REVIEW ARTICLE

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Treatment Costs to Prevent or Treat Upper Gastrointestinal Adverse Events Associated with NSAIDs

A Review

Elham Rahme,[1] *Alan N. Barkun*,[2] *Viviane Adam*[3] and *Marc Bardou*[4]

1 Department of Medicine, McGill University and Research Institute, McGill University Health Center, Montreal, Quebec, Canada
2 Department of Medicine, Division of Gastroenterology, McGill University and the McGill University Health Center, Montreal, Quebec, Canada
3 Research Institute, McGill University Health Center, Montreal, Quebec, Canada
4 Department of Medicine, Clinical Pharmacology Unit, Faculty of Medicine, Dijon, France

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Abstract

The widespread use of nonselective NSAIDs and cyclo-oxygenase (COX)-2 inhibitors has a substantial impact on healthcare budgets worldwide. The cost of their gastrointestinal (GI) adverse effects is a major component of their direct cost and has received much attention in the literature. Published studies have often differed in their methodologies and results. It is important for decision makers to understand the reasons for these differences in order to make informed decisions.

We conducted a literature review to summarise data that evaluate the direct costs of NSAID-related GI adverse effects worldwide. This resulted in 789

articles from which 29 studies met the inclusion criteria and were fully reviewed. Of these 29, the 9 studies that assessed the cost of COX-2 inhibitors were all based on decision economic models, compared with only 7 of the remaining 20 studies, which assessed the cost of nonselective NSAIDs. In most studies, the perspective was that of the healthcare payer and the costs assessed were reimbursement costs. Costs of GI events almost doubled between regular users and non-users of nonselective NSAIDs and were much higher in high-dose versus low-dose users. The ratio of the total cost of nonselective NSAIDs to their acquisition cost reported in all studies varied from 1.36 to 2.12. Both of these numbers were reported in one single study assessing several different NSAIDs in France. Thus, the GI adverse events attributable to nonselective NSAIDs are substantial, and their costs often exceed the cost of the nonselective NSAID itself.

The acquisition cost of the COX-2 inhibitors was the main driver of their total cost. The GI adverse effects with the COX-2 inhibitors added 10–20% to their acquisition cost in North America, while this increase was about 50% in some European countries. Decision analysis models showed that the direct costs of COX-2 inhibitors were lower than those of nonselective NSAIDs in patients at risk of NSAID gastropathy but higher in patients at no to low risk of gastropathy. Thus, from an economic perspective, the healthcare system would benefit from treating patients at risk of NSAID gastropathy with COX-2 inhibitors, but not those at no to low risk.

1. Background

NSAIDs are widely used in the treatment of several acute and chronic disorders including arthritis and pain,[1] and aspirin (acetylsalicylic acid) is increasingly being used for the prophylaxis of vascular events. NSAIDs are classified into two groups: (i) the conventional NSAIDs, also known as the nonselective NSAIDs; and (ii) the newer selective NSAIDs known as the cyclo-oxygenase (COX)-2 inhibitors. In this review, unless otherwise stated, 'NSAIDs' refers to non-aspirin nonselective NSAIDs. Because of their widespread use and their substantial impact on healthcare budgets worldwide, several authors have studied the costs of NSAIDs and COX-2 inhibitors. Often, published studies have differed in their methodologies and results. It is important for decision makers to understand the reasons for these differences in order to make informed decisions. The purpose of this review is to summarise studies that have evaluated the direct costs of NSAIDs and COX-2 inhibitors and highlight the possible sources that led to differences in their results.

1.1 Gastrointestinal (GI) Adverse Effects of NSAIDs

NSAIDs inhibit two isoforms of cyclo-oxygenase: COX-1 and COX-2. COX-1, the constitutive form of COX, generates prostaglandins believed to be involved in gastrointestinal (GI) mucosal protection, while COX-2 is induced at sites of inflammation and generates prostaglandins that mediate inflammation and pain.[2-5] The inhibition of COX-1 is believed to be primarily responsible for NSAID-induced GI adverse events.[6] GI adverse events are the most frequent complication of any drug therapy and occur mostly in the upper GI tract.[7] These events can be minor, such as dyspepsia and abdominal discomfort, or very serious, such as perforation, ulcer or bleeding (PUB).[1,8-10] Other, rarer, types of GI adverse effects related to NSAIDs exist, such as intestinal diaphragms and NSAID colitis, but these will not be discussed in this review.[11] A PUB often requires hospitalisation and can be fatal in some patients. Therefore, co-prescription with a gastroprotective agent (GPA) is recommended in patients at high risk for NSAID gastropathy including the elderly (aged ≥60 years), those with a history of peptic ulcer or GI bleeding,

those with co-morbid conditions such as cardiac and renal dysfunction and those taking corticosteroids or anticoagulants.[12] Dyspepsia and abdominal pain resulting from NSAIDs are not life threatening but are often responsible for decreased patient comfort and a subsequent lack of compliance with treatment. They are a common reason for co-treatment with a GPA. The GPAs that have been used to heal or prevent an ulcer or to suppress abdominal pain and dyspepsia are misoprostol, histamine H_2 receptor antagonists, sucralfate and proton pump inhibitors (PPIs).[13-19]

1.2 The Cyclo-Oxygenase (COX)-2 Inhibitors

The COX-2 inhibitors specifically inhibit COX-2 but have little effect on COX-1,[20-23] although this selectivity varies between agents. Rofecoxib and celecoxib are two COX-2 inhibitors that are widely used worldwide. Clinical trials have demonstrated that COX-2 inhibitors have the same efficacy as the nonselective NSAIDs and an improved GI safety profile.[24,25] It has been shown that among patients with a recent history of ulcer bleeding, treatment with COX-2 inhibitors might be as effective as treatment with nonselective NSAIDs in combination with a PPI with respect to the prevention of recurrent bleeding.[26] Observational studies using administrative databases have also demonstrated that the COX-2 inhibitors have fewer GI adverse effects than conventional NSAIDs.[2,20,25,27-30] Recently, the GI safety of celecoxib has been challenged and the conduct and results of the CLASS (Celecoxib Long-term Arthritis Safety Study) that compared celecoxib with ibuprofen and diclofenac were criticised.[31]

1.3 Gastroprotective Agent Co-Prescription with the COX-2 Inhibitors

After the introduction of the COX-2 inhibitors, a reduction in GPA utilisation resulting from a decrease in prophylaxis against NSAID gastropathy was expected but not observed, perhaps because some physicians remain cautious about the GI safety of these agents. Ironically, an increase in GPA prescriptions was reported in the US and elsewhere[32] after the introduction of the COX-2 inhibitors, although some of the GPA use is for indications not associated with NSAIDs or COX-2 inhibitors.

Some studies have observed a higher occurrence of cardiovascular events with COX-2 inhibitors compared with nonselective NSAIDs.[25,33] Unlike nonselective NSAIDs, COX-2 inhibitors are believed to have no effect on platelet function.[34] Therefore, patients in need of antiplatelet therapy and prescribed a COX-2 inhibitor are advised to take aspirin at an antithrombotic dose as well.[25] However, the CLASS study demonstrated that patients taking celecoxib and aspirin had the same GI adverse event rate as patients taking nonselective NSAIDs; therefore, prophylaxis against gastropathy is advised in these patients.

Among the nonselective NSAIDs some, such as meloxicam, have an *in vitro* COX-2/COX-1 selectivity that is intermediate between that of conventional NSAIDs and the COX-2 inhibitors.[35] These agents are less widely used.[36,37]

1.4 Costs and Iatrogenic Cost Factors

The elderly are in general the highest consumer group of drugs including NSAIDs, COX-2 inhibitors and GPAs.[38] The cost of gastropathy with these drugs has therefore been best characterised in this population. Several authors have evaluated the additional costs associated with NSAID use to prevent or treat GI events. The cost of COX-2 inhibitor utilisation has not yet been adequately addressed because of the relatively short time that they have been available.

The acquisition costs of COX-2 inhibitors are much higher than that of most NSAIDs. If costs were not an issue, all elderly patients would receive COX-2 inhibitors and/or co-therapy of NSAIDs with PPIs as these agents represent the most effective and safest alternatives for the gut. Unfortunately, because of limited budgets, systematic, non-differential prescription of costly therapies is only affordable at the expense of other health benefits. Economic assessments of the impact of therapies are needed to help determine management strategies. To compare two equally efficacious therapies, the overall costs must be determined. These include the direct, indirect and intangible costs. Direct costs include the acquisition cost of the drug and the costs directly associated with the detection, treatment and prevention of its adverse events. The direct cost has been termed the shadow price.[39] Unless otherwise

stated, in this paper acquisition costs include the dispensing costs. Indirect costs include productivity losses attributable to drug adverse events. The burden of the drug on patients and their relatives or friends in terms of loss of quality of life because of adverse events represents the intangible cost. Both indirect and intangible costs are difficult to assess and are seldom included in cost-assessment studies.

In the cost assessment of NSAIDs and COX-2 inhibitors, authors have concentrated on direct costs. Given that the GI events are the most frequent and important adverse events attributable to NSAIDs, the costs of other adverse events have often been ignored. Therefore, in this review, unless otherwise stated, the direct cost or shadow price of NSAIDs will refer to their acquisition costs plus the costs of primary care, specialist visits, hospitalisations, diagnostic tests and GPA utilisation to prevent or treat associated GI adverse events. Iatrogenic cost factors (ICFs) are reported in some studies. The ICF of a drug is the ratio of its shadow price to its direct acquisition cost.[39] An ICF of 1.5, for example, means that for every $1 (or any other country-specific currency) spent on the drug an additional $0.50 will be spent to prevent or treat its adverse events. It is a simple measure that is useful when comparing costs of adverse events across different health insurance systems. However, the ICF can be misleading when comparing drugs with different acquisition costs. If two drugs from the same class administered to similar populations resulted in the same cost of adverse events, then the drug with a lower acquisition cost would have a higher ICF.

The direct costs of NSAIDs or COX-2 inhibitors depend on the perspective adopted (who the payer is – patient, society, or healthcare payer [third-party payer]) and differ according to population age and illness, healthcare policies and costs of services. As GI events can occur independently of NSAID use, it is often difficult to separate those GI events that are caused by NSAIDs from those that are not. Therefore, in assessing the direct costs of NSAIDs or COX-2 inhibitors it is important to have a control group in which the baseline costs of GI events can be estimated.

2. Objective

We conducted a literature review to summarise data that evaluated the direct costs of NSAID-related GI adverse effects worldwide, to highlight the possible sources of variability in the results and to identify knowledge gaps in the literature.

3. Methods

3.1 Literature Search

NSAIDs are associated with a number of GI adverse events, the best characterised of which are the upper GI mucosal disorders.[12] These events have been referred to as NSAID gastroduodenopathy, PUB, gastropathy and, more recently, clinical upper GI events.[12] We searched MEDLINE for articles published in the English language using the MeSH terms: 'cost and NSAID', 'cost nonsteroidal and anti-inflammatory drugs' and 'cost and nonsteroidal anti-inflammatory drugs'. Abstracts were reviewed when available and full articles were obtained when the abstract discussed the problem of interest or when an abstract was not available for review.

3.1.1 Inclusion Criteria

Since the focus of the review was the costs of upper GI adverse events of NSAIDs, we excluded economic evaluations of arthritis or other illnesses that required NSAID or COX-2 inhibitor use and where the cost of GI events could not be specifically extracted. We also restricted our search to studies published during or after 1990 because the management of GI adverse events with NSAIDs has changed over the years, with prophylaxis being increasingly prescribed and the PPIs, a major class of GPAs, for the most part, were launched in the early 1990s. Review articles were not included.

3.1.2 Outcome Measures

We included studies that assessed the costs of some or all of the following events: primary care and specialist visits for upper GI mucosal disorders, hospitalisations for PUB, upper GI diagnostic tests and GPA utilisation to prevent or treat upper GI mucosal disorders in patients taking NSAIDs or COX-2 inhibitors. Because GI events are referred to using many different terminologies, and because

there was no standardisation of terminology across the different articles, we quote the GI events as they are given in the study.

3.1.3 Costs

Study results are divided into two sections, separating those that studied NSAIDs either before or during the COX-2 inhibitor era but with no mention of the COX-2 inhibitors, and those trials that studied COX-2 inhibitors. The costs are presented by country, and the studies that used decision analytic models with hypothetical cohorts were grouped in a separate section. The main methodological characteristics of a given study that could have affected estimates of the direct costs are highlighted in order to understand possible between-study differences in results. Management of patients differs according to healthcare policies, in which drug use can be dictated by specific rules. For example, in the Canadian province of Ontario, prescriptions of COX-2 inhibitors are only reimbursed for patients who do not respond to or are intolerant of NSAIDs; in contrast, in the neighbouring province of Quebec, no such restrictions exist. The costs of resources used also differ greatly between countries and sometimes within the same country according to healthcare policies. For example, the cost of an endoscopy was estimated at $US1000 in the US in 1998[40] while the cost of an endoscopy with biopsy in Canada approximates $Can130[41] (1998 values: $US1 = $Can1.48).[42]

The guidelines published in 1996 by the American College of Rheumatology recommended the use of prophylaxis with NSAIDs in patients at high risk of NSAID gastropathy.[43-45] At least in theory, an increase in the use of prophylaxis was expected to have followed the publication of these guidelines. The guidelines aimed to decrease NSAID-induced gastropathy and consequently the application of these guidelines may have decreased physician visits and hospitalisations for GI events. Moreover, more effective drugs with higher acquisition costs are now increasingly used to prevent and heal NSAID-induced ulcers. Therefore, management of patients in need of NSAIDs or those with NSAID gastropathy has changed over the years and costs calculated in the early 1990s cannot simply be projected to the late 1990s by only considering inflation. Nonetheless, to allow for some level of comparison over time and across countries, country-specific costs have been converted, in this review, to US dollars of the same year using the foreign exchange rates published by the Bank of Canada.[42] Costs were then expressed into 2002 equivalents by accounting for the inflation rate published by the US Department of Labor, Bureau of Labor statistics.[46] Because some studies conducted in Europe published their results in US dollars using the foreign exchange rates, we chose to use the foreign exchange rates and not the purchasing power parity to convert costs to US dollars to facilitate comparability.

3.2 Assessment

In this article, we report the type of NSAID or COX-2 inhibitor studied; the perspective; the country in which the study was conducted; the reimbursement policy; the year of the study; the main characteristics of the population (age, condition for which treatment was prescribed [e.g. all conditions, osteoarthritis and/or rheumatoid arthritis] and number of patients included); the GI adverse effects considered (hospitalisations, visits, drugs); the type of GPA used (H_2 antagonists, misoprostol, PPIs); the source of data (administrative database, clinical trials, literature); the methodology used; and the results. We comment on the assumptions used in the study when they were likely to have contributed to differences between study results.

4. Results

The MEDLINE search resulted in 789 articles whose abstracts, when available, were reviewed. Of these, 29 studies met the inclusion criteria and were fully reviewed.

4.1 Direct Costs of Upper GI Adverse Events of NSAIDs

4.1.1 US and Canada

US

Johnson et al.[47] estimated the occurrence and costs of GI adverse events associated with NSAIDs in a cohort of patients aged 65 years or older enrolled in a health maintenance organisation (HMO)

in 1992 (table I). All costs were calculated from the HMO perspective and were provided in 1992 US dollar values. The costs of medications included acquisition and dispensing costs to the HMO. The most commonly used NSAID was ibuprofen. Rates and costs of treating a gastropathy episode were calculated from an existing database that had abstracted records of HMO members in 1987. These data were extrapolated to the cohort of 1992 by using an inflation factor of 1.45 for outpatient services and procedure costs and 1.52 for drug costs. Cost estimates were based on data from 11 members of the 1987 cohort who met the criteria for having a gastropathy not more than 14 days after the last day of NSAID supply. The total direct costs included the acquisition and dispensing costs of NSAIDs and anti-ulcer drugs for the entire cohort plus the outpatient, inpatient and anti-ulcer drug costs attributable to patients with a possible gastropathy. Four types of gastropathy were found: stomach or duodenal ulcer with no perforation or haemorrhage, peptic ulcer or upper GI bleeding with no mention of site. The average direct cost of treating an NSAID-associated GI episode was $US2172. About 14 000 patients were included in the study (exact number not provided). The acquisition and dispensing cost of NSAIDs amounted to $US679 636. The total GPA and outpatient and inpatient costs to treat NSAID-related gastropathies was $US612 781 and the total non-gastropathy-related anti-ulcer drug cost was $US444 124.

The author calculated the ICF to be 1.35. The ICF in this paper was derived from the ratio [cost of gastropathy]/[total cost] = 612 781/1 736 541 = 0.35. The author concluded that for each dollar spent on the direct costs of NSAIDs the HMO spent $0.35 on the 'indirect' costs of NSAID-associated gastropathy. We should note that the definitions of ICF and 'indirect' cost used by Johnson et al.[47] differ from those provided by De Pouvourville[39] and adopted in this review (ICF = shadow price/acquisition cost = 1 736 541/679 636 = 2.55, or 1.90 if we ignore the costs of GPA not related to gastropathy) and should be interpreted accordingly. The calculation provided by Johnson et al.[47] means that if the HMO spends a total of $US1 on the direct cost of NSAIDs (acquisition + cost of GI events), 35% of this dollar would have been spent to treat the NSAID-related gastropathy, while the remaining $0.65 would have been spent on acquisition and dispensing costs of the NSAIDs and GPAs not related to the NSAID gastropathies (although some of this may perhaps be related to prophylaxis and dyspepsia).

Simon et al.[48] used a national claims database to compare the costs of inpatient and outpatient services for GI events from a healthcare payer perspective in patients with arthritis who used etodolac, nabumetone or oxaprozin between 1992 and 1994. They divided the GI events into NSAID-related and possibly NSAID-related and compared the median costs between the three drugs ([median cost of treating the event × number of patients with events]/total number of patients). The costs were adjusted to 1994 US dollar values using the inflation rates of 5.9% and 4.8% for 1993 and 1994, respectively. The median per-patient costs of NSAID-related (and possibly NSAID-related) events during the 9-month follow-up in the etodolac, nabumetone and oxaprozin groups were as follows: acquisition costs of $US122.00, $US161.85 and $US141.00, respectively; NSAID-related inpatient admission costs for ulcers of $US18.90, $US6.42 and $US6.84, respectively; and possible NSAID-related inpatient admission costs for ulcers of $US30.35, $US34.00 and $US28.24, respectively. These costs were based on small numbers of NSAID-induced and possible NSAID-induced claims (two and seven claims, respectively, in 1597 etodolac recipients; 7 and 21 claims, respectively, in 2200 nabumetone recipients; and one and four claims, respectively, in 734 oxaprozin recipients). The number of claims for outpatient services for upper GI bleeding was found to be similar between the three groups (0.08, 0.09 and 0.11 claims/patient in etodolac, nabumetone and oxaprozin recipients, respectively). The costs of outpatient services for GI events and the costs of GPAs were not provided separately. The authors assumed that the patients did not use etodolac, nabumetone and oxaprozin prior to the start of the study and that patients stayed with their insurance programme during the 9-month follow-up; however, this was a dynamic population and the number of privately insured individuals covered by the database varied from 2.8 million in 1992 to 4.2 million in 1994.

Table I. Population-based studies (costs were converted to 2002 US dollar values of the same year using foreign exchange rates and accounting for the inflation rate[42,46])

Study (location)	Year of costing	Study characteristics: treatment, perspective, population, healthcare utilisation and cost of services assessed	Direct costs (acquisition + dispensing + adverse events) [2002 $US]
Johnson et al.[47] (US)	1992	Direct cost of NSAIDs (ibu most common) from a payer (HMO) perspective in seniors[a] enrolled in 1992. Adverse events included GPA utilisation and outpatient and inpatient services to treat a gastropathy. Ignores costs of outpatient visits for dyspepsia	Costs for approximately 14 000 patients: Acquisition: 870 884 Non-gastropathy-related GPAs: 569 099 NSAID-related gastropathy: 785 216 Total: 2 225 199
Simon et al.[48] (US)	1994	Direct cost of eto, nab, oxa from a payer perspective in patients with arthritis in 1992–1994. Outpatient costs included those of musculoskeletal and other disorders. Only acquisition and inpatient costs for NSAID-induced and possibly NSAID-induced ulcers are reported in the review	Median costs per patient in 9-month follow-up: Acquisition: 148 (eto); 197 (nab); 171 (oxa) NSAID-related admissions for ulcers: 23 (eto); 7 (nab); 8 (oxa) Possibly NSAID-related admissions for ulcers: 36 (eto); 41 (nab); 34 (oxa)
Smalley et al.[49] (US)	1989	Direct cost of NSAIDs from a payer (Medicaid) perspective in seniors[a] enrolled in 1988–1989. Adverse events included GPA use (ome and mis not reimbursed then), outpatient upper and lower GI tract examinations and hospitalisations/emergency department visits for gastritis/duodenitis and PUB	Mean costs of GI events per year based on NSAID use: 194 (non-users); 261 (occasional users); 354 (regular users) Cost by prescribed dose in regular users of NSAIDs: 275 (low dose); 368 (medium dose); 422 (high dose)
Kephart et al.[50] (Canada)	1994	Direct cost of aspirin and non-aspirin NSAIDs from the payer perspective in seniors[a] in Nova Scotia in 1993–1994. Assessed only the reimbursement cost of medications	Reimbursement per year for 29 342 patients: NSAIDs and aspirin: 2 292 777 GPAs: 584 863
Rahme et al.[51,52] (Canada)	1997	Direct cost of NSAIDs from a payer perspective in seniors[a] in Quebec in 1993–1997. Adverse events included GPA utilisation, upper GI investigations (visits, procedures) and hospitalisation for PUB. Control group (patients receiving paracetamol)[51] Self control (patients during non-exposure)[52]	Cost/patient-day on NSAID: Acquisition: 1.03 NSAID-related GI events: 0.68[51] ICF: 1.66[51] NSAID-related GI events: 0.76[52] ICF: 1.73[52]
Rahme et al.[53] (Canada)	1997	Direct cost of a fixed combination of dicl/mis vs other NSAIDs from a payer perspective in seniors[a] in Quebec in 1993–1997. Adverse events included GPA utilisation, upper GI investigations (visits, procedures) and hospitalisation for PUB	The ratio of the adjusted costs of the dicl/mis group to that of the NSAID group was 1.15 (95% CI 0.89, 1.48). Costs were adjusted for patient characteristics at baseline

Continued next page

Table I. Contd

Study (location)	Year of costing	Study characteristics: treatment, perspective, population, healthcare utilisation and cost of services assessed	Direct costs (acquisition + dispensing + adverse events) [2002 $US]
Chevat et al.[54] (Europe)	1998	Direct costs of NSAIDs from a payer and society perspective (we report payer perspective only) in patients with arthritis in Europe and Australia in 1998. Adverse events included GPA utilisation, upper GI investigations and hospitalisation for PUB	Costs varied substantially between countries because of differences in unitary costs and divergence in expert opinion. Range of costs per event: GI discomfort: 52 (The Netherlands) to 750 (Finland) Anaemia: 159 (France) to 840 (UK) Ulcer treatment: 253 (France) to 877 (Finland) Hospitalisation: 1971 (Switzerland) to 7422 (The Netherlands)
De Pouvourville[39] (Europe)	1990	Direct cost of NSAIDs from a payer perspective (Assurance-Maladie) in France in 1990. Adverse events included GPA utilisation, upper GI investigations and hospitalisation for PUB	Mean cost per 6-months' treatment: Acquisition: 176 (nap); 159 (sul); 104 (dicl); 132 (pir); 138 (ket); 119 (eto) Total: 239 (nap); 234 (sul); 171 (dicl); 220 (pir); 274 (ket); 254 (eto) ICF: 1.36 (nap); 1.48 (sul); 1.65 (dicl); 1.67 (pir); 2.00 (ket): 2.12 (eto)
Sturkenboom et al.[55] (Europe)	1998	Direct cost of NSAIDs from a payer perspective (national health organisation) in patients aged <90 years in Italy in 1998. Adverse events included GPA use, hospitalisation for PUB and outpatient diagnostic procedures	Total cost for 12 459 713 person-days of NSAID exposure: Acquisition cost: 6 105 617 (0.49/patient-exposed day) NSAID-related GI events: 3 548 704 (0.28/patient-exposed day) ICF: 1.58
Jönsson and Haglund[56] (Europe)	1997	Cost of NSAIDs from a societal perspective in Sweden in 1997. Two approaches considered: top-down and bottom-up	Total costs per year for about 200 000 NSAID users, 60 000 of them experiencing GI adverse events: Bottom-up: 47 million (90% were direct costs) Top-down: 48–86 million (76–83% were direct costs)
Vargas et al.[57] (Europe)	1998	Costs of NSAID-related hospitalisations for PUB from a payer perspective (hospital) in Spain in 1998	36% of all patients with GI bleeding were previously exposed to NSAIDs. Cost per patient with GI bleeding: 3207
Herings and Klungel[58] (Europe)	1998	Direct costs of NSAIDs from a payer perspective in The Netherlands in 1989–1998. Adverse events included GPA use and hospitalisation for PUB	Number of NSAID person-days in 1998: 140 million. Acquisition cost: 82 million GPA and hospitalisation cost: 55 million ICF: 1.74

a Seniors: age ≥65 years.

dicl = diclofenac; **eto** = etodolac; **GI** = gastrointestinal; **GPA** = gastroprotective agent; **HMO** = health maintenance organisation; **ibu** = ibuprofen; **ICF** = iatrogenic cost factor; **ket** = ketoprofen; **mis** = misoprostol; **nab** = nabumetone; **nap** = naproxen; **ome** = omeprazole; **oxa** = oxaprozin; **pir** = piroxicam; **PUB** = perforation, ulcer or bleeding; **sul** = sulindac.

Smalley et al.[49] conducted a retrospective cohort study using Tennessee Medicaid data of 1988–1989 to quantify medical care costs for the diagnosis and treatment of GI disorders attributable to the use of NSAIDs in patients ≥65 years from the Medicaid perspective. Patients in the cohort were classified according to their 1988 total number of days of NSAID use expressed as a percentage of total number of days in a year: non-users (no use), occasional users (<75%) or regular users (≥75%). Costs of GI disorders that occurred in these patients in 1989 were calculated. Non-users who received an NSAID in 1989 were censored at that date. The study accounted for hospitalisations/emergency department visits for peptic ulcers, gastritis/duodenitis and GI bleeding; outpatient upper and lower GI tract radiological and endoscopic examinations; and H_2 antagonist, sucralfate, and antacid prescriptions (omeprazole and misoprostol were not reimbursed at the time of the study). Costs were expressed in 1989 US dollar values. Among non-users of NSAIDs, the adjusted mean annual payment for all types of medical care for GI disorders was $US134. This increased to $US180 among occasional users and to $US244 among regular users. Doses of all NSAIDs received were standardised and costs were compared among those patients who received <1, 1–2 and >2 standard units per day. Among regular NSAID users, excess payments (costs in the group minus costs in the non-NSAID group) increased with baseline NSAID dose from $US56 in those receiving <1 standard unit per day to $US120 for those receiving 1–2 standard units per day and reached $US157 in patients receiving >2 standard units per day. The acquisition costs of NSAIDs were not provided. This study estimated the costs of gastropathy that occurred during 1989 for patients who received NSAIDs in 1988. GI events that occurred in 1988 following NSAID use were ignored, which may have led to an underestimation of the costs.

Canada

Kephart et al.[50] studied the co-prescription rate and costs of GPAs (misoprostol, sucralfate, H_2 antagonists and omeprazole) with NSAIDs in Nova Scotia's senior population (age ≥65 years) in 1993–1994 using data from the Nova Scotia Seniors Pharmacare programme database. The author considered aspirin (prescribed for its anti-inflammatory properties, i.e. excluding 325mg tablets) among the NSAIDs. Co-prescription was determined based on overlapping prescription periods for NSAIDs and GPAs. Aspirin accounted for 25.2% of the total days' supply of NSAIDs followed by diclofenac (18.8%) and naproxen (12.9%). Overall, 17.1% of the total days' supply of NSAIDs was co-prescribed with a GPA. H_2 antagonists accounted for most of the co-prescribed days' supply (83.6%) followed by sucralfate (8.1%), misoprostol (4.5%) and omeprazole (2.3%). Costs were expressed in 1994 Canadian dollar values ($US1 = $Can1.37).[42] Costs were calculated from the healthcare payer perspective and excluded patient co-payments. The total reimbursed cost for 29 342 NSAID users between April 1993 and March 1994 was $Can2 589 341 for aspirin and NSAIDs and $Can660 513 for GPAs. This study included only the costs of medications and found that the cytoprotective and anti-ulcer drugs co-prescribed with NSAIDs accounted for 25.5% of the total expenditure for NSAIDs.

Rahme et al.[51] assessed the direct cost and ICF of NSAIDs in comparison with paracetamol (acetaminophen), which was considered to be devoid of any GI toxicity of its own, using data from the Quebec Health Insurance Agency (RAMQ) in patients aged ≥65 years during 1993–1997. Unlike the situation in Nova Scotia, in Quebec, aspirin is rarely prescribed at dosages higher than 325 mg/day and aspirin use was not considered with NSAIDs in this study. A fixed combination of diclofenac/misoprostol was considered among the NSAIDs. Costs were calculated from a single-payer perspective and were expressed in 1997 Canadian dollar values ($US1 = $Can1.39).[42] The costs included those of GPA use, upper GI investigations, visits to gastroenterologists and GI hospitalisations. Outpatient costs were reimbursement by RAMQ. The hospitalisation per-day cost was estimated at $Can500 in a regular ward and $Can1000 in the intensive care unit. Patients with prior GI events, cancer or concomitant anticoagulant or corticosteroid therapy were excluded from the study. To estimate the cost of NSAID-related GI adverse events, costs during NSAID therapy were compared with those during paracetamol therapy. It was found that the average daily direct cost of GI events attributed to NSAID therapy was

$Can0.84. The average daily acquisition cost of NSAIDs reimbursed by RAMQ in those years was $Can1.28. Recent controversial studies have associated paracetamol with an increased incidence of dyspepsia[59,60] and in one trial with serious GI events.[61] Therefore, the baseline cost of GI events is likely to have been overestimated as a result of adding some of the cost of dyspepsia caused by high doses of paracetamol. Thus, the costs of NSAID-related GI events (cost of gastropathy in the NSAID group minus baseline cost of gastropathy) and the ICF of NSAIDs are likely to have been underestimated. Moreover, patients with prior GI events and concomitant anticoagulant therapy were excluded from the study. Indeed, GI events are known to be much more severe in this important risk group and prescription of NSAIDs is therefore usually contraindicated in patients receiving anticoagulant therapy.

In another study using the same data, Rahme et al.[52] considered each patient as his/her own control and compared the costs of GI events that occurred while the patient was receiving NSAID therapy with those that occurred while he/she was not. Again, the study excluded patients with prior known GI risk factors. The average direct costs of GI adverse events per patient-day while receiving NSAIDs were 3.5 times higher than those attributable per patient-day while not receiving NSAIDs. The direct cost of GI adverse events per patient-day while receiving NSAIDs was $Can1.34, of which >70% ($Can0.94) was attributed to GI events resulting from NSAID treatment. The ICF was 1.73. This is perhaps also an underestimation since some of the GI events that occurred during the days when the patients did not have an NSAID prescription could reflect a carryover from a GI event that started during NSAID therapy.

In a third study, Rahme et al.[53] found that the occurrence and costs of GI adverse events with a fixed combination of diclofenac/misoprostol were similar to those with other NSAIDs.

4.1.2 Europe

Chevat et al.[54] assessed the direct costs of treating GI events associated with the use of NSAIDs in patients with arthritis over a 6-month period across 11 countries (Australia, Belgium, Finland, France, Germany, Italy, The Netherlands, Spain, Sweden, Switzerland and the UK) in 1999. Estimates of average GI-related resource utilisation were based on the results of questionnaires filled in by general practitioners and specialists from each of these countries and were compared with results from the published literature for further validation. Resources considered included inpatient and outpatient medical visits and procedures and outpatient medications. Resource utilisation was converted into costs considering individual country requirements, national guidelines and the availability of cost information. The costs were calculated from the society and/or third-party payer perspective. Only the cost from the third-party payer perspective will be reported in this review. Reimbursement rules were applied to tariffs removing patient co-payments and costs were expressed in 1998 US dollar values. Resource utilisation varied significantly across countries for all types of events considered (GI discomfort, ulcer, anaemia and hospitalisations); the total costs per event also varied by country. France, Germany, The Netherlands and Belgium had the lowest total per-event costs for all events except hospitalisation. The total per-event costs varied from $US47 in The Netherlands to $US680 in Finland for GI discomfort, from $US144 in France to $US762 in the UK for anaemia, from $US229 in France to $US795 in Finland for ulcer treatment, and from $US1787 in Switzerland to $US6729 in The Netherlands for hospitalisations. The total overall or per-patient costs of GI events were not provided but can be derived by multiplying the average resource utilisation by the total number of NSAID users and by the cost per event. We did not do this exercise because of the large number of countries included and because costs and rates were not all explicitly provided: only graphs were displayed. The main conclusion from this study was that the treatment and costs of resource utilisation differ substantially across countries. While most of this difference could be because of the between-country variability attributable to specific healthcare policies and pricing, some of it is perhaps a result of the methodology used in assessing the management of GI diseases. This was based on administrative databases in Italy where only outpatient and medication data were available and on administrative

databases in The Netherlands for both medication and inpatient data; in other countries it was based on expert opinions collected through interviews of various types (face-to-face, expert panel interviews or mailings). A sensitivity analysis was unfortunately not performed to assess the robustness of the results.

France

De Pouvourville[39] used data collected in a clinical trial as well as approximations from national databases to estimate the ICF for various NSAIDs in the French population. Direct costs of NSAIDs were calculated from a healthcare provider perspective. Costs were expressed in 1990 French franc (FF) values [$US1 = FF5.45).[42] The prevalence rate of ulcers reported by the clinical trial was discounted by 40% to account for non-symptomatic ulcers; the prevalence rate of ulcers in the general population was then subtracted to estimate the prevalence of ulcers resulting from NSAID use. When several epidemiological estimates of the rate of GI adverse events were available the conservative estimate was chosen. The cost of medication was that reimbursed by the public health insurance agency (Assurance-Maladie) in 1990, which amounted to 70% of the retail price. Diclofenac was the least expensive NSAID, with a reimbursed daily therapy price of FF2.29, and naproxen was the most expensive, with a reimbursed daily therapy price of FF3.87. The selected GPA medication for healing gastroduodenal ulcers was the least expensive H_2 antagonist in the class (in this case, ranitidine 300 mg/day). The cost of GI hospitalisations was obtained through audits at two hospitals. For patients with ulcers, it was assumed that the ulcer would occur halfway through NSAID therapy and that the patient would have an NSAID cost equivalent to 3 additional months added to the cost of treating the ulcer to calculate shadow pricing. The shadow price per patient for 6 months of therapy was lowest for diclofenac (FF678.87) and highest for ketoprofen (FF1087.61). The ICFs were estimated at 1.36 for naproxen, 1.48 for sulindac, 1.65 for diclofenac, 1.67 for piroxicam, 2.00 for ketoprofen and 2.12 for etodolac.

Italy

Sturkenboom et al.[55] conducted a retrospective cohort study in Italy to estimate the direct costs of GI toxicity (GPA use, hospitalisation for PUB and outpatient diagnostic procedures) in patients aged <90 years treated with NSAIDs and registered with the National Health Service (NHS) between 1 August 1996 and 31 July 1998. Costs were calculated from the NHS perspective and were expressed in 1998 euro values (rate provided in the study: $US1 = €1). Outpatient procedures (gastric endoscopies and breath tests) were registered in the database if reimbursed by the NHS (private, non-reimbursed procedures were excluded). NSAIDs were reimbursed only for patients with rheumatoid arthritis, osteoarthritis, gout, selected arthropathies and neoplastic pain, while GPAs were reimbursed only for patients with gastritis, ulcers, Zollinger-Ellison syndrome or reflux esophagitis (with misoprostol also reimbursed for prevention of GI bleeding in patients receiving long-term NSAID therapy). Costs were said to be directly attributable to NSAIDs when an event occurred during a risk window that consisted of the treatment period plus a carryover effect that varied with the type of prescription. Costs were indirectly attributable to NSAIDs if they occurred outside the risk window but followed an attributable event. To obtain baseline-reimbursed GI event costs, the costs generated by GI-related hospitalisations and prescriptions of GPAs for a period of time spanning 4–6 months before study entry were estimated in all patients who had not used NSAIDs for at least 9 months prior to enrolment. The total number of days of NSAID therapy for the cohort was 12 459 713. The acquisition cost of NSAIDs amounted to €6 587 533 (€0.53/person-day). The total costs of medical interventions for upper GI events following NSAID use amounted to €3 828 803 (€0.31/person-day), of which 57.5% were direct costs. The costs of GI events represented a 58% addition to the daily NSAID treatment costs. The baseline GI event cost/day was €0.028. The cost was driven by GPA use, which accounted for 78.6% of total costs. This cost increased with age (from €0.06 in patients <30 years of age up to €0.39 in those >80 years old) and was 1.4 times higher in men than in women (€0.39 vs €0.27), 11.8 times higher among patients with a positive history of GI disorders (€1.01 vs €0.09) and 45.1 times higher in cancer patients than in those without cancer (€13.66 vs €0.30).

The cost attributed to NSAIDs may have been underestimated since in 1997 outpatient procedures were not reimbursed and therefore were not accounted for in the total cost of NSAID gastropathy. In addition, baseline hospitalisations and prescriptions of GPAs were estimated in the 4–6 months before study entry in patients who had not taken NSAIDs in the prior 9 months. Many patients were enrolled in 1997 and may have received NSAIDs in 1996 for pain that were not reimbursed by NHS and therefore these patients were classified as non-users. In addition, over-the-counter use of NSAIDs and GPAs may have been substantial in this population because of the restrictive reimbursement policy. Therefore, some of the baseline costs might have been overestimated because of the use of over-the-counter or non-reimbursed NSAIDs. However, the baseline costs were very small and did not affect the costs attributed to NSAIDs.

Sweden

Jönsson and Haglund[56] estimated the economic burden of NSAID-induced gastropathy in Sweden in 1997 considering both prevalence (top-down) and incidence (bottom-up) approaches. The top-down approach considered the total cost of gastropathy in Sweden and calculated the component attributable to NSAIDs based on estimates of the proportion of patients using NSAIDs among those who experienced dyspepsia or ulcers. The bottom-up approach was based on decision analytic models that used estimates of the risk and cost to treat or prevent NSAID-induced GI adverse events to calculate the total costs of NSAID-induced gastropathy (outpatient and drug costs for non-ulcer dyspepsia and outpatient, inpatient and drug costs for peptic ulcers) in the entire population. Costs were expressed in 1997 Swedish kronor (SEK) and were calculated from a societal perspective (direct and indirect costs) [in 1997 $US1 = SEK7.64].[42] The top-down approach gave an estimate of the total cost of NSAID-induced gastropathy ranging from SEK329 million to SEK586 million per year, of which 76–83% were direct costs. The cost estimate varied depending on the data source. The bottom-up approach gave an estimate of SEK320 million per year, of which SEK290 million (91%) were direct costs. The total number of NSAID users was estimated to approximate 200 000, with one-third of these patients (60 000) presumed to have experienced abdominal pain.

The top-down approach used an estimate of physician visits for non-ulcer dyspepsia derived by Nyrén et al.[62] in 1985, and adjusted for the year 1997. The GPA costs for non-ulcer dyspepsia estimated by this method were SEK130.2 million, while the estimate from Apoteket AB (Swedish Pharmaceutical Statistics) was SEK480 million for 1997. In the cost assessment of non-ulcer dyspepsia the author included the costs of drugs derived from Apoteket AB for 1997. This finding emphasises the fact that the management and costs of patients with ulcer or non-ulcer dyspepsia has changed over time. Indeed, the incidence method was based on a decision analytic model developed in 1992 that was itself based on assumptions from earlier literature. Costs were then projected to 1997.

Spain

Vargas et al.[57] estimated the hospital costs related to the treatment of digestive haemorrhages potentially caused by NSAIDs by reviewing the clinical history of all patients admitted to two tertiary Spanish hospitals during 1998. All resources consumed during the hospitalisations (concomitant medication, complementary examinations and tests, surgery, blood product consumption, inpatient consultations and hospital length of stay) were recorded. Costs were expressed in 1998 pesetas (Pta) [in 1998 $US1 = Pta149.41].[42] Thirty-six percent of patients admitted for GI bleeding had taken some NSAID on the same day of their hospitalisation (85.4%) or in the previous 15 days (14.6%). The cost related to the treatment of these patients amounted to Pta434 407/patient. The study only considered the cost of hospitalisation for GI bleeding. The bleeding was attributed to the NSAID if the patient was exposed to the NSAID during that day or on the previous day. No control group was considered.

The Netherlands

Herings and Klungel[58] took an epidemiological approach to assess the economic burden of NSAID-induced GI events in The Netherlands between 1989 and 1998. Costs were calculated from the perspective of a third-party payer and were expressed in 1998 euro values (in early January 1999 $US1 = €1.19).[42]

Costs were those of GPA use and hospitalisation for PUB. They were reimbursement costs for drugs and per-day costs for a GI hospitalisation. The costs were extrapolated to the entire population using the population attributable risk (PAR).[63,64] To estimate the PAR in each risk-specific group, the prevalence of NSAID utilisation and the effect (odds ratio) of each risk factor on GPA use and hospitalisation were needed. Two case-control studies were performed to estimate the odds ratios using data from the Dutch PHARMO system. The total annual cost of GPA use and hospitalisations for GI events attributable to the use of NSAIDs was €59.3 million, which represented 14% of the total costs for GPAs and hospitalisations for GI events in The Netherlands. The total cost of NSAID use in The Netherlands in 1998 was estimated at €88 million (€0.60 per patient per day) for a total of 140 million person-days of NSAID use. Long-term users of NSAIDs (patients who used NSAIDs for uninterrupted periods of 100 days or more) formed 9.3% of all NSAID users and accounted for 65% of the total cost of NSAIDs. Patients aged >65 years accounted for 60% of the total costs. The ICF was estimated at 1.74. This study used a simple epidemiological approach to assess the cost of NSAID gastropathy. However, this approach was based on assumptions that tend to oversimplify the reality to an even greater extent than decision analysis models, which we discuss in section 4.2.

4.2 Decision Analysis Models

Decision analysis models have been used to assess the cost of NSAIDs and COX-2 inhibitors over periods of time during which direct data are not available or are difficult to obtain. Such models rely heavily on assumptions and estimates derived from expert opinions and clinical trials and/or observational studies performed in varying circumstances (that include different populations, protocols and doses). A hypothetical cohort of patients is considered and events are assumed to happen to this cohort based on a pathway dictated by the assumed probabilities. In general, clinical trials assess endoscopically diagnosed lesions that would not necessarily develop into an overt clinical event. Moreover, ulcer-like symptoms caused by dyspepsia, for example, can be present in the absence of any endoscopic lesion. These symptoms are highly prevalent and drive health service consumption and expenditures. Some but not all models incorporate estimates of the rates of these symptoms. Moreover, prophylactic use of GPAs is prevalent in patients taking NSAIDs. Very few decision analysis models incorporate the rate of GPA prophylaxis in the model. The effects of a departure from model assumptions and estimates on the overall results are tested through sensitivity analyses. Decision analysis models over-simplify the medical pathway of the patient. These models typically assume 100% compliance with the regimen assigned and attribute at most a single event to each patient. However, in the absence of direct data, as is the case for new drugs, decision analysis models constitute a useful tool for cost estimations and comparisons.

4.2.1 Decision Analysis Models to Assess the Cost of NSAIDs

US

Bentkover et al.[65] used a decision analysis model to compare the 3-month direct costs of nabumetone, ibuprofen and ibuprofen plus misoprostol from the perspective of a healthcare payer (table II). Costs were calculated in 1992 US dollars. The probabilities for the occurrence of various adverse events were derived from a clinical study that compared the efficacy and safety of nabumetone, ibuprofen and ibuprofen plus misoprostol in 171 elderly patients with osteoarthritis over a 3-month period.[1] Endoscopic lesions were discounted by 40% to account for symptomatic ulcers. Direct costs of medical resources were estimated using the 1992 Medicare reimbursement amount. The costs of medications were estimated from the wholesale acquisition costs. The costs per patient-day of treatment with nabumetone, ibuprofen and ibuprofen plus misoprostol were as follows: total costs including the cost of osteoarthritis were $US2.03, $US2.83 and $US3.00, respectively; of these, the acquisition costs were $US1.30, $US0.50 and $US2.20, respectively; and the GI adverse event costs were $US0.22, $US1.86 and $US0.32, respectively. Sensitivity analyses demonstrated that direct costs with nabumetone approached those for the other two regimens if the price of nabumetone increased by 60%.

Table II. Decision analysis models (costs were converted to 2002 US dollar values of the same year using foreign exchange rates and accounting for the inflation rate[42,46])

Study (location)	Year of costing	Study characteristics: treatment, perspective, population, healthcare utilisation and cost of services assessed	Direct costs per patient-day (unless otherwise stated) [2002 $US]
NSAIDs			
Bentkover et al.[65] (US)	1992	Direct costs of nab, ibu, ibu + mis from a payer perspective in seniors with OA	Acquisition:[a] 1.67 (nab); 0.64 (ibu); 2.82 (ibu + mis) GI events: 0.28 (nab); 2.34 (ibu); 0.41 (ibu + mis)
Brixner[66] (US)	1994	Direct costs of nab and ibu from a payer (HMO) perspective in arthritis patients aged >60y enrolled with the HMO	Acquisition: 1.80 (nab); 0.63 (ibu); 1.70 (ibu + mis) Total: 2.55 (nab); 3.52 (ibu); 3.15 (ibu + mis)
Goldstein et al.[67] (US)	1996	Direct costs of dicl/mis, NSAID, NSAID + H_2RA and NSAID + mis from a payer perspective in patients requiring long-term NSAID therapy	Total: 5.96 (dicl/mis); 6.47 (NSAID); 10.07 (NSAID + H_2RA); 8.62 (NSAID + mis) Acquisition (not provided)
Liaropoulos et al.[68,69] (Europe)	1998	Direct costs of nim and dicl from a payer (social security system) perspective in patients with arthritis in Greece. PUB hospitalisation rate was assumed to be 0 with nim	Acquisition: 1.06 (nim); 0.92 (dicl) GI events: 0.18 (nim); 1.88 (dicl)
Peris et al.[70] (Europe)	1996	Direct costs of ace vs other NSAIDs from a payer perspective in patients with arthritis or AS in Spain. Outpatient costs of adverse events included those of GI ulcers, constipation, diarrhoea, vomiting, oesophageal reflux, dermatitis, dizziness and headache	Acquisition: 0.84 (ace); 0.21 (ind)–0.56 (dicl) [other NSAIDs] Direct cost: 1.00 (RA)–1.91 (AS) [ace]; 1.10 (RA)–1.27 (AS) [other NSAIDs]
McCabe et al.[71] (Europe)	1995	Direct costs of nab vs ibu from a payer perspective in patients with arthritis in the UK. Outpatient costs of adverse events included those of headache	Acquisition: 1.43 (nab); 0.26 (ibu)
		Model 1: Co-prescribe a GPA if minor event	Direct costs model 1: 1.57 (nab); 0.73 (ibu)
		Model 2: Switch to a better tolerated therapy if minor event	Direct costs model 2: 1.33 (nab); 0.86 (ibu)
COX-2 inhibitors			
Pellissier et al.[72] (US)	1998	Direct cost of rofe vs NSAIDs from a payer perspective in patients with OA	Acquisition: 2.67 (rofe); 1.62 (NSAIDs) Direct cost: 3.15 (rofe); 3.01 (NSAIDs) Iatrogenic cost factor: 1.18 (rofe); 1.83 (NSAIDs)
Fendrick et al.[40] (US)	1998	Direct cost of a generic vs a better tolerated NSAID from a payer perspective in long-term NSAID users with no GI risk factors at baseline	Acquisition: 0.18 (generic NSAID); 2.21 (better tolerated NSAID)
		Strategy 1: if treatment fails, then give better tolerated NSAID	Direct cost (strategy 1): 0.72
		Strategy 2: give better tolerated NSAID to all patients	Direct cost (strategy 2): 2.51
Marshall et al.[73] (Canada)	1999	Direct cost of rofe vs nonselective NSAIDs from a payer perspective (Ontario Ministry of Health) in seniors with OA that did not respond to para in Ontario. Costs included those of prophylactic drugs	Acquisition: 1.09 (rofe); 0.72 (NSAIDs) Direct cost: 1.21 (rofe); 1.15 (NSAIDs)
Zabinski et al.[74] (Canada)	1998	Direct costs of cele vs NSAIDs, dicl/mis, NSAIDs + H_2RAs, NSAIDs + mis or NSAIDs + PPIs from a payer perspective (Provincial Ministry of Health) in seniors with arthritis in Ontario	Acquisition: 0.93 (cele); 1.14 (dicl/mis); 0.56 (NSAIDs); 2.88 (NSAIDs + PPIs) Direct cost: 1.13 (cele); 1.51 (dicl/mis); 1.09 (NSAIDs); 3.03 (NSAIDs + PPIs)

Continued next page

Table II. Contd

Study (location)	Year of costing	Study characteristics: treatment, perspective, population, healthcare utilisation and cost of services assessed	Direct costs per patient-day (unless otherwise stated) [2002 $US]
Chancellor et al.[75] (Europe)	1999	Direct costs of cele vs NSAIDs from a payer perspective in patients with arthritis in Switzerland	Acquisition: 1.40 (cele); 1.39 (dicl/mis); 1.29 (NSAIDs); 5.40 (NSAIDs + PPIs) Direct cost: 1.74 (cele); 2.09 (dicl/mis); 2.03 (NSAIDs); 5.65 (NSAIDs + PPIs)
Pettitt et al.,[76] Haglund and Svarvar,[77] Svarvar and Aly[78] (Europe)	1998	Generic model to compare the cost of cele vs NSAIDs or NSAIDs + GPAs from the payer perspective in patients with arthritis. The model was applied in Sweden[77] and Norway.[78] Only results in OA patients are reported in this table because of limited space and the fact that rofe was not available for RA. Costs were not calculated per day because the total number of days of therapy was not given	Costs per OA patient-year: Acquisition (Sweden): 198 (cele); 287 (rofe); 168 (NSAIDs) Cost of GI events (Sweden): 100 (cele); 100 (rofe); 181 (NSAIDs) Acquisition (Norway): 221 (cele); 270 (rofe); 196 (NSAIDs) Cost of GI events (Norway): 89 (cele); 89 (rofe); 200 (NSAIDs)
You et al.[79] (Asia)	2001	Direct costs of cele vs NSAIDs, NSAIDs + PPIs, NSAIDs + mis and NSAIDs + H_2RAs from a payer (public health organisation) perspective in patients with arthritis in Hong Kong	Acquisition: 0.78 (cele); 0.26 (NSAIDs); 1.69 (NSAIDs + PPIs); 0.27 (NSAIDs + H_2RAs) Direct cost: 1.12 (cele); 1.16 (NSAIDs); 2.07 (NSAIDs + PPIs); 1.02 (NSAIDs + H_2RAs)

a Acquisition plus dispensing costs (first study only).

ace = aceclofenac; **AS** = ankylosing spondylitis; **cele** = celecoxib; **dicl** = diclofenac; **GI** = gastrointestinal; **GPA** = gastroprotective agent; **H_2RA** = histamine H_2 receptor antagonist; **HMO** = health maintenance organisation; **ibu** = ibuprofen; **ind** = indomethacin; **mis** = misoprostol; **nab** = nabumetone; **nim** = nimesulide; **OA** = osteoarthritis; **para** = paracetamol; **PPI** = proton pump inhibitor; **PUB** = perforation, ulcer or bleeding; **RA** = rheumatoid arthritis; **rofe** = rofecoxib.

Brixner[66] used a decision analysis model to compare the direct cost of a 3-month treatment with nabumetone with that of ibuprofen in arthritis patients aged >60 years registered with an HMO in the US. The author used HMO data to determine the population characteristics, and data from a clinical trial by Roth[1] comparing nabumetone with ibuprofen to determine the GI adverse event probabilities. The rate of endoscopic ulcers was discounted by 40% to estimate the symptomatic ulcers that would be treated in practice. Costs were derived from the paper by Bentkover et al.[65] Costs were provided from the HMO perspective and were expressed in 1994 US dollars. The model predicted that if a patient in this HMO was treated for 3 months with nabumetone, the direct cost would be $US186 ($US2.10/day) compared with $US260 ($US2.90/day) for ibuprofen and $US230 ($US2.60/day) for ibuprofen plus antiulcer therapy. The daily acquisition costs of nabumetone, NSAIDs and antiulcer therapy were $US1.48, $US0.52 and $US1.40, respectively. The costs for NSAIDs and anti-ulcer therapy were the average weighted costs of these drugs.

Goldstein et al.[67] conducted a decision analysis model to compare the 6-month costs associated with a fixed-dose formulation of diclofenac/misoprostol versus NSAID or NSAID plus H_2 antagonist or NSAID plus misoprostol. The costs were those of the drugs, hospitalisations for PUB and outpatient treatment of symptomatic ulcers without complications. The rates of these events were estimated from the literature when available or by expert opinion. Patients were assumed to be receiving continuous therapy throughout the 6 months unless they had an endoscopic finding, at which time they were treated with 4 weeks of omeprazole therapy, and had two follow-up visits. A proportion of those with ulcers or hospitalisations was assumed to have discontinued NSAID therapy and the remaining patients were assumed to have received NSAID and misoprostol thereafter. Costs were expressed in 1996 US dollars and were calculated from a single-payer perspective. Costs of NSAIDs were average wholesale price, with the cost of branded diclofenac used as the NSAID cost. The diclofenac/misoprostol cost was preliminary and provided by the manufacturer (not explicitly given in the paper). The 6-month per-

patient cost in the diclofenac/misoprostol arm was $US939.00 ($US5.20/day assuming all patients were exposed for 180 days, which is not necessarily the case for those who experienced GI events) compared with $US1017.00 ($US5.65/day) in the NSAID arm. These costs were lower than those of either the NSAID plus H_2 antagonist arm ($US8.79/patient-day) or the NSAID plus misoprostol arm ($US7.52/patient-day). Sensitivity analyses indicated that the model was not sensitive to the assumptions used. The author did not provide the acquisition costs of diclofenac/misoprostol considered in the model. In some places such as Quebec, Canada the cost of diclofenac/misoprostol does not differ from that of diclofenac alone.[80] Therefore, under such conditions and assuming that the tolerability of diclofenac/misoprostol would be similar to that of an NSAID plus misoprostol, it is not surprising to find that diclofenac/misoprostol was cost saving.

Greece

Liaropoulos[69] and Liaropoulos et al.[68] used a decision analysis model to compare the direct costs of nimesulide with those of diclofenac in patients with rheumatic disease and osteoarthritis, respectively, in Greece. Both studies used the same model and cost sources and yielded the same results. In both studies, the probabilities of GI adverse events used in the model were derived from a meta-analysis of published clinical trials.[68] Only one of these trials in the meta-analysis compared nimesulide with diclofenac. None of the trials that studied nimesulide reported PUB adverse events. Two of the trials that studied diclofenac reported PUB incidence rates of 0.3% and 1.58%. The probabilities of GI adverse events were based on the cumulative incidence calculated from the trials (ratio of total number of new cases over the total number of patient-weeks at risk).[81] Therefore, the model assumed that no serious GI events requiring hospitalisation would have occurred with nimesulide. Costs were calculated from the social security system perspective and were provided in 1998 US dollars (in 1998 $US1 = 310 Greek drachmas [Dr]; rate provided in the paper). The model considered a treatment period of 15 days and calculated the costs of NSAIDs and other drugs (prophylaxis, analgesics, etc.), medical consultations, examinations and hospital-based treatments for arthritis as well as the costs of treating GI adverse events. Ambulatory costs were calculated using expert opinion on the management of GI adverse events. Hospital costs were estimated from the hospital records of 43 patients admitted with a diagnosis of gastric bleeding who did not experience severe non-GI complications. Medical and nursing costs and the cost of surgery were not included since hospital care in Greece is heavily subsidised to keep costs to social security low.

It was found that 15-day treatment with diclofenac for rheumatic disease (or osteoarthritis) was 56% more expensive than treatment with nimesulide. The daily acquisition cost of nimesulide was $US0.96 and that of diclofenac $US0.83. The cost of GI adverse events during the 15-day treatment was $US2.42/patient for nimesulide ($US0.16/patient-day) versus $US25.46/patient for diclofenac ($US1.70/patient-day). Hospitalisation for PUB accounted for $US0 for nimesulide and $US20.85/patient for diclofenac. Some of the studies included in the meta-analysis were conducted as early as 1982 and only one was a head-to-head comparison of diclofenac versus nimesulide. Therefore, the difference in adverse events between diclofenac and nimesulide observed in these studies could be because of differences in study populations and protocols (age, prior GI risk factors and daily dose of the NSAID used).

Spain

Peris et al.[70] used a decision analysis model to study the clinical and economic consequences of aceclofenac and other NSAIDs in Spain in patients with arthritis or ankylosing spondylitis. Probabilities of non-compliance, lack of efficacy and adverse events were obtained from 12 comparative, randomised, double-blind clinical trials and were accounted for in the model. An expert panel estimated resource utilisation. Direct costs included substitution treatment costs for patients not achieving clinical efficacy and inpatient and outpatient medical costs of adverse events. The GI adverse events considered were abdominal pain, constipation, diarrhoea, gastroduodenal ulcer, vomiting and oesophageal reflux. Dermatitis, dizziness and headache were also considered. The model covered a 3-month period. All costs were in 1996 US dollars

and were calculated from a single-payer perspective ($US1 = Pta166.08; rate provided by the author). The cost of lack of efficacy was estimated at $US0.42/day. The daily acquisition cost of aceclofenac was $US0.73 while that of other NSAIDs ranged from $US0.18 for indomethacin to $US0.49 for diclofenac. The mean direct cost of aceclofenac treatment varied according to the clinical trial from which the rates were derived. It ranged from $US0.87/day when compared with indomethacin ($US0.96) in rheumatoid arthritis to $US1.67/day when compared with indomethacin ($US1.11) in ankylosing spondylitis.

The ICFs were calculated for each branch of the decision tree. They were then log-transformed and the mean ICF was calculated for each clinical trial by calculating the mean of the log-transformed values and then transforming this mean back to the original scale. The results were quite different from those given by directly dividing the direct cost for the clinical trial by the acquisition cost of the NSAID. The ICFs for aceclofenac given in the paper ranged from 1.17 to 1.83 and were significantly lower than those for diclofenac, indomethacin, naproxen, tenoxicam and ketoprofen, but similar to that of piroxicam. The ratio of the ICF of piroxicam to the other NSAIDs ranged from 0.58 (versus ketoprofen) to 0.93 (versus diclofenac). The authors concluded that the overall costs of NSAIDs bear little relationship to drug acquisition costs. This conclusion was not supported by the results since, for example, the acquisition cost of aceclofenac amounted in one study to 85% of the direct cost (ICF 1.17). The ICF was the main outcome in this study and was in some cases misleading. For example, indomethacin had a lower daily acquisition cost than aceclofenac ($US0.18 vs $US0.73) and a lower daily total cost in patients with ankylosing spondylitis ($US1.11 vs $US1.67). Yet its ICF was much higher (6.16 vs 2.29 if calculated directly or 2.43 vs 1.83 using the log-transformation method).

UK

McCabe et al.[71] constructed two decision analysis models using data from a clinical trial and published cost data to compare the direct costs of nabumetone with those of ibuprofen in patients with arthritis in the UK. Costs included those of minor GI and non-GI (headache) adverse events and those of serious GI adverse events (PUB). Costs were expressed in 1995 pound sterling values (in 1995 $US1 = £0.63)[42] and were calculated from a single-payer perspective. In the first 'co-prescription' model, patients who experienced minor adverse events continued taking their original NSAID and received co-therapy, while in the second 'switching' model they were switched to a better tolerated NSAID (for the particular outcome that they had experienced) and faced different probabilities of adverse events. In both models, patients with serious adverse events received treatment but in the switching model, they also remained at risk for recurrence. Acquisition costs of nabumetone and ibuprofen were £0.76/day and £0.14/day, respectively. The co-prescription model estimated that the direct costs per patient for a 3-month treatment were £35.17 (£0.39/day) for ibuprofen versus £75.99 (£0.84/day) for nabumetone. These costs were slightly lower in the switching model: £41.64 (£0.46/day) for ibuprofen versus £64.20 (£0.71/day) for nabumetone.

4.2.2 Decision Analysis Models to Compare the Costs of COX-2 Inhibitors with those of NSAIDs

The COX-2 inhibitors have been relatively new additions to the market, and data on real life adverse events are still scarce. To our knowledge, only decision analysis models have been conducted to study the economic impact of these agents. Some of these models were conducted before the launch of the COX-2 inhibitors and were based on data from phase III trials. We review these models in the following sections.

US

Pellissier et al.[72] studied the potential economic implications of the use of rofecoxib versus NSAIDs for the treatment of osteoarthritis from the perspective of a third-party payer. They used a decision analysis model based on rofecoxib clinical data and the published literature. Only GI events that led to either a diagnostic test or therapeutic intervention were included. The rate of clinical ulcers was 40% that of endoscopic ulcers. The rate of GPA prophylaxis was assumed to be 25.5% with NSAID use. PPIs and misoprostol were assumed to be equally effective in reducing the risk of gastroduodenal ulcer by 40% and H_2 antagonists were assumed to

have no effect. The GPA prophylaxis rate was assumed to be 75% less with rofecoxib than with NSAIDs. Healthcare resource utilisation and costs associated with these GI events were estimated based on published reports. Direct costs were calculated over 1 year and expressed in 1998 US dollars. The daily acquisition costs of rofecoxib, NSAIDs, omeprazole, misoprostol and H_2 antagonists were $US2.42, $US1.47, $US3.77, $US3.05 and $US1.54, respectively. The direct cost of rofecoxib was $US2.86/patient-day compared with $US2.73/patient-day for NSAIDs. The ICF of NSAIDs was 1.83 compared with 1.18 for rofecoxib. Rofecoxib was found to be cost saving when compared with NSAIDs plus PPIs or NSAIDs plus misoprostol (cost offset $US2.91 and $US2.38, respectively). In analyses based on endoscopic data, rofecoxib was found to be cost saving compared with NSAIDs. Sensitivity analyses showed that the model was affected by the rate of GPA prophylaxis. The cost offset with rofecoxib varied from $US0.60/day to $US1.10/day when the GPA prophylaxis rate reduction with rofecoxib versus NSAID varied from 50% to 100%.

Fendrick et al.[40] constructed a decision analysis model to compare, from the payer's perspective, the costs of two treatment strategies over a 1-year period in long-term NSAID users who did not have any risk factors for gastropathy at baseline. The year of costing was not explicitly given in the paper but costs were concurrent to the conduct of the study that we assumed occurred in 1998. The model was symptom driven and considered two strategies. Strategy one assumed that a generic NSAID was used initially, and a better tolerated NSAID with a higher acquisition cost was reserved for treatment failures resulting from symptomatic gastropathy. Strategy two assumed that a better tolerated NSAID with a higher acquisition cost was used in all instances. The better tolerated NSAID was not explicitly named. The use and impact of antisecretory (PPI and H_2 antagonist) medications were included in the model. Sensitivity analyses were used to evaluate the key clinical outcomes and costs. The rate of PUB with the generic NSAID was assumed to be 2.7%. The better tolerated NSAID was assumed to be associated with a 3.7-fold reduction in the monthly endoscopic ulcer rate when compared with the generic NSAID. These assumptions were based on the published literature comparing nabumetone, rofecoxib and celecoxib with nonselective NSAIDs. PPIs were assumed to have been prescribed if a symptomatic ulcer was identified at endoscopy. For patients with symptoms but without endoscopic evidence of ulceration, H_2 antagonists were prescribed. Ulcer healing rates were estimated at 0.52 for H_2 antagonists and 0.66 for PPIs. Ulcer prevention rates were 0.20 for H_2 antagonists and 0.72 for PPIs. The daily acquisition costs were assumed to be $US0.16 for the generic NSAIDs, $US2.00 for the better tolerated NSAID, $US0.23 for the generic H_2 antagonists and $US3.33 for PPIs.

The model calculated that the cost per patient treated over the 1-year period with the restricted strategy (strategy one: $US239 [$US0.65/day]) was significantly lower than that of the strategy that permitted unrestricted use of the better tolerated NSAID (strategy two: $US831 [$US2.28/day]).[40] This difference was driven for the most part by the substantial difference in acquisition costs between the two NSAIDs. The strategy that permitted unrestricted use of the better tolerated NSAID prevented an additional symptomatic ulcer at an incremental cost of $US31 900. The incremental cost per complicated ulcer avoided was $US56 700. The authors conducted extensive sensitivity analyses, which showed that the results were not reliant on assumptions about effectiveness and costs of antisecretory therapy, the likelihood that an ulcer was complicated or the cost of non-drug services. The results were sensitive to the relative level of GI protection provided by the better tolerated NSAID and the risk level for ulcer development in the patient population.

Canada

Marshall et al.[73] evaluated the direct costs of rofecoxib in Ontario, Canada, for patients with osteoarthritis ≥65 years of age whose condition did not respond to paracetamol therapy. They used a decision analysis model to compare the GI adverse events with rofecoxib versus nonselective NSAIDs. The model had a 1-year horizon and assessed direct costs from the perspective of the Ontario Ministry of Health. Event rates were estimated from a pooled analysis of eight phase IIb/III clinical trials. The

number of PUBs with each strategy was used as the primary measure of effectiveness. Costs were expressed in 1999 Canadian dollars ($US1 = $Can1.49).[42] Asymptomatic ulcers that were detected via scheduled study endoscopies were not considered in the model. All perforations were assumed to require hospital admission. The model assumed that the rate of co-prescription of GPA with rofecoxib would be 10% of the rate with nonselective NSAIDs and that 57.2% of GPAs would be H_2 antagonists, 2.8% sucralfate, 22.4% misoprostol and 17.6% PPIs. Misoprostol and PPIs were assumed to reduce ulcer occurrence by 40%, while no reduction in ulcer rate was assumed with H_2 antagonists and sucralfate. The annual direct costs per patient were $Can584.91 ($Can1.60/day) in the NSAID group versus $Can609.36 ($Can1.67/day) in the rofecoxib group. The daily acquisition costs of NSAIDs were $Can1.00 and of rofecoxib were $Can1.51. The incremental cost to avoid one additional PUB by substituting rofecoxib for NSAIDs was $Can2247. The rofecoxib strategy became dominant (safer and less costly) if a GPA was prescribed to more than 27.5% of the patients receiving NSAIDs or if no GPAs were prescribed with rofecoxib while the rate of GPA co-prescription with NSAIDs exceeded 25%. The authors conducted extensive sensitivity analyses to test their assumptions. They have assumed a 10% rate of co-prescription of GPAs with rofecoxib compared with that with nonselective NSAIDs. However, other studies have found a higher rate of co-prescription of GPAs with rofecoxib depending on patients' prior GI risk factors.[82] The assumed rate of H_2 antagonist utilisation for prophylaxis (58% of total prophylaxis rate) was also high in this study. It was based on GPA utilisation in the general population in Ontario, in which a higher proportion of H_2 antagonists could have been prescribed for indications other than NSAID prophylaxis. Since no reduction in ulcer rate was assumed with these drugs this may have increased the costs in the NSAID arm. Other studies have reported some reduction in NSAID-induced ulcers with H_2 antagonists.[83] The assumed rate of H_2 antagonist utilisation for prophylaxis and the possibility of a positive rate of duodenal ulcer reduction attributable to high-dose H_2 antagonists were not tested in the sensitivity analyses.

Zabinski et al.[74] constructed a decision analysis model to compare the costs of treating arthritis patients aged >65 years with celecoxib versus NSAIDs or NSAIDs in combination with GPAs over a 6-month period. The costs were calculated from the perspective of a provincial Ministry of Health and were expressed in 1998 Canadian dollars ($US1 = $Can1.48).[42] The model accounted for the costs of the drugs (including patient co-payment), dyspepsia, PUB, symptomatic ulcers and anaemia. The mortality rate resulting from serious GI events was assumed to be 10%. Probabilities of clinical outcomes were derived from the results of eight phase III clinical trials and from other medical literature. Resource use for the treatment of GI complications was estimated after consulting with experts from several Canadian provinces and standard unit costs for Ontario were applied. The daily acquisition costs of NSAIDs, diclofenac/misoprostol and celecoxib were $Can0.75, $Can1.53 and $Can1.25, respectively.

The cost of a serious GI event requiring hospitalisation and resulting in death was considered equal to the cost of the hospitalisation itself. The model showed that overall NSAIDs were the least expensive regimen (per patient, $Can262/6 months or $Can1.46/day) followed by celecoxib (per patient, $Can273/6 months or $Can1.52/day) and diclofenac/misoprostol (per patient, $Can365/6 months or $Can2.02/day). Celecoxib was the least costly in patients at moderate to high risk for GI complications. However, celecoxib is often not prescribed alone in patients with moderate to high risk of GI complications.[82] Prophylaxis prescription was not accounted for in this model and would have increased the cost in the celecoxib arm.

Switzerland

Chancellor et al.[75] predicted the cost effectiveness of celecoxib versus NSAIDs (naproxen, diclofenac and ibuprofen) in patients with arthritis in Switzerland. They developed a decision analysis model to estimate the GI adverse event rates and costs. The model had a 6-month time horizon. Probabilities of GI adverse events were derived from the pooled Kaplan-Meier estimates from the celecoxib comparative clinical trials.[84] The model incorporated the patients' GI risk factors and ex-

cluded mild GI discomfort. The cost of resources used to manage the GI events was taken from a published study.[54] The direct costs were calculated from the perspective of a healthcare payer and were expressed in 1999 Swiss francs (SwF) [$US1 = SwF1.5].[42] The year of costing was not explicitly stated by the authors but drug costs were those of 1999. The 6-month costs per patient were SwF435.06 (SwF2.42/day) for celecoxib compared with SwF509.94 (SwF2.83/day) for NSAIDs, SwF521.95 (SwF2.90/day) for diclofenac/misoprostol and SwF1414.72 (SwF7.86/day) for NSAIDs plus PPIs when the same efficacy was assumed for all treatments. Patient contribution estimated at a fixed 10% of the total cost was discounted. It is important to note that the daily cost of celecoxib at an average daily dose of 240mg was SwF1.94 (SwF1.27 for 200 mg/day and SwF2.96 for 400 mg/day), that of diclofenac/misoprostol was SwF1.93, and that of NSAIDs was SwF1.79, with that of naproxen set at SwF2.85. The daily cost of PPIs, misoprostol and H_2 antagonists were SwF5.71, SwF3.19 and SwF4.32, respectively. Since the cost of NSAIDs is not much lower than that of celecoxib in Switzerland and the clinical trials have shown a lower rate of occurrence of GI events with celecoxib versus NSAIDs, it is not surprising that celecoxib was found to be cost effective compared with NSAIDs or NSAIDs plus GPAs. However, in most countries, the acquisition cost of celecoxib is much higher than that of most NSAIDs.

Scandinavia

Pettitt et al.[76] constructed a pharmacoeconomic model, the Arthritis Cost Consequence Evaluation System (ACCES) to predict and evaluate the costs associated with the use of celecoxib versus NSAIDs or NSAIDs in combination with a GPA in patients with arthritis, adopting a payer perspective. The model can be customised to a variety of practice patterns, resource utilisations and costs. The model accounts for treatment efficacy (switches between treatments) and discontinuation because of misoprostol adverse effects and incorporates the costs of dyspepsia and anaemia as well as those of serious GI events. Multiple levels of sensitivity analyses can be performed in this model. The ACCESS model has been applied by Haglund and Svarvar[77] and Svarvar and Aly[78] to predict the economic impact of celecoxib in Sweden and Norway, respectively, in patients with arthritis. In Sweden, expected resource utilisation was estimated using questionnaires sent to clinical experts. Costs were based on 1998 pricing and expressed in 1998 Swedish kronors ($US1 = SEK7.95).[42] It was shown that the expected per-patient cost of celecoxib (SEK3804/year or SEK10.42/day) was slightly higher than that of NSAID monotherapy (SEK3691/year or SEK10.11/day) in rheumatoid arthritis but was lower than that of NSAIDs in osteoarthritis (celecoxib: SEK2152/year or SEK5.90/day vs NSAIDs: SEK2519/year or SEK6.90/day). The cost of NSAIDs and PPIs was about twice as high as that of celecoxib in both osteoarthritis and rheumatoid arthritis. Rofecoxib was found to be more costly than celecoxib because of its higher acquisition cost. Similar rates of adverse events were assumed for both drugs.

Similar methods and results were reported by Svarvar and Aly in Norway.[78] Celecoxib was found to be cost saving compared with NSAID monotherapy in both osteoarthritis (celecoxib: Norwegian kronor [NOK] 2125/patient-year [NOK5.82/day] vs NSAIDs: NOK2705/patient-year [NOK7.41/day]) and rheumatoid arthritis (celecoxib: NOK3729/patient-year [NOK10.21/day] vs NSAID: NOK4243/patient-year [NOK11.62/day]) [$US1 = NOK7.55].

Asia

You et al.[79] conducted a study in Hong Kong to compare the cost of celecoxib with that of NSAIDs in arthritis patients over a 6-month period using a decision analysis model. The analysis was conducted from the perspective of a public health organisation. The model accounted for GI discomfort, symptomatic ulcer, anaemia with occult bleeding and serious GI complications. It considered six different regimens: NSAID, NSAID plus PPI, NSAID plus H_2 antagonist, NSAID plus misoprostol and celecoxib. The probabilities of the clinical outcomes were based on work done by Burke et al.[84] as in the model by Chancellor et al.[75] The probabilities (%) in the NSAID, NSAID plus H_2 antagonist, NSAID plus misoprostol, NSAID plus PPI and celecoxib arms were GI discomfort 14.54, 10.32, 17.30, 9.31 and 9.40; symptomatic ulcer 6.28, 4.08, 2.51, 2.07 and 1.74; serious GI event 0.59, 0.58, 0.36, 0.29 and 0.23; and anaemia 1.09, 0.71, 0.44, 0.36 and 0.30,

respectively. Resource utilisations (except for anaemia) were retrieved from patient medical records. Resource utilisation for anaemia was determined through expert opinion. The costs were provided in 2001 Hong Kong dollars ($HK) [$US1 = $HK7.8; rate provided in the paper] (the year of costing was not explicitly stated and was assumed to be the year of the survey). The daily acquisition costs of NSAIDs, celecoxib, H_2 antagonists, misoprostol and PPI were $HK2.00, $HK6.00, $HK0.80, $HK6.20 and $HK11.00, respectively, with the daily cost of NSAIDs being the average of that for naproxen, diclofenac and ibuprofen. The costs associated with resources were approximated using the charges for public hospitals listed in the Hong Kong Gazette. The expected direct costs per patient per 6 months were lowest in the NSAID plus H_2 antagonist arm ($HK1404 or $HK7.80/day), compared with celecoxib ($HK1545 or $HK8.58/day), NSAID ($HK1610 or $HK8.94/day), NSAID plus misoprostol ($HK2213 or $HK12.29/day) and NSAID plus PPI ($HK2857 or $HK15.87/day).

5. Discussion

The direct costs of NSAIDs and COX-2 inhibitors have been studied by many authors using various approaches and methodologies. The populations studied, the perspectives considered and the inclusion of resources often differed between studies. Because the most important adverse events with NSAIDs are related to their GI toxicity, several authors refer to the direct costs of NSAID as their acquisition costs plus the costs of treating and preventing the associated gastroduodenal toxicity. The COX-2 inhibitors have been shown to have the same efficacy and fewer GI adverse events compared with nonselective NSAIDs but with higher acquisition costs. We reviewed studies that assessed the costs of some or all of the following NSAID-associated healthcare events: primary care and specialist visits for upper GI mucosal disorders, hospitalisations for PUB, upper GI diagnostic tests, and GPA utilisation to prevent or treat upper GI mucosal disorders. In the reviewed studies, probabilities of GI events were estimated from administrative databases, patient chart reviews or published studies. Resource utilisation was estimated from administrative databases and patient chart review when available or otherwise was based on expert opinion. GPA utilisation and GI event management depended on the country-specific healthcare policy. Healthcare policies sometimes differed between regions within the same country. The attribution of costs to the healthcare services depended on the perspective adopted in the study. In most studies the perspective was that of the healthcare payer. Therefore, the costs assessed were often reimbursement costs and did not consider patient-related or societal contributions. To calculate the cost of gastropathy attributable to NSAIDs, a comparison with a control group was not always considered. These factors created significant heterogeneity between studies, which limited comparability. Therefore, the results should be interpreted within the context of each study. To allow for some level of comparison, specific costs have been converted to 2002 US dollar values and expressed per patient per day of treatment in table I and table II. The treatment of NSAID gastropathy and the prescription of prophylaxis have changed over time, and the exchange rates do not adequately reflect the purchasing power parities of the respective currencies. Therefore, these converted costs are only included to facilitate part of the interpretation of results across studies and do not render cross-study results fully comparable in most cases.

It was evident from all reviewed studies that the GI adverse events attributable to NSAIDs have a substantial effect on the healthcare budget and can sometimes exceed the cost of the NSAID itself. The economic impact of the COX-2 inhibitors has only been studied in hypothetical populations using decision analysis models where the probabilities of event occurrences were based on published clinical trials and/or expert opinions. These models showed that, from an economic perspective, the healthcare system would benefit from treating patients at risk of NSAID gastropathy with COX-2 inhibitors. COX-2 inhibitors would not be cost beneficial in patients at no risk or low risk for developing a GI event. These results now need confirmation in a real-life setting, where actual drug prescription and event management could differ from their respective assumptions incorporated in the models.

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Correspondence and offprints: Dr *Elham Rahme*, Division of Clinical Epidemiology, Montreal General Hospital, 1650 Cedar Ave., Montreal, H3G 1A4, Quebec, Canada.
E-mail: elham.rahme@mcgill.ca