Saudi Pharmaceutical Journal (2015) **23**, 381–387

King Saud University

**Saudi Pharmaceutical Journal**

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

# Assessing prescribing patterns for the prevention of chemotherapy-induced nausea and vomiting in the national center for cancer care and research

**Manal Zaidan [a,*], Lana Soufi [a], M. Hafeez [a], M. Abdelwahid [a], Kakil I. Rasul [b]**

[a] *Pharmacy Department, National Center for Cancer Care and Research (NCCCR), Doha, Qatar*
[b] *Department of Medical Oncology, National Center for Cancer Care and Research (NCCCR), Doha, Qatar*

Received 29 October 2014; accepted 1 January 2015
Available online 10 January 2015

**KEYWORDS**

CINV;
5HT3 receptor antagonists;
Anti-emetic guidelines

**Abstract** *Purpose*: Chemotherapy is the mainstay of cancer treatment; however, chemotherapy treatment may cause nausea and vomiting, which could cause 25–50% of patients to consider delaying or refusing further cancer treatment. Chemotherapy-induced nausea and vomiting (CINV), can be prevented in 70–80% of patients with evidence-based anti-emetic regimen. The purpose of this study is to assess prescribing patterns with regard to prevention of CINV, in the national center for cancer care and research (NCCCR), and develop and implement a standardized evidence-based guideline for the management of CINV. *Methods*: 25 anti-emetic prescriptions were audited to assess their conformity with either of the published guidelines; Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), or the National Comprehensive Cancer Network (NCCN), to establish baseline data. A multidisciplinary team of clinical pharmacists and oncologists developed and implemented a guideline for the prevention of CINV. The guideline was promoted using a variety of strategies; education, pocket cards, academic detailing and pharmacist intervention. Physician anti-emetic orders were audited by pharmacists, to assess their conformity with NCCCR anti-emetic guidelines. A data collection form was developed to capture relevant information including; patient demographics, type and emetogenic level of chemotherapy, and the conformity of anti-emetic order with NCCCR guidelines. SPSS statistical software was used to analyze the data. *Results*: The conformity of anti-emetic physician order with NCCCR anti-emetic guidelines increased from 0% baseline in June 2008 to an average

* Corresponding author at: Pharmacy, National Center for Cancer Care and research, HMC, P.O. Box 3050, Doha, Qatar. Tel.: +974 44397275; fax: +974 44397276.
E-mail address: mzaidan@hmc.org.qa (M. Zaidan).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.01.003

of 60.006% ($n$ = 331) by December 2010 and consistently increased reaching 94.3827% ($n$ = 792) by December 2013, ($p$ value 0.0002). *Conclusion*: The introduction of anti-emetic guidelines succeeded in standardizing CINV management, toward an evidence-based approach.



## 1. Introduction

Chemotherapy is the mainstay of treatment for many cancers; however, chemotherapy treatment could cause many unwanted side effects among which nausea and vomiting are the most feared by patients. Chemotherapy-induced nausea and vomiting (CINV) are classified into three classes according to the pattern and time in which it occurs; acute which occurs within 24 h of chemotherapy, delayed occurs after 24 h of chemotherapy, and anticipatory nausea and vomiting (Naeim et al., 2008; Wiser and Berger, 2005). As many as 70–80% of all patients treated, experience nausea and vomiting of varying severity (Berger and Clark-Snow, 2004). Nausea and vomiting, can lead to dehydration, fatigue, difficulty concentrating, slow wound healing, loss of appetite, as well as distress and disruption in daily activities which may cause 25–50% of patients to consider delaying or refusing possible lifesaving further cancer treatment (Jordan et al., 2007a; Naeim et al., 2008).

Yet considerable progress has been made in the treatment of CINV in patients receiving standard doses of chemotherapy following the introduction of newer drugs; 5-hydroxytriptamine-3 antagonist (5-HT3) antagonists, and neurokinin 1 (NK(1)) antagonists i.e. Aprepitant, which are more effective in controlling and even preventing nausea and vomiting (http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional/page 6 Accessed June 2008, Poli-Bigelli et al., 2003; Richard et al., 1999; Kaiser, 2005). In fact, CINV can be prevented in 70–80% of patients with the appropriate use of anti-emetics (Jordan et al., 2007a; Perwitasari et al., 2011). Meaning that 20–30% of the patients will still suffer CINV despite being prescribed the appropriate anti-emetic regimen according to the guidelines (Jordan et al., 2007b; Kaiser, 2005).

Guidelines for the management of CINV that integrate clinical research into practices have been developed by reputable institutions including; the Multinational Association of Supportive Care in Cancer (MASCC), (http://www.mascc.org/antiemetic-guidelines, accessed June 2008), American Society of Clinical Oncology (ASCO), (Basch et al., 2011), and National Comprehensive Cancer Network (NCCN) (http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf, accessed June, 2008). These guidelines categorize chemotherapeutic agents into four categories according to their likelihood to induce nausea and vomiting; high (90%), moderate (30–90%), low (10–30%), and minimal ( < 10%). These figures represent the percentage of patients who would experience CINV if not prescribed appropriate prophylaxis. The guidelines further suggest anti-emetic regimens that would provide the best control of all types of nausea and vomiting; acute, delayed and anticipatory putting into consideration the likelihood of the chemotherapeutic agent to cause nausea and vomiting (Roila et al., 1998; Frederick, 2003; Jordan et al., 2007b) however, the implementation of these guidelines is less than optimal for a variety of reasons including, disagreement with the guidelines due to concerns about the underlying evidence, lack of knowledge and unclear guidelines (Jordan et al., 2007a; Lugtenberg et al., 2009). Physician adherence to guidelines may also vary according to type of patient and length of physician experience (Mackinlay et al., 2007). Some studies show that as low as 50% of patients receive according to recommended guidelines (McGlynn et al., 2003); however, "greater adherence to evidence-based guidelines is critical to improving healthcare" (Kenefick et al., 2008).

Expert panels have identified major barriers to physician adherence as; "physicians rewarding systems that are based on service volume (quantity) rather than quality of outcomes; lack of information technology systems which would make it easier to access guidelines; lack of staff training; the likelihood of physicians to base clinical decisions on their personal experience, rather than evidence-based clinical practice guidelines; physicians' belief that their own practice is good which could be attributed to lack of feedback about the quality of their practice compared to their peers, and lack of physician involvement in guideline development process which would otherwise improve adherence" (Kenefick et al., 2008).

The same article suggests several strategies to improve physician adherence; information technology innovations to improve access to guidelines, support clinical decision-making, involvement of physicians in guideline development and review process; staff awareness and training to re-orient practice toward guidelines and measurement of health care performance (Kenefick et al., 2008).

An audit of 25 anti-emetic prescriptions conducted at the National Center for Cancer Care and Research (NCCCR), in May, June 2008, revealed considerable variation in individual physician's approach toward management of CINV which implies that, management of CINV is not standardized and is mostly guided by individual physician opinion and experience, which could lead to either suboptimal control of CINV, or unnecessary over-treatment.

The primary purpose of this study is to assess the current clinical practice in NCCCR with regard to the management of CINV, in terms of the rate of physician orders conforming to either of the published anti-emetic guidelines; MASCC, ASCO, or NCCN, and develop and promote a standardized evidence-based guideline for the management of CINV in NCCCR.

## 2. Materials and methods

This quality improvement project was conducted in the national center for cancer care and research, Doha, Qatar, in the period July 2008 to December 2013. The project was conducted with the permission of the Medical Research Center at Hamad Medical Corporation (PR # 14353/14).

**Table 1** Percentage physician order conformance to NCCCR anti-emetic guidelines 2nd Quarter 2008–4th Quarter 2013.

| Year | Quarter | Number of. Ph. O. audited guidelines | Number of Ph. O. conformant to NCCCR antiemetic guidelines | % Ph. O. conformant to NCCCR antiemetic guidelines | % Yearly Ph. O. conformant to NCCCR antiemetic |
|---|---|---|---|---|---|
| 2008 | 3rd Q | 66 | 7 | 10.6 | 18.64 |
| | 4th Q | 45 | 12 | 26.67 | |
| 2009 | 1st Q | 53 | 24 | 45.28 | 65.34 |
| | 2nd Q | 53 | 39 | 73.58 | |
| | 3rd Q | 53 | 34 | 64.15 | |
| | 4th Q | 60 | 47 | 78.33 | |
| 2010 | 1st Q | 50 | 40 | 80 | 75.36 |
| | 2nd Q | 50 | 36 | 72 | |
| | 3rd Q | 60 | 43 | 71.67 | |
| | 4th Q | 63 | 49 | 77.78 | |
| 2011 | 1st Q | 56 | 48 | 85.71 | 91.72 |
| | 2nd Q | 44 | 42 | 95.45 | |
| | 3rd Q | 66 | 59 | 89.39 | |
| | 4th Q | 82 | 79 | 96.37 | |
| 2012 | 1st Q | 68 | 64 | 94.12 | 94.57 |
| | 2nd Q | 80 | 78 | 97.5 | |
| | 3rd Q | 62 | 58 | 93.55 | |
| | 4th Q | 58 | 54 | 93.1 | |
| 2013 | 1st Q | 52 | 51 | 98.08 | 96.71 |
| | 2nd Q | 44 | 44 | 100 | |
| | 3rd Q | 99 | 94 | 94.94 | |
| | 4th Q | 129 | 121 | 93.8 | |

Q = Quarter
Ph. O. = Physician order

**National Center for Cancer Care and Research (NCCCR)**

**Anti-Emetic Protocol for Chemotherapy Induced Nausea and Vomiting**

| | High Risk Chemotherapy | Moderate Risk Chemotherapy | Low Risk Chemotherapy |
|---|---|---|---|
| Day 1 (Pre – Chemo) | • Dexamethasone 12 mg PO or IV<br>• + 5-HT3 antagonist: Ondasetrone 16-24 mg PO or 8-12mg (max. 32 mg) IV OR Granisetrone 1-2 mg PO or 0.01mg/kg (max. 9mg) IV<br>• + Aprepitant 125mg PO<br>• ± Lorazepam 0.5-2mg PO or IV either every 4 or every 6 hr | • Dexamethasone 12mg PO or IV<br>• + 5-HT3 antagonist: Ondasetrone 16-24 mg PO or 8 - 12mg IV (max. 32mg/day) OR Granisetrone 1-2 mg PO or 0.01mg/kg (max. 9mg) I<br>• ± Aprepitant 125mg PO<br>• ± Lorazepam 0.5-2mg PO or IV Either every 4 or every 6 hr. | • Dexamethasone 12mg PO or IV daily OR<br>• Metoclopramide 10-40mg PO or IV every 4 /6 hr or 1-2mg/kg IV every 3/4 hr OR<br>• Prochlorperazine 10mg PO or IV every 4 or 6 hr<br>• ±Diphenhydramine 25-50mg PO or IV every 4/6hr<br>• ± Lorazepam 0.5-2mg PO or IV every 4 or 6 hr |
| Day 2 – 4 (Post – Chemo) | • Dexamethasone 12mg PO or IV daily<br>• + Aprepitant 80 mg PO daily days 2-3<br>• ±Metoclopramide 10-40 mg PO/IV every 4 or 6 hrs PRN<br>• ±Lorazepam 0.5-2 mg PO/IV either every 4 or 6 hrs PRN | • Dexamethasone 12mg PO daily<br>• ± 5-HT3 antagonist: Granisetrone 1-2mg PO daily or 1mg PO bid OR Ondasetrone 8mg PO bid or 16mg PO daily<br>**If Aprepitant given as pre-chemo, then**<br>• Aprepitant 80mg PO daily, days 2-3 ± Dexamethasone 12mg PO daily You can add to 1 OR 2 above:<br>• ±Metoclopramide 10-40 mg PO/IV every 4 or 6 hrs PRN<br>• ±Lorazepam 0.5-2 mg PO/IV either every 4 or 6 hrs PRN | |

**Figure A1** NCCCR anti-emetic guidelines for chemotherapy induced nausea and vomiting.

To establish baseline data, 25 anti-emetic prescriptions were audited in June 2008 to assess their conformity with either of the published guidelines; Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), or the National Comprehensive Cancer Network (NCCN). The rate of physician adherence to these guidelines was found to be 0%.

A multidisciplinary team of oncologists and pharmacists, reviewed NCCN, ASCO, and MASCC antiemetic guidelines, and developed and implemented a customized antiemetic guideline based on available evidence as well as availability of the required medications in the hospital formulary with the objective of achieving the best possible control of CINV (Figs. A1–A3). The guideline was promoted among care providers using a variety of strategies to overcome potential barriers to physician adherence to the guidelines; educational sessions, interactive workshops, posting laminated copies of the guidelines and reminders in nurse stations, treatment rooms and pharmacy work areas, distribution of pocket size copies of the guideline to all physicians and pharmacists in addition to academic detailing to provide objective clinical knowledge to individual physicians to improve their conformance to the guidelines (Fischer and Avorn, 2012). Pharmacists were instructed to communicate with prescribers to correct any variation from the guidelines before dispensing and document their interventions. The guideline and the data collection process were piloted for one month and eventually launched in July 2008.

Actions

All anti-emetic regimens prescribed for oncology patients receiving first cycle of chemotherapy in the day-care unit (DCU) were audited by dispensing pharmacists for conformity with NCCCR anti-emetic guidelines. A specially designed data collection form was made available in all pharmacy work areas to be filled by dispensing pharmacists (Fig. B1). Collected information included; patient demographics, Diagnosis, Name and emetogenic level of the chemotherapy protocol, anti-emetic medications prescribed, and conformity of the prescribed anti-emetic regimen with NCCCR anti-emetic guidelines.

### 2.1. Inclusion criteria

All anti-emetic regimens prescribed for oncology patients receiving first cycle of chemotherapy in the day-care unit (DCU).

**Emetogenic risk of individual chemotherapeutic agents**

| Risk level | Agents | Agents |
|---|---|---|
| **High Emetic Risk** (> 90 % frequency of emesis) | • Combination of either Doxorubicin or Epirubicin with Cyclophosphamide<br>• Procarbazine (oral) | • Cisplatin 50 mg/m$^2$<br>• Cyclophosphamide > 1,500mg/m$^2$<br>• Dacarbazine |
| **Moderate Emetic Risk** (30- 90 % frequency of emesis) | • Aldesleukin > 12- 15 million units/ m$^2$<br>• Amifostine > 300 mg/ m$^2$<br>• Busulfan > 4 mg/ d<br>• Carboplatin<br>• Cisplatin < 50 mg/ m$^2$<br>• Cyclophosphamide 1,500 mg/ m$^2$<br>• Cyclophosphamide (oral)<br>• Cytarabine >1 g/m$^2$<br>• Dactinomycin<br>• Vinorelbine (oral) | • Daunorubicin<br>• Doxorubicin<br>• Epirubicin<br>• Etoposide (oral)<br>• Ifosfamide<br>• Imatinib (oral)<br>• Irinotecan<br>• Lomustine<br>• Melphalan > 50 mg/m$^2$<br>• Methotrexate 250 - > 1,000mg/m$^2$<br>• Oxaliplatin > 75 mg/m$^2$<br>• Temozolomide (oral) |
| **Low Emetic Risk** (10- 30 % frequency of emesis) | • Amifostine 300 mg<br>• Capecitabine<br>• Cytarabine 100- 200 mg/m$^2$<br>• Docetaxel<br>• Doxorubicin (liposomal)<br>• Etoposide<br>• Fludarabine (oral)<br>• Pclitaxel | • Nilotinib.<br>• 5- Fluorouracil<br>• Gemcitabine<br>• Methotrexate> 50 mg/ m< 250 mg/m$^2$<br>• Mitomycin<br>• Mitoxantrone<br>• Pemetrexed<br>• Topotecan |
| **Minimal Emetic Risk** (< 10 % frequency of emesis) | • Hydroxyurea (oral)<br>• Melphalan (oral low- dose)<br>• Methotrexate 50 mg/ m$^2$<br>• Pentostatin<br>• Rituximab<br>• Thalidomide<br>• Trastuzumab<br>• Vinblastine | • Vincristine<br>• Vinorelbine<br>• Alpha Interferon<br>• Asparaginase<br>• Bevacizumab<br>• Bleomycin<br>• Bortezomib<br>• Cetuximab<br>• Chlorambucil<br>• Dasatinib<br>• Erlotinib<br>• Lapatinib<br>• Alemtuzumab<br>• Sorafinib<br>• Thioguanine |

**Figure A2** Emetogenic risk of individual chemotherapeutic agents.

**Emetogenic risk of combination chemotherapy**

| High Risk | Moderate Risk |
|---|---|
| • AC – Doxorubicin + cyclophosphamide | • FOLFOX = Fluorouracil + Oxaliplatin |
| • CAF- cyclophosphamide + Doxorubicin + Fluorouracil | • FOLFIRI = Fluorouracil + Irinotecan |
| • FEC – Fluorouracil + Epirubicin + Cisplatin | • NAV+CARBOPLATIN |
| • CMF – Cyclophosphamide + Methotrexate + Fluorouracil | • TAXOL +CARBOPLATIN |
| • BEP – Bleomycin + Etoposide + Platinum ( cisplatin) | • GEM+TAXANE |
| • ABVD – Doxorubicin + Bleomycin + Vinblastin + Dacarbazine | • GEM+CARBOPLATIN |
| • CHOP – Cyclophosphamide + Doxorubicin + Vincristin + Prednisolone | |

**Figure A3** Emetogenic risk of combination chemotherapy.

*2.2. Exclusion criteria*

Patients receiving chemotherapy in medical wards.

## 3. Results

The rate of conformity of anti-emetic physician orders to NCCCR anti-emetic guidelines following the implementation of NCCCR anti-emetic guidelines, increased from an average of 60.006% ($n$ = 331) in the period July 2008–December 2010 to 94.3827% ($n$ = 792) in the period January 2011–December 2013, ($p$ value 0.0002) Table 1, Fig. C1.

## 4. Discussion

The rate of conformity of anti-emetic physician orders to NCCCR antiemetic guidelines showed a slow but consistent improvement at the beginning, taking as long as 18 months to reach the initial 75% target. This could be attributed to the fact that the project involved a change in physician mindset and prescribing habits. However, the rate of anti-emetic order conformity with the guidelines, showed a consistent improvement exceeding the initial target. Consequently the target was raised to 90% in January 2011, and again to 100% in January 2012 as the rate of conformity to the guidelines improved exceeding the 90% target. The multidisciplinary approach, periodic education, pocket cards, introduction of novel drugs (Aprepitant), and pharmacist intervention were the major success factors. The hospital management adopted physician adherence to the anti-emetic guidelines as a patient safety indicator which provided an excellent chance to keep the implementation efforts as a standing agenda to be discussed in the monthly hospital quality improvement and patient safety committee (QIPS) meetings. The audit results, intervention strategies, and specific action plan to improve physician order conformance to the guidelines were periodically discussed with prescribers during the regular physician morning report meetings. To further ensure that patients receive adequate antiemesis therapy, the guideline has been incorporated into preprinted chemotherapy protocols which considerably contributed to the maintenance of the current rate of conformance (94.3%), since January 2011.

The guideline is a proactive approach to the prevention of CINV, providing specific drug recommendations for the management of acute, delayed as well as anticipatory nausea and vomiting to achieve maximum control of CINV without undue over or under-use of hospital resources. It has been developed based on medications available on the hospital formulary; however, the study team stays vigilant to new advancements in the management of CINV. In due course, Aprepitant-P/neurokinin 1 (NK1) receptor antagonist was added to the formulary in April 2009 and the guideline was updated accordingly. To improve patient accessibility to required medications, all chemotherapy pre-medications used to prevent acute and anticipatory CINV are provided free of charge to all patients as an integral part of the chemotherapy protocol.

The guideline also emphasizes an evidence based clinical decision making approach rather than personal opinion guided practice and would encourage other healthcare entities to develop clinical practice guidelines to optimize drug therapy.

As evidenced by multiple studies consistent implementation of the guidelines reduces the incidence and severity of CINV improving thus, patient adherence to chemotherapy, reduce

المركز الوطني لعلاج وأبحاث السرطان
National Center for Cancer Care & Research

**Anti-emetic guidelines data collection tool**

Patient name:……HC no:……Gender……
Date:…… Location:……
Diagnosis:……Chemotherapy protocol:……Cycle no:……

| Chemotherapy Medication/s |
|---|
| 1- |
| 2- |
| 3- |

**Emetogenic Risk:** ☐ High ☐ Moderate ☐ Low

Antiemetic therapy prescribed

| Pre-chemotherapy antiemetics | Post-chemotherapy antiemetics |
|---|---|
| ☐ Granisetron: | ☐ Granisetron: |
| ☐ Ondansetrone: | ☐ Ondansetrone: |
| ☐ Metoclopramide: | ☐ Metoclopramide: |
| ☐ Dexamethasone: | ☐ Dexamethasone: |
| ☐ Diphenhydramine: | ☐ Diphenhydramine: |
| ☐ Hydrocortisone: | ☐ Hydrocortisone: |
| ☐ Lorazepam: | ☐ Lorazepam: |
| ☐ Aprepitant 125mg | ☐ Aprepitant 80mg |

Physician order conformance to guidelines ☐Yes ☐No
Prescriber:……
Pharmacist signature:…… Date: ……

**Figure B1** Data collection form.

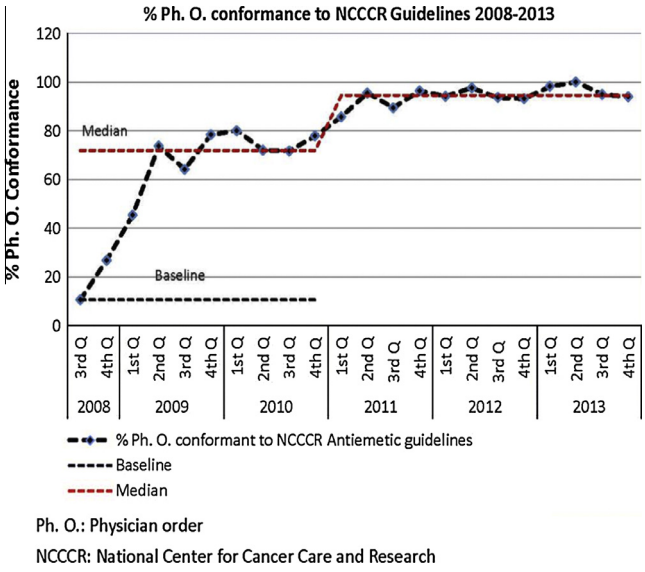


**Figure C1** % Ph. O. conformance to NCCCR guidelines 2008–2013.

treatment delays and improve clinical outcomes; however, further study is required to assess the impact of consistent conformance with antiemetic guidelines in NCCCR.

## 5. Conclusion

The introduction of the guidelines was an important shift toward evidence-based practice, as evidenced by the implementation of the clinical practice guidelines for the management of chemotherapy induced nausea and vomiting in NCCCR, and although, the program involved a change in physicians' prescribing practices which is rather a slow process, the program succeeded in achieving its defined goals. This could be attributed to a firm and consistent support from hospital management as well as consistent educational activities to promote the guidelines. Availability of new products specifically for the treatment of CINV, which provide extra options for the prescribers and improves physician conformance with guidelines, in addition to active involvement of pharmacists to discuss variations from prescribing guidelines were critical to improvement.

## Disclosure

Study has been approved for publication by the Research Strategy and Assurance Committee at Hamad Medical Corporation (RP #/14353/14).

## Acknowledgements

The team would like to thank all NCCCR physicians for their invaluable input toward the development of the guideline, the hospital management and QIPS members' for their support and continued encouragement, pharmacists for their consistency and dedication for data collection and follow-up with prescribers, and pharmacy secretary as well for preparing all the required materials.

## Appendix A

See Figs. A1–A3, B1, and C1.

## References

Basch, Ethan et al, 2011. Antiemetics: ASCO clinical practice guideline update. J. Clin. Oncol. 29 (31), 4189–4198. http://dx.doi.org/10.1200/JCO.2010.34.4614.

Berger, A.M., Clark-Snow, R.A., 2004. Nausea and vomiting. In: DeVita, V.T., Jr.Jr., Hellman, S., Rosenberg, S.A. (Eds.), Cancer: Principles & Practice of Oncology, seventh ed. Lippincott Williams & Wilkins, Philadelphia.

Fischer, M.A., Avorn, J., 2012. Academic detailing can play a key role in assessing and implementing comparative effectiveness research findings. Health Aff. (Millwood) 31 (10), 2206–2212. http://dx.doi.org/10.1377/hlthaff.2012.0817.

Frederick, M. Schnell, 2003. Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. Oncologist 8 (2), 187–198.

Jordan, K., Sippel, C., Schmoll, H.J., 2007a. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist 12 (9), 1143–1150.

Jordan, Karin, Sippel, Christoph, Schmoll, Hans-Joachim, 2007b. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist 12 (9), 1143–1150. http://dx.doi.org/10.1634/theoncologist.12-9-1143.

Kaiser, Rolf, 2005. Antiemetic guidelines-are they being used? Lancet Oncol. 6 (8), 622–625. http://dx.doi.org/10.1016/S1470-2045(05)70284-9.

Hope Kenefick, Jason Lee, Valerie Fleishman, 2008. Improving Physician Adherence to Clinical Practice Guidelines, Barriers and strategies for change, New England Healthcare Institute, February 2008. <http://www.nehi.net/writable/publication_files/file/cpg_report_final.pdf>.

Lugtenberg, Marjolein et al, 2009. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. Implement Sci. 4, 54. http://dx.doi.org/10.1186/1748-5908-4-54, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2734568/>.

Mackinlay, J.B. et al, 2007. Sources of variation in physician adherence with clinical guidelines: results from a factorial experiment. J. Gen. Intern. Med. 22 (3), 289–296. http://dx.doi.org/10.1007/s11606-006-0075-2.

Multinational Association of Supportive Care in Cancer. MASCC Anti-emetic Guidelines. <http://www.mascc.org/antiemetic-guidelines> (accessed June 2008).

McGlynn, E.A., Asch, S.M., Adams, J., et al, 2003. The quality of health care delivered to adults in the United States. N. Engl. J. Med. 348 (26), 2635–2645.

Naeim, A. et al, 2008. Evidence-based recommendations for cancer nausea and vomiting. J. Clin. Oncol. 26 (23), 3903–3910. http://dx.doi.org/10.1200/JCO.2007.15.9533.

National Cancer Institute; Prevention of Acute/Delayed Nausea and Vomiting (Emesis). <http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional/page> 1 (accessed June 2008).

NCCN Clinical Practice Guidelines in Oncology; Antiemesis. <http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf> (accessed June 2008).

Perwitasari et al, 2011. Anti-emetic drugs in oncology: pharmacology and individualization by pharmacogenetics. Int. J. Clin. Pharm. 33 (1), 33–43. http://dx.doi.org/10.1007/s11096-010-9454-1.

Poli-Bigelli, S., et al., 2003. Aprepitant Protocol 054 Study Group. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer, 97(12), 3090-3098, <http://www.ncbi.nlm.nih.gov/pubmed/12784346>.

Richard, J. Gralla et al, 1999. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. J. Clin. Oncol., <http://jcoascopubs.org/content/17/9/2971.full>.

Roila, F., Del Favero, A., Gralla, R.J., Tonato, M., 1998. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the Perugia Consensus Conference. Oxford J. Med., Ann. Oncol. 9 (8), 811–819.

Wiser, W., Berger, A., 2005. Practical management of chemotherapy-induced nausea and vomiting. Oncology (Bethesda, Maryland) 19 (5).