

Lorazepam, Diphenhydramine, and Haloperidol Transdermal Gel for Rescue From Chemotherapy-Induced Nausea/Vomiting: Results of Two Pilot Trials

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Chemotherapy-induced nausea and vomiting (CINV), a significant medical problem,¹⁻⁴ has been commonly cited by patients as being among the “most unpleasant and distressing” side effects associated with chemotherapy.⁵ Acute nausea occurs in approximately 30%–50% of patients receiving chemotherapy, and acute emesis occurs in about 15% of such patients, especially those receiving highly emetogenic chemotherapy.⁶ CINV may impair quality of life significantly and necessitate chemotherapeutic dose reductions, treatment delays, and discontinuation of therapy.^{7,8} Finally, it may cause a substantial number of lost work days for patients and considerable costs to the healthcare system, resulting in a substantial economic burden.^{9,10}

Currently, the mainstay of prophylactic antiemetic therapy for CINV involves the combined use of 5-hydroxytryptamine (5-HT₃)-receptor antagonists (eg, dolasetron [Anzemet], granisetron [Kytril], ondansetron, palonosetron [Aloxi], the investigational agent tropisetron), dexamethasone, and neurokinin-1 antagonists (eg, aprepitant [Emend]).^{3,6,11-17} The various 5-HT₃ serotonin antagonists have similar efficacy and adverse effects; in fact, recent guidelines stated that these drugs may be used interchangeably.^{15,18} Other therapies that have shown some benefit in preventing CINV

Abstract Despite their use of prophylactic antiemetic therapies, cancer patients continue to consider chemotherapy-induced nausea and vomiting (CINV) to be a significant problem. Patients frequently use various “breakthrough” medications for these symptoms. Unfortunately, there is a paucity of trials regarding treatment of breakthrough CINV. This study investigated the efficacy of “ABH,” a topical gel containing lorazepam (Ativan), diphenhydramine (Benadryl), and haloperidol (Haldol), in reducing breakthrough CINV. Adults receiving standard recommended prophylactic antiemetics as outpatients were instructed to use 0.5 mL of the gel topically when they experienced significant CINV. Patients then were contacted retrospectively to respond to a questionnaire rating their nausea and/or vomiting and their response to ABH-gel treatment. The results were collected during two trials: Trial I began in April 2003, and Trial II began in March 2006. During Trial I, 23 patients were evaluated; 17 patients (74%) reported that use of the gel decreased their CINV, with 15 (70%) reporting relief within 30 minutes of its application. Three patients believed that the gel caused sedation; no troubles with skin irritation or muscle spasms were reported. In Trial II, all 10 patients believed that the treatment was effective. When the severity of CINV was quantified on a scale of 0–10, the mean CINV score decreased significantly from a 6.1 before gel application to a 1.7 as evaluated 30 minutes following gel application ($P < 0.005$). Topical use of ABH gel appears to be a promising and safe rescue therapy for breakthrough CINV that occurs despite prophylactic antiemetic therapy. These results warrant further confirmation in a large, randomized, placebo-controlled trial.

include benzodiazepines,¹⁹ phenothiazines,²⁰ acupuncture,²¹ cannabinoids,²² and metoclopramide.²³

Even with the availability of these prophylactic therapies, nausea and/or vomiting continues to remain a significant problem for cancer patients receiving chemotherapy.^{6,8,24,25} However, few trials have assessed the best treatment for breakthrough CINV occurring despite use of prophylaxis. Ideally, in such situations, patients need rescue medications to quickly relieve CINV.

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Table 1**Pharmacologic Composition of ABH Gel as Used in Trials I and II**

DRUG*	DOSE
Lorazepam	120 mg
Diphenhydramine	1,500 mg
Haloperidol	120 mg
Lecithin organogel	12 mL
Ethoxydiglycol	5 mL
Water	1 mL
Pluronic gel 20% qs	60 mL

*Yields 120 doses of 0.5 mL in amber syringes. The dose of the active agents in the 0.5-mL aliquot was 2 mg of lorazepam, 25 mg of diphenhydramine, and 2 mg of haloperidol.

Abbreviations: ABH = lorazepam (Ativan), diphenhydramine (Benadryl), and haloperidol (Haldol); qs = quantity sufficient

Guidelines issued by the American Society of Clinical Oncology¹⁵ and the National Comprehensive Cancer Network (NCCN)²⁶ recommend that physicians use agents of different classes for breakthrough CINV. For example, they recommend that additional agents (eg, the dopamine antagonists, lorazepam [Ativan], corticosteroids) be considered. In addition, the NCCN guidelines recommend that physicians consider using an intravenous (IV) or rectal route of administration for patients with vomiting, since an oral route may not be practical.²⁶ However, they do not specify whether these agents should be used sequentially or in combination, what the duration of therapy should be, or which route of administration would be best. IV medications are difficult to give to patients at home, and rectal suppositories often are uncomfortable and unpleasant for some patients.

A topical compound consisting of lorazepam, diphenhydramine (Benadryl), and haloperidol (Haldol; ABH) has yielded promising results when used anecdotally in hospice patients. A similar compound, consisting of lorazepam, diphenhydramine, haloperidol, and metoclopramide (Reglan; ABHR), was tolerated by hospice patients.²⁷

Weschules²⁸ noted that of 11,181 ABHR prescriptions provided for patients, 6,529 (58.4%) were for a topical gel, and 4,312 (38.6%) were for a rectal suppository. Less than 0.5% of patients discontinued treatment due to adverse side effects. This study reported ABHR gel to be tolerable, but it did not analyze the effectiveness of this formulation. Another retrospective study²⁹ reported use of an ABHR gel to be 98% effective in hospice patients. There were no adverse reactions; however, problems arose when patients with bowel obstructions were treated. Apart from these results, prospective data about the efficacy of ABHR are lacking.

All of the components of ABH gel appear to be beneficial in patients with CINV. Haloperidol is a competitive dopamine-receptor antagonist that particularly affects the mesolimbic dopaminergic system and mediates its antiemetic effects via blockade of postsynaptic dopamine.³⁰⁻³² Diphenhydramine is another antiemetic that predominantly works by blocking histamine-1 receptors; however, it also has some anticholinergic

Table 2**Questionnaire Used in Trial I**

Nausea	
Did you experience any nausea?	
How would you rate your nausea before using the gel?	0 (no nausea) 1 2 3 4 5 (worst possible nausea)
Did you feel relief from nausea after using the gel?	
How long was it before you felt relief?	10 minutes 20 minutes 30 minutes 45 minutes 1 hour > 1 hour Other
How would you rate your nausea after using the gel?	0 (no nausea) 1 2 3 4 5 (worst possible nausea)
Was the gel helpful in controlling your nausea?	
Vomiting	
Did you experience any acute vomiting before using the gel?	
How many episodes of vomiting did you have before using the gel?	0 to 1 time 2 to 5 times ≥ 6 times
Did you experience relief from vomiting after using the gel?	
How long did it take to feel better?	10 minutes 20 minutes 30 minutes 45 minutes 1 hour > 1 hour Other
How would you rate your vomiting after using the gel?	0 (no nausea) 1 2 3 4 5 (worst possible nausea)
Was the gel helpful in controlling your vomiting?	

effects.³³ Lorazepam is a benzodiazepine that binds to the γ -aminobutyric acid receptor in the central nervous system and helps to prevent anticipatory nausea^{34,35}; although it is not an antiemetic, per se, it reportedly augments the efficacy of other antiemetics, including haloperidol.³⁶

Combined use of these agents in one compound has several potential advantages. First, the compound effectively manages CINV in cancer patients, as suggested by anecdotal reports and retrospective review.²⁷ Second, the incidence of extrapy-

Table 3**Trial II: Patient Diagnoses, Chemotherapy, and Antiemetic Regimens**

CANCER DIAGNOSIS	CHEMOTHERAPY	ANTIEMETICS
Non-small cell lung	Cisplatin, etoposide	Palonosetron, dexamethasone, ondansetron
Pancreatic (metastatic)	Gemcitabine, bevacizumab, oxaliplatin, FOLFIRI (study N034A)	Palonosetron, dexamethasone, aprepitant, ondansetron
Colon (metastatic)	FOLFOX, bevacizumab	Dexamethasone (as needed), granisetron
Follicular lymphoma	CHOP, rituximab	Dexamethasone, palonosetron, aprepitant, ondansetron
Hodgkin's lymphoma	Vinblastine, lomustine	Dolasetron, dexamethasone, granisetron
Ovarian	Paclitaxel, carboplatin	Palonosetron, dexamethasone, ondansetron, aprepitant
Leiomyosarcoma	Cisplatin (low dose with radiation)	Dexamethasone, ondansetron, palonosetron
Merkel-cell	Cisplatin, etoposide	Palonosetron, dexamethasone, aprepitant, ondansetron
Liposarcoma	Ifosfamide, doxorubicin, mesna	Promethazine, ondansetron, prochlorperazine, chlorpromazine, aprepitant
Astrocytoma	Carmustine	Dexamethasone, granisetron, prochlorperazine

Abbreviations: FOLFIRI = 5-fluorouracil (5-FU), leucovorin, and irinotecan; FOLFOX = 5-FU, leucovorin, and oxaliplatin; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone

ramidal side effects observed with haloperidol should be lower with use of this combination due to the anticholinergic effects of diphenhydramine.^{28,37} Third and finally, the combination is available as a topical agent, which makes it a convenient product for patients experiencing CINV.

This report describes a pilot study examining the efficacy of topical ABH in reducing CINV among cancer patients.

Methods

The two different, but related, trials of this study defined nausea as any sickness of the stomach that created an urge to vomit. Vomiting was defined as any emesis whatsoever that occurred. Both studies used the same gel formulation; the gels were distributed to patients in the same manner.

TRIAL I

All patients involved in this trial were adults; they were diagnosed with different types of cancers, were treated with a variety of chemotherapy regimens as outpatients, and were given standard prophylactic antiemetics similar to those recommended in established guidelines.^{3,6,11-17} This method was initiated in the clinical practice of one physician (PTS), who noted that hospice patients appeared to benefit from this therapy. To obtain more detailed information about whether this therapy was alleviating CINV, a protocol was developed and approved by the Creighton University Institutional Review Board (IRB) in April 2003.

The patients were given a prescription for six prefilled, capped, 1.0-cc, tuberculin syringes of ABH gel when they received emetogenic chemotherapy. The components of the gel they received are listed in Table 1.

The patients were instructed to use the ABH gel when they developed significant nausea and/or vomiting in the days following chemotherapy and were given the option of repeating the treatment at 6-hour intervals. They were instructed to place 0.5 mL of the gel on the palmar aspects of their wrists using a prefilled syringe (without a needle). After applying the gel, the subjects were instructed to rub their wrists together gently for approxi-

mately 1–3 minutes to facilitate its transdermal absorption.

Thereafter, patients were contacted by telephone by an investigator, generally within 1 month of using the gel. No written consent was required by this IRB; however, the patients provided verbal informed consent when called to answer questions about their progress with the ABH gels. The investigator conducted a directed interview using a standardized questionnaire (Table 2) that asked patients to rate their CINV and to indicate whether they believed the gel to cause sedation, skin irritation, or muscle spasms.

TRIAL II

The second trial was approved by the Creighton University IRB in March 2006. This trial involved adult patients who had been given a prescription for ABH gels when they received emetogenic chemotherapy; the patients were not chosen for any particular diagnoses. The chemotherapy and antiemetic regimens, along with patients' diagnoses, appear in Table 3.

Two of the 10 patients received high-dose cisplatin-based chemotherapy, and 1 patient received low-dose cisplatin. The two patients given high-dose cisplatin received dexamethasone, a 5-HT₃ antagonist, and aprepitant, whereas the others were given a standard antiemetic regimen consistent with practice guidelines. The patients were instructed to apply the

Table 4**Questionnaire Used in Trial II**

The involved patients were asked, on a scale of 0–10, with 0 being "no nausea or vomiting" and 10 being "the worst nausea and/or vomiting experienced" to rate the following:

Nausea/vomiting prior to applying ABH gel
Nausea/vomiting 30 minutes after applying ABH gel
Nausea/vomiting 4 hours after applying ABH gel
Did you feel the treatment was effective?
Did you have any side effects from the drug?

Abbreviation: ABH = lorazepam (Ativan), diphenhydramine (Benadryl), and haloperidol (Haldol)

Table 5

Trial I: Nausea/Vomiting Scores Before and After Using ABH Gel

PATIENT NUMBER	RATING BEFORE GEL	RATING AFTER GEL	CHANGE
1	4	0	-4
2	3	3	0
3	5	1	-4
4	5	3	-2
5	5	3	-2
6	5	3	-2
7	5	1	-4
8	3	2	-1
9	3	1	-2
10	5	0	-5
11	3	1	-2
12	2	0	-2
13	5	2	-3
14	4	0	-4
15	2	1	-1
16	5	5	0
17	5	5	0
18	4	1	-3
19	3	1	-2
20	3	0	-3
21	5	5	0
22	5	5	0
23	3	3	0
Mean	4	2	-2
Median	4	1	-3

Abbreviation: ABH = lorazepam (Ativan), diphenhydramine (Benadryl), and haloperidol (Haldol)

Table 6

Trial I: Nausea Relief and Time to Relief After Using ABH Gel (n = 23)

	n (%)
Patients experiencing relief	17 (74%)
Time (min) to relief	
10	6 (26%)
20	4 (17%)
30	6 (26%)
45	1 (4%)
No relief	6 (26%)

Abbreviation: ABH = lorazepam (Ativan), diphenhydramine (Benadryl), and haloperidol (Haldol)

ABH gel if they developed nausea and/or vomiting in the days after chemotherapy administration.

Again, following receipt of verbal consent, an investigator used a structured interview methodology (by telephone or in person); the questions addressed in this second trial (Table 4) were applicable to the first dose of the ABH gel. Patients then were asked to rate the severity of their CINV on a combined

Table 7

Trial II: Nausea/Vomiting Scores Before and After ABH Gel Use (n = 10)

PATIENT NUMBER	NAUSEA/VOMITING (SCALE 0-10)		
	BEFORE APPLYING GEL	AFTER 30 MINUTES	AFTER 4 HOURS
1	3	0	0
2	4	0	0
3	8	4	6
4	8	5	0
5	10	4	8
6	2	0	0
7	6	2	0
8	10	0	5
9	10	2	2
10	8	0	0
Mean	6.1	1.7	2.1
Median	7	1	0

Abbreviation: ABH = lorazepam (Ativan), diphenhydramine (Benadryl), and haloperidol (Haldol)

scale at baseline, 0.5 hours, and 4 hours after applying the ABH gel. The rating scale that patients used ranged from 0 (no nausea or vomiting) to 10 (worst imaginable nausea or vomiting).

STATISTICAL METHODS

All statistics were performed using statistical software JMP (version 6.0; SAS Institute; Cary, NC), which reports continuous variables as means and categorical variables in numbers and percentages. Given the small sample size and uncertainty about normal distribution of the study sample, a nonparametric statistical test (Wilcoxon signed rank test) was used to calculate the mean difference in the nausea score before and after treatment. A *P* value of < 0.05 was considered to be statistically significant.

Results

TRIAL I

In all, 24 patients were contacted for the first trial between April 2003 and August 2003. One had not developed any CINV and was excluded from analysis. Nausea scores for the remaining 23 patients are provided in Table 5. A total of 74% (17/23) of the patients believed that the gel decreased their nausea, and 70% (16/23) experienced relief from vomiting. Further, 70% (16/23) of all patients obtained relief within 30 minutes after applying the gel (Table 6). The mean reported nausea score significantly decreased from a 4 before patients applied the gel to a 2 when patients assessed their condition 30 minutes following its application (*P* < 0.0001).

Three patients (13%) reported mild fatigue after using the gel; no patients reported skin irritation or muscle spasms.

TRIAL II

A total of 10 patients were involved in the second trial, which took place between March 2006 and July 2006. Table 7

includes data on patients' CINV scores reported before the ABH gel was used and 30 minutes and 4 hours after it was applied. The mean reported nausea score significantly decreased from a 6.1 at baseline to a 1.7 when patients assessed their condition 30 minutes after using the gel ($P < 0.0005$). All 10 patients reported that the treatment was effective. None of the patients reported any significant side effects.

Discussion

Extensive literature searches provided no proof of appropriate evidence-based practice for use of rescue medications for CINV. In the current two trials, the vast majority of subjects reported a significant decrease in their severity of CINV after applying transdermal ABH gels. The patients' side effects from using these topical agents were minimal; patients experienced

only slight sedation.

Importantly, this study was a *pilot* retrospective study with a *small* sample size that sought data to support initiation of a more formal, randomized, placebo-controlled clinical trial to better determine the utility of this approach. A randomized, double-blind, controlled trial to evaluate ABH gel versus placebo in a cooperative group setting is being planned to better evaluate the efficacy and toxicity associated with using this gel in clinical practice. The data from the current trial support an additional study using this approach; however, currently available data are not sufficiently definitive to recommend use of ABH gels for routine clinical practice. Additional studies may explore the role of this formulation for treating cancer patients with chemotherapy-independent nausea and/or vomiting and for anyone suffering from acute nausea and/or vomiting.

References

PubMed ID in brackets

- Kris MG, Gralla RJ, Tyson LB, et al. Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenhydramine: results of consecutive trials in 255 patients. *Cancer* 1985;55:527-534. [3880660]
- Kris MG, Gralla RJ, Clark RA, Tyson LB, Groshen S. Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: a double-blind, randomized trial. *Cancer* 1987;60:2816-2822. [3315176]
- Kris MG, Hesketh PJ. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy. *Support Care Cancer* 2005;13:85-96. [15565277]
- Sridhar KS, Donnelly E. Combination antiemetics for cisplatin chemotherapy. *Cancer* 1988;61:1508-1517. [3280112]
- Morrow GR, Hickok JT, Burish TG, Rosenthal SN. Frequency and clinical implications of delayed nausea and delayed emesis. *Am J Clin Oncol* 1996;19:199-203. [8610650]
- Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer* 2004;100:2261-2268. [15139073]
- Roila F, Del Favero A. Antiemetics revisited. *Curr Opin Oncol* 1997;9:321-326. [9251881]
- Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol* 2006;24:4472-4478. [16983116]
- O'Brien BJ, Rusthoven J, Rocchi A, et al. Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: survey of five Canadian centres. *CMAJ* 1993;149:296-302. [8339175]
- Ihbe-Heffinger A, Ehlen B, Bernard R, et al. The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. *Ann Oncol* 2004;15:526-536. [14998860]
- Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *American Society of Clinical Oncology. J Clin Oncol* 1999;17:2971-2994. [10561376]
- Loprinzi CL, Alberts SR, Christensen BJ, et al. History of the development of antiemetic guidelines at Mayo Clinic Rochester. *Mayo Clin Proc* 2000;75:303-309. [10725961]
- Lindley C, Goodin S, McCune J, et al. Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy: comparison of ondansetron, prochlorperazine, and dexamethasone. *Am J Clin Oncol* 2005;28:270-276. [15923800]
- Aranda Aguilar E, Constenla Figueiras M, Cortes-Funes H, et al. Clinical practice guidelines on antiemetics in oncology. *Expert Rev Anticancer Ther* 2005;5:963-972. [16336087]
- Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *American Society of Clinical Oncology. J Clin Oncol* 2006;24:2932-2947. [16717289]
- Italian Group For Antiemetic Research. Randomized, double-blind, dose-finding study of dexamethasone in preventing acute emesis induced by anthracyclines, carboplatin, or cyclophosphamide. *J Clin Oncol* 2004;22:725-729. [14966097]
- Palonosetron (Aloxi) for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drugs Ther* 2004;46:27-28.
- Jordan K, Kasper C, Schmoll HJ. Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. *Eur J Cancer* 2005;41:199-205.
- Abali H, Oyan B, Guler N. Alprazolam significantly improves the efficacy of granisetron in the prophylaxis of emesis secondary to moderately emetogenic chemotherapy in patients with breast cancer. *Chemotherapy* 2005;51:280-285. [16103667]
- Bregni M, Siena S, Di Nicola M, Bonadonna G, Gianni AM. Tropicisetron plus haloperidol to ameliorate nausea and vomiting associated with high-dose alkylating agent cancer chemotherapy. *Eur J Cancer* 1991;27:561-565. [1828962]
- Josefson A, Kreuter M. Acupuncture to reduce nausea during chemotherapy treatment of rheumatic diseases. *Rheumatology (Oxford)* 2003;42:1149-1154. [12777644]
- Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001;323:16-21. [11440936]
- Bruera E, Moyano JR, Sala R, et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manage* 2004;28:381-388. [15471656]
- Glaus A, Knipping C, Morant R, et al. Chemotherapy-induced nausea and vomiting in routine practice: a European perspective. *Support Care Cancer* 2004;12:708-715. [15278682]
- López-Jiménez J, Martín-Ballesteros E, Sureda A, et al. Chemotherapy-induced nausea and vomiting in acute leukemia and stem cell transplant patients: results of a multicenter, observational study. *Haematologica* 2006;91:84-91. [16434375]
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Antiemesis. V.1.2007. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed December 19, 2007.
- Tolen L, McMath JA, Alt C, Weschules DJ, Knowlton CH, McPherson ML. Initial selection of antiemetics in end-of-life care: a retrospective analysis. Presented as a poster at the 2005 Annual Assembly of the American Academy of Hospice and Palliative Medicine and the Hospice and Palliative Nurses Association; January 19-23, 2005; New Orleans, LA. Abstract 731.
- Weschules DJ. Tolerability of the compound ABHR in hospice patients. *J Palliat Med* 2008;8:1135-1143. [16351526]
- Moon RB. ABHR gel in the treatment of nausea and vomiting in the hospice patient. *Int J Pharm Compounding* 2006;10:95-99.
- Neidhart JA, Gagen MM, Wilson HE, Young DC. Comparative trial of the antiemetic effects of THC and haloperidol. *J Clin Pharmacol* 1981;21:385-425. [627183]
- Snyder SH. Dopamine receptors, neuroleptics,

and schizophrenia. *Am J Psychiatry* 1981;138:460–464. [6111227]

32. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. *Clin Pharmacokinet* 1999;37:435–456. [10628896]

33. Garnett WR. Diphenhydramine. *Am Pharm* 1986;NS26:35–40. [3962845]

34. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981;6:89–105. [6111408]

35. Maher J. Intravenous lorazepam to prevent nausea and vomiting associated with cancer chemotherapy. *Lancet* 1981;1:91–92.

36. Friedlander ML, Kearsley JH, Sims K, et al.

Lorazepam as an adjunct to antiemetic therapy with haloperidol in patients receiving cytotoxic chemotherapy. *Aust N Z J Med* 1983;13:53–56. [6136266]

37. Davies A, Adena MA, Keks NA, Catts SV, Lambert T, Schweitzer I. Risperidone versus haloperidol: I. Meta-analysis of efficacy and safety. *Clin Ther* 1998;20:58–71. [9522104]