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Title: Systematic review of [the efficacy of](#) antiemetics in the treatment of nausea in patients with far advanced cancer

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ABSTRACT

Objectives: To systematically review studies of antiemetics used in the treatment of nausea in patients with far-advanced cancer.

Data Sources: Randomized controlled trials (RCT) and uncontrolled studies identified by electronic and hand searching.

Review methods: Identified studies were appraised for quality and effect size.

Results: Twenty-one studies were included. Two were systematic reviews, seven were randomised controlled trials (RCT) and 12 were uncontrolled studies or case series. Differences in interventions and outcomes amongst the RCT precluded any quantitative data synthesis and all seven studies were prone to bias. Whereas uncontrolled studies indicated a high response rate to standard regimens (75-93% for both nausea and vomiting), RCT produced much lower response rates to these agents (23-36% for nausea, 18-52% for vomiting). The two methods of antiemetic choice (choice based on either the inferred mechanism or else empiric) were equally effective. There is reasonably strong evidence for the use of metoclopramide in cancer-associated dyspepsia and steroids in malignant bowel obstruction. There was conflicting evidence about the efficacy of serotonin antagonists compared with standard treatments (e.g. metoclopramide, dopamine antagonists or dexamethasone). There is little or no evidence about the efficacy of some commonly used and seemingly effective drugs such as haloperidol, cyclizine, or methotrimeprazine.

Conclusion: Evidence supporting the existing consensus-based guidelines for management of nausea and vomiting in advanced cancer is sparse. Current approaches to treatment based on the neuropharmacology of the emetic pathway may be inappropriate in this setting. Well-designed studies of the impact of “standard” management and novel agents on nausea and vomiting in palliative populations are needed.

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1. INTRODUCTION

Nausea and vomiting are common experiences of patients with advanced cancer, independent of exposure to chemotherapy. Approximately 60% of patients with advanced cancer report nausea and 30% report vomiting,[Davis] often rating them as a source of great distress.[Portenoy] The management of nausea and vomiting is prominent in palliative care textbooks [Mannix] but these symptoms are under-treated in patients with advanced cancer [Reuben]. The development, dissemination and implementation of evidence-based clinical practice guidelines (CPG) based on specialist palliative care practice may empower health care professionals to improve the management of nausea and vomiting in patients with advanced cancer.

A key feature of specialist palliative care is that the assessment and treatment of symptoms is based on a sophisticated understanding of symptom pathophysiology. The pathophysiological mechanism is inferred from careful assessment of the patient's history, physical examination and diagnostic test results. This approach is best studied for pain,[Ashby] but may provide a useful paradigm for the assessment and management of other symptoms. The differential diagnosis of nausea and vomiting in patients with advanced cancer is long. Antiemetic choice is based on identifying the likely mechanism of the symptoms from the clinical picture and applying knowledge of the neuropharmacology of the emetic pathway [Grunberg, Peroutka]. Experts in the field claim that the cause of nausea and vomiting can be determined clinically in 90% cases [Bentley, Lichter1], although they recognise that the cause is usually multifactorial. It is claimed that more than 80% of patients can have their nausea and vomiting controlled when treated in this way [Bentley, Lichter2]. The evidence upon which this claim is made warrants review.

Based on the success of educational interventions for assessing and treating cancer pain, we propose to develop an evidence-based CPG for non-specialist clinical providers of palliative care to guide their assessment and treatment nausea in patients with advanced cancer. The purpose of this systematic review (SR) was to evaluate all known controlled and non-controlled trials pertaining to the efficacy of pharmacological therapy for nausea in advanced cancer, in order to inform the development of the CPG. It was expected that the number of studies identified would be small and that the variation in study methodology would preclude a quantitative meta-analysis.

2. METHODS

The review conformed to the QUOROM statement's standards for improving the quality of reports of meta-analyses [Moher] and the criteria for informing CPG development outlined by the National Health and Medical Research Council (NHMRC) of Australia [NHMRC]. The assessment of study quality was based on the level of evidence provided, validity of the results and the effect sizes reported.

2.1 Search strategy

The search was carried out in three steps. The search strategy for the identification of studies included (a) electronic searching of the US Clinical Guidelines Repository [www.guideline.gov] and the Cochrane Library's Systematic Review And Clinical Trial Registry, (b) the Ovid Medline and EmBase electronic databases of the medical literature, and (c) hand-searching of targeted sources.

The search of the Clinical Guidelines Repository and the Cochrane Library used the search terms *nausea*, *cancer* and *palliative care*. The Ovid Medline (1966-week 4, June 2003) search used combinations of the key words and exploded Medical Subject Headings (MeSH) terms *nausea*, *vomiting*, *antiemetics*, *palliative care*, *hospices*, *hospice care*, *terminal care*, and *neoplasms*. The initial search was limited to studies in humans published in English. The identified citations were then further limited to meta-analyses, randomised-controlled trials and clinical studies. The same terms were used for the EmBase (1980 - 2003 week 26) search.

To identify any articles missed by the electronic search, the bibliographies of the electronically identified articles and consensus-based guidelines, and the chapter on nausea and vomiting of the Oxford textbook of Palliative Medicine (2nd edition) [Mannix] were hand-searched. The Table of Contents of all issues of five palliative care journals that publish experimental data (Palliative Medicine, Journal of Pain and Symptom Management, Journal of Palliative Care, Journal of Palliative Medicine, Supportive Care in Cancer) and three major oncology journals from 1993 to mid-2003 (Journal of Clinical Oncology, Cancer, British Journal of Cancer; all 1993-present) were also hand-searched.

2.2 Study characteristics and selection

Publications from the various sources were screened for retrieval according to their titles. Systematic reviews, randomised controlled studies, Phase I/II clinical trials, well-designed cohort/case-control studies and case series were considered. Single case-reports, clinical examples and expert opinions were excluded. If the title of the study appeared relevant, the abstract was read and screened for the following pre-determined inclusion/exclusion criteria:

- (i) the study involved clinical research in humans
- (ii) the study participants had cancer at an advanced stage
- (iii) the study objective was to evaluate a pharmacological intervention aimed at controlling emesis and the intervention was clearly described
- (iv) the study objective was not primarily aimed at evaluating (a) antiemetics for the control of nausea and vomiting caused by emetogenic chemotherapy (b) agents for the treatment of bowel obstruction other than the standard antiemetics (such as surgery, tubes, or drugs intended to control secretions such as hyoscine or octreotide), and
- (v) the Results section reported a clearly-described measurement of the baseline symptoms and the treatment effect (reduction of nausea or vomiting, measured either subjectively or objectively).

The full article was retrieved for more detailed evaluation only if it met all of these criteria and was published in English.

2.3 Validity assessment

The level of evidence was determined using the NHMRC criteria (Table 1). The risk of bias in the randomised trials and the quasi-experimental studies was evaluated independently by two of the authors (PG, GP) according to the *Methods for Evaluating Research Guideline Evidence (MERGE)* document (Table 2).[Liddle] The results were then compared and disagreements resolved by consensus. The major source of bias to be identified in the case of the SR was publication bias. The major

sources of bias to be identified in primary trials included non-concealment of treatment allocation (in the case of randomised trials) and loss to follow up and failure to carry out an intention-to-treat analysis (in both randomised and non-randomised trials).

2.4 Data abstraction and quantitative data synthesis

The first author abstracted the data. It was anticipated that the quality of the studies and the nature of the data would preclude quantitative data synthesis. If quantitative data synthesis appeared possible, it was planned to consult a biostatistician to assess the data for heterogeneity, to combine the results and to quantify the extent of any publication bias; no *a priori* sensitivity or subgroup analyses were under consideration prior to the commencement of the review.

3. RESULTS

3.1 Trial flow.

The search of the web-based Clinical Guideline Repository yielded 50 citations, of which three concerned nausea and one of which appeared relevant [Finnish]. However, this guideline was not evidence based, contained no data and provided no references and was therefore excluded. The search of the Cochrane Library resulted in 48 citations regarding nausea and vomiting in cancer, however none was deemed relevant to the topic of this review. A Cochrane review of steroids for the relief of bowel obstruction was missed by the search but was subsequently identified as a Topic Review while performing the Medline search.

The initial Medline and EmBase searches for nausea and vomiting in advanced cancer produced a list of more than 1100 citations, of which only 22 (1.9%) had titles that appeared relevant to the topic of the review. Limiting the search to meta-analyses revealed seven citations, only one of which appeared relevant [44], the others all relating to chemotherapy-induced emesis. A systematic review of haloperidol, published as a letter and not coded electronically as a systematic review, was found subsequently when searching for uncontrolled studies [Critchley].

Limiting the electronic search to RCT resulted in the identification of five relevant publications out of almost 400 citations that were retrieved for closer evaluation.[Hardy 02, Bruera 94, Bruera 00, Mystakidou, Mystakidou]. Seven uncontrolled studies were also located electronically that met the review criteria [Bentley, Wilson, bruera, lichter, Jackson. Currow], .

Hand searching revealed one randomized trial [Corli] and two uncontrolled studies [Porcel, TwyX] that had been missed by the electronic search. No meta-analyses or SR were missed. Three guidelines or algorithms were also identified that were not included in the online repository.[TGA, Regnard, Twyx&Back]. None was evidence-based.

A second electronic search for studies specifically about nausea in inoperable bowel obstruction revealed 77 publications of which 12 (16%) appeared relevant. Five of the twelve met the inclusion criteria consisting of one meta-analysis,[Feuer] the two RCT considered in the meta-analysis [Hardy 98, laval] and two case series.[baines, ventafriidda]. Hand searching identified another case series missed by the electronic search.[Fainsinger]

3.2 Study characteristics

Twenty-two studies were initially assessed (see Tables 2 and 3). There were nine studies providing NHMRC Level I or II evidence and 11 studies providing Level III or IV evidence (uncontrolled studies or cases series). The Level I/II studies consisted of two SR [Critchley, Feuer] and eight RCT, six on nausea [Hardy 02, Bruera 94,00; Corli, MystakX2] and two on bowel obstruction [Hardy 98, Laval]. One RCT on nausea that met the inclusion criteria was excluded after retrieval when it was found to contain duplicate data published in another included study [Mystak]. The electronically identified “meta-analysis” turned out to be an uncontrolled study [Wilson]. Ultimately, 21 studies were included in the review: two systematic reviews, seven RCT and 12 uncontrolled studies.

3.3 Quality appraisal

The quality of the Level I-III studies was appraised. The SR were at low risk of publication bias but the evidence they provide on the control of nausea is weak. The results of the quality appraisal of the Level II-III studies are shown in Table 2. The majority of the primary RCT were at low-moderate risk of bias. Strengths of the RCTs included: blinding, use of valid and objective measures and use of intention to treat analysis. The main weaknesses of the studies were failure to state how the allocation of randomisation was concealed, loss to follow-up, and failure to undertake studies at more than one centre so that reproducibility of the results is unknown. The two assessors agreed on 40/56 (71%) ratings of methodologic quality for the seven RCT; the differences were resolved by consensus.

The Level III studies were even more susceptible to bias: all were rated as being of at least moderate-to-high risk of bias. The main strengths of the Level III studies were that refusals were well documented, and there was complete follow-up. The main weaknesses were that the populations were poorly defined, the measures were not validated, there was no adjustment for confounders, and they were all single centre studies.

All but one of the RCT were small (<100 patients) and few had the sample size based on a power calculation. Measurement of effect was generally simplistic (e.g. percentage of responses to treatment). Confidence intervals or other indicators of the precision of these estimates of effect size were not given in any of the studies.

3.4 Quantitative data synthesis

The five RCT on nausea compared very different populations, treatment regimens and outcome measures, so a quantitative data synthesis was impossible. Qualitative syntheses of the study results are summarised in Table 3 and 4. Whereas the uncontrolled studies had high response rates (75-93%) to standard regimens, the RCTs had much lower response rates (23-36% for nausea, 18-52% for vomiting). Similar response rates were achieved whether drug selection was empiric [Bruera, Bruera, Corli, Mystakidou] or based on the patient’s clinical picture.[Hardy, Bentley, Ichieter, Wilson]

Metoclopramide was superior to placebo in one of two small, controlled studies.[Hardy 02, Bruera 00] The evidence for many other anti-emetics that are used routinely in palliative care, such as haloperidol, prochlorperazine, cyclizine and

methotrimeprazine is weak or non-existent [Cirtchley, Lichter, Bentley, Twycross]. This is also the case for newer agents like olanzepine and synthetic cannabis derivatives [Jackson, passik, Walsh).

One RCT of the dopamine-antagonist levosulpride found it to be superior to metoclopramide [Corli]. A small body of experimental data suggests serotonin antagonists may be at least as effective in the management of nausea in advanced cancer - if not more so - as the traditionally used antiemetics such as metoclopramide, dopamine antagonists and dexamethasone.[Currow, hardy, Mystak, porcel].

In the case of bowel obstruction, steroids appear to be effective in hastening its resolution but there is no data as to whether they are anti-emetic *per se* {Feuer, Hardy 98, Laval] **While there is Level I evidence for the use of steroids in bowel obstruction, the effect size obtained was small and showed a non-significant statistical trend for efficacy.**

4. DISCUSSION

This review has shown that the evidence base for the pharmacological treatment of nausea and vomiting in advanced cancer practiced by palliative care specialists is generally weak and contradictory. The small number of well-designed studies, the variation in the interventions studied and the lack of uniformity in outcome measurement precluded a formal meta-analysis of the results of the review being performed. Not surprisingly, the response rates to anti-emetic treatment were lower in the controlled studies than the uncontrolled ones. The findings of this review have major implications for clinicians and researchers.

There are two possible approaches to drug selection for controlling symptoms such as nausea. The “mechanistic” approach, favoured by palliative care specialists, attempts to infer the pathophysiological abnormality producing nausea from the patient’s clinical picture and anti-emetic selection is based on the current understanding of the neuropharmacology of the emetic pathway [Lichter1]. Alternatively, an empiric approach can be followed, trialing various anti-emetics without regard to the underlying cause of the nausea. The two prospective audits of current practice [Bentley, lichtner2] suggest the mechanistic approach is effective. The empiric approach may also be highly effective [Bruera, bruera, Mystak, Corli] however and the two have not been directly compared. If a mechanistic approach is to be followed, it is unclear whether an accompanying algorithm for prescribing is needed [bentley] or not [Lichter2]; either way, 80-90% of nausea responds to treatment. Empiric use of anti-emetics acting on multiple receptors, such as methotrimeprazine, olanzepine and levosulpride may be as effective as more specific agents selected by the mechanistic approach, but research on this possibility is needed.

Support for adhering to a mechanistic approach to drug selection is provided by the studies of metoclopramide, which has been the most widely studied agent. Metoclopramide appears to be more effective than placebo,[Bruera 00, hardy] with a 75% response rate when used for a gastroparetic mechanism (the cancer-associated dyspepsia syndrome,[Bruera00]) compared to a 30% response rate when prescribed empirically [Bruera 96, Mystak]. There is very little evidence from well-designed

studies for other anti-emetic agents that are widely prescribed in palliative care such as haloperidol, cyclizine and methotrimeprazine [While a systematic review of haloperidol has been published \[Critchley\], the current evidence base is weak. Well-designed studies testing the efficacy of these agents are urgently needed.](#)

The efficacy of steroids as antiemetics is also dependent on the approach to drug selection that is taken. Used empirically, steroids have been used as adjuvants in patients with nausea not responding to other therapy, although the results are conflicting [Bruera, mystak]. Taking a mechanistic approach, there is Level I evidence for the effectiveness of steroids in symptomatic malignant bowel obstruction. This conclusion is based on just two controlled studies involving a total of only 89 patients [Feuer] and the effect size was small (NNT 6, 95% CI 3 to ∞). Studies of scopolamine and octreotide in malignant bowel obstruction were intentionally excluded from the review because of the scope of the proposed CPG (Ripamonti, mercadente).

The previously limited use of 5HT₃ receptor antagonists in palliative care practice may need to be reviewed given that there have now been two RCT supporting the findings of previous positive case series and case reports. Although one of the studies found only a non-significant trend favouring ondansetron over placebo, it may have been statistically under-powered to detect a difference [Hardy 02]. In the other study, tropisetron was more effective than conventional agents like metoclopramide and chlorpromazine but drug selection was empiric and deficiencies in the study design, as reported, meant the results were at a high risk of bias [Mystak]. Because the chronic nausea associated with advanced cancer is multifactorial and involves many different receptor systems, the large body of evidence for the treatment of acute nausea and vomiting due to highly emetogenic chemotherapy has not been considered [Bartlett]. Because of concerns over toxicity, such as constipation, and the cost of therapy, more well designed studies of the 5HT₃ receptor antagonists for the nausea associated with far-advanced cancer are needed.

While there remains such a paucity of data from well-designed and clearly described studies, the management of nausea in advanced cancer will continue to be based on expert opinion rather than evidence. Inference from the basic science of the emetic pathway will also continue, even though it may not be the appropriate paradigm. At least most of the standard antiemetics are inexpensive and well tolerated. More research is needed before expensive agents like the serotonin antagonists and olanzepine can be recommended.

As with many areas of palliative care, the lack of evidence for current practice is due to an absence of data rather than a body of negative results. The implication of this review is not to cease current practice in treating nausea in patients with advanced cancer. Rather, it highlights that well-designed, high-quality studies to test and refine the hypotheses raised by more than thirty years of clinical experience are urgently needed. Only then will it become clear how relevant are our current approaches and how we can best use currently available treatments.

Based on the results of this review, the following nine recommendations, graded with supporting evidence, as the basis for CPG, using the grades of recommendations

proposed by the US Department of Health and Human Services' Agency for Health Care Policy and Research:[AHCPR]

- the current mechanistic approach to the management of nausea in advanced cancer which is based on the neuropharmacology of the putative “emetic pathway” should be the basis for choosing first-line antiemetic drugs (*grade of recommendation: B; references: Bentley, Lichter*)
- utilizing a CPG may be effective for the management of nausea and vomiting in patients with advanced cancer (*C; Finland, Regnard, Twy&Back, TGL*)
- metoclopramide is effective in the management of nausea in advanced cancer (*A; Bruerax3, Hardy*)
- haloperidol may be effective in the management of nausea in advanced cancer (*C; Bentley, Lichter, Vf, Critchley*)
- other standard antiemetics recommended for the management of nausea in advanced cancer, including cyclizine, steroids and methotrimeprazine may be effective in the management of nausea in advanced cancer (*B; Lichter, Bentley, Twyx*)
- serotonin antagonists are more effective than metoclopramide and chlorpromazine in the management of nausea and vomiting from advanced cancer (*A; Hardy, Mystak*)
- the novel agent olanzepine may be effective in the management of nausea in advanced cancer (*B; Passik, Jackson*)
- cannabinoids like nabilone may be effective in the management of nausea in advanced cancer (*C; Walsh*)
- steroids are effective in hastening the resolution of bowel obstruction (*A; Feuer*)

Grade of recommendations:

A: at least one RCT as part of a body of literature of good quality and consistency addressing the specific recommendation

B: well conducted clinical studies but no RCT on the topic of the recommendation

C: evidence from expert committee reports or opinions, or opinions of respected clinical authorities; no directly applicable clinical evidence of good quality

Like any SR, this summary of evidence is prone to publication bias. Although the two main medical electronic databases (Medline, EmBase) were accessed, other databases (e.g. Cancer Lit, CINAHL, Current Contents) could also have been searched. Ideally, the searches would have been re-run using the MeSH terms of the studies that were identified by the hand-search. However, only two such articles were found,[9,13] the sensitivity of the search was good, and its specificity was extremely low. Other data sources could have been pursued including searching for unpublished studies through conference abstracts, theses and contacting authors. Such an exhaustive approach was beyond the available resources.

The extensive hand searching undertaken was a strength of this study, given the relatively high rate of published palliative care articles that do not appear on electronic databases. Only one investigator carried out the publication retrieval, which is a potential methodological weakness. However, in view of the low specificity of the

search strategy it was not feasible for more than one person to retrieve the publications within the available resources.

It is clear that much more research needs to be done on the pharmacological management of nausea in patients with advanced cancer. Well-designed studies using standard regimens and agreed outcomes of all agents – standard and novel – are needed. Placebo-controlled studies may be justified but are unlikely to be acceptable in clinical practice and to institutional review boards. It is particularly important to compare newer, more expensive drugs (eg serotonin antagonists, olanzepine, aprepitant [Chawka]) with conventional, cheaper drugs (eg metoclopramide, haloperidol, cyclizine).

More research is needed on the epidemiology and assessment of nausea and vomiting. There are few studies on the incidence, prevalence or frequency of nausea and vomiting. There are currently no well-established assessment tools. The results of this study also reinforce the need, recognised by others,[Bruera 87] to rethink our approach to the management of nausea in advanced cancer which is currently based on the mono-mechanistic paradigm of chemotherapy induced emesis. While this may be appropriate in some circumstances, e.g. opioid-induced emesis, in many cases, the cause of nausea in advanced cancer is multifactorial and multidimensional and involves systems other than the “emetic pathway” that determines chemotherapy-induced emesis. Even if the neuropharmacology of the emetic pathway is appropriate for advanced cancer, the previous insistence on using single agents to affect specific receptors may be *passee*, as many of these agents are known to affect multiple receptors [Peroutka, twycross]. Clinical trials of “dirty” drugs like methotrimeprazine are needed.

If drugs like the serotonin antagonists become more important in palliative care, then the emerging field of pharmacogenomics will also become more relevant to palliative care [McLeod]. These and many other drugs commonly used in palliative care (e.g. codeine, dexamethasone, NSAID) are metabolized by, induce or inhibit enzymes in the Cytochrome P450 system [Rogers] and the effect of genetic polymorphism on this system are also being recognized [Bernard]. A pharmacodynamic interaction between morphine and 5HT3 antagonists has recently been identified [Shoji].

Conclusion

Evidence supporting the existing consensus-based guidelines for management of nausea and vomiting in advanced cancer is sparse. Current approaches to treatment based on the neuropharmacology of the emetic pathway may be inappropriate in many cases of nausea in this setting. Well-designed studies of the impact of standard management and novel agents on nausea and vomiting in palliative populations are needed.

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Table 1. Designation of levels of evidence (adapted from reference 31).

Level of evidence	Study design
I	Systematic review of all relevant RCT
II	At least one properly-designed RCT
III-1	Well designed pseudo-randomised trials
III-2	Non-randomised comparative studies, cohort studies, case-control studies, interrupted time series with a control group
III-3	Comparative studies with historical control, two or more single arm studies, interrupted time series without a control group
IV	Case series, either post test or pre-test/post test

Table 2. Quality assessment of the Level II and level III studies, using MERGE criteria to evaluate various aspects of study design (columns 2-9) and overall quality assessment (column 10)

1. RCT

Author, year [reference number]	CRA	Blinding	Reliable, valid measures	Objective measures	Adjust for confounders	Loss to follow-up	Intention to treat analysis	Homogenous results across sites	OVERALL <i>QUALITY</i> ASSESSMENT
1. N&V									
Hardy 2002 [19]	A	B	A	A	B	C	A	?	BB
Bruera 2000, [8]	?	A	B	A	A	B	A	?	BB
Mystakidou 1998 [29]	?	?	B	A	B	B	A	?	CC
Corli 1995 [9]	D	B	A	A	A	A	A	?	BB
Bruera 1994 [6]	?	A	A	A	A	B	A	?	BB
2. BO									
Laval 2000 [22]	?	B	D	?	C	C	A	D	CC
Hardy 1998 [18]	?	A	A	A	A	B	A	D	BB

2. Cohort or before-after studies

Author, year [reference number]	Participants well- defined	Refusals	Reliable, valid measures	Adjust for confounders	Loss to follow-up	Intention to treat analysis	Homogenous results across sites	OVERALL <i>QUALITY</i> ASSESSMENT
1. N&V								
Bentley 2001 [4]	B	A	B	N/A	B	A	?	BB
Wilson 2002 [44]	B	?	B	B	C	A	?	DD
Bruera 1996 [7]	B	A	B	D	A	N/A	?	CC
Lichter 1993 [24]	C	A	D	D	A	N/A	?	CC
2. BO								
Baines 1985 [2]	A	A	C	A	A	N/A	?	CC

Legend:

N&V: nausea and vomiting

BO: bowel obstruction

CRA: concealment of randomization allocation

Evaluation criteria

A: criterion entirely fulfilled

B: criterion mostly fulfilled

C: criterion mostly not fulfilled

D: criterion not fulfilled

?: not described adequately to classify

n/a: criterion not applicable to this study design

Overall assessment of quality

AA: all or most criteria fulfilled

BB: some criteria not fulfilled

CC: some criteria fulfilled

DD: few or no criteria fulfilled

Table 3. Summary of results of studies providing Level I or II evidence

Table 3A. – Level I studies (systematic reviews)

<i>Author, year</i>	<i>Ref. No.</i>	<i>Agent(s)</i>	<i>N</i>	<i>Risk of Publication Bias</i>	<i>Effect</i>
a. N&V Critchley, 2001	10	Haloperidol	3	Low	Uncertain (very few good quality data available)
b. BO Feuer, 2003	14	Steroids	3	Low	Resolution of BO; no data for nausea

Table 3B. – Level II studies (RCT)

<i>Author</i>	<i>Ref. No.</i>	<i>Agent(s)</i>	<i>N</i>	<i>Effect</i>
a. N&V Hardy, 2002	19	Ondansetron vs. metoclopramide vs. placebo	92	No significant difference between agents
Mystakidou, 1998	29	Metoclopramide vs. Chlorpromazine vs. Tropisetron	288	Tropisetron superior to metoclopramide and chlorpromazine
Bruera, 2000	8	Metoclopramide vs. Placebo	26	Metoclopramide superior to placebo
Bruera, 1994	6	CR metoclopramide vs. IR metoclopramide	34	CR formulation at least as effective as IR
Corli, 1998	9	Levosulpride vs. Metoclopramide	30	Levosulpride superior
b. BO Hardy, 1998	18	Steroids + cyclizine/ haloperidol vs. placebo	35	Steroids superior
Laval, 2002	22	Steroids vs. placebo	52	Steroids superior

Legend:

CR = controlled release

IR = immediate release

Table 4: Summary of results of studies providing Level III or IV evidence.

Table 4A - Level III studies

<i>Author, year</i>	<i>Ref. No.</i>	<i>Agent(s)</i>	<i>Study design</i>	<i>N</i>	<i>Effect</i>
a. N&V					
Passik, 2002	32	Olanzapine	Phase II	15	20-50% ↓ in nausea scores 66%*
Wilson, 2002	44	Metoclopramide	Phase II	48	
Bentley, 2001	4	Various	Cohort	40	
Bruera, 1996	7	Metoclopramide + Dexamethasone	Retrospective cohort	100	
Lichter, 1993	24	Various	Cohort	100	
b. BO					
Baines, 1985	2	Various	Cohort	40	90%

Table 4B. – Summary of level IV studies

<i>Author, year</i>	<i>Ref. No.</i>	<i>Agent(s)</i>	<i>N</i>	<i>Effect</i>
a. N&V				
Jackson, 2003	21	Olanzapine	6	100%*
Porcel, 1998	33a	Ondansetron	10	90%*
Currow, 1997	11	Ondansetron	16 [#]	81% *
Twycross, 1997	40	Methotrimeprazine	29	83% *
b. BO				
Ventafridda, 1990	43	Haloperidol	15	80%*
Fainsinger, 1994	13	Various	15	22% ↓ in nausea scores

Legend for Tables 4a and 4b:

* = percentage of patients responding to treatment

n/a = not applicable