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Economics and health-related quality of life in antiemetic therapy: recommendations for trial design

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Abstract

Emesis (nausea and vomiting) is one of the most important toxicities associated with chemotherapy. Although it is not life threatening, it has a major impact on a patient's health-related quality of life (HRQL) and overall response to chemotherapy. New antiemetics are expensive and well-conducted comparative health economic studies are rare. The aim of the study was to review the literature in the area of chemotherapy-induced emesis in cancer patients and to offer recommendations for the inclusion of these outcomes in the design of clinical trials for new antiemetic therapies. The economic literature was reviewed based on methodological standards for economic evaluation. Many studies did not comply with standards, specifically with regard to the choice of alternatives, chosen perspective, setting, type of emesis, measurement of costs and defining outcomes (including health-related quality of life). These issues are described for each study and recommendations for trial design are presented. The role of economic data is to support decision making in choosing between competing antiemetic therapies. It is the combination of clinical outcomes, costs and health-related quality of life, which will allow treating physicians to comprehensively assess the relative value of antiemetic therapies and to provide the most cost-effective therapy for their patients. © 2000 Published by Elsevier Science Ltd. All rights reserved.

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1. Introduction

Economic analysis has become increasingly important in the assessment of cancer therapies over the past decade. Most industrialised countries spend 3–6% of their gross domestic product (GDP) on cancer care [1]. Budgetary pressures, compounded by the limited curative potential and increasing competition between existing therapies, have shifted payers' and providers' attention to the evaluation of treatment effects using endpoints other than clinical efficacy. The purpose of economic analysis is to aid decision makers in choosing between competing therapies within the constraints of a fixed pool of resources. It allows for the objective comparison of alternative treatments in terms of costs and effects [2].

The area of supportive cancer care is particularly prone to economic analysis. Because supportive therapies offer no curative effect, they are often the targets of cost-containment policies, which typically focus on the high immediate direct costs of acquiring these drugs, yet fail to incorporate into their decision analysis the long-term economic impact of therapies over the full course of treatment. The evaluation of supportive care requires a move away from the perception of a cure as a success and an incurable condition as a failure [1]. Ideally, resource allocation decisions in this area should encompass a comprehensive assessment of direct and indirect costs as well as reliable measurements of clinical benefit which take into account patients' preferences and needs. In this respect, health-related quality of life (HRQL) is recognised as a primary outcome for the evaluation of supportive care therapies.

Emesis (vomiting and nausea) is one of the most important toxicities associated with anticancer therapy. Although not life threatening, it has a major impact on cancer patients' well being and overall response to chemotherapy. In a study of patients' perceptions of the side-effects of chemotherapy, vomiting was the most severe symptom reported by patients [3]. When the

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study was repeated in 1995, nausea was reported as the most troublesome symptom, followed by tiredness and hair loss, and vomiting moved down to fifth place [4]. Chemotherapy-induced emesis can be divided into acute ($\leqslant$24 h post chemotherapy), delayed ($>$24 h post-chemotherapy) and anticipatory (before chemotherapy) emesis [5]. Complete control rates of 75–90% of acute emesis can be achieved with currently available antiemetics, namely the 5-HT3-receptor antagonists combined with dexamethasone. There exists four widely accepted 5-HT3-receptor antagonists and, despite numerous clinical trials, no data have shown any real differences in efficacy between them [6–8]. The use of 5-HT3-receptor antagonists beyond the acute phase of emesis (24 h) has been contested by experts as being expensive and not optimally effective. Indeed, the complete control of nausea and vomiting remains insufficient, as patients still sustain delayed emesis (22–89% incidence) as well as acute emesis (20–40% incidence) and the total control of emesis over several cycles of chemotherapy is often not achieved [6,7]. In a recent review by Gralla, cost was considered one of the main considerations in selecting antiemetic treatment [9,10]. However, data from well-conducted comparative economic studies are lacking [9]. The purpose of this study was to review the economic and HRQL literature in the area of cancer chemotherapy-induced emesis in order to formulate recommendations for the inclusion of these outcomes in the design of future clinical trials for antiemetic therapies.

2. Methods

A literature search was conducted using *MEDLINE*, *CancerLit* and *EMBASE* for the period 1990–1997. Seventy-five publications with the key words 'emesis', 'nausea' or 'vomiting', 'cost' or 'quality of life' were retrieved, of which 63 were retained which addressed issues of cost or economic evaluation and 17, of HRQL. These latter two groups of papers were used as the basis for this study.

Economic publications were assessed based on methodological standards for economic analysis in cancer care outlined in Williams and Colleagues [11]. These standards pertain mainly to the methodology and presentation of economic analyses, specifically in terms of the choice of alternatives, the chosen perspective, the setting of the study, the measurement of costs, the proper definition of outcomes, discounting and performing sensitivity analyses. We also looked at the type of emesis under study. HRQL studies were assessed based on the choice of methodology and hypotheses under study. Based on these assessments, recommendations for the design of trials assessing antiemetic therapies were made. These are presented in the Discussion.

3. Results

3.1. Economic evaluation of antiemetic therapies

The rationale for the economic evaluation of antiemetic therapy is based on the following hypotheses:

1. Effective antiemetic therapy allows for the prevention of the side-effects associated with emesis, namely malnutrition, dehydration, electrolyte imbalance and aspiration pneumonia. This may translate into less healthcare utilisation, less indirect costs in terms of work-days lost or caregiver time, and improved HRQL.
2. Emesis can be a dose-limiting and therapy-limiting toxicity for chemotherapy. The successful prevention of emesis can thus allow for patients to continue with their projected course of therapy unabated. The corollary of this argument is that the unsuccessful control of emesis may limit the potential for anticancer therapy to be administered and thus compromise the potential efficacy in patients. These added benefits and avoided costs of complications and therapy delays or disease progression should be factored into the model for supportive care.

The economic evaluations of antiemetic therapy contained in the literature span a wide range of methods and approaches, depending on the objectives of the study and scope of analysis. An overview of reviewed studies is provided in Table 1. Some of the main methodological issues with these studies are described below.

3.1.1. Presentation of treatment alternatives

As the purpose of economic analysis is to aid decision-makers in their selection of competing therapies, it is imperative that economic studies clearly present the treatment options which are being considered. In the existing studies on antiemetics, a 5-HT3-receptor antagonist is usually included.

There have been a few direct randomised clinical trials comparing ondansetron and granisetron, and no difference in efficacy was found. A meaningful comparison between two antiemetic regimens can also only be made once the optimal doses for each product have been established and are currently applied in clinical practice. Although several studies have looked at the efficacy of both ondansetron and granisetron, they vary in terms of dosages and regimens applied and compared. One difficulty is that there is wide variability in the approved single doses for the administration of ondansetron and granisetron in different countries. The question remains whether low-dose levels are already on the therapeutic plateau or whether there is a defined dose–response curve for these agents [20]. Moreover, even if recommendations for dose levels are made, postmarketing

Table 1
Economic studies of emesis and antiemetics in the literature (1990–1997)

Author [Ref]	Setting	Perspective	Comparison	Clinical data source (*n*)	Methods	Duration covered	Costs included	Measure of effects	Key findings and comments
Cox [12]	UK, inpatient setting	Hospital perspective	Study 1: i.v. ondansetron versus i.v. metoclopramide in HEC. Study 2: i.v. dexamethasone and i.v. ondansetron versus i.v. dexamethasone and iv. metoclopramide in MEC	Study 1: study of Cunningham [13]. Study 2: retrospective study	Incremental cost-effectiveness	Study 1: 24 h. Study 2: 5 days	Direct medical costs + costs of adverse events + costs of emetic episodes	Number of patients treated successfully	Study 1: see below study Cunningham [13]. Study 2: The average costs per patients were £141 in the ondansetron group and £48 in the metoclopramide group. Taking the costs per successfully treated patients as outcome, the costs for ondansetron therapy amounted to £184 and for metoclopramide to £160. However, giving ondansetron orally twice daily was more cost-effective (£133 versus £160). The results showed that ondansetron is at least as cost-effective as metoclopramide.
Cunningham [13]	UK, inpatient setting, two centres	Hospital perspective	i.v. ondansetron versus metoclopramide i.v. in HEC, cisplatin-naïve	Open multicentre randomised parallel study in two UK centres ($n = 32$)	Cost-effectiveness	24 h	Direct medical costs (drug acquisition + administration costs), treatment of adverse events and emetic episodes. No hospitalisation costs included	Successful treatment = at most one emetic episode and no adverse events in 24 h post-chemotherapy	The cost per patient amounted to £47.60 in the ondansetron group and to £20.28 in the metoclopramide group. The cost per successfully treated patient was £95.20 for ondansetron and £92.18 for metoclopramide. The most expensive cost component in both groups was the antiemetic drug. Other direct medical costs, nursing and treatment costs for emetic episodes were significantly larger in the metoclopramide group, which only achieved 22% total response rate. Whereas a crude comparison of drug costs yields a ratio of 3.7:1.0 for ondansetron, the consideration of all direct medical costs per patient yields a ratio of 2.3:1.0. The ratio per effectively treated patient yields a ratio of 1.03: 1.0: Flaws of the study: no sensitivity analysis and a small sample size.
O'Brien [14]	Canada, five centres	Societal and healthcare system perspective	Observational study for patients receiving dexamethasone or other non-5-HT3-receptor antagonist therapies	Prospective survey of patients receiving chemotherapy ($n = 107$)	Cost analysis	5 days	Full direct medical costs, indirect costs (time lost from usual activities) for patients + non-medical direct costs (home care)	Total number of patients with no significant emesis. FLIE scores also collected	It provides a very comprehensive 'burden of illness' study which incorporates indirect as well as non-medical direct costs. The direct costs amounted to £63 and the indirect costs amounted to £121. These data can be used as baseline data to assess the impact of newer and more costly antiemetic therapies.

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Table 1
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Author [Ref]	Setting	Perspective	Comparison	Clinical data source (n)	Methods	Duration covered	Costs included	Measure of effects	Key findings and comments
Sykes [15]	UK, single centre	Hospital perspective	Oral ondansetron versus chlorpromazine + dexamethasone in single-fraction radiotherapy; with ondansetron for 3 days after radiotherapy	Randomised clinical trial ($n = 66$)	Cost-minimalisation, cost-utility (FLIE)	4 days	Direct medical costs and costs of rescue treatment during 4-day period	Total avoidance of emesis (nausea and vomiting) over 4 days. Patient FLIE scores and perceptions of treatment effectiveness by patients and investigators also recorded	In the ondansetron group the average cost per patient was £16.58 and in the chlorpromazine + dexamethasone group £3.44. The cost per successfully treated patient over 4 days was £20.24 in the ondansetron versus £18.13 for the chlorpromazine + dexamethasone group. FLIE scores were in favour of the ondansetron arm, whereas no differences were found in the FLIC. 98% of patients and investigators in the ondansetron arm said they would use the therapy again, compared with 75% in the combination arm. Flaw: no sensitivity analysis.
Zbronek [16]	USA, inpatient setting only	Hospital perspective	i.v. ondansetron versus metoclopramide in high-dose cisplatin chemotherapy (100 mg/m^2)	Meta-analysis of clinical trial results	Incremental cost–utility	24 h	Direct medical costs	Total number of episodes of nausea and vomiting avoided	The basic-case cost of treating a 70-kg patient with prophylactic antiemetic therapy amounted to $211 for ondansetron and to $155 for metoclopramide. This resulted in an incremental cost-utility ratio of $407 667 (cost per QALY) of ondansetron compared with metoclopramide. Flaws: Utility values were hypothetical and the overall methodology is questionable (e.g. hospitalisation costs for emetic episodes excluded, pooling of results which used different doses of antiemetic drug, inappropriate use of rescue therapy, inappropriate setting). Effects were measured over the full life of the patient, whereas costs were only measured during the 24 h of antiemetic treatment. Costs and effects of the underlying therapy were not included.

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Author [Ref]	Setting	Perspective	Comparison	Clinical data source (*n*)	Methods	Duration covered	Costs included	Measure of effects	Key findings and comments
Plosker [17]	UK	Review of all ondansetron-based studies	Three main studies reviewed for ondansetron	Clinical trials, not all randomised, some comparative	Cost-effectiveness and cost–utility	24 h	Direct medical costs	Patients treated successfully	The results of two studies of i.v. ondansetron versus metoclopramide in HEC are presented. Ondansetron had the same cost per successfully treated patient as metoclopramide at an acquisition cost 4 or 5 times that of metoclopramide (£10). The combination study favoured ondansetron, although clinical data were not derived from randomised clinical trials and findings would need to be confirmed in a head-to-head study.
Jones [18]	UK, one hospital	Hospital perspective	Several alternatives of 5-HT3-receptor antagonists (ondansetron or granisetron) +/− metoclopramide and dexamethasone. Alternatives include: i) HEC versus MEC, ii) acute versus delayed emesis, iii) extension to patients < 30 years	Literature review of clinical trial results and expert opinion of three UK oncologists	Decision analytical model (cost analysis). Scenario analysis based on alternatives described in preceding column	24 h + delayed phase	Only the costs of antiemetic acquisition and administration are considered in addition to full costs of chemotherapy administration (drugs, staff, hospitalisations, procedures)	Cost analysis	The decision-tree analysis used hypothetical data to test different scenarios for administration of antiemetic therapies in one UK hospital. The additional cost of 5-HT3-receptor antagonists was £32–£106 per patient and for acute and delayed emesis it was £118–£342 per patient. The authors found that the administration of 5-HT3-receptor antagonists (RA) would only increase the hospital budget by 3–10% if restricted to the prevention of acute emesis, whereas this increase would be 12–34% if extended to the delayed emesis phase. Costs were highly sensitive to the doses administered. The only two strategies which had a major budgetary impact (increment of +£50 per patient) were the addition of 5-HT3-RA antagonists to MEC, and to delayed emesis. This is a very interesting and original model for decision analysis, which highlights the need to make decision based on marginal cost-effectiveness. Flaw: no measure of outcome is included.

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Author [Ref]	Setting	Perspective	Comparison	Clinical data source (*n*)	Methods	Duration covered	Costs included	Measure of effects	Key findings and comments
Ballatori [19]	Italy	Hospital perspective	Ondansetron and dexamethasone versus metoclopramide, dexamethasone and diphenhydramine	Retrospective analysis ($n = 289$)	Cost-effectiveness	Study period	Direct medical costs, costs of rescue medication and adverse events	Patients treated successfully	The costs of the ondansetron regimen were higher than the costs of the metoclopramide regimen (L120 874 versus L32 085; L = Italian liras (L); 1 US$ = 1241 L, base year = 1991). However, taking into account the costs per successfully treated patient the costs of the ondansetron regimen decreases remarkable. In the first cycle in the ondansetron group it cost L180 062 and in the metoclopramide group L76 920. The incremental cost-effectiveness in the first cycle amounted to 458 048. Flaw: no evaluation of delayed emesis and indirect costs.

FLIE, Functional Living Index–Emesis; HEC, high emetogenic chemotherapy; MEC, mild emetogenic chemotherapy; QALY, quality adjusted life year.

data indicate that up to 45% of the doses applied for ondansetron were unapproved [21,22].

3.1.2. Perspective and setting

Economic analysis can be done to measure the impact of emesis on the hospital budget only, the healthcare system in general, third-party payers, the patient and his family or society at large. Most studies reviewed chose to limit their analysis to the hospital perspective. As oral administration becomes the standard route for antiemetic therapy, broadening the perspective to encompass the outpatient and home setting for patient care will become necessary for any results to be meaningful to clinical practice. There remains some uncertainty, however, about what proportion of antiemetic therapy is administered on an inpatient basis. Some studies had shown that outpatient chemotherapy was the norm in 80–90% of patients in the USA, whereas an observational study revealed that ondansetron was given as inpatient therapy in 76% of 670 patients in 23 American University hospitals [23]. In the study of antiemetic therapy administered for radiotherapy, the setting for the study becomes particularly important as many patients who receive radiotherapy on an outpatient basis and have good performance status may be admitted for at least an overnight stay due to anticipated emesis [15].

3.1.3. Type of emesis targeted: acute, delayed, anticipatory

Few of the cost-effectiveness comparative studies identified describe costs and effects for the full duration of antiemetic therapy. Moreover, authors unanimously state in the discussion of their findings that the cost-effectiveness ratio for the extension of the product in question to the prevention of delayed as well as acute emesis would not be as favourable. Given the medical need to reduce the occurrence of emesis beyond 24 h after chemotherapy (43% failure rate of existing antiemetics) [4], it is recommended that economic studies encompass the full period of anticancer treatment in their assessment of both costs and efficacy.

3.1.4. Measurement of costs

Several authors [12,13] have compiled a summary table of the direct medical costs to be considered in an economic analysis of antiemetics. Table 2 presents these costs in addition to non-medical direct costs and indirect costs associated with antiemetic treatment.

The comprehensiveness of the costs covered in an economic analysis obviously impacts on the results obtained. Most studies reviewed were limited to the evaluation of direct medical costs. This is linked to the fact that the setting chosen was most often that of inpatient care, and that the perspective was most often that of the hospital or of the healthcare system. Patient impact in terms of family life or time lost from usual activities was rarely included in the analysis. Issues related to the valuation of costs include:

1. *Acquisition costs*: The cost of an antiemetic can vary significantly from drug to drug or even from centre to centre.
2. *Duration of observation period*: Integration of medical costs further down the line after antiemetic therapy, namely costs of emetic episodes avoided or unsuccessfully treated, costs of adverse events and any change in healthcare use due to delays or dose reductions in chemotherapy regimens would ideally allow for a more accurate depiction of the full economic impact of antiemetics.
3. *Hospital costs*: The additional time spent in hospital due to emesis and/or adverse events is difficult

Table 2
Direct and indirect cost components of antiemetic therapies

Medical resource	Description
Direct costs	
Antiemetics	Acquisition cost of the antiemetic(s)
Antiemetic administration	Disposable items used in the administration of the antiemetic (i.e. alcohol swabs, needles, syringes, intravenous sets, normal saline solution)
Materials	Items used after an emetic episode or adverse event (i.e. mouthwash, linen, clothing)
Additional medication	Drugs used for 'rescue' treatment of emesis or for the management of adverse events associated with antiemetic therapy
Nursing staff	Time spent by nursing staff dealing with adverse events, emetic episodes (i.e. administer and empty vomit bowl, provide bed bath, change linen and clothes, clean floor) and comforting patients
Medical staff	Time spent by medical staff dealing with emesis and adverse events
Hospitalisation	Additional time spent in hospital due to inadequate control of emesis and/or adverse events
Formal home care (paid)	Assistance received by the patient in his or her home from nursing staff or other healthcare workers to cope with emesis and its sequelae
Informal home care (unpaid)	Assistance received from caregiver to help patient cope with emesis and its after-effects.
Indirect costs	
Time lost to usual activities	Time lost to usual activities, whether these be employment (work-days lost) or other non-remunerated activities.

to identify and is rarely included in economic analyses of antiemetic therapies.

4. *Non-medical costs and indirect costs:* Perhaps more importantly, limiting the costs to the hospital setting is not representative of today's clinical practice, where both antiemetic therapy and chemotherapy may be frequently administered on an outpatient basis and patients must cope with the effects of chemotherapy in their home environment [24]. The consideration of non-medical costs and of indirect costs is the most adequate reflection of the impact of emesis on the patient and on society in general.

3.1.5. Choice of economic methodology

The methods chosen to evaluate antiemetic therapies may include partial economic evaluation (cost analysis or cost–consequence analysis) or full evaluation in the form of cost–minimisation analysis, cost-effectiveness analysis, cost–utility analysis or cost–benefit analysis [2]. In the case of supportive care evaluation, it is difficult to apply standard cost–effectiveness or cost-utility methodologies, as the aim of therapy is not to impact on survival but to alleviate symptoms, which renders the expression of outcomes in terms of the traditional 'cost per life year gained' or 'cost per Quality Adjusted Life Year (QALY) inappropriate. Three studies reported the cost-utility of antiemetics [16,25,26]. Zbronek and associates calculated the cost–utility of ondansetron versus metoclopramide [16]. Data on incidence of emesis and costs were based on a literature review. The utility of one day of ondansetron treatment was estimated to be a gain of 0.05 unit compared with metoclopramide (0.05 per day = 0.00014 QALY). With an estimated cost difference of $56 for patients weighting 70 kg, the calculated incremental costs per QALY for ondansetron treatment amounted to $407 677 for these patients.

The study of Zbronek and associates was criticised by Grunberg and colleagues [26]. They performed a pilot study to generate a first approximation of a utility score for nausea/vomiting. Patients were asked to rate on a visual analogue scale their global HRQL during their previous cycle of chemotherapy with hypothetical absence or presence of nausea/vomiting as the only variable. The difference between the two health states was 0.52. A 25% reduction in emesis would result in an incremental utility score of 0.153. Furthermore, they assumed the benefit lasted the entire course of chemotherapy (3.5 weeks) instead of just 1 day. This resulted in a gain of 0.067 life-years and 0.010 QALYs. With a similar cost difference as in the study of Zbronek and associates, the cost:utility ratio for ondansetron is $5463 per QALY for patients weighing 70 kg. These studies show that caution must be paid when interpreting cost–utility outcomes. With equal costs and incidence of emesis, changing the assumptions of the utility value and its duration leads to a change in cost–utility from US $407 677 per QALY to US $5463 per QALY.

In order to express outcomes of antiemetic therapy in terms of a meaningful cost-to-effects ratio, the full integration of all costs and effects of antiemetic therapy should be projected over a sufficiently large period, namely from the onset of therapy throughout the full course of chemotherapy and beyond until the patient's eventual cure or death. This way, the dose-limiting or regimen-limiting impact of emesis can be projected. However, the limited timeframe of clinical trials from which costs and effects data may be derived does not allow for a comprehensive assessment of this sort. The building of a model for antiemetic treatment may prove to be helpful to extrapolate beyond results derived from clinical trials and project a full framework for the evaluation of antiemetic therapy. Several models have been presented [12,18,25]. Despite differences in underlying assumptions and applications, all these models allow the visualisation of the economic (and clinical) impact of antiemetic therapies over the full course of anticancer therapy.

3.2. HRQL studies of antiemetic therapies

Emesis may have a strong influence on a patient's HRQL, both in terms of direct impact through uncomfortable symptoms and by limiting a patient in fulfilling or enjoying his or her activities of daily living. The term emesis refers to three different phenomena that often occur simultaneously: nausea, vomiting and retching. The 1997 Perugia Consensus Conference on antiemesis [10] recommended that nausea be measured in terms of severity only (not frequency), whereas vomiting should be measured in terms of frequency. These data should be collected directly from patients in patient diaries. These measurements may, however, be complemented by more qualitative assessments of emesis using an emesis-specific instrument, or by measurements of the impact of emesis on HRQL, using a HRQL instrument.

3.2.1. Instruments used in HRQL studies

Seventeen reports were identified which addressed HRQL related to chemotherapy-induced emesis. Three studies were not taken into account; two studies were abstracts and one study only described utilities. Therefore, 14 studies were reviewed. In three studies, the EORTC QLQ C-30 was used, in one study, the Rotterdam Symptom Checklist and in six studies, the Functional Living Index — Cancer (FLIC) and Functional Living Index — Emesis (FLIE) alone or in combination were used. One study considered the RSCL, the FLIC and the FLIE. Other studies used a diary ($n = 2$), a Visual Analogue Scale (VAS) or a study-specific questionnaire to measure emesis. The studies showed a great

Table 3
Quality of life studies of emesis and antiemetics in the literature (1990–1997)

Author [Ref]	Cancer type, number of patients	Emetogenicity of chemotherapy	Antiemetic regimen	Instrument of assessment	Time of assessment	Interview schedule	Key findings and comments
Osoba [27]	Not reported, $n=433$	Highly or moderately	Various	EORTC QLQ C-30	7 days	Baseline day 8	Pretreatment HRQL has a predictive value on how patients will experience chemotherapy-induced emesis. In the week following chemotherapy, cognitive function, global HRQL, fatigue, anorexia, insomnia and dyspnoea were worse in the group experiencing emesis than in the group that remained free of emesis.
Osoba [28]	Various, $n=832$	Highly or moderately	5-HT_3 antagonists	EORTC QLQ C-30	7 days	Baseline	Study demonstrated that prechemotherapy HRQL scores, patient and treatment characteristics impacted on post-chemotherapy nausea and vomiting. Patients should be screened for these factors in order to improve control of nausea and vomiting.
Crucitt [29]	Breast lymphoma, $n=133$	Cyclophosphamide (moderately)	Ondansetron versus prochlorperazine	FLIC/FLIE	FLIC: 1–14 days FLIE: 3 days	Baseline day 3	Total control of emesis (vomiting only) during days 1–3 was 60% in the ondansetron group versus 20% in the prochlorperazine group. Nausea scores were also in favour of the ondansetron group on days 1 and 2, but the differences were not statistically significant. No differences were found for average pre- and post-treatment FLIC scores, nor for the FLIE nausea subscores. However, there was a difference of 19 points in favour of the ondansetron group after treatment on the FLIE vomiting subscale (with equal pretreatment values).
Bruntsch [30]	Various, $n=87$	Highly	Tropisetron	Diary	Day	Daily from days 1–7	Although tropisetron in combination with dexamethasone was significantly superior in preventing both acute and delayed vomiting and nausea, no changes from pre-treatment to post-treatment scores on mental or physical condition were observed, irrespective of the treatment arm.
Clavel [31]	Breast, $n=183$	Moderately	Ondansetron versus conventional antiemetics	RSCL FLIC/FLIE	RSCL: 7 days FLIC: 1–14 days FLIE : 3 days	Baseline day 3	The paper reviewed five clinical trials; HRQL was measured in two of the five studies. Ondansetron provides HRQL benefits compared with conventional antiemetics particularly as these patients are often treated on an outpatient basis and can be treated with oral ondansetron at home.
Clavel [32]	Breast, $n=259$	Moderately	Ondansetron versus alizapride	FLIC/FLIE	FLIC: 1–14 days FLIE: 3 days	Baseline day 4	Control of acute, delayed and overall emesis was significantly better in the ondansetron group. Significant differences in favour of ondansetron were found for the change in FLIE scores, but not for the change in FLIC scores. Both groups experienced deterioration in FLIC and FLIE scores from pretreatment to day 4, but the decline in FLIE scores was significantly less in the ondansetron group.
Soukop [33]	Breast, $n=187$	Moderately	Ondansetron versus metoclopramide	RSCL	7 days	Baseline day 5	Ondansetron was significantly superior in preventing both vomiting and nausea, in the day 1 analyses (acute phase) as well as in the day 1–5 analyses (overall) over all six courses. The differences were reflected in the HRQL data. There was a significant difference in the psychological subscale in favour of the ondansetron group after the first course, becoming more pronounced over the series of courses. No differences were observed after the first course on the functional activity and the physical subscales. Over the series of courses, there were trends in favour of the ondansetron group on both of these subscales.

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Table 3
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Author [Ref]	Cancer type, number of patients	Emetogenicity of chemotherapy	Antiemetic regimen	Instrument of assessment	Time of assessment	Interview schedule	Key findings and comments
Berry [34]	Various, $n=190$	Highly or moderately	Ondansetron compassionate-use programme	FLIE	3 days	Retrospectively	Total FLIE scores were transformed to a 100-point scale, where a score of 100 means is the best. The mean FLIE score was 65.5 for ondansetron treatment compared with 39.5 for previous treatment ($P<0.01$). The difference in scores is probably overestimated because of the time of assessment (both after treatment with ondansetron).
Garbe [35]	Melanoma, $n=90$	Highly	Tropisetron 5 mg versus 10 mg	Scale 0–8 in diary	Day	Day-1 end treatment (=days 1, 5 or 10)	Patients rated their mood, their food intake and their overall quality of life using numerical scales. No differences were found between groups in the incidence of acute and delayed nausea and vomiting, nor in patient scores.
Sorbe [36]	Various, $n=259$	Highly	Tropisetron versus metoclopramide/ dexa cocktail	Study-specific questionnaire	Not reported	Baseline day 7 both courses	Total control of acute vomiting was comparable in both treatment arms. Total control of acute nausea was significantly lower in the tropisetron group. Both delayed vomiting and delayed nausea were comparable between the treatment arms. Patients reported more nausea, vomiting, being ill, being tired or sleepy and having more problems with eating post-treatment versus pretreatment.
Barrenetxea [37]	Breast, $n=182$	Moderately	Three ondansetron regimens	FLIC or FLIE	1/14 days	Daily days 1–5	The FEC regimen was expected to be more emetogenic than the CMF regimen. Therefore, analyses were performed by regimen. For patients receiving the FEC regimen, the best emetic control was obtained with schedule A, both in the acute and in the delayed phase. Patients treated with schedule A had the best FLIC scores during days 1–4, but the difference was only significant on day 3 compared with schedule B. When patients receiving CMF therapy were considered, emetic control with schedule C was significantly less compared with A and B, both in the acute phase and in the delayed phase. FLIC scores in this patient group followed the same pattern: significantly lower scores on every day of follow-up compared with A and B.
Lindley [38]	Various, $n=162$	Weakly moderately highly	Various	FLIC, FLIE	3 days both	Baseline day 3	The mean difference between pretreatment FLIC scores was — 18 points for those with emesis and — 2 points for those without emesis. The mean changes in FLIE scores were — 30 points and — 1 point, respectively. These results support validity for the FLIE and the contribution of nausea and vomiting to the decline in general functioning (FLIC) scores.
Pater [39]	Various, $n=407$	Moderately	Four different regimens	EORTC QLQ C-30	7 days	Baseline days 4 or 8	Results were reported only for the comparison of dexamethasone alone groups versus dexamethasone plus 5-HT_3 antagonist groups. Of all functioning and symptom scales measured by the QLQ C-30, only two were significantly different between these two groups: the decline in social functioning in the dexamethasone alone group was — 6.0 points (on a 100-point scale) compared with — 0.8 point in the dexamethasone plus 5-HT_3 group. Conversely, patients in the 5-HT_3 group had a greater increase in obstipation compared with the dexamethasone alone group (+26 points versus +13 points).

(continued)

Table 3
(continued)

Author [Ref]	Cancer type, number of patients	Emetogenicity of chemotherapy	Antiemetic regimen	Instrument of assessment	Time of assessment	Interview schedule	Key findings and comments
O'Brien [14]	Various, $n=128$	Moderately highly	—	FLIE	3 days	Baseline day 1	On day of chemotherapy 41% of the patients experienced emesis with or without nausea. Over the 5-day study period at least 78% of the patients reported at least one episode of nausea or emesis. The FLIE scores indicated a decline in functional status after chemotherapy. On the day after treatment the main impact was from emesis, particularly with regard to leisure activities, household tasks and hardship to the family. Nausea had a greater improvement than emesis on overall functioning.

HRQL, health-related quality of life; CT, chemotherapy; FLIC, Functional Living Index on Cancer; FLIE, Functional Living Index–Emesis; RSCL, Rotterdam Symptom Checklist; dexa, dexamethasone; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

variability with respect to study design and completeness of reporting the outcomes. An overview of the studies is given in Table 3. In the study of Sykes and colleagues FLIE scores are presented [15]. However, the results of this study have already been described in Table 1.

3.2.2. Choice of instrument

The choice of instrument used to assess the influence of emesis on HRQL is dependent on the chosen scope of analysis. If one wishes to measure the impairment caused by emesis as such, an instrument specific to emesis should be used. If one wishes to look at the influence of emesis and antiemetic therapy on HRQL, a HRQL instrument should be used. Most studies chose the latter approach, however they isolated the specific items on emesis from HRQL instruments which were designed to measure a broader scope of domains than purely emesis. For example, the Rotterdam Symptom Checklist and the EORTC QLQ C-30 both contain one question about vomiting and one question about nausea [40,41], and the Functional Living Index on Cancer (FLIC) has only one question about nausea [38]. Isolation of the 'emesis' items from these instruments does not constitute appropriate measurement of emesis as such, and the entire profile of the domains obtained through the instrument should be looked at to evaluate HRQL. The only emesis-specific instrument identified was the Functional Living Index — Emesis (FLIE) [38]. This module, originally intended to be administered with the FLIC, consists of 18 items regarding the severity of nausea and vomiting and the impact of these symptoms on several domains of functioning and activities. The timeframe used in this module is 'the past 3 days' and each item is scored on a 7-point scale ranging from 'not at all' to 'a great deal'.

3.2.3. Interpretation of findings from HRQL studies

There are several issues concerning the measurement of HRQL alongside clinical antiemetic trials. First, HRQL is a multidimensional concept, and the impact of antiemetic therapies must be viewed in terms of patient scores in all domains contained in the chosen instrument. A second difficulty is the interpretation of a difference in HRQL between treatment arms or over time once such a difference is found: if a deterioration in HRQL after treatment is observed compared with pretreatment values, it is difficult to determine which part of the decline is attributable to nausea/vomiting alone and which part to other effects of treatment or the combination/accumulation of all treatment effects. Moreover, because antiemetics do not directly influence treatment outcomes with respect to the disease itself, patients in most antiemetic trials are not homogeneous with respect to cancer type, stage of disease and chemotherapy regimen, although comparability between treatment arms is either aimed at by stratification, or corrected for in the analyses. Finally, antiemetics may impact over a period of 1–5 days, whereas anticancer therapy will usually be administered in 3-weekly cycles. The time of assessment HRQL and the interview schedule will determine whether the the impact of antiemetics on HRQL could be measured adequately. Thus, the attribution of differences in HRQL scores to antiemetic therapies may only be verified if sufficient correction for the confounding effects of the anticancer regimen, cancer type and patient characteristics are made.

4. Discussion

4.1. Recommendations for trial design

Phase III comparative trials are the ideal setting for the prospective collection of economic and HRQL data. Of the studies described in Table 1, none involved prospective economic data collection alongside a randomised clinical trial. Most studies combined prospective clinical data with economic assumptions or data collected in separate costing studies. In other words, economic data collected from one source are matched to clinical trial data from a separate source. This combination of data poses obvious methodological problems, and the prospective, parallel collection of clinical, economic and quality of life outcomes is clearly a preferable methodology.

In phase III trials, the most critical issue is the relevance of the comparator chosen. The literature is rich in recommendations and comparative studies of efficacy between antiemetic therapies [6,7,10]. It is critical to respect these recommendations in order to ensure that trial results are as meaningful as possible to practising physicians and their patients.

In order for economic data collection to be relevant, it is important that resource use is recorded in a reliable way during the full course of therapy. Ideally, resource use and clinical data should be recorded during the administration of antiemetic therapy, as well as in-between chemotherapy cycles, in order to assess fully the impact of antiemetic treatment over the full course of chemotherapy. The collection of economic resource data should not be restricted to the hospital, as most therapy is now given on an outpatient basis. In order to adequately assess the impact of emesis on the patient and his/her family, patients must be asked to record use of home care, caregiver time and indirect costs in diaries. The collection of this information may be done simultaneously with that of emetic episodes, intensity of the emetic episodes and HRQL or emesis-specific instruments. However a cautionary note should be added as the use of diaries to collect patient data

although useful is associated with a number of pitfalls such as the recording of inaccurate or incomplete data.

The presentation of results from economic studies must include a full description of which effects are measured, and specifically state whether the trial objective is to assess acute only or acute, delayed and anticipatory emesis. The recommendations of the Perugia consensus panel [10] are to encompass all three dimensions of emesis in the trial setting. Emesis must also include measurement of vomiting and nausea, using patient diaries and any additional tools.

Additional tools may include HRQL measurements, such as the RSCL, the EORTC QLQ-C30 or the FLIC, or specific measures of the impact of emesis on daily functions, such as the FLIE. The choice of instrument will depend on the chosen scope for measurement, namely HRQL in general or the specific impact of emesis on functioning. These data may complement data retrieved from patient diaries and help differentiate between competing therapies. The advantage of the FLIE is that the patient is asked how much his daily life has been disrupted *due to* vomiting and nausea and it thus allows for specific measurement of the impact of emesis or antiemetic therapies on functioning. Assuming that a patient is able to distinguish between reduced functioning caused by emesis and reduced functioning due to other causes, this makes the interpretation of the outcomes easier. However, experience with the FLIE in clinical trials is limited and further research is needed to assess the responsiveness of this instrument in the clinical trial setting. Moreover, publications on the psychometric properties of the FLIE are fairly scarce.

An important consideration in the selection of instruments to complement the evaluation of emesis is the timeframe of each instrument and that of the clinical trial in which it is administered. The timeframe of the questionnaire should be carefully considered and, if necessary, be adapted to the purpose of the specific study (acute control versus delayed control or overall control). If patient groups are not stratified for risk factors of developing chemotherapy-induced emesis before treatment, the distribution of these factors (including pretreatment HRQL scores) should be considered as potential confounders at the time of analysis.

Finally, if a full economic evaluation is intended, a suitable methodology would be to evaluate the incremental cost-effectiveness of a novel antiemetic versus existing antiemetics in combination with chemotherapy regimens. The outcome can then be expressed in terms of incremental costs per incremental outcome, and the most methodologically sound outcome would be the number of patients in whom total control of nausea and vomiting is achieved over the full course of antiemetic treatment, i.e. a cost per totally-controlled patient. Comparative analyses can then be done to measure the marginal cost-effectiveness of applying this therapy to different chemotherapy regimens (high, moderate, mild emetogenicity) and different patient populations (adult, paediatric) or for different durations of emesis control (acute, delayed, anticipatory emesis). However, the specificity of such a measure precludes the comparison of results with those from other cancer therapies. Nevertheless, it could help in allocating resources to competing antiemetic therapies in the clinical setting.

5. Conclusion

Over the past few years, emesis and the comparison of antiemetic therapies has been a relatively interesting area for economic research. However, the data available quickly become obsolete with the changing recommendations for new therapies. Furthermore, economic endpoints have become a must for the promotion of these therapies, and cost considerations are an intrinsic part of the product profile in a crowded antiemetic market. Developers of these new products can facilitate the inevitable choices which hospital budget holders and clinicians will face in choosing between antiemetics by providing timely, methodologically sound and meaningful economic data in tandem with the proof of the clinical efficacy of their products.

Cost data, HRQL data and a clear measurement of the impact of therapy on patients as well as of patient preferences for competing therapies are equally important. It is this combination of data, which will allow treating physicians to comprehensively assess the relative value of old and new antiemetic therapies and optimally, provide the most cost-effective therapy to their patients.

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