] Oral sumatriptan was statistically and clinically significantly more efficacious than oral caffeine/ergotamine for all the events studied (including the primary efficacy measure), except for relief of vomiting at 2 hours, for which no significant

difference was found (table I). When data from all randomised controlled trials involving oral sumatriptan were tallied, the probability of the primary efficacy measure being achieved was found to be 55.8%.[12-23]

It is notable that sumatriptan was associated with significantly higher recurrence rates compared with caffeine/ergotamine. The recurrence rate within 48 hours for oral sumatriptan, pooled from all clinical trials, was 40.6%.[12-23]

Model

A decision tree (fig. 1) was constructed to derive expected costs and utilities of alternative therapies.[24] The decision tree is relatively simple, yet we believe it to be an adequate model of the clinical situation.

Both the societal and health-departmental perspectives were adopted. The societal perspective was included, since it is the broadest and is always relevant.[25] The health-departmental perspective was included, since a major audience for this study is government-funded drug plans, i.e. provincial/national government insurers and other third-party payers. Discounting of costs and effects is unnecessary, since the time horizons did not exceed 1 year.[11] All costs are in 1995 Canadian dollars ($Can1 = $US0.74).

Assumptions

General

1. The decision tree is an accurate model of the clinical situation.
2. The probability of relief when using a comparator drug is equal to the probability of relief with

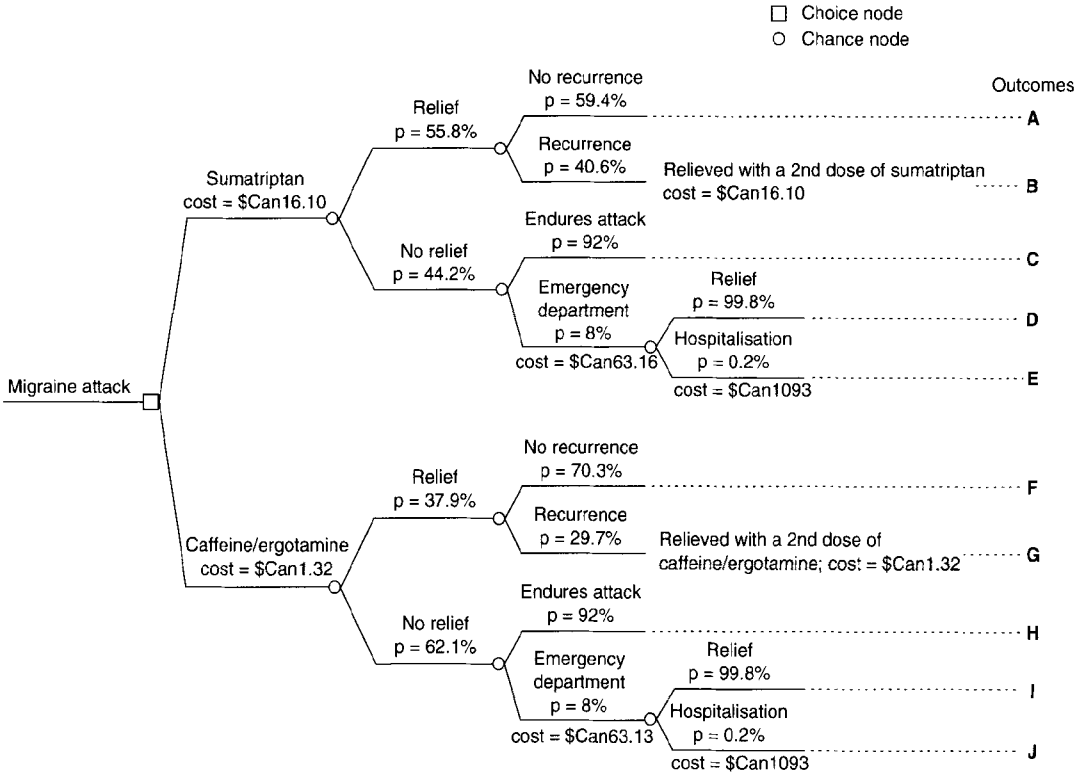

Fig. 1. Decision tree used in the model.

sumatriptan, minus the absolute risk difference for the primary efficacy measure.[12]

3. Patients with migraine have a mean of 21 attacks per year. Of these, 45% (9.45 attacks per year) are moderate or severe. When a moderate or severe attack occurs and relief is not obtained within 2 hours, the patient misses 1 day of work, or is so incapacitated at work that it is equivalent to missing a day of work. It is further assumed that the risk of missing work is dependent solely on the response to the first-line treatment; and when there is recurrence, relief is prompt and work is not missed.[4]

4. The mean duration of an attack is 24 hours.[4]

5. Costs and utilities are normally distributed.

6. Probabilities have logistic-normal distributions.

7. Each abortive migraine drug is only given once to abort an attack, and once again if there is a recurrence (this is the recommended use of sumatriptan). However, for caffeine/ergotamine, repeat doses are commonly administered. Therefore, it was expected that this assumption would introduce a bias against sumatriptan.

8. When a patient does not experience relief from first-line therapy and chooses to endure the attack, no other treatments are taken.

9. The age- and gender-specific earnings of patients with migraine are the same as for Canadians as a whole.

10. Any differences in indirect costs between comparator groups, with the exception of decreased production, are negligible.

11. Moderate and severe headaches have the same value of utility.

12. Mild headaches have the same value of utility as no headaches (this value is 1.0).

13. The probability of visiting an emergency department during an attack is 8%.

14. The probability of hospitalisation while at an emergency department is 0.2%.

15. There are no costs associated with occurrences of adverse events.

Efficacy Rates

1. The probability of conversion of a moderate or severe headache to a mild or no headache at all within 2 hours with oral sumatriptan is 55.8%.[12-23]

2. The probability of conversion of a moderate or severe headache to mild or no headache at all within 2 hours with oral caffeine/ergotamine is 55.8% – 17.9% = 37.9%.[12]

Recurrence Rates

1. The probability of recurrence within 48 hours after relief with oral sumatriptan is 40.6%.[12-23]

2. The probability of recurrence within 48 hours after relief with oral caffeine/ergotamine is 40.6% – 10.9% = 29.7%.[12]

Definitions

1. Probability = the product of all the individual branch probabilities leading to the final outcome.

2. Cost = the sum of all the individual branch costs leading to the final outcome.

3. Expected cost = probability (note 1) × cost (note 2).

4. Incremental effect = the pooled risk difference for the primary efficacy measure.

5. Incremental cost = expected cost for sumatriptan – expected cost for caffeine/ergotamine.

6. Expected utility = probability (note 1) × utility of the final outcome.

7. Incremental utility = expected utility for sumatriptan – expected utility for caffeine/ergotamine.

Other Considerations

Since the dispensing fee would be the same for both medications, this has been ignored. The numbers shown are rounded, but in the calculations, there was minimal rounding error.

Data Sources

The sources of the cost data are listed below.

1. Retail drugs and medical supplies: random telephone survey of 20 Canadian community pharmacies located in: Halifax, Nova Scotia; Montreal, Quebec; Toronto, Ontario; Regina, Saskatchewan; and Vancouver, British Columbia. The lowest price

Table II. Table of utilities (outcomes are shown in figure 1)

Outcome	Mean utility	Standard deviation
A	1.0	0.00
B	0.9	0.01
C	−0.3	0.10
D	0.1	0.10
E	−0.3	0.10
F	1.0	0.00
G	0.9	0.01
H	−0.3	0.10
I	0.1	0.10
J	−0.3	0.10

for the currently available brand was used for each of the 2 agents.

2. Hospital drugs and medical supplies: nonrandom survey of wholesalers and hospitals.

3. Other hospital costs [the 'intermediate method' of using the *per diem* tariff relating to hotel costs (since these are relatively invariant across patients) combined with a more precise calculation of the medical treatment costs associated with migraine therapy was used]:[25,26] Statistics Canada Annual Hospital Returns[27] database (nonteaching, acute care hospitals with 100 to 299 beds); and Canadian Institute for Health Information.[28]

4. Physician costs: provincial physician fee schedules obtained from a telephone survey of provincial health departments across Canada.

5. Average earnings: Statistics Canada reports.[29,30]

Economic Analyses

Cost-Effectiveness Analysis

The time horizon was 48 hours from the onset of an attack. The following formulae were used to calculate the cost-effectiveness ratios.

Societal perspective: incremental cost-effectiveness ratio = (incremental cost − incremental productive output)/incremental effect (Eq. 1)

Health-departmental perspective: incremental cost-effectiveness ratio = incremental cost/incremental effect (Eq. 2)

Cost-Utility Analysis

The major advantage of a cost-utility analysis is its ability to simultaneously incorporate changes in the quantity of life and the quality of life [using the quality-adjusted life-year (QALY)]. Since a migraine does not directly affect the patient's lifespan, it is only necessary to consider changes in the quality of life. This permits more freedom in choosing the time horizons for an analysis, and a 1-year time horizon was used.

Utilities were assigned to various health states using a multi-attribute utility instrument called the Quality of Well-Being Scale, developed by Kaplan and Anderson (table II).[31] It was preferred because it measures the social value of particular health states, as opposed to the value of those health states to individual patients. As such, the cost-utility ratios produced encapsulate considerations of distribution as well as efficiency; therefore, questions regarding the allocation of resources can be addressed (questions regarding clinical decisions for individual patients are another matter). Other reasons for using this scale are: (ii) it can be used for very short-time horizons (e.g. 1 day); (iii) the scale lists many of the symptoms associated with migraines; and (iv) it is reliable and fairly valid.[32] However, the scale has been observed to assign unexpectedly low values to trivial states of illnesses that intuition would suggest should be higher.[33] This is quite likely, but it is not problematic in our study, since migraine symptoms are not trivial.

The authors reached a consensus on the probabilities of various symptoms occurring during a migraine attack. This was based largely on epidemiological data from a study by Pryse-Phillips et al.[4]

The utility (U) at a given point in time for an individual was calculated using the following formula:

$$U = I + (CPXwt) + (MOBwt) + (PACwt) + (SACwt)$$

where CPX is the symptom/problem complex, MOB is the degree of mobility, PAC is the physical-activity scale, SAC is the social-activity scale and wt is the preference-weighted measure for each factor. The utility of complete health was defined as 1.0, and the utility of death was defined as 0. It

Table III. Calculation of the baseline utility of an 'average' migraine attack

Quality of Well-Being (QWB) category[31]	Weight (provided by QWB scale)	Prevalence of symptoms[4] (% of patients)	Weight × prevalence of symptoms
Symptom/Problem Complex (CPX)			
Sick or upset stomach, vomiting or loose bowel movement	–0.290	61	–0.177
General tiredness or weakness	–0.259	100	–0.259
Headache	–0.244	100	–0.244
Pain or discomfort in 1 or both eyes or any trouble seeing after correction	–0.230	65	–0.150
Pain in ear or any trouble hearing	–0.170	74	–0.126
Taking medication	–0.144	100	–0.144
Mobility Scale (MOB)			
Did not drive a car; did not ride in a car as usual (for age) [younger than 15 years]; did not use public transportation; or had (or would have used) more help than usual (for age) in order to use public transportation	–0.062	100	–0.062
Physical Activity Scale (PAC)			
In bed, chair, or couch for most or all of the day	–0.077	100	–0.077
Social Activity Scale (SAC)			
Performed no major role activity but did perform self-care activities	–0.061	100	–0.061
Total			**–1.30**
Utility			1 – 1.30 = –0.30

is possible for some health states to have a utility of less than 0. Table III shows the calculation of the baseline utility for an 'average' migraine attack.

The following formulae were used to calculate cost-utility ratios from a societal perspective (note that attack frequency cancels out of the equations):

incremental cost-utility ratio = (incremental cost – incremental productive output) × attack frequency/incremental QALYs

= (incremental cost – incremental productive output) x attack frequency/(incremental utility x attack frequency/365 days)

= (incremental cost – incremental productive output) x 365/incremental utility (Eq. 3)

The following formulae were used to calculate cost-utility ratios (note that attack frequency cancels out of the equations) from a health departmental perspective:

incremental cost-utility ratio = incremental cost × attack frequency/incremental QALYs

= incremental cost × attack frequency/(incremental utility × attack frequency/365 days)

= incremental cost × 365/incremental utility (Eq. 4)

The cost-utility analysis from the health-departmental perspective has been used in many studies

Table IV. Grades of recommendation for adoption of a new healthcare technology, based on cost-utility (C-U) ratios from the health-departmental perspective[34]

Description	Criteria
Compelling evidence for adoption	Less costly and as effective or more effective than existing technologies
Strong evidence for adoption	More effective than existing technologies; C-U ratio is less than $Can20 000/QALY
Moderate evidence for adoption	More effective than existing technologies; C-U ratio is $Can20 000 to $Can100 000/QALY
Weak evidence for adoption	More effective than existing technologies; C-U ratio is more than $Can100 000/QALY
Compelling evidence for rejection	More costly and as effective or less effective than existing technologies

Abbreviations: QALY = quality-adjusted life-year; $Can = Canadian dollars.

evaluating various health technologies. Because of this, it is possible to derive rough guidelines on how attractive a new technology should be for its adoption into general usage. Laupacis et al.[34] have done this by formulating 'grades of recommendation' as shown in table IV.

Cost-Benefit Analysis

In a cost-benefit analysis, the incremental benefit (expressed in monetary units) is compared with the incremental costs incurred. The net economic benefit is calculated as incremental benefits minus incremental costs. Since it is difficult to assign a monetary value to some intangible benefits (such as having less pain and so forth), the incremental benefit is taken as the incremental productive output of the average patient as a result of not being ill. This is known as the human-capital approach.[26]

The incremental productive output is calculated as the incremental amount of time in productive work, multiplied by the average earnings per day for Canadian patients with migraine.[35] The latter piece of information was obtained using Statistics Canada 1991 census data on mean age- and gender-specific earnings,[29] indexed to 1995 according to the Consumer Price Index.[30] For convenience, a 1-year time horizon was used. Only the societal perspective was taken, since it would be meaningless to take the health-departmental perspective. The following formula was used to calculate net economic benefit from the societal perspective:

Net economic benefit = incremental productive output per year – incremental cost per year

= (mean earnings per day × mean attacks per year × incremental effect) – (incremental cost × mean attacks per year)

= mean attacks per year × [(mean earnings per day × incremental effect) – incremental cost] (Eq. 5)

Sensitivity Analysis

A sensitivity analysis was carried out to test the robustness of the conclusions to variations in the assumptions made. Both simple sensitivity analysis and probabilistic sensitivity analysis were conducted.

Table V. Efficacy of oral sumatriptan and oral caffeine/ergotamine (assessed as percentage probability of conversion to mild or no headache at 2 hours) according to severity of migraine attack

Attack severity	Sumatriptan	Caffeine/ergotamine
Moderate	77.3	59.0
Severe	45.3	27.0

The simple sensitivity analysis was conducted by varying 1 input variable, while keeping the other input variables constant, and determining how much the output variables change. The following variables were independently varied over relatively wide ranges:

- drug acquisition costs
- hospitalisation and emergency department costs
- utilities
- relative effectiveness of different therapies
- average earnings
- attack frequency.

The probabilistic sensitivity analysis (Monte Carlo simulation)[36] was carried out to determine the sensitivity of the conclusions to simultaneous changes in all the input variables. 1000 simulations were executed. The distributions of the computer-generated results were then analysed using Microsoft Excel Version 5.0.

Subgroup Analysis – Severity of Attack

Work conducted by the manufacturer (personal communication, Catherine Berka, Health Economist, Glaxo-Wellcome Inc., Missassauga, Ontario, Canada, December 1995) in which attacks documented in randomised controlled trials were stratified according to whether they were moderate or severe, indicates that severity affects drug efficacy. Using the primary efficacy measure, oral sumatriptan and oral caffeine/ergotamine are each approximately twice as efficacious for moderate pain than for severe pain (table V). An economic analysis was also carried out on these subgroup data.

Table VI. Outcome values of the decision tree (outcomes are shown in figure 1) [all costs are expressed in 1995 Canadian dollars ($Can)]

Outcome	Probability (%)	Cost ($Can)	Expected cost ($Can)	Utility	Expected utility
Sumatriptan					
A	33.1	16.10	5.34	1.00	0.33
B	22.7	32.20	7.29	0.90	0.20
C	40.7	16.10	6.55	−0.30	−0.12
D	3.5	79.26	2.80	0.10	0.0035
E	0.007	1172	0.08	−0.30	−0.000021
Total	**100**		**22.06**		**0.42**
Caffeine/ergotamine					
F	26.6	1.32	0.35	1.00	0.27
G	11.3	2.64	0.30	0.90	0.10
H	57.1	1.32	0.75	−0.30	−0.17
I	5.0	64.45	3.20	0.10	0.0050
J	0.010	1157	0.11	−0.30	−0.000030
Total	**100**		**4.71**		**0.20**

Results

Base-Case Evaluation

The outcome values of the decision tree are shown in table VI. Assuming an incremental effect with the use of sumatriptan of (55.8 − 37.9%) = 17.9%, the incremental cost was $Can17.34, and the incremental utility was 0.22.

Table VII shows the incremental cost-effectiveness and cost-utility ratios, and the net economic benefit, associated with using sumatriptan in place of caffeine/ergotamine.

From the societal perspective, the use of oral sumatriptan resulted in net savings as well as improved health outcomes, as evidenced by the negative cost-effectiveness and cost-utility ratios and the positive net economic benefit.

From the health-departmental perspective, the use of oral sumatriptan resulted in net costs for improved health outcomes. The cost-effectiveness ratio was $Can98 per attack aborted, and the cost-utility ratio was $Can29 366 per QALY. This cost-utility ratio translates into a 'moderate' recommendation for adoption according to Laupacis et al.[34] (table IV).

Sensitivity Analyses

The simple sensitivity analysis (table VIII) showed that from the health-departmental perspective, the results are not sensitive to changes in the various input variables. However, from the societal perspective, the results were sensitive to large changes in relative effectiveness. A threshold analysis indicated that the net economic benefit

Table VII. Incremental cost-effectiveness and cost-utility ratios, and the net economic benefit, associated with using sumatriptan in place of caffeine/ergotamine [all costs are expressed in 1995 Canadian dollars ($Can)]

Societal perspective	
Cost-effectiveness ratio (Equation 1)	[$Can17.34 − ($Can122.52 × 17.9%)]/17.9% = −$Can25 per attack aborted
Cost-utility ratio (Equation 3)	{[$Can17.34 − ($Can122.52 × 17.9%)] × 365}/0.22 = −$Can7507 per QALY
Net economic benefit (Equation 5)	9.45 × [($Can122.52 × 17.9%) − $Can 17.34] = $Can42 per year
Provincial health department	
Cost-effectiveness ratio (Equation 2)	$Can17.34/17.9% = $Can98 per attack aborted
Cost-utility ratio (Equation 4)	($Can17.34 × 365)/0.22 = $Can29 366 per QALY

Abbreviation: QALY = quality-adjusted life-year.

Table VIII. Results of a simple sensitivity analysis [all costs are expressed in 1995 Canadian dollars ($Can)]

	Cost-effectiveness ratio ($Can per attack aborted)	Cost-utility ratio ($Can/QALY)	Net economic benefit ($Can/year)
Societal perspective			
Baseline	−25	−7 507	42
Drug prices:			
if sumatriptan costs $Can20 and caffeine/ergotamine costs $Can1.20 per dose	2	574	−3
if sumatriptan costs $Can14 and caffeine/ergotamine costs $Can1.60 per dose	−41	−12 247	68
Hospitalisation and emergency department costs:			
if these are doubled	−27	−8 236	46
if these are halved	−24	−7 143	40
Utilities:			
if utilities of 'no relief' branch are increased by 0.3	NA	−9 998	NA
if utilities of 'no relief' branch are decreased by 0.3	NA	−6 010	NA
Relative effectiveness:			
if the risk difference is at lower bound of 95% CI (9.1%)	10	4 731	−13
if the risk difference is at upper bound of 95% CI (26.8%)	−46	−11 558	97
Average daily wage:			
if increased by 20%	−49	−14 882	83
if decreased by 20%	−0.4	−133	1
Attack frequency:			
if decreased to 4 per year	NA	NA	18
if increased to 21 per year	NA	NA	93
Provincial health-departmental perspective			
Baseline	98	29 366	NA
Drug prices:			
if sumatriptan costs $Can20 and caffeine/ergotamine costs $Can1.20 per dose	124	37 447	NA
if sumatriptan costs $Can14 and caffeine/ergotamine costs $Can1.60 per dose	82	24 627	NA
Hospitalisation and emergency costs:			
if these are doubled	95	28 637	NA
if these are halved	99	29 730	NA
Utilities:			
if utilities of 'no relief' branch are increased by 0.3	NA	39 107	NA
if utilities of 'no relief' branch are decreased by 0.3	NA	23 510	NA
Relative effectiveness:			
if the risk difference is at lower bound of 95% CI (9.1%)	133	60 839	NA
if the risk difference is at upper bound of 95% CI (26.8%)	76	18 950	NA

Abbreviations: CI = confidence interval; NA = not applicable; QALY = quality-adjusted life-year.

would change from positive to negative if the risk difference was less than 11.2%.

The probabilistic sensitivity analysis (table IX) showed a small to moderate amount of dispersion in the results. There was a 74% chance of a positive net economic benefit, and there was a 73% probability of positive health benefits being achieved with net savings to society. However, there was less than a 1% probability of net savings to health departments from the use of sumatriptan rather than caffeine/ergotamine.

Figure 2 shows the distribution of outcomes in terms of the grade of recommendation (table IV) that each outcome would correspond to. Compared with oral caffeine/ergotamine, oral sumatriptan predominantly has a 'moderate' recommendation

Table IX. Results of probabilistic sensitivity analysis [all costs are expressed in 1995 Canadian dollars ($Can)]

	Societal perspective			Provincial health-departmental perspective	
	cost-effectiveness ratio	cost-utility ratio	net economic benefit	cost-effectiveness ratio	cost-utility ratio
Baseline	−25	−7 507	42	98	29 366
95% confidence interval:					
lower bound	−58	−22 020	−45	65	14 384
upper bound	35	11 686	123	123	79 567
Percentage of output with:					
+ve numerator/+ve denominator (%)	26.1	21.8	NA	99.1	94.1
+ve numerator/−ve denominator (%)	0.0	4.3	NA	0.0	5.0
−ve numerator/+ve denominator	73.9	72.8	NA	0.9	0.5
−ve numerator/−ve denominator	0.0	1.1	NA	0.0	0.4
+ve net economic benefit	NA	NA	73.9	NA	NA

Abbreviation: NA = not applicable.

for adoption. However, there is an 18% chance of a 'strong' recommendation.

Subgroup Analysis - Severity of Attack

The results of the economic calculations according to the severity of attack (using the probabilities in table V) are shown in table X. It can be seen that for oral sumatriptan, the values are somewhat better when treating severe attacks than during treatment of moderate attacks.

Discussion

From the societal perspective, oral sumatriptan resulted in a positive net economic benefit compared with oral caffeine/ergotamine. From the health-departmental perspective, improved health outcomes were achieved at 'moderately' acceptable incremental costs.

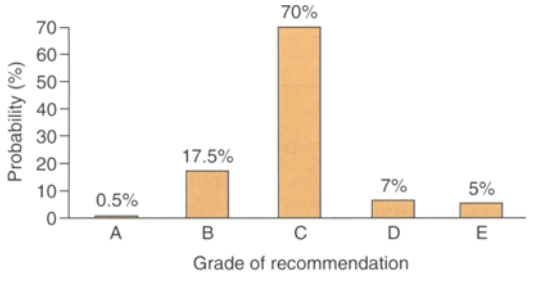

Fig. 2. Proportion of cost-utility ratios from the health-departmental perspective (derived in the probabilistic sensitivity analysis) that fall within each of the 5 grades of recommendation for adoption (see table IV for grades).

Methodology

The results of the 3 methods used for the economic evaluation are consistent with each other. Cost-effectiveness analysis yields the incremental cost for a specific outcome (i.e. relief of an attack). Cost-utility analysis measures outcomes in generic units called QALYs. Cost-benefit analysis attempts to produce a 'bottom line' monetary figure of net gain or loss to society as a result of introducing a healthcare programme.

However, these techniques do not provide much information on whether sumatriptan is affordable. A separate analysis of this question suggests that the total incremental drug cost is between $Can10 000 000 and $Can19 000 000 per million population (i.e. $Can10 to $Can19 per person), assuming sumatriptan is only used to treat moderate and severe attacks, and not mild attacks.[37] How much of this incremental cost would be paid by drug plans varies with the different coverage criteria and reimbursement policies of each plan.

Study Limitations

The purpose of this study was to inform decision-making, not to replace it. Much judgement is

still required in order to make sound decisions, and other factors that should be considered are discussed below.

Generalisability

The results of this study apply to individuals aged 18 to 65 years who experience moderate or severe migraines, with or without aura. The results are not generalisable to children, adults over 65 years of age, pregnant women, patients with mild symptoms or those who have complicated migraines, since the clinical trials excluded these types of patients. Furthermore, conclusions cannot be drawn regarding the treatment of only those who fail other treatments and are trying sumatriptan as a last resort (as is the current policy of many provincial drug plans in Canada).

Distributional Issues

The social issues of distribution are ignored in this analysis. For example, the calculations do not take into account whether benefits are received by one group while costs are borne by another. Nor is any consideration given to the fact that society may want to value certain lives over others for certain purposes, such as the poor over the wealthy. Consequently, these social decisions must be made outside the quantitative framework of the economic evaluation.[38]

Efficacy Measures

Only the primary efficacy measure was used in the decision tree. Other efficacy measures, such as pain relief at 4 hours and relief of nonpain symptoms, were not used in the decision tree. This was done to make the modelling manageable. However, the primary efficacy measure chosen is almost always the most important outcome for the patient.

Human-Capital Approach

The human-capital approach was used instead of the willingness-to-pay approach. The human-capital approach to valuing indirect costs may grossly underestimate the true cost attributable to migraine, since it ignores intangible costs such as pain, discomfort and anxiety. The willingness-to-pay approach would capture these intangible costs, as well as other indirect costs, more effectively than the human-capital approach. However, time and resources did not permit the conduct of a willingness-to-pay study.

Tolerability Issues

Tolerability differences between agents were ignored in the calculations. Since the availability and quality of data on adverse reactions is different for the 2 drugs studied, it was decided not to incorporate safety data in the quantitative analysis. However, the literature indicates that sumatriptan is probably better tolerated than caffeine/ergotamine.[39-43] Thus, any bias introduced into the analysis because of this omission was almost certainly against sumatriptan. The results are therefore more conservative because of this.

Caveats on Cost-Utility Analysis

The cost-utility analysis actually incorporated values about healthcare outcomes into the quantitative part of the analysis. This ability to assign numbers to the relative worth of very different healthcare activities is one of the attributes that makes this tool attractive for policy-making. In doing so, however, it introduces 2 potential pitfalls.[14] First, decision-makers may not fully understand the implications of the values incorporated. Second, they may not realise that other important values are not incorporated into the analysis.

Table X. Economic values according to severity of attack [all values are 1995 Canadian dollars ($Can)]

Attack severity	Societal perspective			Provincial health-departmental perspective	
	cost-effectiveness ratio (Eq. 1)	cost-utility ratio (Eq. 3)	net economic benefit (Eq. 5)	cost-effectiveness ratio (Eq. 2)	cost-utility ratio (Eq. 4)
Baseline	–25	–7505	42	98	29 366
Moderate	–19	–5651	32	104	31 191
Severe	–30	–8798	50	93	27 464

In particular, decision-makers should bear in mind that:[14] (i) the utilities are average values, not individual values, so there are potentially large numbers of individuals who will strongly disagree with the decisions, because the average values do not represent their views; (ii) since the assumption is made that the quality, as well as the duration, of life is important, less value is placed on lower quality life than on life of higher quality – individuals who strongly believe in the prolongation of life for life's sake may find themselves at odds with some of the resulting policy implications; (iii) the assumption is made that relieving very severe, but very temporary, distress is much less important than relieving more prolonged distress; and (iv) the assumption is made that for a given degree of suffering, those whose illnesses happen to be less expensive to treat will be treated in preference to those whose treatments are more expensive.

Conclusion

This economic evaluation shows that incremental health benefits are obtained from using oral sumatriptan rather than oral caffeine/ergotamine, and these benefits are achieved at *moderately* acceptable incremental costs to third party payers, if past decisions on the adoption of other health technologies into general usage are used as a guide. When society as a whole is considered, rather than just the third party payer perspective, the health benefits also result in a net reduction of overall costs to society.

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