

Evaluation of a nurse-led intervention (SNA \leftrightarrow P)
to improve patients' experiences of chemotherapy-
related nausea and fatigue

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by

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Abstract

Despite a rise in breast cancer incidence, mortality rates have fallen. This improvement in mortality is due to the success of anti-cancer treatments such as chemotherapy and radiotherapy. Such treatments, however, are known to be associated with a range of symptoms. A number of studies exploring patients' chemotherapy-related symptom experiences have shown that patients consistently rate nausea and fatigue highly, not only in relation to severity, but also in relation to the associated distress they experience.

The subjective and non-observable nature of both nausea and fatigue complicates their assessment. While a range of assessment tools exists to evaluate patients' experiences of these two symptoms, there is currently no gold standard assessment tool for assessing either symptom. Moreover, while a range of pharmacological and non-pharmacological interventions have been developed for both symptoms, further evaluation is often needed to provide the level of evidence required to recommend their implementation in real life clinical environments.

The SNA↔P (structured nursing assessment into practice) study arose in response to this clinical situation. The SNA↔P study was a longitudinal study that evaluated the impact of a complex evidence-based intervention, incorporating structured multidimensional symptom assessment and multiple symptom management techniques, on patients' experiences of nausea and fatigue during a course of chemotherapy for breast cancer. Using complementary quantitative and qualitative research methods not only allowed in-depth understanding of patients' experiences and patterns of nausea and fatigue during a course of chemotherapy, but also

facilitated a rounded evaluation of the intervention, incorporating both statistical elements and those of personal significance. The use of these methods showed that the implementation of the SNA↔P intervention in routine clinical practice has significant potential for improving patients' symptom experiences during a course of chemotherapy. In so doing, it also highlighted a number of areas in which clinical practice can be influenced, and research conducted, to further improve patients' symptom experiences.

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Steering group (Nora Kearney, Walter Sermeus, Dickon Weir-Hughes, Sara Lister, Faith Gibson, Derek Hoy) who allowed me to draw on the design and intervention of the WISECARE+ study.

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Preface – The development of the SNA↔P study

This PhD study arose from my involvement in a European cancer nursing study called WISECARE+ (2001-2003). The WISECARE+ study aimed to evaluate the impact of structured symptom management on patients' chemotherapy-related symptoms. WISECARE+ was pan-European, involving five clinical sites in Denmark, England, Ireland and Scotland, and was funded by the Royal Marsden NHS Foundation Trust.

To ensure clarity about the relationship between WISECARE+ and my PhD, in this preface I will outline:

- The aims and design of WISECARE+
- The roles of those involved in WISECARE+
- The inter-relationship between WISECARE+ and this thesis

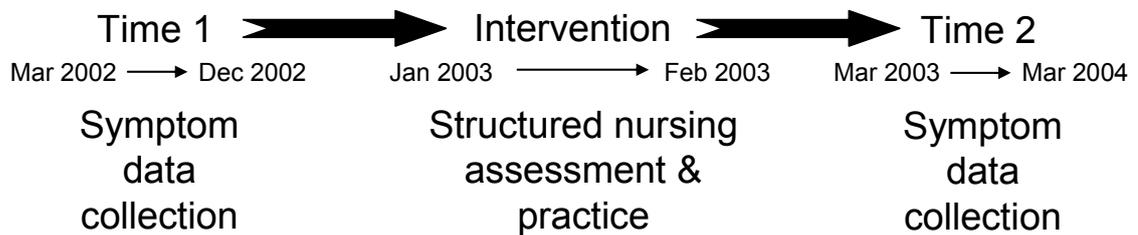
The aims and design of WISECARE+

The aim of WISECARE+ was to evaluate the impact of structured symptom assessment and management, facilitated by the WISETool, on patients' chemotherapy-related symptoms. The study focused on four physical chemotherapy-related symptoms identified by nurses involved in the study as problematic in their daily clinical practice: nausea, vomiting, fatigue and oral problems. These have also been consistently identified in the literature as prevalent and troublesome symptoms experienced by those receiving chemotherapy (Coates et al. 1983; Love et al. 1989; Griffin et al. 1996; Tierney et al. 1991; Cooper and

Georgiou 1992; Sitzia et al. 1995; Foltz et al. 1996; de Boer-Dennert et al. 1997; Lindley et al. 1999; Carelle et al. 2002).

WISECARE+ followed a before and after design with data collection taking place over two distinct time periods (times 1 and 2). The intervention took place between these two time periods (see Figure 1).

Figure 1: WISECARE+ Design



A convenience sample of patients was recruited from all five clinical sites and the samples from times 1 and 2 were not matched. The inclusion/exclusion criteria for the sample are presented in Table 1 below.

Table 1: WISECARE+ patient inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> • Aged 18 years or over • Aware of their cancer diagnosis • Able to give informed consent • Able to read/write English • Scheduled to receive chemotherapy for breast, lung, ovarian or colorectal cancer, osteosarcoma, leukaemia or lymphoma 	<ul style="list-style-type: none"> • Patients deemed by any member of the clinical team as being physically or psychologically unfit to participate in the study • Patients who had previously received a course of chemotherapy

Ethical approval was granted in each clinical site and all patients gave written informed consent prior to their recruitment to, and participation in, WISECARE+.

Patients completed a daily structured symptom questionnaire for 14 days following each cycle of chemotherapy. The questionnaire asked patients about the incidence, severity and distress of any nausea, vomiting, fatigue or oral problems that they experienced that day. A total sample of 249 patients was recruited from the 5 clinical sites. These patients (127 participating during period 1 and 122 during period 2) completed a total of 12,227 symptom questionnaires. All participating patients completed at least 1 cycle of chemotherapy, and so, were included in the analysis. The impact of the intervention was evaluated by comparing symptom outcomes between times 1 and 2, and found statistically significant improvements in nausea, vomiting and oral problems, but not fatigue.

Those involved in the WISECARE+ study

WISECARE+ was managed by a Steering Group (see Appendix A) who met on a four-six monthly basis to plan and oversee the study. The Steering Group was comprised of myself (Research Fellow, MM), Professor Nora Kearney (Principle Investigator), Professor Walter Sermeus (statistical and IT advisor), Derek Hoy (software design and support), Dickon Weir-Hughes and Sara Lister (representing the funding body and advising on general study conduct), and Dr Faith Gibson (paediatric advisor, as it was envisaged that future development of WISECARE+ would involve a paediatric aspect, and advisor on all study aspects). Professor Nora Kearney is also one of my PhD supervisors. In addition to the Steering Group there was also a group of nurses from each of the clinical sites involved in the

WISECARE+ study. While these nurses met face-to-face only at the start and end of the study, they frequently communicated by e-mail, discussing their involvement in the study and providing each other with peer support.

My role in the research ideas for the WISECARE+ study started before funding had been received. I was responsible for developing the research proposal and working with clinical sites to secure their involvement in WISECARE+. Thus, I had considerable influence over the research design and choice of research methods. I was solely responsible for the development and introduction of the intervention for the WISECARE+ study in all 5 clinical sites. During the planning of the WISECARE+ study and throughout its duration, I also had a close working relationship with Derek Hoy, who was responsible for the development and maintenance of the WISETool. The WISETool was the electronic patient record, designed specifically for WISECARE+, into which patient data was entered. The WISETool had an integral role in the study's intervention, as it provided nursing staff with feedback of patients' symptom outcomes, as well as prompts for appropriate nursing interventions. Liaising between Derek and nursing staff involved in the study, it was my responsibility to ensure that the WISETool was user-friendly and provided the nursing staff with relevant patient and symptom information. It was also my role to ensure that the nursing staff were competent in their use of the WISETool, so using it to its full potential. During the implementation of the WISECARE+ study, I was responsible for working with the nursing staff in each clinical site to ensure adherence to the data collection process. Working with the nurses involved visits to each clinical site and, at least, weekly e-mail contact. The

number of visits varied between each clinical site, depending on the nurses' previous research experience, and geographical location of the clinical sites.¹

The inter-relationship between the WISECARE+ study and my PhD

As this thesis arose from my involvement in the WISECARE+ study, it inevitably draws on the design of WISECARE+ and the WISECARE+ intervention (structured nursing assessment and practice) which I developed and implemented across the 5 clinical sites involved in the WISECARE+ study. However, this thesis describes the SNA↔P study (Structured Nursing Assessment into Practice study). Figure 2 demonstrates the inter-relationship between the WISECARE+ study and the SNA↔P study.

¹ As Principal Investigator for the study I can confirm that although the idea for the study was not generated by Morven she had significant input to the subsequent development and execution of the study and as a consequence was involved in refining the methods for the study. She had responsibility for the development of the intervention, development of links and ongoing collaboration with the clinical sites throughout the study, development and integration of the literature reviews and symptom management information into the WISETool. In addition she led the clinical team in ensuring feasibility and acceptability of the WISETool across the clinical sites. Professor Nora Kearney February 2008

Figure 2: Inter-relationship between WISECARE+ and SNA↔P studies

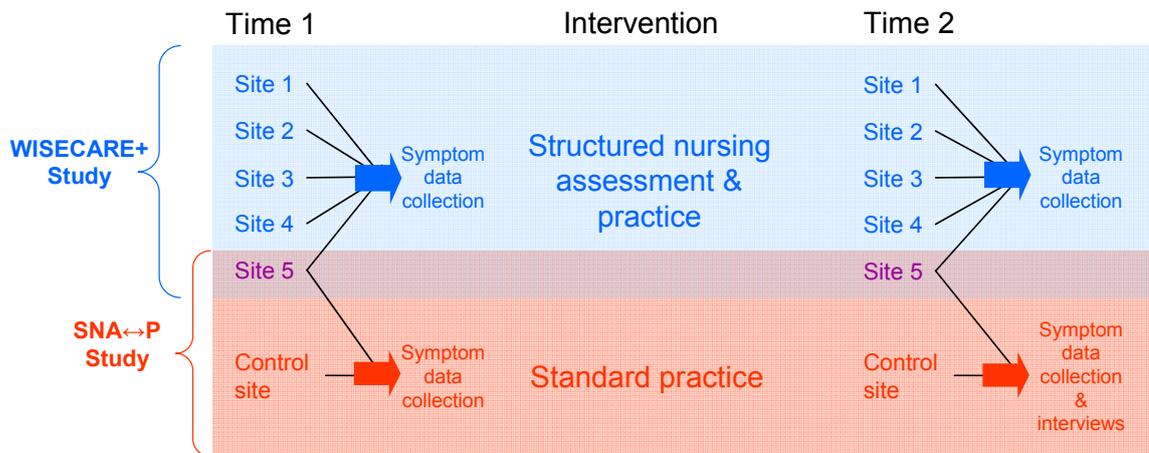


Figure 2 shows that the SNA↔P study involved one site from the WISECARE+ study. The intervention from the WISECARE+ study, developed and implemented by me, was also utilised in the SNA↔P study. However, the SNA↔P study differs significantly from the WISECARE+ study in 3 ways:

1. It focuses only on women receiving chemotherapy for breast cancer

WISECARE+ involved a heterogeneous sample of patients receiving chemotherapy. While this sample reflected the patient populations of the clinical sites involved in the WISECARE+ study, I felt it was important to explore the impact of the intervention in a more homogenous population. I chose women with breast cancer for a number of reasons. Firstly, I had developed a particular interest in this patient population through my clinical experience. Secondly, they represented the largest patient population in the clinical sites that I had identified for my study, so giving me access to the greatest number of patients during the data collection period, and so increasing the power of the study.

2. It includes a control group

Before and after designs are made stronger with the addition of a control group that receives the same measurement but not the intervention (Burns and Grove 2005). This design increases the strength of the confidence that any improvement observed in symptoms during time 2 was due to the intervention rather than other variables, such as a change in policy for example, between the two timepoints.

3. It incorporates simultaneous quantitative and qualitative exploration of symptom experiences

Through my involvement in the WISECARE+ study I grew to appreciate that, although measuring symptoms in a structured fashion was helpful in evaluating the impact of an intervention, it did not describe *how* symptoms are experienced, or their impact on the lives of those experiencing them. Thus, in the design of the SNA↔P study, I included structured interviews with a sub-sample of patients to explore the relationship between the quantitative measurement of symptoms and the personal significance and meaning of symptoms to individuals. This novel method of exploring symptoms, that is, using quantitative data to facilitate the qualitative exploration of the meaning of specific symptom scores for individual patients, produced illuminating results.

As the SNA↔P study arose from my involvement in the WISECARE+ study, it is constrained to some extent by the methods utilised in the WISECARE+ study. I have, (in the relevant methods and discussion chapter), highlighted these methods. The remainder of this thesis will focus on my study: the SNA↔P study.

1 CHAPTER 1 – INTRODUCTION

Cancer remains one of the most feared of illness, and receiving a diagnosis has been shown to be a dramatic and life-changing experience (Saegrov and Halding 2004).

Breast cancer is the most common malignancy among women, with an average lifetime risk of approximately 10% (Benson 2007). Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for a tenth of all new cancers and 23% of all female cancer cases (Ferlay et al. 2004). Breast cancer incidence rates vary considerably, with the highest rates in the developed world and the lowest rates in Africa and Asia (Ferlay et al. 2004). In Scotland, during 2002 (where and when the SNA↔P study was performed), 3,691 women were diagnosed with breast cancer and 1,105 women died of the disease (Information and Statistics Division 2007a; Information and Statistics Division 2007b). However, despite the continued rise in incidence of the disease, with almost half a million deaths annually worldwide, mortality rates have fallen over the last two decades (Benson 2007). The most recent estimate suggests around 172,000 women are alive in the UK having had a diagnosis of breast cancer (Micheli et al. 2002), and in Scotland, at the end of 2003, there were 32,821 women living with breast cancer, which equates to 1.249% of the female population (Information and Statistics Division 2007c). The improvements in survival are due to the success of a range of strategies, including screening, and cancer therapies such as chemotherapy and radiotherapy.

However, anti-cancer therapies are associated with a range of symptoms that have been shown to have a negative effect on quality of life (Dikken and Sitzia 1998; Department of Health 2000; National Institute for Clinical Excellence 2004). This finding, in tandem with the shift in the administration of chemotherapy from in-

patient to out-patient services, means that the majority of patients receiving chemotherapy cope with chemotherapy-related symptoms while they are at home without the direct support of trained oncology health professionals (McCaughan and Thompson 2000). It is such chemotherapy-related symptoms, specifically nausea and fatigue, that are the focus of this thesis.

1.1 Plan of Thesis

In the following chapter of this thesis, the evidence concerning chemotherapy-related symptoms will be reviewed. A considerable body of research utilising a variety of research methods has generated evidence that shows chemotherapy is associated with a plethora of physical and psychosocial symptoms. However, despite the range of research methods and methodological limitations, chemotherapy-related nausea and fatigue have been consistently identified by patients as high ranking symptoms of concern. As both these symptoms are non-observable they present a considerable challenge to health professionals in their assessment and management.

Chapters 3 and 4 explore the current evidence concerning chemotherapy-related nausea and fatigue, respectively. The causes of nausea and fatigue will be considered in these chapters, before critical analysis of the available assessment and management techniques demonstrate that, not only is there a variety of effective ways of assessing nausea and fatigue, there is also growing evidence of effective interventions. However, despite advances in assessment and management, exploration of the symptom experience for both nausea and fatigue continues to show the overriding negative impact these symptoms have on the lives of those

experiencing them. Explanations for the minimal impact of interventions on experiences will be offered and the potential role for nursing staff in these interventions will be explored. Chapter 5 provides a brief summary of this literature review and presents a rationale for the development of the SNA↔P study.

Chapter 6 describes the design and methods used in the SNA↔P study, a study undertaken to evaluate the impact of a nurse-led intervention incorporating structured assessment and practice on chemotherapy-related nausea and fatigue. Details of the pilot study will be given before the methods used in the main study, both quantitative and qualitative, are detailed. The intervention itself is described in detail in chapter 7. The results of the SNA↔P study are presented in chapter 8.

Finally, the overall conclusions from the SNA↔P study are discussed in chapter 9. Key aspects of the study and its implications for practice in relation to symptom assessment and management are presented. Areas for future research are also identified.

2 CHAPTER 2 – EXPERIENCES OF CHEMOTHERAPY - RELATED SYMPTOMS

2.1 Introduction

Chemotherapy is one of the most common and successful anti-cancer treatments, however it is associated with a range of related symptoms. This chapter will, firstly, consider ‘symptoms’ and the ‘symptom experience’ in general, before moving on to review the body of research, developed over the last 3 decades, that specifically explores patients’ experiences of chemotherapy-related symptoms.

2.2 Symptoms and the symptom experience

Multiple definitions of ‘symptom’ have been developed, but they all agree that symptoms can be defined as a subjective experience reflecting changes in the biopsychosocial functioning, sensations or cognition of an individual (Giardino and Wolf 1993; Hegyvary 1993; McDaniel and Rhodes 1995; Larson et al. 1999; Dodd et al. 2001a; Fu et al. 2004; Larson et al. 1994). Lexical information and the literature support the assumption that a symptom is an experience that is perceived and verified only by the individual experiencing the phenomenon (Fu et al. 2004), making a symptom subjective and experiential.

Symptoms motivate people to seek care, they cause distress and they disrupt quality of life (Caldwell and Miaskowski 2000). There is a growing body of evidence that supports the concept of symptom clusters, which can be defined as: three or more concurrent symptoms that are related to each other (Dodd et al. 2001b). This

concept of symptom clusters will be returned to in the discussion chapter of this thesis. Because symptoms, either alone or arising in combination, can interfere with every element of a person's life (Teel et al. 1997; Hyden and Sachs 1998; Dodd et al. 2001b), the term 'symptom experience' broadens the definition of symptom to include altered social interactions, diminished functional status and/or decreased economic capabilities. Indeed, in an analysis of multidisciplinary knowledge relating to chronic illness, the centrality of the symptom experience to the patient was highlighted (Dluhy 1995), a position supported by numerous authors (Bury 1991; McWilliam et al. 1996; Liaschenko 1997). Moreover, the significance attached to a symptom by the patient strengthens the need for those caring for them to value, as well as relieve or control, the symptom (Baumann et al. 1989; Vessey and Richardson 1993; Peay and Peay 1998; Russell et al. 1998). Thus, symptoms are more than 'simply the windows into a disease process... and demand more than control or elimination' (Haworth and Dluhy 2001, p303). Instead, managing symptoms from a nursing perspective requires understanding the person's experience and the meanings they associate with each symptom. This concept of understanding and appreciation of the symptom experience is reflected in the symptom experience component of the Symptom Management Model (Larson et al. 1994).

2.3 The Symptom Management Model

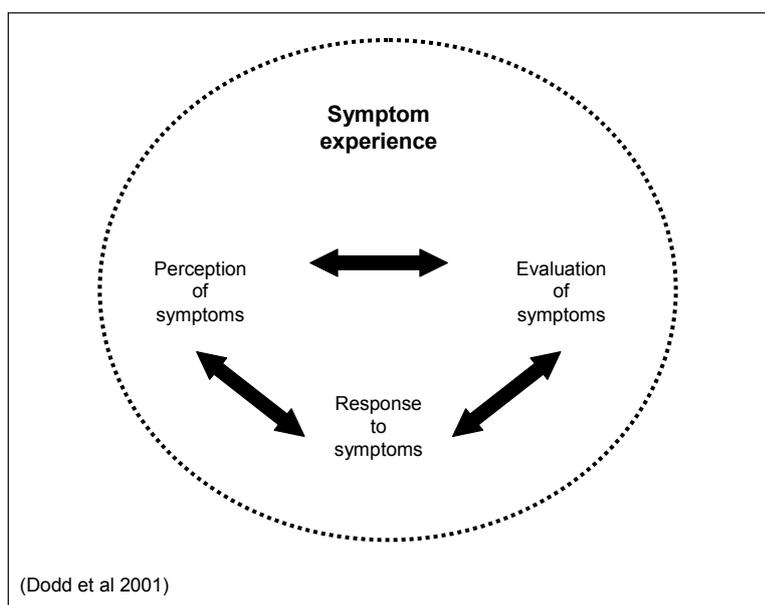
The Symptom Management Model (SMM), first published in 1994 by Larson and her colleagues and later revised by Dodd and her colleagues in 2001, provides a holistic perspective of symptoms. It has been developed and tested using a wide range of symptoms, including cancer and cancer-treatment related symptoms (Wells

et al. 2007; Im 2006), and is practical and straightforward, so useful for clinical practice, both of which make the model appropriate for consideration within this thesis. It provides a generic conceptual framework based on the premise that effective management of any given symptom requires that symptom experience, symptom management strategies and symptom outcomes are considered. The model presents a comprehensive organising structure that includes a broad array of variables well suited to understanding and characterising symptoms. The symptom experience component is comprised of the perception, evaluation and response to a symptom; the symptom management component investigates interventions used to manage the symptom experience; while the resulting outcomes component evaluates symptom status, including quality of life, mortality and morbidity.

2.3.1 Component parts of the symptom experience

Understanding the symptom experience includes developing an appreciation of the inter-relationship between an individual's perception of a symptom, evaluation of the meaning of the symptom, and response to a symptom (see Figure 3). Based on work undertaken following the initial development of the model by Larson et al (1994), Dodd et al (2001) described the perception and evaluation of and response to symptoms.

Figure 3: The symptom experience component of the SSM



Perception of symptoms refers to whether an individual notices a difference from the way they usually feel or behave. For a valid self-report of symptoms, the person reporting must be responding to their perception of the symptom (Dodd et al. 2001a). Indeed, differences in symptom perceptions have been consistently shown between patients, family and professional carers (Vogelzang et al. 1997; Stone et al. 2003; Eisenberg et al. 2003; Grunberg et al. 2004; Fromme et al. 2004; Liao et al. 2005). Additionally, factors such as culture and developmental stage also have a bearing on perceptions of symptoms (Dodd et al. 2001a).

Evaluation of symptoms is undertaken by making judgements about the severity, cause, treatability and the effect of symptoms on an individual's life and involves a complex set of factors that characterise the symptom experience, including

intensity, location, temporal nature, frequency, and affective impact (Dodd et al. 2001a).

Finally, response to symptoms can be physiological, psychological, sociocultural or behavioural. Indeed, one or more of these responses can be seen with a single symptom (Dodd et al. 2001a).

However, it is important to note that the most intense or frequent symptom experiences are not consistently the most distressing for patients (Rhodes et al. 1984), a concept that could be lost within the SMM. The reason for differences between intensity, frequency and distress may be because symptom distress relates to meanings that the symptom or illness itself holds for individuals as well as the fact that the meanings ascribed to symptoms are relative to one's personal life situation (McClement et al. 1997), that is, the individual human response to symptom occurrence. Thus, the extent of physical or mental anguish related to a symptom is dependent upon the individual's subjective perceptions. Consequently, the symptom experience is subjective, and so, understanding patients' experiences of chemotherapy-related symptoms, a key component of this thesis, relies on reports from patients themselves. The SMM was used to guide the choice of the symptom questionnaire and development of the interview schedule used within the SNA↔P study (details of which are presented in chapter 6) to ensure that the essential variables were included in order to understand and characterise patients' symptom experiences. A growing body of evidence has been built concerning patients' experiences of chemotherapy-related symptoms and is presented in the following section.

2.4 Patients' experiences of chemotherapy-related symptoms

Health professionals need to understand patients' experiences of symptoms to allow them to meet their symptom management needs. During the previous 3 decades, efforts have been made to better understand which chemotherapy-related symptoms patients perceive as being the most important or troubling. Ranking techniques, that is, asking patients to rank symptoms in order of importance, have been used in a number of studies (Coates et al. 1983; Griffin et al. 1996; de Boer-Dennert et al. 1997; Carelle et al. 2002), while other techniques including interviews, symptom diaries and questionnaires have also been implemented (Love et al. 1989; Tierney et al. 1991; Cooper and Georgiou 1992; Sitzia et al. 1995; Foltz et al. 1996; Lindley et al. 1999; Tierney et al. 1992). The results of these studies are presented below according to the techniques they adopted.

2.4.1 Studies using ranking techniques

Four groups of medical researchers have explored patients' experiences of chemotherapy-related symptoms using a near-identical survey and ranking technique (Coates et al. 1983; Griffin et al. 1996; de Boer-Dennert et al. 1997; Carelle et al. 2002). This technique involved using 2 groups of cards (Group A: 45 cards listing physical chemotherapy-related symptoms, and Group B: 28 cards listing non-physical chemotherapy-related symptoms), and asking patients to select any card that they attributed to their current chemotherapy. Patients were asked to rank the cards they had selected from each group, and the top 5 cards from each group were combined. Patients were then asked to identify the 5 most severe symptoms regardless of group, putting them in order from most to least severe. In an effort to obtain a ranking of the relative severity of symptoms, a scale was

defined by which 5 points were allocated to the symptom ranked as most severe, decreasing to one point for that symptom ranked as 5th. The points allocated to each symptom were then added and expressed as a percentage of the number of patients in the group to give an overall score. The results of these studies are presented in Table 2.

Table 2: Comparison of symptom ranking studies

	Coates et al (1983)	Griffin et al (1996)	de Boer-Dennert et al (1997)	Carelle et al (2002)
1	Being sick (vomiting)	Feeling sick (nausea)	Feeling sick (nausea)	Affects my family or partner
2	Feeling sick (nausea)	Constantly tired	Loss of hair	Loss of hair
3	Loss of hair	Affects my family or partner	Being sick (vomiting)	Constantly tired
4	Thought of coming for treatment	Not reported	Constantly tired	Affects my work, home duties
5	Length of time treatment takes at clinic	Being sick (vomiting)	Having to have an injection	Affects my social activities
6	Having to have an injection	Not reported	Constipation	Loss of sexual feelings
7	Shortness of breath	Not reported	Thought of coming for treatment	Giddiness on standing up
8	Constantly tired	Not reported	Affects family or partner	Diarrhoea
9	Difficulty sleeping	Not reported	Feeling low, miserable (depression)	Weight gain
10	Affects my family or partner	Not reported	Feeling anxious or tense	Shortness of breath

Table 2 demonstrates the plethora of symptoms that patients identify when asked to rank the symptoms they experience during chemotherapy treatment. However, it should be recognised that the pool of symptoms from which patients were invited to choose was developed by Coates et al (1983), and, although designed to be comprehensive, they were, necessarily, limited. Moreover, they were developed by the researchers themselves without patient involvement and so, were inherently open to personal and professional biases. That said, patients did not add to this list of symptoms when asked to do so following their involvement in the study.

Comparison of the studies is complicated by differences in the study populations that differ with respect to diagnosis, chemotherapy treatment, number of chemotherapy treatments received, age, and gender. The original work by Coates and colleagues included only patients with advanced cancer which, although appropriate at the time when most chemotherapy was given with palliative rather than curative intent, does not apply to today's climate of treatment intent. Indeed, it is important to consider whether symptom experiences are likely to differ according to the aim of treatment, be it curative or palliative. This question could have been addressed by Griffin et al (1996), who included both patients receiving curative and palliative chemotherapy, however, as they aimed to compare their results with Coates' earlier work, they failed to report the results of those patients receiving curative treatment. While this was a sensible decision from a methodological perspective, it failed to address a clinically interesting and important question. Neither de Boer-Dennert (1997) nor Carelle (2002) described their population in relation to treatment intent. However, all 4 studies did involve a range of cancer diagnoses and, although heterogeneity within a sample is not always problematic, in such studies where the cancer diagnosis and chemotherapy regime is likely to have a

bearing on patients' symptoms experiences, it may reduce the power of the analyses and the conclusions which can be drawn from them.

Inconsistent use of terminology also complicates the comparison of these ranking studies. During the initial ranking process, patients were asked to rank their symptoms according to 'severity' (Coates et al. 1983; Carelle et al. 2002), 'troublesomeness' (Griffin et al. 1996), or 'distress' (de Boer-Dennert et al. 1997), while the second ranking was, in the main, based on 'severity' of the symptoms (Coates et al. 1983; Griffin et al. 1996; Carelle et al. 2002). However, ranking according to distress continued to be used by de Boer-Dennert and his colleagues (1997). Indeed, while de Boer-Dennert and his colleagues sought to validate their results by comparing them with those of Coates (1983) and Griffin (1996), one can question whether this comparison is feasible, given the differences in terminology (severe, troublesome and distressing) used in the three studies.

It is also important to note that all these studies, apart from that by Coates et al in 1983, were conducted following the introduction of 5HT₃ receptor antagonists during the early 1990s, heralded as significant progress in the management of chemotherapy-related nausea and vomiting, and expected to significantly improve patients' experiences of these two symptoms (Kaiser et al. 1994; Campora et al. 1994; Franchi and Zamboni 1995; Morrow et al. 1995). While Chapter 3 explores the actual impact of 5-HT₃ receptor antagonists on nausea, the general picture presented from these ranking studies suggests that although patients' experiences of vomiting improved, nausea remained a symptom of significant concern.

Furthermore, one can question whether 'symptoms' such as 'the thought of coming for treatment', 'length of time treatment takes at clinic' and 'having to have an

injection' are actual symptoms of chemotherapy or whether they are consequences of service delivery. Certainly, within the summary definition of symptoms used in this thesis (see page 11) that identifies a symptom as a subjective experience reflecting changes in the biopsychosocial functioning, sensations or cognition of an individual, such physical processes involved with chemotherapy administration would not be considered symptoms at all. Such 'symptoms' were not included in the second group of studies that used a range of techniques to explore patients' symptom experiences during chemotherapy.

2.4.2 Studies using miscellaneous techniques

Perhaps in recognition of the limitations of the ranking technique described above, a number of studies adopted alternative methods to explore patients' perceptions of chemotherapy-related symptoms. These studies vary widely in their choice of methods, and a combination of structured and unstructured approaches to explore symptoms was frequently used (see Table 3). In all studies, the questionnaires and interview schedules were developed specifically for the study, and in all but one (Sitzia et al. 1995), little detail was provided of the process of development and testing of the tool.

Table 3: Miscellaneous methods of exploring symptom experiences

Authors	Methods used
Love et al (1989)	Longitudinal semi-structured interviews, daily diary containing 13 symptoms to be rated 0-11 for severity
Tierney et al (1991, 1992)	Interviews and single questionnaire at end of treatment
Cooper & Georgiou (1992)	Symptom and quality of life questionnaires (no further detail provided)
Sitzia et al (1995)	Longitudinal ranking of physical symptoms over at least 3 cycles of chemotherapy
Foltz et al (1996)	Self-care diary
Lindley et al (1999)	5 point likert scale for 41 chemotherapy-related symptoms, serial ranking questionnaire adapted from Coates et al 1983

The results of these studies, as well as the component of the symptom experience that each study sought to explore (symptom distress, severity or frequency), can be seen in Table 4. As with the ranking studies described in Table 2, Table 4 shows the plethora of physical symptoms that patients experience as a consequence of their chemotherapy.

Table 4: Results of symptom experience studies

Love et al (1989)	Tierney et al (1991)	Cooper & Georgiou (1992)		Sitzia et al (1995)	Foltz et al (1996)
Most distressing symptoms	Most frequent symptoms	Most frequent symptoms	Most distressing symptom	Most troublesome symptoms	Most severe symptoms
Nausea, alopecia & tiredness experienced by >80% of patients.	Tiredness	Alopecia	Tiredness	Tiredness	Alopecia
	Nausea	Tiredness	Alopecia	Hair loss	Fatigue
	Loss of appetite	Lack of energy	Nausea	Nausea	Nausea
	Mouth sores	Decreased sexual interest		Night sweat	Taste change
	Pain			Difficulty sleeping	Appetite loss
	sickness			Feeling generally unwell	Sleep problems
	Sore eyes			Difficulty concentrating	Constipation
				Dry mouth	Headache
				Weight up	Sore mouth
				Physical weakness	Pain

There are a number of positive aspects of these studies that should be highlighted. The first of these is the longitudinal evaluation of symptom experiences (Love et al. 1989; Sitzia et al. 1995) that takes into consideration the potential for changes in symptoms over time. Through such longitudinal evaluation, Love and colleagues (1989) demonstrated that patients perceive an increase in the ‘difficulty’ of chemotherapy over time due to their symptom experiences, with the number of different symptoms acting as the best predictor of the level of ‘difficulty’. It was

also positive that Tierney and her colleagues (1991, 1992) sought to explore symptom experiences within a homogenous population of women with breast cancer. However, this sample was compromised somewhat, as it included women receiving both curative and palliative chemotherapy. Finally, Cooper and Georgiou (1992) attempted to capture a multidimensional picture of symptom experiences through exploring both the frequency and associated distress of patients' chemotherapy-related symptoms.

Nevertheless despite these shortcomings, these studies do replicate many of the limitations of the previous symptom ranking research. There was continued arbitrary selection of symptoms for inclusion within questionnaires and interviews (Love et al. 1989; Tierney et al. 1991; Tierney et al. 1992; Cooper and Georgiou 1992; Foltz et al. 1996) with Sitzia and his colleagues (1995) being the only researchers to involve patients in the identification of symptoms to be evaluated. Also, there was variation in the terminology used with regards to which component of the symptom experience was being evaluated (see Table 4). Furthermore, the heterogeneous populations involved in each study with respect, not only to diagnosis, but also chemotherapy treatment, treatment intent, in-/out-patient treatment, gender and age, complicates drawing comparisons between each of the studies.

2.4.3 Comparing and contrasting results from ranking studies and those employing miscellaneous approaches

Despite the limitations of both the ranking replication studies and those that employed a range of approaches, or perhaps because of them, it is clear that, regardless of diagnosis, chemotherapy treatment, treatment intent, age, gender and

the component of the symptom being explored, patients experience a wide range of symptoms as a consequence of their chemotherapy. The results of both the ranking studies and those that adopted multiple methods to explore symptom experiences have been combined and are presented in Table 5. This table shows that patients identified 32 physical and psychological symptoms, social consequences, or physical processes involved with chemotherapy administration. Physical symptoms were, by far, the most commonly identified, perhaps as they were the focus of the studies that employed miscellaneous approaches to explore symptom experiences. Indeed, as the researchers were predominantly responsible for determining the symptoms for ranking or discussion within each of the studies, it is likely that the focus on physical symptoms is due to the preferences, conscious or otherwise, of the researchers themselves, rather than those of the patients.

Combining the results of these 10 studies (as seen in Table 5) provides illuminating results. Three symptoms stand out from the others with regards to the frequency of their reports: tiredness, nausea and alopecia being identified 10, 9 and 8 times respectively out of a possible 10. However, not only are they the most frequently identified symptoms, tables 2 (page 17) and 4 (page 22), in which symptoms were ranked in order of importance to the patient, demonstrate that in 8 out of the 10 studies, fatigue, alopecia and nausea were consistently ranked by patients within their top 4 symptoms of concern. Although these are three completely different symptoms, nausea and fatigue are similar in the fact that they are non-observable and, as such, present a considerable challenge to oncology health professionals in relation to their assessment and subsequent management. These symptoms were consequently chosen as the symptoms of focus within this thesis.

Table 5: Combined results of ranking and miscellaneous studies exploring chemotherapy-related symptoms

		Ranking technique: times symptom identified (out of a possible 4)	Miscellaneous techniques: times symptom identified (out of a possible 6)	Total times symptom identified (out of a possible 10)	
Physical symptoms					
Symptom class	Descriptor				
Tiredness	Constantly tired	4	--	4	10
	Tired	--	6	6	
	Lack of energy	--	1		1
	Difficulty sleeping	1	2		3
	Physical weakness	--	1		1
Appearance	Alopecia	3	5		8
	Weight gain	1	1		2
Upper gastrointestinal	Nausea	3	6		9
	Vomiting	3	1		4
	Mouth sores	--	2		2
	Appetite loss	--	2		2
	Dry mouth	--	1		1
	Taste change	--	1		1
Lower gastrointestinal	Constipation	--	1		1
	Diarrhoea	1	--		1
Pain	Pain	--	2		2
	Headache	--	1		1
Respiratory	Shortness of breath	2	--		2
Other	Giddiness on standing up	1	--		1
	Night sweat	--	1		1
	Sore eyes	--	1		1
	Generally unwell	--	1		1
Psychological symptoms					
Depression		1	--		1
Anxiety		1	--		1
Difficulty concentrating		--	1		1
Social consequences					
Affects family/partner		4	--		4
Affects work/home duties		1	--		1
Affects social activities		1	--		1
Loss of sexual feelings		1	1		2
Physical process involved with chemotherapy administration					
Thought of coming for treatment		2	--		2
Length of time treatment takes at clinic		1	--		1
Having to have an injection		2	--		2

2.5 Conclusion

This chapter firstly presented a summary definition of symptoms in general as well as highlighting and describing the component parts that should be considered when exploring patients' symptom experiences. Thereafter, it demonstrated the plethora of symptoms that patients experience as a consequence of chemotherapy through a number of studies that employed a range of research techniques. Comparing and contrasting this body of research evidence, despite its methodological flaws, has shown that chemotherapy-related nausea and fatigue were not only the most frequently identified symptoms but were also consistently highly ranked symptoms.

Ranking and ordering of symptoms are helpful in understanding the variety of symptoms that patients experience, as are their perceptions regarding which symptoms are most severe or distressing. However, this approach does not provide insight into why patients have ranked specific symptoms and how it feels to experience them. It also raises questions with regards to currently available intervention strategies for managing or alleviating these symptoms and so improving patients' symptom experiences. Such issues are especially important for chemotherapy-related nausea and fatigue, as they are non-observable symptoms, a fact which challenges their assessment and complicates their management. The following two chapters will provide further detail on chemotherapy-related nausea and fatigue respectively, with regards to current assessment and interventions, and will seek to understand patients' experiences of these symptoms.

3 CHAPTER 3 – CHEMOTHERAPY-RELATED NAUSEA

3.1 Introduction

This chapter will consider chemotherapy-related nausea. Chapter 2 demonstrated that chemotherapy-related nausea is not only one of the most frequently reported symptoms by patients, but is also highly ranked. However, such a ranking process does not explain why patients have identified the symptom, how it feels to experience that symptom, nor the available interventions or techniques that have the potential to improve this symptom experience.

This chapter will briefly detail definitions of chemotherapy-related nausea, vomiting and retching as well as the various forms that chemotherapy-related nausea can take. It will then consider the current assessment tools and management interventions for chemotherapy-related nausea, demonstrating the various methods available to improve patients' experiences. Thereafter, the literature detailing patients' experiences of chemotherapy-related nausea and its impact on quality of life will be reviewed. Finally, possible reasons for patients' continued negative experiences of chemotherapy-related nausea, despite currently available assessment and interventions, will be explored.

3.2 Defining chemotherapy-related nausea

The term 'emesis' has been used to collectively describe vomiting and retching (Hesketh et al. 1998) as well as nausea, vomiting and retching (Multinational Association of Supportive Care in Cancer 1998). However, nausea, vomiting and retching are 3 distinct symptoms that should be clearly defined and understood to

ensure accurate assessment and subsequent management. Thus, to ensure clarity throughout the remainder of this thesis, the following definitions will be used for each.

Nausea has been defined as a subjective and unobservable phenomenon of an unpleasant sensation often associated with a feeling that vomiting is imminent (Andrews 1996). This definition is appropriate for this thesis as it highlights the subjective and non-observable nature of nausea while recognising that it is an unpleasant sensation. It is also in keeping with the summarised definition of a symptom given in chapter 2, as it refers to subjective experiences and a change in sensation. However, it is important to note that chemotherapy-related nausea does not always culminate in vomiting. Moreover, while essentially non-observable, nausea can be accompanied by objectively observable activity of the autonomic nervous system causing pupil dilation, cutaneous vasoconstriction, sweating, salivation, tachycardia, and gastric relaxation (Morrow et al. 2002). Vomiting is the forceful expulsion of the contents of the stomach through the oral or nasal cavity (Rhodes and McDaniel 2001), while retching is the attempt to vomit, and has been described by patients as ‘dry heaves’ and ‘gagging’ (Rhodes and McDaniel 2001).

Chemotherapy-related nausea has been classified into 5 distinct categories:

- Acute - occurring within the first 24 hours following chemotherapy administration (Jordan et al. 2005);
- Delayed - beginning the day following chemotherapy administration and may last 6-7 days (Kris et al. 1994; National Comprehensive Cancer Network 2007b);

- Anticipatory – learned from previous experiences or associations and experienced at any time prior to the administration of chemotherapy or when the patient thinks of aspects relating to chemotherapy (Morrow et al. 1998);
- Breakthrough – nausea that occurs despite optimal preventative therapy in the acute or delayed phase and that requires additional therapy (Aapro 2002);
- Refractory – failure to respond to prevention and/or intervention during the previous cycle of chemotherapy (Aapro 2002).

This thesis focuses on an intervention to improve patients' experiences of chemotherapy-related nausea following chemotherapy administration and, as such, the remainder of this chapter will not include literature that addresses anticipatory nausea. Much of the literature addressing nausea also includes vomiting, however, where possible, only the evidence concerning nausea will be presented.

3.3 Assessing chemotherapy-related nausea

Assessment and documentation of nausea, as well as an evaluation of the effectiveness of any treatment, are essential components of optimal symptom control (Rhodes 1997) and, as such, are important tasks for nurses caring for people with chemotherapy-induced nausea. This assessment is necessarily an ongoing process, beginning with the patient's initial consultation and continuing throughout their entire treatment journey, and involves skilful observation and effective, efficient methods of information collection. During chemotherapy treatment the ideal assessment tool would be quick to complete and review while simultaneously

capturing the symptom experience. However, three factors complicate the assessment of chemotherapy-related nausea.

3.3.1 Factors complicating the assessment of nausea

The first factor complicating the assessment of chemotherapy-related nausea is its close association with vomiting. Despite the fact that nausea and vomiting are distinct entities with their own physiology, the terms used to describe them are used interchangeably (Hesketh et al. 1998; Multinational Association of Supportive Care in Cancer 1998), leading to confusion both in practice and research. Large randomised trials often fail to distinguish between the two symptoms, assessing and, subsequently, presenting data for these symptoms simultaneously (Hesketh 2000; Gralla et al. 2003). This perpetuates the belief that these symptoms do not occur independently and prevents a full understanding of each symptom in relation to its appropriate assessment and interventions.

Secondly, despite physiological changes such as pupil dilation, sweating, salivation and tachycardia, chemotherapy-related nausea is difficult to observe. Both physicians and nurses have been shown to consistently and substantially underestimate the incidence of both acute and delayed nausea (Eisenberg et al. 2003; Grunberg et al. 2004), especially in relation to moderately emetogenic chemotherapy (Liau et al. 2005). Such a discrepancy between those experiencing nausea and those caring for them is cause for concern and may compromise optimal assessment and management. As such, chemotherapy-related nausea is best measured subjectively by the person experiencing it (Jenns 1994).

Most patients receive chemotherapy as an out-patient, leaving the hospital shortly after chemotherapy administration is complete. However, the practice of symptom assessment is characteristically performed when patients return to the clinical setting for further treatment or review (Brown et al. 2001). This complicates the assessment of nausea, as many patients experience it while at home, away from the presence, support and assessment of oncology health professionals. One could argue that by the time patients return for their subsequent cycle of chemotherapy, usually three-to-four weeks later, their recollection of nausea experiences and its impact on their quality of life will be diminished. Moreover, as health professionals do not witness first hand the severity and distress that can accompany chemotherapy-related nausea, one could argue that they may not fully appreciate the severity or distress associated with the symptom.

Thus, the assessment of nausea is challenging, not only because of its frequent association with vomiting, but also because it is non-observable. Furthermore, patients' experiences of nausea are seldom witnessed first hand by health professionals. However, there are a number of factors that can be assessed to promote the effective management of nausea. The first involves the assessment of specific risk factors associated with higher levels of nausea and the second involves the assessment of actual nausea experiences, so allowing health professionals to initiate appropriate interventions or evaluate the effectiveness of specific management techniques.

3.3.2 Assessment of risk factors associated with chemotherapy-related nausea

One could argue that assessing for personal factors associated with increased susceptibility to chemotherapy-induced nausea would allow nursing staff to ensure that patients with an increased risk are treated with more aggressive interventions. There are a range of individual characteristics, both physiological and psychological, that predispose individuals to experience chemotherapy-induced nausea.

Patients' expectations of developing nausea have been consistently shown to be associated with post-treatment nausea in a number of studies (Rhodes et al. 1988; Haut et al. 1991; Rhodes et al. 1995; Roscoe et al. 2000; Molassiotis et al. 2002a), although earlier studies that refute such an association do exist (Cassileth et al. 1985; Andrykowski and Gregg 1992). A number of other factors have been identified as potentially or partly associated with the development of chemotherapy-induced nausea. These include:

- Age – a younger age (<50 years old or <40 years in some studies) has been shown to be associated with greater nausea (Morrow et al. 1991; Molassiotis et al. 2002a)
- Gender – females are more likely to experience nausea than males (du Bois et al. 1992; Osoba et al. 1997a)
- Susceptibility to nausea when eating certain foods (Jacobsen et al. 1988)
- The taste of drugs during the infusion (Nerenz et al. 1986)
- Low alcohol use (Osoba et al. 1997a)

- Psychological status and stress (Tsavaris et al. 1991; Dibble et al. 2003; Higgins et al. 2007)
- Previous history of labyrinthitis or vestibular dysfunction (Molassiotis et al. 2002a)
- Susceptibility to motion sickness (Morrow 1985; Leventhal et al. 1988; Morrow et al. 1991)
- Experience of acute nausea is predictive of delayed nausea (Molassiotis et al. 2002a)

There is also a growing and frequently updated knowledge base that classifies chemotherapy agents and regimes according to their emetogenic potential (Laszalo 1982; Strum et al. 1984; Craig and Powell 1987; Lindley et al. 1989; Aapro 1993; Hesketh et al. 1997; Grunberg et al. 2004). Indeed, this classification is used to guide clinicians as to the most appropriate pharmacological antiemetic therapies for prescription (National Comprehensive Cancer Network 2007a). However, this classification is calculated solely on the risk of vomiting. While the basis for this classification limits its relevance to this thesis, it provides an example of how experiences of nausea are often overlooked in favour of vomiting.

3.3.3 Assessment of experiences of chemotherapy-related nausea

There are a range of methods available for assessing chemotherapy-related nausea. It is important that an assessment tool clearly distinguishes between the phenomena of nausea, vomiting and retching, using patient-friendly descriptors to dispel the confusion between these three symptoms (Kaye 1991). Indeed, a rounded assessment that describes the patient's symptom experience in terms of frequency, severity and distress will provide the most accurate and complete picture of the

symptom and so facilitate implementation of the most appropriate interventions (Rhodes and McDaniel 1999). The range of tools available to assess chemotherapy-related nausea, with details of their development and usability, can be found in Table 6.

Table 6: Nausea assessment tools

Unidimensional tools		
Instrument/author	Consists of	Clinical utility
CTCAE National Cancer Institute (1999), Trotti et al (2003)	Range of treatment-related symptoms to be graded from 0-4 by a health professional	Quick to complete. Physician-led, relates nausea to patients' functional ability to eat, does not consider frequency, severity or distress, no data to substantiate validity
VAS (Visual Analogue Scale)	A 10cm horizontal line and verbal 'anchors' such as 'no nausea' and 'worst possible nausea' and patients are asked to rate their subjective experience	Simple and quick way of assessing symptoms from the patients' perspective, avoids language descriptors to signify graduations of a subjective phenomena, sensitive, reliable and valid tools when used properly. Verbal anchors should be tested for understanding by and meaningfulness to patients, respondents find the instructions on their use confusing, patients need thorough instruction from trained personnel to ensure reliable answers which has the potential to introduce investigator-related bias, as designed to be used with seated subjects there has been questions raised as to their reliability with supine patients
Ordinal Scales	Grades of nausea such as 'no nausea', 'mild', 'moderate' or 'severe' and patients are asked to indicate which most describes their nausea	Easier than VAS for clinicians and researchers to interpret, requires less patient instruction than VAS. May become less sensitive over time than VAS in detecting change due to their limited responses

Multidimensional tools				
Instrument/author	Domains of factors	No. of items & scaling	Reliability & Validity	Clinical utility
Index of Nausea Vomiting and Retching (INVR) Rhodes and Watson (1984), Rhodes and McDaniel (1999)	Nausea, Vomiting and retching and the components (frequency/ amount, duration, severity, distress) of each symptom	8 total, 5 occurrence, 3 distress 5 point Likert scale	Reliability: Spearman correlation total: 0.87 individual items: 0.71-0.95 Equivalency: 79%-98% (p=0.05) Validity: Spearman's correlation, r=0.87	Ease of use. Provides information about nausea, vomiting and retching total experience, occurrence, distress and individual symptoms. 12 hour time frame. Used with varied populations. No indication of time taken to complete
Morrow Assessment of Nausea and Emesis (MANE) Morrow (1992)	Anticipatory and post-treatment nausea and vomiting, frequency during and after treatment, duration, severity, time when worse	16 Severity – 6 point scale Occurrence – yes/no Duration – number of	Reliability: Test-retest reliability: 0.72-0.96 Validity: Convergent validity 0.26-0.33	Primarily used with antiemetic studies. Long time frame (24 hours). Does not include the concept of symptom distress, No indication of time taken to complete

		hours	Divergent validity 0.04-0.08	
Functional Living Index – Emesis (FLIE) Lindley et al (1992)	Effect of nausea and vomiting on physical activity, social and emotional function and eating	18 9 nausea 9 vomiting 1-7, 7 point scale	Reliability: Cronbach’s alpha 0.9 Pearson item-scale correlations 0.40-0.82 pre-treatment and 0.81-0.96 post-treatment Validity: Factor analysis not reported Pearson correlation with nausea and vomiting 0.65 and 0.68 Correlation with Function Living Index – Cancer nausea factor – 0.83	Ease of use. Provides information about the effect of nausea and vomiting on functional status. Correlates with quality of life measures. Patients were not involved in deciding the concepts addressed within the tool, No information available on time taken to complete the tool.

Table 6 demonstrates the variety of assessment tools. The choice of instrument should be guided by the purpose of the assessment. One could argue that some of the multidimensional specific tools such as the Index of Nausea and Vomiting (INVR) (Rhodes and McDaniel 1999) and the Morrow Assessment of Nausea and Emesis (MANE) (Morrow 1992) are too extensive, limiting their usefulness and appropriateness for daily clinical practice, as they demand both significant patient energy to complete and clinician time to evaluate. Visual analogue scales or ordinal scales may be preferred as an alternative for use in clinical practice, as they are quick and simple for patients to complete and for clinicians to interpret (Molassiotis and Borjeson 2006). A study that compared concordance between VAS and a 4-point ordinal scale for assessing the intensity of nausea demonstrated good similarities between these two methods, making them both appropriate for use in clinical practice (Borjeson et al. 1997), however, no data was provided as to the relative reliability and validity of each method. A more in-depth evaluation of nausea, such as that obtained through multidimensional instruments such as INVR (Rhodes and McDaniel 1999), MANE (Morrow 1992) or Functional Living Index – Emesis (FLIE) (Lindley et al. 1992), while more time consuming to complete, may provide a more thorough and in-depth understanding, and so be wholly appropriate for use within a research setting. It is unfortunate that all the multidimensional assessment tools address nausea and vomiting and, as such, afford clinicians the opportunity to report vomiting data only in their evaluation of antiemetic therapies.

The choice of tool should be based on the needs of the particular situation and should take into consideration patient individuality, that is, which tools are appropriate for which patients and at what specific times (Kaye 1991). Thus,

choosing the most appropriate tool provides clinicians and researchers with information about individuals' experience of chemotherapy-related nausea. The next step is using this information to implement the most appropriate interventions for managing and alleviating chemotherapy-related nausea.

3.4 Current management techniques for chemotherapy-related nausea

The array of assessment tools for chemotherapy-related nausea is matched by a variety of management techniques. Within intervention studies, nausea and vomiting continue to be inextricably linked, with almost all studies exploring the impact of a particular intervention on both symptoms simultaneously (Morrow et al. 1995; Roscoe et al. 2000; The Italian Group for Antiemetic Research 2000; Hesketh et al. 2003; Poli-Bigelli et al. 2003; Olver 2004; DeWalt and Haines 1969; Warr et al. 2005; de Wit et al. 2004). This association between nausea and vomiting makes it difficult to establish the most appropriate interventions for nausea alone. The following sections evaluate the current pharmacological and non-pharmacological interventions for chemotherapy-related nausea, alone when possible, or in tandem with vomiting.

3.4.1 *Pharmacological management of chemotherapy-related nausea*

Chemotherapy-related nausea is most commonly managed with antiemetic drugs. However, if nausea is experienced despite prophylactic treatment, changes in the drugs used can result in an improvement for patients (Koeller et al. 2002; Grunberg et al. 2005). Indeed, a combination of antiemetic drugs with different modes of actions, is often necessary to provide optimal symptom control (Jordan et al. 2005).

Table 7 provides a summary of the main classes of antiemetic drugs, their actions, uses, and clinical considerations.

Table 7: Main classes of pharmacological antiemetic therapies

Class of drug	Mode of action	Clinical uses	Potential side-effects	Clinical considerations
5-HT ₃ receptor antagonists e.g. Dolasetron Granisetron Ondansetron Tropisetron	Inhibits selective 5-HT ₃ receptor sites both centrally and in the GI tract	Moderate to highly emetogenic chemotherapy	Constipation, headache, transient light-headedness may occur during infusion	Ideal for use in elderly patients Use with stool softener, increased fluids and bran to prevent constipation Efficacy increased when used on conjunction with corticosteroids
NK1 receptor antagonist e.g. Aprepitant	Acts centrally	Highly and moderately emetogenic chemotherapy	Weakness, excessive fatigue, dizziness, diarrhoea, constipation, stomach pain or upset, hiccups, loss of appetite.	Impact on chemotherapy-induced acute and delayed nausea remains under question

Class of drug	Mode of action	Clinical uses	Potential side-effects	Clinical considerations
Benzamides e.g. Metoclopramide	Dopamine receptor and 5-HT ₃ receptor (low affinity) inhibition, increase in gastric emptying	Beneficial in managing the effects of low to moderately emetogenic chemotherapy regimens	Associated with extreme extrapyramidal side effects, especially in those aged under 30 years of age	The risk of agitation and dystonic reactions can be minimised by infusing the drug over 30 minutes in conjunction with Diphenhydramine. Enhances gastric emptying so combating the sense of fullness caused by gastric stasis, heartburn caused by chemotherapy and the slowed colonic transit time caused by 5HT ₃ receptor antagonists
Corticosteroids e.g. Dexamethasone Betamethasone	Uncertain	Used for both acute and delayed emesis	May cause psychotic reactions and affect glucose metabolism as well as agitation, insomnia, increased appetite and euphoria	Perirectal burning, commonly felt when Dexamethasone is administered intravenously, can be avoided by increasing the length of infusion time to 10 minutes
Benzodiazepines e.g. Lorazepam Diazepam	Anxiolytic, sedative	Most effective in alleviating anticipatory nausea and vomiting and in reducing anxiety	Causes all levels of CNS depression	Should be used with caution in older patients and those with compromised respiratory status as well as patients with compromised hepatic or renal function

Class of drug	Mode of action	Clinical uses	Potential side-effects	Clinical considerations
Phenothiazines e.g. Prochlorperazine Dixyrazine	Mainly dopamine receptor blockade	Mild emetogenic chemotherapy Can be used in combination with 5HT3 receptor antagonists Sustained release form may prevent delayed nausea and vomiting induced by chemotherapy	Extrapyramidal reactions (especially if aged 30 years or younger)	Prophylactic Diphenhydramine or Benztropine may be given to prevent extrapyramidal reactions Older patients may experience excessive sedation, fatigue and an unsteady gait requiring dose adjustment
Butyrophenones e.g. Haloperidol Droperidol	Mainly dopamine receptor blockade	Most useful when anxiety and anticipatory symptoms aggravate the degree and intensity of the nausea and vomiting experienced by patients	Akathisia, dystonic reactions and severe extrapyramidal effects	When these drugs are used in combination with other central nervous system depressants, their effects can be additive
Cannabinoids e.g. Nabilone Dronabilone	Cannabinoid receptor blockade	May be useful in patients who have a low tolerance or minimal response to other antiemetics	Short-term use of marijuana has been shown to lead to sedation, a high and smoking intolerance in some patients.	Poorly tolerated by older people. Should be used with caution in patients suffering from hypertension or heart disease as well as those patients already receiving sympathomimetic drugs

Despite advances in the anti-emetic therapies detailed in Table 7, nausea remains a significant problem for patients receiving chemotherapy (Morrow et al. 1995; Roscoe et al. 2000; The Italian Group for Antiemetic Research 2000). Two large evaluation studies have demonstrated that while the introduction of 5-HT₃ receptor antagonists were effective in mitigating against vomiting, they were less successful in controlling nausea (Morrow et al. 1995; Roscoe et al. 2000). The evaluation by Morrow et al (1995) highlighted that for all 5HT₃ receptor antagonists except granisetron, a complete response is defined as someone who experienced no vomiting throughout the 24 hours following chemotherapy administration. Consequently, the use of the endpoint ‘complete control’ is potentially misleading as a patient could feel very nauseated yet be judged as a ‘complete responder’. Moreover, in the studies in which nausea was evaluated, its control remained incomplete for approximately half the patients who received a 5HT₃ receptor antagonist (Morrow et al. 1995). This finding was supported by a later study of 1,413 patients’ experiences of nausea (and vomiting) following the introduction of 5HT₃ receptor antagonists. This study showed that although patients’ frequency of vomiting episodes was improved, the frequency of post-chemotherapy nausea did not (Roscoe et al. 2000). Moreover there was an average increase in the duration of nausea following chemotherapy administration (Roscoe et al. 2000). Further large scale research by The Italian Group for Antiemetic Research (2000) involving 705 patients receiving moderately emetogenic chemotherapy showed that despite optimal antiemetic therapy of 5HT₃ receptor antagonists and steroids, 57.1% of patients experienced delayed nausea. Thus, the development of 5HT₃ receptor antagonists did not have the positive impact on patients’ experiences of nausea that was initially anticipated.

More recent pharmacological advances have been seen with the development of aprepitant, a new neurokinin antagonist, with studies commending its 20% improvement in the control of 'emesis' (Olver 2004; Jordan et al. 2005). However, as with the 5HT₃ receptor antagonist research above, a complete response has often been defined as 'no emesis or rescue therapy' with no reference to experiences of nausea (Hesketh et al. 2003; Poli-Bigelli et al. 2003). While a large study involving 1,099 patients receiving highly emetogenic chemotherapy has shown that the addition of aprepitant to the best available antiemetic therapy (a 5HT₃ receptor antagonist and dexamethasone) results in consistently better antiemetic protection using the endpoint of 'no vomiting and no significant nausea', that is, nausea that interferes with normal activities (de Wit et al. 2004), 36.3% of patients receiving aprepitant in tandem with best available antiemetic therapy continued to experience nausea and/or vomiting. Indeed, further clarification of its effects on nausea and vomiting independently are required as a more recent phase II study exploring the effectiveness of aprepitant on the nausea and vomiting experienced by 1,043 patients following moderately emetogenic chemotherapy demonstrated that 40% of patients continued to experience significant nausea as measured by the FLIE, a multidimensional, valid and reliable assessment tool (Warr et al. 2005).

Given the volume of research surrounding the pharmacological management of chemotherapy-induced nausea (and vomiting), one can appreciate the problems clinicians experience in trying to stay informed of the most up-to-date treatments for their patients. A range of antiemetic guidelines have been developed by groups or societies in an effort to facilitate the management of these complex problems in clinical practice (Multinational Association of Supportive Care in Cancer 1998; Gralla et al. 1999; American Society of Health-Systems Pharmacists 1999; ESMO

Guidelines Task Force 2001; National Comprehensive Cancer Network 2007a). Such guideline development involves synthesising an extensive amount of research evidence to provide clinicians with comprehensive, technical documents that detail the most effective pharmacological interventions across a wide range of clinical circumstances. However, these documents are often unwieldy and difficult to use in clinical practice. As an alternative, consensus meetings have been held in which experts from a range of disciplines seek to produce condensed summaries of such guidelines in a succinct and usable format (Koeller et al. 2002; Borjeson 2002). As these summaries are more user-friendly, one could argue that their recommendations are more likely to be implemented in clinical practice. Recent consensus statements based on high quality evidence advocate for the combination of antiemetics to achieve maximum effect (Koeller et al. 2002; Borjeson 2002). However, as even the current best available antiemetic therapy continues to leave a significant percentage of patients experiencing nausea (de Wit et al. 2004; Warr et al. 2005) with vomiting, rather than nausea, as the focus of research, the management of chemotherapy-related nausea remains a significant clinical challenge. Given that many patients' nausea is refractory to available antiemetic therapies, there is a need to seriously consider non-pharmacological interventions that enhance current pharmacological therapies.

3.4.2 Non-pharmacological interventions for chemotherapy-induced nausea

There is a large and mainly convincing body of evidence that explores the effectiveness of non-pharmacological interventions in alleviating or preventing patients' experiences of chemotherapy-related nausea and vomiting. These

interventions involve behavioural and psychoeducational techniques, such as progressive muscle relaxation training, guided imagery and psychoeducational support and information.

3.4.2.1 Progressive muscle relaxation training

Progressive muscle relaxation training (PMRT) involves focusing on and isolating various muscle groups while moving progressively up and down the body to establish a state of deep relaxation. Focused breathing is often used along with PMRT. A meta-analysis of 10 published, randomised, intervention-controlled studies involving 399 patients from the United States, Sweden and the United Kingdom, demonstrated significant beneficial effects of relaxation to decrease nausea (Leubert et al. 2001). A number of studies have explored the impact of PMRT on not only nausea, but also vomiting and anxiety (Arakawa 1995; Arakawa 1997; Molassiotis 2000; Molassiotis et al. 2002b; Yoo et al. 2005; de Carvalho et al. 2007). While these studies employed various methods of delivering PMRT and assessed nausea, vomiting and anxiety using a multitude of assessment tools overall, the results demonstrate that PMRT, in tandem with pharmacological therapy, is effective in reducing the nausea (and vomiting and anxiety) associated with chemotherapy, see Table 8.

Table 8: Summary of studies evaluating progressive muscle relaxation training

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Arakawa (1995)	To explore the effects of PMRT on nausea, vomiting and anxiety	Pilot RCT	8 Japanese women receiving chemotherapy for a range of cancer diagnoses	The experimental group received training in relaxation techniques and performed these twice a day either before meals or two hours after meals. Assessments were made using MANE and Spielberger State-Trait Anxiety Inventory	Both groups showed a reduction in nausea and vomiting. Average decrease in state anxiety in the experimental group.	Snapshot view of a single cycle of chemotherapy. Small sample size. Heterogeneity in relation to cancer diagnosis, treatment and antiemetics received. Reliability of MANE not tested in Japanese population.
Arakawa (1997)	To explore the effects of PMRT on nausea, vomiting and anxiety	RCT	60 Japanese patients receiving chemotherapy for a range of cancer diagnoses	The experimental group received training in relaxation techniques and performed these twice a day either before meals or two hours after meals. Assessments were made using MANE and Spielberger State-Trait Anxiety Inventory	The experimental group showed a decrease in nausea and vomiting.	Snapshot view of a single cycle of chemotherapy. Heterogeneity in relation to cancer diagnosis, treatment and antiemetics received. Reliability of MANE not tested in Japanese population.

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Molassiotis (2000)	To assess effectiveness of PMRT in management of chemotherapy-induced nausea and vomiting	Pilot RCT	8 Chinese women with breast cancer scheduled to receive moderately emetogenic chemotherapy	Control group received standard anti-emetics and were asked to complete the Morrow Nausea and Vomiting Scale daily for 6 days. The Experimental group received PMRT with a trained research nurse 1 hour before chemotherapy as well as standard anti-emetics. The nurse visited patients at home for the next 5 days giving them a session of PMRT. They also completed the questionnaire for 6 days	Duration and intensity of nausea were lower in the experimental group, although the former was at a borderline level of significance. Duration and intensity of vomiting were lower in the experimental group	Not conclusive results for nausea. Small sample. No exploration of extraneous variables that could have influenced the results.

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Molassiotis et al (2002)	To assess effectiveness of PMRT in management of chemotherapy-induced nausea and vomiting	RCT	71 Chinese women with breast cancer scheduled to receive moderately emetogenic chemotherapy	<p>Control group received standard anti-emetics. The Experimental group received standard antiemetics as well as PMRT one hour before chemotherapy administration and thereafter for 5 consecutive days. Each session lasted 25 minutes and was followed by 5 minutes of imagery techniques</p> <p>All patients completed the Morrow Nausea and Vomiting Scale daily for 7 days, the Chinese version of the Profile of Mood States and State-Trait Anxiety Inventory before chemotherapy and at days 7 and 14 after chemo.</p>	No difference between the experimental and control groups in relation to intensity of nausea and vomiting. However, there was a significant reduction in the duration and frequency of nausea and vomiting. These differences were noted most during days 1-4 of the cycle of chemotherapy.	Intervention was conducted only on the first cycle of chemotherapy. Patients received antiemetic therapy that was not in keeping with current guidelines at that time. Consequently, the results may only be applicable to patients with a poor control of nausea and vomiting.

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Yoo et al (2005)	To evaluate the efficacy of PMRT and guided imagery on experiences of anticipatory and post-chemotherapy nausea and vomiting	RCT	30 patients with breast cancer randomised to either control or experimental group	Patients in the experimental group received a PMRT and guided imagery session for one hour immediately before each cycle of chemotherapy as well as a tape recording of their first session for home use. Patients completed Multiple Affect Adjectives Checklist, anticipatory nausea and vomiting and post-chemotherapy nausea and vomiting were recorded using a 7 point Likert scale. Patients also rated their nausea and vomiting for 3 days following each cycle of chemotherapy and completed the Functional Assessment of Cancer Therapy – Breast at baseline and after 3 and 6 months	The experimental group experienced significantly less nausea and vomiting before and after chemotherapy. 6 months following treatment, the quality of life of those in the experimental group was higher than that of the control group.	Small sample size and a short-term follow up. Cost of the intervention not considered.

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
de Carvalho et al 2007	To evaluate the effects of PMRT on the nausea and vomiting	Descriptive study	30 patients with a range of cancer diagnoses who were receiving chemotherapy	Pre-relaxation data (demographic data, vital signs, salivation, perspiration, pupil dilation, skin colour, muscle reaction and patients' spontaneous comments) were collected. Patients also completed a 10cm visual analogue scale for nausea and then for vomiting. Following the PMRT these physiological measures of nausea and vomiting were collected again as well as the patient's self-assessed nausea and vomiting levels using the visual analogue scale.	Statistically significant differences were seen in physiological and muscular measures, except for skin colour following PMRT. Statistically significant reductions in self-report of nausea and vomiting using the visual analogue scales were seen following PMRT.	No control group and a heterogeneous population with respect to chemotherapy and antiemetic therapy received. It is unclear as to during which cycle of chemotherapy patients participated.

Only Yoo and colleagues (2005) recognised the need for longitudinal evaluation of PMRT and conducted a study that included 6 months post-chemotherapy follow-up. The remaining studies focused on a single cycle of chemotherapy and so provided a limited view of the potential of PMRT. Future research involving longitudinal follow up would allow conclusions to be drawn concerning the benefits of long term use of PMRT. Self report was the most common method of exploring patients' experiences of nausea using a variety of assessment tools such as MANE (Arakawa 1995; Arakawa 1997; Molassiotis 2000; Molassiotis et al. 2002b), Likert scales (Yoo et al. 2005), the Spielberger State-Trait Anxiety Inventory (Arakawa 1995; Arakawa 1997; Molassiotis et al. 2002b), the Profile of Mood States (Molassiotis et al. 2002b), and the Functional Assessment of Cancer Therapy – Breast (Yoo et al. 2005), with just one study choosing to add objective measures of patients' vital signs, salivation, perspiration, pupil dilation, skin colour and muscle reactions to evaluate the impact of PMRT on nausea (de Carvalho et al. 2007). While in research terms this inconsistent use of assessment tools can be criticised, it demonstrates that, no matter how experiences of nausea are assessed, PMRT positively influences patients' experiences of this symptom.

However, the practicalities of implementing PMRT outwith a research setting are not considered in these studies, for example, the availability of trained staff, the time required to provide the service, or the availability of a quiet space in which to deliver PMRT. Neither are the cost implications of providing a PMRT service addressed in any research reports. Thus, although effective, the issues associated with the delivery of such a service in the real clinical setting are not addressed by

those exploring the intervention. Future studies that seek to implement and evaluate PMRT in real clinical settings are urgently required.

3.4.2.2 Psychoeducational support and information

A meta-analysis of 116 intervention studies indicated that psychoeducational and psychosocial care have beneficial effects for nausea and vomiting associated with cancer (Devine and Westlake 1995). More recent supportive evidence for the use of psychoeducational interventions in the reduction of chemotherapy-related nausea is presented in Table 9.

Table 9: Summary of studies evaluating psychoeducational support and information

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Gaston-Johansson et al 2000	To determine whether a comprehensive coping strategy programme was effective in reducing pain, fatigue, psychological distress and nausea	RCT	110 patients with breast cancer undergoing autologous bone marrow transplant	Patients in the experimental group were taught a coping strategy programme at least 2 weeks before admission to hospital for treatment. This included relaxation training and guided imagery which was also given as an audiotape to patients. Patients were instructed to use the tape at least once a day. Evaluation tools used were: the Gaston-Johnasson Painometre; a 100mm VAS for nausea severity and fatigue; the State-Trait Anxiety Inventory; and the Beck Depression Inventory	Nausea was significantly lower in patients who participated in the coping strategy programme compared with those receiving standard care, even after controlling for relevant variables	The sample population is a very specific group, making it difficult to generalise the results. No consideration given to the practicalities or cost of the intervention

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Williams and Schreier 2004	To evaluate the effectiveness of informational audiotapes on patients' self-care behaviours, anxiety and the occurrence and intensity of common symptoms associated with chemotherapy	RCT	Women with breast cancer (n=70) about to start a course of chemotherapy	Patients in the experimental group (n=38) received standard education and they were mailed two 20-minute audiotapes about the nutritional management of symptoms and exercise and relaxation techniques to manage fatigue, anxiety and difficulty sleeping. They were instructed to listen to the tapes 12-24 hours before each cycle of chemotherapy and as often as they wanted during their entire course of treatment. Patients were interviewed using the State-Trait Anxiety Instrument and the modified Nail Self-Care Diary 3 times by phone by the same interviewer: before the start of their treatment; at one month following the start of treatment; and two months thereafter	In the experimental group, the number of women reporting nausea and vomiting almost halved between the second and third interviews. However, more nausea and vomiting was reported in the experimental group than the control group at the second interview and only marginally less nausea and vomiting was reported by the experimental group during the third interview. While this study supports the use of audiotapes as teaching tools, it does not provide conclusive proof of the benefits for managing nausea and vomiting	Nausea and vomiting were addressed as a single symptom. While data collection was longitudinal it did not span the whole duration of chemotherapy. Assessment relied on patient recall over a long period of time

These studies were longitudinal, although did not always span the entire duration of patients' chemotherapy treatment (Gaston-Johansson et al. 2000; Williams and Schreier 2004). Furthermore, they did not consider the practicalities of implementing these interventions in the real clinical setting or conduct a cost/benefit analysis of sustaining such services. They did, however, demonstrate innovative methods of presenting educational material, for example, via audiotape (Gaston-Johansson et al. 2000; Williams and Schreier 2004), which is especially relevant, given that the majority of patients receive chemotherapy as an out-patient, and so spend the majority of their time at home, a factor that limits the time available for patient education by health professionals.

3.4.2.3 Acupuncture and Acupressure

Acupuncture and acupressure have been shown to have a positive effect on nausea and vomiting (Vickers 1996; Dibble et al. 2000; Roscoe et al. 2003; Ezzo et al. 2005; Molassiotis et al. 2007). They are based on traditional Chinese medical concepts of meridians which carry energy throughout the body and involve stimulation of a specific point by fine needles or pressure (Vickers 1996; Klein and Griffiths 2004; Ezzo et al. 2005). Two reviews have been conducted that summarise the efficacy of acupuncture for the management of chemotherapy-related nausea (Vickers 1996; Ezzo et al. 2005). Taking a general approach to nausea, Vickers describes 12 high quality randomised controlled trials that explored the antiemetic benefits of acupuncture for nausea associated with surgery, chemotherapy or pregnancy. In 11 of these 12 studies, involving nearly 2,000 patients, acupuncture had a positive effect on nausea. More recently Ezzo, and her colleagues (2005) focused on chemotherapy-induced nausea and in a review of 11 trials of

acupuncture and acupressure involving 1,247 patients, they concluded that acupuncture has a demonstrable benefit for acute chemotherapy-related nausea, however, studies that evaluate the impact of acupuncture in tandem with current best antiemetic therapies, as well as studies exploring the impact of acupuncture on delayed nausea, are required to establish the usefulness of this intervention in clinical practice.

Acupressure was explored in a mini systematic review reporting on 2 randomised controlled trials involving 482 patients receiving chemotherapy, which concluded that acupressure may decrease chemotherapy-related nausea (Klein and Griffiths 2004). Details of a more recent study evaluating the impact of acupressure wristbands are found in Table 10.

Table 10: Summary of studies evaluating acupressure

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Molassiotis et al 2007	To evaluate the impact of acupressure wristbands	RCT	36 patients with breast cancer having chemotherapy	Patients in the intervention group wore wrist bands for 5 days following chemotherapy administration. The revised Rhodes Index of Nausea, Vomiting and Retching (INVR) was used to measure patients' experiences and was completed every evening for 5 days following chemotherapy administration	Nausea was experienced significantly less often in the experimental group. Only at day 3 following treatment did both groups have the same level of nausea. Nausea also occurred significantly less frequently in the experimental group across the 5 assessment days (day 3 had similar levels of nausea between the 2 groups). The experimental group reported significantly less distress associated with their experience of nausea than did the control group	Small sample size. Non-standardised antiemetics days 2-5. No rationale given for attrition rate of 34%. Only explored during first cycle of chemotherapy

Such results demonstrate the positive impact that acupressure can have on the various dimensions of the experience of chemotherapy-related nausea, although it is unfortunate that there was no longitudinal follow up to explore whether its positive effects can be maintained across chemotherapy cycles. The multidimensional evaluation of nausea by Molassiotis and his colleagues (Molassiotis et al. 2007) clearly demonstrated the positive impact of acupressure on all dimensions of the symptom experience. However, the lack of cost/benefit analysis and small sample size (Molassiotis et al. 2007) compromise these studies, and future research that addresses these methodological flaws is necessary.

Nevertheless, despite the problems associated with small sample sizes and the variety of assessment tools used, the results from acupuncture and acupressure studies show positive outcomes, indicating that they offer a viable adjunct to optimal antiemetic therapy.

3.4.2.4 Other non-pharmacological interventions

There are a range of other non-pharmacological interventions that have been evaluated for their efficacy for chemotherapy-induced nausea, including guided imagery (Troesch et al. 1993), music therapy (Standley 1992; Ezzone et al. 1998; Sahler et al. 2003), and massage (Billhult et al. 2007) - see Table 11.

Table 11: Summary of studies evaluating other non-pharmacological interventions

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Troesch et al 1993	To explore whether the addition of guided imagery to a standard antiemetic regime decreased the occurrence of nausea, vomiting or retching and distress	Pilot RCT	Convenience sample of 28 patients receiving Cisplatin-based chemotherapy	Both groups received the standard antiemetic therapy while the experimental group participated in guided imagery. This consisted of listening to a 20 minute audiotape 60 minutes before treatment, the following morning before breakfast and the following evening. Patients were asked to complete 5 INV-2 for each cycle of chemotherapy. Patients also completed the Chemotherapy Experience Survey (developed for the study) to evaluate overall perceptions of the chemotherapy experience. Descriptive statistics of both groups were compared and differences explored	Statistical significance was not demonstrated with respect to symptom occurrence and distress with the addition of guided imagery. Patients in the guided imagery group described their overall chemotherapy experience more positively than those subjects who did not receive the guided imagery	Involving only patients receiving cisplatin based chemotherapy as well as the small sample size limits generalisability of results. Researchers were unable to control hospital activities that may have influenced or disrupted the patient when listening to the guided imagery tape

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Standley et al 1992	To explore the effects of music on the frequency and degree of anticipatory nausea and vomiting and nausea and vomiting during and after chemotherapy	Descriptive study	15 subjects who received 4 or more chemotherapy sessions	Participants were randomly assigned to one of 4 groups: listening to music during chemotherapy cycles 1-4; listening to music chemotherapy cycles 2-5; did not listen to music cycle 1 & 2; did not listen to music cycle 2 – 5. Data were collected at 4 time points: entering the treatment room; immediately prior to infusion of chemotherapy; 15 minutes after start of chemotherapy; at the end of treatment. Data were also collected by telephone interview 48 hours after chemotherapy	Both music groups reported less nausea than the 2 no music groups. The length of time before nausea began was longer for the music groups compared to the no music groups	All the patients volunteered for the study so this may have biased the results

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Ezzone et al 1998	To explore the effects of music on patients undergoing bone marrow transplant	RCT	33 patients undergoing bone marrow transplant	Patients were assigned to either the control group (n=17) who received antiemetics according to the standard antiemetic protocol or the experimental group (n=16) who received standard antiemetics plus music intervention during the 48 hours of high-dose cyclophosphamide administered as part of the preparatory chemotherapy regime. Incidence of nausea was measured on a visual analogue scale	The experimental group experienced less nausea.	Results are limited to this particular population and a short period of time

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Sahler et al 2003	To explore the impact of music therapy and relaxation imagery on the nausea experienced by patients	Case control study	Patients (n=23) undergoing bone marrow transplant	The intervention incorporated a 45 minute session of integrated music therapy and relaxation imagery provided twice weekly from enrolment in the study to day of discharge from the bone marrow transplant unit. Sessions were designed to be a non-disruptive as possible and were scheduled around patients' treatment needs. Antiemetics were given to all patients as per routine protocol. The music was the patient's choice. Nausea was assessed at the beginning and end of each session using a 10cm visual analogue scale with the anchors 'worst nausea' and 'least nausea'	Patients' self-reports of nausea significantly decreased following music therapy	The sample was not randomised and the frequency of the intervention was lower than planned due to a misconception among staff that some patients were 'too sick' to participate. The study included both paediatric and adult patients, age range 5-65 years (mean 47.5) with no detail was given as to the breakdown of these ages. One can question whether the visual analogue scale would be an appropriate scale for both adults and children

Author	Aim	Design	Sample	Procedure & Instrument	Findings	Limitations
Billhult et al 2007	To evaluate the effects of massage on nausea, anxiety and depression	RCT	Patients with breast cancer receiving chemotherapy (n=39)	Patients were randomly assigned to a massage group (20 minutes of massage on 5 occasions) or a control group (five 20 minute visits). Nausea and anxiety were assessed using a visual analogue scale before and after each intervention with the verbal anchors 'no nausea' and 'worst nausea'. Patients also completed the Hospital Anxiety and Depression Scale	A significant reduction in nausea between the intervention and control groups when improvement was measured as a percentage of all 5 treatments. It is not clear whether there was an improvement following each of the 5 treatments alone. There was no difference between groups in relation to anxiety or depression.	Small sample. Unidimensional measurement of nausea does not fully capture the experience of nausea. Cost or practicalities not considered

While guided imagery does appear to have benefits concerning overall experiences of chemotherapy, used in isolation it does not appear to impact directly on experiences of nausea (Troesch et al. 1993). While there is a growing evidence base for the use of music therapy as demonstrated within Table 11, future research will be required to overcome the methodological flaws of existing studies, such as small sample sizes and patient self-selection, to increase confidence in the results. Finally, although initial results demonstrated a positive impact of massage on chemotherapy-related nausea (Billhult et al. 2007), this is based on a single study and continued research is required before definite conclusions can be drawn as to its efficacy.

It is clear then, that non-pharmacological interventions have a valuable role in the management of chemotherapy-related nausea. However, despite the positive impact on chemotherapy-related nausea that these interventions have almost consistently demonstrated, they are not often integrated into the care of patients receiving chemotherapy (Molassiotis et al. 2002b). A variety of reasons have been given for lack of integration in practice including: health professionals' unfamiliarity with the techniques; the time required to administer the interventions; lack of education in the necessary techniques; and the associated costs of delivering them (Molassiotis et al. 2002b). However, given the positive impact that such interventions have on patients' experiences, innovative methods are necessary to overcome the practicalities of providing these non-pharmacological interventions. For example, the use of tape recordings for the delivery of PMRT may be helpful in overcoming staff shortages and the time taken to deliver the intervention (Gaston-Johansson et al. 2000; Cheung et al. 2003; Williams and Schreier 2004).

3.4.3 Summary of current management techniques for chemotherapy-related nausea

New developments in the pharmacological management of nausea and vomiting have had limited impact on patients' experiences of nausea with significant percentages of patients receiving chemotherapy continuing to experience nausea during their treatment (Morrow et al. 1995; Roscoe et al. 2000; The Italian Group for Antiemetic Research 2000; de Wit et al. 2004; Warr et al. 2005). However, a wide range of non-pharmacological interventions have been successfully evaluated as an adjunct to standard anti-emetic therapies, resulting in improved experiences of chemotherapy-related nausea. Unfortunately, these non-pharmacological therapies are rarely implemented in routine clinical practice. Indeed, the research that explores the efficacy of these interventions consistently fails to address the practicalities of introducing and maintaining these services in day-to-day clinical practice. Given these facts, it is important to consider patients' actual experiences of chemotherapy-related nausea.

3.5 Patients' experiences of chemotherapy-related nausea

Chemotherapy-related nausea not only aggravates patients' general health and cancer-related symptoms such as cachexia, lethargy and weakness (Griffin et al. 1996; American Society of Clinical Oncology 1996; Roscoe et al. 2000), but has also been shown to impair quality of life and cause emotional distress (Grunberg et al. 1996; Osoba et al. 1997a; Rusthoven et al. 1998; Dibble et al. 2003; Glaus et al. 2004; Bergkvist and Wengstrom 2006; Ballatori et al. 2007). This section will

explore the research to date that explores patients' experiences of nausea during chemotherapy.

Little research explores in depth the ways in which nausea is experienced and its impact on the quality of patients' daily lives. No rationale for this is evident within the literature, however, it may be the result of a number of factors. Firstly, as already highlighted, nausea is inextricably linked with vomiting. Chemotherapy-related vomiting is simpler to quantify and describe than nausea and studies that set out to explore both nausea and vomiting often focus on vomiting as it is easier than nausea to evaluate and report (Hesketh et al. 2003; Poli-Bigelli et al. 2003).

Secondly, clinicians and researchers may believe that the significant developments in antiemetic therapies have alleviated patients' nausea. However, such perceptions are erroneous. As already shown, while chemotherapy-related vomiting has been improved, nausea remains a significant symptom for patients (Morrow et al. 1995; Roscoe et al. 2000; The Italian Group for Antiemetic Research 2000; Hesketh et al. 2003; Poli-Bigelli et al. 2003). Finally, the majority of current research concerning chemotherapy-related nausea focuses on evaluating or comparing therapies and interventions rather than describing patients' experiences. These three factors together may explain the relative lack of research that explores the lived experience of chemotherapy-related nausea. However, there is some evidence that can be drawn together to gain an understanding of patients' experiences of chemotherapy-related nausea. While a minority of this literature focuses solely on nausea (Dibble et al. 2003), the majority explores both nausea and vomiting (Grunberg et al. 1996; Farley et al. 1997; Osoba et al. 1997a; Rusthoven et al. 1998; Glaus et al. 2004; Bergkvist and Wengstrom 2006; Ballatori et al. 2007), however, where possible, only the evidence relating to nausea will be considered.

There is a consistent body of evidence that supports the negative effects of nausea on patients' quality of life (Grunberg et al. 1996; Osoba et al. 1997a; Farley et al. 1997; Rusthoven et al. 1998; Dibble et al. 2003; Glaus et al. 2004; Lee et al. 2005; Bergkvist and Wengstrom 2006; Ballatori et al. 2007). A large study involving 832 patients receiving chemotherapy demonstrated the deleterious effects of nausea on cognitive and social functioning and global quality of life, as well as fatigue, anorexia and insomnia, as measured using the European Organisation for Research and Cancer (EORTC) core quality of life questionnaire (QLQ-C30) (Osoba et al. 1997a). Indeed, patients with nausea scores equal to or greater than the median did not show greater deterioration in quality of life scores than did those with nausea scores below the median, suggesting that even a relatively low amount of nausea has a negative effect on quality of life (Osoba et al. 1997a). Similarly, using the EORTC QLQ-C30, Rusthoven and his colleagues demonstrated a decline in physical, social and role functioning as well as global quality of life in tandem with declines in symptom scores for fatigue, anorexia and insomnia in patients reporting nausea 2 days following chemotherapy (Rusthoven et al. 1998). These declines in functioning continued to be reported 6 days following chemotherapy with constipation and dyspnoea also reporting declining symptom scores (Rusthoven et al. 1998).

Other methods of evaluating the impact of nausea on quality of life support the results from the QLQ-C30. Asking patients receiving chemotherapy (n=30) to rate their quality of life in the hypothetical presence and absence of nausea, highlighted the impact of nausea on quality of life with a mean quality of life score of 79/100 in the absence of nausea, and just 27/100 in its presence (Grunberg et al. 1996). Using the Functional Living Index for Emesis (FLIE), patients (n=115) reported their

experiences of nausea (and vomiting) 72 hours following the administration of highly or moderately emetogenic chemotherapy, describing their inability to complete usual household tasks (Farley et al 1997). Again using the FLIE, patients (n=248) receiving moderately and highly emetogenic chemotherapy described their nausea as too severe to allow normal daily functioning on a physical, psychological and social level (Glaus et al. 2004). Significant decreases in patients' functional status (physical functioning, role limitations, general health, vitality and social functioning), as measured by the Medical Outcomes Study Short Form (SF-36), were shown to be associated with the experience of delayed nausea in a longitudinal (2 cycles of chemotherapy) study involving 303 women receiving chemotherapy for breast cancer (Lee et al. 2005). Qualitative data of indepth interviews with patients (n=9) receiving chemotherapy support the impact of nausea on quality of life, demonstrating the negative impact of chemotherapy-related nausea on eating, weight loss, reduced social interaction, anxiety, sleep patterns and exhaustion (Bergkvist and Wengstrom 2006). Using both the FLIE and a daily diary, 33% of patients with acute nausea, 61% of patients with delayed nausea and 92% of patients with both acute and delayed nausea reported an impact on their daily lives (Ballatori et al. 2007). These results suggests that delayed nausea has a greater impact than acute nausea, and may mean that the duration of nausea plays a significant role in its impact on patients' lives.

Just 3 studies have explored patterns of nausea experiences in relation to quality of life, and nausea on the third day following chemotherapy has been identified by patients as the worst (Dibble et al. 2003; Glaus et al. 2004; Lee et al. 2005).

However, while an increase in nausea over successive cycles of chemotherapy has been demonstrated (Rhodes et al. 1987), there has been no attempt to correlate this

with a longitudinal evaluation of quality of life. As patients commonly receive between 6-8 cycles of chemotherapy over 6-8 months, such a limited perspective, such as that gleaned from 2 cycles of chemotherapy (Dibble et al. 2003; Lee et al. 2005), or snap-shots from various cycles of chemotherapy (Farley et al. 1997; Bergkvist and Wengstrom 2006; Ballatori et al. 2007), cannot wholly reflect patients' actual experiences. Longitudinal evaluation could identify how changes in nausea impact on patients' quality of life over time.

It is also noteworthy that the majority of these studies have a predominantly female population: 66% in Osoba et al; 73% in Grunberg et al; 76% in Rusthoven et al; 77.5% in Glaus et al; 100% in Dibble et al and Bergkvist and Wengstrom. As highlighted earlier in this chapter, women are more susceptible to developing chemotherapy-related nausea. Thus, caution should be taken before applying the results of these studies unconditionally to men receiving chemotherapy.

The antiemetics received by patients during these studies should also be considered. For example, 21% of patients did not receive prophylactic antiemetics for delayed nausea in the study by Osoba and his colleagues, no details were given of the antiemetics received by patients in Rusthoven's study, and less than half of the patients participating in Ballatori's study received appropriate prophylaxis for delayed nausea and vomiting. One can question the effects that such under-treatment has on experiences of nausea and the subsequent impact on patients' quality of life.

Finally, a concept that has not been addressed within this evidence-base that may affect patients' perceptions of nausea and its impact on their quality of life is that of treatment intent. Treatment intent has been shown to have an impact on patients'

satisfaction with care during chemotherapy (Holtedahl et al. 2005). Thus, whether a patient is receiving chemotherapy with curative or palliative intent may impact on how they perceive chemotherapy-related nausea. Further research that explores this concept is much needed.

However, despite these methodological flaws, there is evidence to suggest that chemotherapy-related nausea is an unpleasant symptom for patients and is associated with reduced quality of life and distress (Grunberg et al. 1996; Osoba et al. 1997a; Rusthoven et al. 1998; Dibble et al. 2003; Glaus et al. 2004; Lee et al. 2005; Bergkvist and Wengstrom 2006; Ballatori et al. 2007). The following section will consider potential explanations for why nausea persists despite the available range of therapies and interventions and why it is one of the most frequently reported and highly ranked symptoms associated with chemotherapy (as shown in chapter 2).

3.5.1 Potential explanations for continued negative experiences of nausea

Regardless of the extensive research over the last 3 decades exploring chemotherapy-related nausea, it remains a major problem for patients. Reasons for this lack of improvement have not been addressed per se in the literature, however, there are a number of explanations that either alone or together have the potential to inhibit optimal patient outcomes.

The first of these is poor assessment of nausea in the clinical setting: both in relation to evaluating the likelihood of patients' developing nausea and measuring their actual experiences. While there are established classifications of chemotherapy

emetogenicity, these are based on the likelihood of vomiting so fail to acknowledge nausea (Hesketh et al. 1997; Hesketh 1999; Grunberg et al. 2005), and there are no established assessment tools for personal factors that increase an individual's susceptibility for chemotherapy-related nausea. As such, structured and consistent assessment of personal factors that contribute to experiences of nausea in clinical practice is at best sporadic, meaning that patients at increased risk of nausea may or may not be identified for greater attention and interventions. Assessing actual experiences of chemotherapy is also problematic: the range of available assessment tools give little indication as to the clinical situations for which they are most appropriate; how and when to administer them; and what to do with the results (Rhodes and McDaniel 1999; Morrow 1992; Lindley et al. 1992; National Cancer Institute 1999; Trotti et al. 2003).

Secondly, the array of available antiemetic drug therapies may cause confusion for health professionals. Antiemetic guidelines that condense and consolidate the vast amounts of research that compares and contrasts antiemetic therapies are often unwieldy and difficult to use in day-to-day practice (Aapro 2002). While consensus statements simplify this process (Koeller et al. 2002; Borjeson 2002), there is no doubt that patients continue to receive inappropriate antiemetic therapy. For example, even within studies whose primary focus was nausea and vomiting, patients have been shown to receive inappropriate antiemetic therapy (Osoba et al. 1997b; Molassiotis et al. 2002a; Ballatori et al. 2007).

Thirdly, while currently available anti-emetic therapies have positively impacted on patients' experiences of vomiting, the same is not true of nausea (Morrow et al. 1995; Roscoe et al. 2000; The Italian Group for Antiemetic Research 2000; de Wit

et al. 2004; Warr et al. 2005). Acknowledging that nausea and vomiting are two distinct symptoms that can be addressed and researched independently may encourage studies that explore interventions solely to improve experiences of nausea.

The final potential explanation for continued negative experiences of nausea may be that the non-pharmacological interventions that have proven successful in the research setting are difficult to translate into day-to-day clinical reality as they involve unfamiliar techniques for many health professionals with the required training being costly in terms of staffing, time and money (Molassiotis et al. 2002b). Moreover, it could be argued that some of the interventions are simply not practical for the real world of clinical practice, for example one hour of PMRT for 5 days following chemotherapy with a trained therapist (Molassiotis 2000).

3.6 Conclusion

This chapter has provided definitions of chemotherapy-related nausea, vomiting and retching and briefly described the various forms that chemotherapy-related nausea can take. It has shown the range of available assessments for chemotherapy-related nausea, both before and during chemotherapy, highlighting their appropriateness to clinical or research environments, while demonstrating that nausea is seldom assessed in isolation as all the currently available multidimensional assessment tools assess nausea and vomiting. Pharmacological developments in the management of chemotherapy-related nausea have been shown to have limited impact on patients' experiences of nausea with a significant percentage of patients continuing to experience nausea following chemotherapy administration. Optimistically, non-

pharmacological techniques have been shown to enhance experiences of nausea, however, it is disappointing that these remain rooted in research with little translation into day-to-day clinical practice. Therefore, it is not surprising that chemotherapy-related nausea continues to be experienced by a significant proportion of patients and that it has a deleterious effect on their quality of life. Potential explanations for this continued negative effect have been offered.

Chemotherapy-related nausea and fatigue are the two most frequently identified symptoms by patients receiving chemotherapy and are consistently highly ranked. They are both non-observable and subjective. Thus one can question whether the picture for fatigue reflects that of nausea or whether there are fresh challenges for health professionals in its assessment and management. Chapter 4 will consider chemotherapy-related fatigue, its assessment and management, as well as patient experience of fatigue.

4 CHAPTER 4 – FATIGUE

4.1 Introduction

This chapter will consider chemotherapy-related fatigue. Chapter 2 showed that fatigue is not only the most frequently identified symptom by patients receiving chemotherapy, but it is also consistently highly ranked as a symptom of concern to them. The emergence of fatigue as the most common unrelieved symptom associated with cancer is likely due to advances in cancer symptom management, such as improved pain management (Smets et al. 1993; Dean and Stahl 2002; Ryan et al. 2007), longer cancer survival (de Jong et al. 2002), as well as increased attention to quality of life (Iop et al. 2004). However, acknowledging fatigue as a highly ranked symptom does not provide insight into why patients began to identify fatigue as a symptom of concern or what fatigue means to patients in their daily lives.

This chapter will firstly consider the terminology surrounding cancer-related fatigue, briefly describe the main theoretical concepts for fatigue, and reflect on potential aetiologies. As with nausea in chapter 3, the current assessment techniques for fatigue will be considered before available therapeutic interventions are evaluated. Finally, patients' experiences of chemotherapy-related fatigue will be explored in light of existing interventions.

4.2 Defining fatigue

'Fatigue' is defined as extreme tiredness or weariness resulting from physical or mental activity or illness (Concise Oxford English Dictionary 2006). In a healthy

person fatigue occurs as an indispensable sensation that prompts the desire to rest to protect against overexertion or promote healing. However, as the focus of this chapter is cancer- and, more specifically, chemotherapy-related fatigue, it is important to consider specific definitions of these.

In contrast to ‘normal’ fatigue, cancer-related fatigue is perceived as being of greater magnitude, disproportionate to activity or exertion, and not completely relieved by rest (Irvine et al. 1994; Glaus et al. 1996; Morrow et al. 2005; Johnston and Coward 2001; Holley 2000a). Defining cancer- and chemotherapy-related fatigue is complicated, as it is non-observable and subjectively experienced, as well as multidimensional and multifactorial (Ryan et al. 2007). There is also a linguistic problem in some European countries, as the term ‘fatigue’ does not exist in German, Italian or Swedish, meaning there is no universal word that can be shared by the scientific community. However, various definitions of cancer-related fatigue pepper the literature - indeed, it is cancer-related rather than cancer treatment-related fatigue that is defined throughout.

In response to myriad definitions, a concept analysis was conducted in 1996 which concluded that cancer-related fatigue was ‘*a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals’ ability to function to their normal capacity*’ (Ream and Richardson 1996 p527). More recently, the National Comprehensive Cancer Network defined cancer-related fatigue as ‘*a persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning*’ (National Comprehensive Cancer Network 2007b, pFT-1). Both these

definitions are suitable for use within this thesis, as they highlight the persistence and subjectiveness of fatigue and demonstrate its detrimental impact on patients' normal or usual lives. They also concur with the description of symptoms proposed in chapter 2, as it stresses the subjectivity of symptoms as well as their impact on functioning. However, as this thesis addresses fatigue associated with chemotherapy, the latter definition from the NCCN will be used because it identifies the role of cancer treatment in causing fatigue.

4.3 Theoretical models of, and potential aetiologies of, chemotherapy-related fatigue

4.3.1 *Theoretical models*

There are a few theoretical models of fatigue, but despite studies exploring the causes of fatigue, no clear support for any of the major hypotheses have emerged (Nail 1997). The accumulation hypothesis proposes that fatigue is due to a build up of waste products within the body (Simonson 1971); the depletion hypothesis is based on the supposition that muscular activity is impaired when certain substances such as carbohydrates, fats, proteins, adenosine triphosphate and adrenal hormones are not readily available (Simonson 1971); the biochemical and physiochemical hypotheses suggest changes in the production, distribution, use, balance and movement of substances such as muscle proteins, glucose, electrolytes and hormones are important factors that influence the experience of fatigue (Taylor and Rachman 1988); the hypothesis of adaptation and energy reserves proposes that every individual has a certain amount of energy available for adaptation to fatigue and, that when that energy supply is depleted, resting for a time allows energy to be

replenished so that adaptation can continue (Nail et al. 1991), and; the psychobiologic-entropy hypothesis defines fatigue in relation to energy and function and seeks to associate activity, fatigue, symptoms and functional status (Winningham 1992; Lucia et al. 2003).

However, the most established and commonly cited model for cancer-related fatigue is the Integrated Fatigue Model (IFM) (Piper et al. 1987), which provides a comprehensive framework for explaining fatigue associated with cancer. A deductive approach was used to develop the model blending the knowledge from the 5 primary areas of fatigue research: psychology, ergonomics, physiology, medicine and care. The IFM, a synthesis of much of the available data on cancer-related fatigue (Berger and Walker 2001), encompasses 6 manifestations or dimensions of subjective fatigue: temporal, sensory, cognitive or mental, affective or emotional, behavioural or severity, and physiologic (Piper et al. 1987). The IFM delineates the multiple inter-related factors that lead to fatigue in patients with cancer, such as life event patterns, social patterns, environmental patterns, regulation or transmissions factors, psychological patterns, symptom patterns, oxygenation patterns, innate host factors, accumulation of metabolites, energy or energy substrate patterns, activity and rest patterns, sleep and wake patterns, and disease and treatment patterns (Piper et al. 1987; Berger et al. 2003). The significant outcome of Piper's model is the Revised Piper Fatigue Scale (Piper et al. 1998) – an assessment instrument which is reviewed in the assessment section of this chapter (page 86). Psychometric evaluation of this tool involving 715 survivors of breast cancer confirmed 4 key subscales for the model associated with cancer-related fatigue: behavioural/severity, affective meaning, sensory and cognitive mood (Piper et al. 1998).

Thus, while there is a range of hypotheses that are all potentially relevant in the explanation of cancer-related fatigue, with the exception of Piper's Integrated Fatigue Model, they have not been fully evaluated in patients with cancer. Consequently, they present no more than conjecture of possible theories of cancer-related fatigue. There is, however, a developing body of knowledge surrounding specific causes of fatigue.

4.3.2 *Potential aetiologies of fatigue*

Specific mechanisms for the development of fatigue are not completely known or understood. Indeed, it is likely that there are a number of factors that contribute to the fatigue experienced by each individual. A growing number of potential causes are being explored. These can be categorised as physiological and biochemical, psychosocial, or demographic factors.

4.3.2.1 *Physiological and biochemical factors*

Anaemia, a deficiency of red blood cells or haemoglobin which leads to a reduction in the oxygen-carrying capacity of the blood, is one of the most studied physiological factors contributing to fatigue in patients with cancer. Anaemia in cancer can be the result of haemorrhage, haemolysis or nutritional deficiencies, as well as the increased production of cytokines which reduce the production of erythropoietin and contribute to impaired iron utilisation (Heinz and Fritz 1998). It is commonly associated with chemotherapy with over one third of patients becoming anaemic after 3 cycles of chemotherapy (Glaspy et al. 2002). Haemoglobin concentration has been shown to have an impact on patients' experiences of fatigue. A study of patients with solid or haematological

malignancies (n=50) demonstrated that those with haemoglobin levels of <12g/dl reported significantly more fatigue, worse physical and functional wellbeing, and generally reduced quality of life compared with patients whose haemoglobin levels were >12g/dl (Cella 1997). The relationship between haemoglobin levels and quality of life were further defined in a retrospective analysis from 2 community studies involving 4,382 patients with cancer and anaemia (Crawford et al. 2002). In these patients, the maximum quality of life gain was in those whose haemoglobin levels were increased to 12g/dl (range 11-13g/dl) (Crawford et al. 2002). However, while involving a larger number of patients and so increasing confidence in the results, this study measured quality of life using the Linear Analogue Scale Assessment and the more detailed Functional Assessment of Cancer Therapy-Anaemia scale, and did not directly evaluate fatigue (Crawford et al. 2002). A study of 444 patients with different cancer diagnoses and stage of disease as well as treatment modalities compared levels of anaemia with patient reports of fatigue intensity measured using the Fatigue Assessment Questionnaire (Glaus and Muller 2000). This large study established that patients with a higher level of fatigue had haemoglobin levels of <11g/dl, indicating that fatigue was a function of the grade of anaemia. This correlation was most noted in relation to patients' physical functioning. While there is a growing body of evidence that suggests a link between haemoglobin level and fatigue, further large prospective studies are required to evaluate whether fatigue and haemoglobin are correlated, or whether a number of factors are responsible for influencing fatigue.

Cancer treatments have also been linked to patients' fatigue experiences. A systematic review of cancer-related fatigue during anticancer therapy identified 40 studies employing either cross-sectional or longitudinal designs and in a range of

patient populations with respect to diagnosis and treatment (Prue et al. 2006). They concluded that cancer-related fatigue was evident in patients during treatment and, through the use of comparison groups, that patients' fatigue was more severe than 'normal' fatigue (Prue et al. 2006). In relation to chemotherapy-related fatigue, there have been some efforts to establish whether patterns of fatigue can be detected. Studies have failed to agree on a single pattern. For example, a sharp rise in fatigue immediately following chemotherapy that declined midway through each cycle of chemotherapy was experienced by two studies of women (n=72, n=31) receiving chemotherapy for breast cancer (Berger 1998; Schwartz 2000), whereas, a peak in fatigue was reported just 3 days post-chemotherapy by Chinese patients (n=42) receiving chemotherapy (Molassiotis and Chan 2001). A third study differs, indicating the constant presence of fatigue for 14 days following chemotherapy shown to increase with subsequent cycles detected in a longitudinal exploration of chemotherapy-related symptoms in a heterogeneous sample of 249 patients (Miller et al. 2007). The variation in patterns between these studies is likely due to small samples (apart from Miller's study), heterogeneity of the samples, differences in factors such as chemotherapy treatment and dose, cancer diagnosis, and the tools and timing of the fatigue assessment. Thus, while there is substantial evidence to support the impact of treatment on fatigue (Prue et al. 2006), there is no consistent body of evidence that supports specific patterns of chemotherapy-related fatigue.

The cancer itself should also be considered as a factor in experience of fatigue.

Comparing four groups of patients (n=227), differences in the prevalence of severe fatigue was clearly demonstrated: 15% in women recently diagnosed with breast cancer, 16% in men recently diagnosed with prostate cancer, 50% in those with inoperable non small cell lung cancer and 78% in patients receiving specialist

inpatient palliative care (Stone et al. 2000a). Moreover, a study of people older than 65 (n=841), newly diagnosed, with a range of cancer diagnoses, has shown that those with late stage disease have greater levels of fatigue (Given et al. 2001). While these studies suggest that disease burden has an impact on fatigue experiences, these findings have been refuted in studies including patients (n=95) with a range of advanced cancer diagnoses, including lung, breast and prostate cancer (Stone et al. 1999) and patients with advanced lung cancer (n=157) (Okuyama et al. 2001). However these results may be due to the small numbers of patients of each type and stage of disease in both these studies. Thus, while there is not a consistent body of evidence that supports a link between the cancer and fatigue, there is evidence from these studies that is suggestive of some form of relationship between the stage of cancer and its impact on the level of fatigue experienced by patients.

Cytokines are the final biochemical factor that potentially contributes to fatigue. Pro-inflammatory cytokines are proteins that mediate cell-to-cell communication and are released in greater amounts in patients with cancer due to the host response to the tumour, in response to tissue damage, or due to the depletion of immune cell subsets associated with cancer treatments. Support for the role of cytokines in the aetiology of fatigue comes from reports of elevated cytokine levels in patients with chronic fatigue syndrome (Ryan et al. 2007), and, although one study has found no evidence of correlations between serum cytokine levels in patients with breast cancer, this may be due to the fact that measurements of fatigue were made at just 3 timepoints during one cycle of chemotherapy, rather than throughout the course of chemotherapy (Pusztai et al. 2004). Further research is required before definite

conclusions can be drawn in relation to the role of cytokines in cancer-related fatigue.

4.3.2.2 Psychosocial factors

A number of studies have shown fatigue to be associated with psychosocial factors of anxiety and/or depression (Hann et al. 1999; Stone et al. 2000a; Stone et al. 2000b; Roscoe et al. 2002; Haghghat et al. 2003) and sleep problems (Berger and Farr 1999; Jacobsen et al. 1999; Berger and Higginbotham 2000). However, while these studies utilised multidimensional fatigue measures with established reliability and validity, such as the Piper Fatigue Scale (Berger and Farr 1999), the Multidimensional Assessment of Fatigue (Roscoe et al. 2002), the Cancer Fatigue Scale (Haghghat et al. 2003), FACT-F (Stone et al. 2000b) and the Fatigue Symptom Checklist (Roscoe et al. 2002), as well as measures of depression and wakefulness/activity, the majority based their conclusions on small samples ranging from 14-78 (Berger and Farr 1999; Hann et al. 1999; Jacobsen et al. 1999; Berger and Higginbotham 2000; Stone et al. 2000a; Roscoe et al. 2002). Moreover, these studies failed to demonstrate whether fatigue results in the development of anxiety and/or depression, as well as sleep problems, or whether they contribute to patients' experiences of fatigue. Both options are possible, and further research that fully explores their complex relationships is necessary.

4.3.2.3 Demographic factors

There is conflicting evidence of a relationship between fatigue and demographic factors, such as age and gender. While the majority of studies report no relationship between age (Smets et al. 1998; Jacobsen et al. 1999; Stone et al. 2000a; Haghghat

et al. 2003; Donovan et al. 2004) and fatigue, one longitudinal study that specifically explored mental fatigue in women (n=157) with breast cancer receiving adjuvant chemotherapy demonstrated an association between increasing age and lower fatigue (de Jong et al. 2005). Thus, further research to specifically explore and clarify the relationship between age ranges and each dimension of fatigue is necessary.

While one study failed to establish a link between fatigue and gender (Smets et al. 1998) this finding has been refuted by other studies. A small study of 20 patients undergoing a range of cancer treatments demonstrated that women reported significantly higher mean levels of fatigue compared with men (Glaus 1993), while a study of 81 patients receiving radiotherapy for a range of cancers showed that women experienced more fatigue than men, both at the end of therapy, and 1 and 3 months following radiotherapy (Furst and Ahsberg 2001). Fatigue disruptiveness, measured using the fatigue symptom inventory, has also been shown to be higher in women than men in a study of 77 men and women aged 60 and above (Respini et al. 2003). Extending the age range of those involved and replicating this study would clarify whether this is an issue for all ages or just older age groups, and the reasons for their fatigue. Thus, the evidence that supports a relationship between gender and fatigue is based on small sample sizes, and further work that includes larger samples and explores fatigue longitudinally across a range of cancer treatments is necessary before firm conclusions can be drawn as to the relationship between fatigue and gender.

Thus, several mechanisms for the development of fatigue have been proposed. However, while there is a growing body of evidence of potential aetiologies for

fatigue, the necessary quality of evidence that allows firm conclusions to be drawn about definite causative factors is not currently available. Indeed, it is likely that the aetiology of fatigue is multifactorial, involving a combination of these potential mechanisms (Ryan et al. 2007). So, while the identification of these proposed mechanisms may be helpful in developing appropriate assessment and therapeutic interventions to combat fatigue, further research is necessary to fully understand the interrelationships between them and the development of cancer-related fatigue. This situation contrasts with other cancer-related symptoms such as pain, for which there is clear understanding (Smets et al. 1993; Donnelly et al. 1995; Dean and Stahl 2002). Despite this lack of understanding, however, there are already a number of assessment tools and interventions for fatigue. The assessment of fatigue will be addressed in the following section with an evaluation of available interventions following.

4.4 Assessing fatigue

Decisions about managing fatigue are based on understanding the level of fatigue a person experiences and its impact on their life (Nail 2002). Indeed, if interventions are to be implemented, there should be measures available to evaluate their effects. However, the goals of clinical and research-based assessment of fatigue are different. Clinical assessment of fatigue seeks to measure levels of fatigue and its distress with minimum effort from patients, who may be already significantly fatigued, in order that patients can be educated and/or interventions that will improve patients' fatigue experiences initiated and evaluated. Research-based assessment seeks to understand, in-depth, patients' experiences of fatigue and/or evaluate which interventions in what circumstances can alleviate or minimise

patients' fatigue experiences. Although both approaches require assessment instruments that are valid and sensitive to change, assessment tools that are appropriate for one approach are unlikely to meet the needs of the other. For example, while validated multidimensional tools provide an in-depth method of assessing fatigue, they are often unwieldy for use in clinical practice, as they not only take patients a considerable time to complete, but also require sophisticated analysis. Such tools are more practical for use within a research setting. A more basic assessment, yet one which incorporates incidence, severity and associated distress, has been proposed for use in clinical practice (Portenoy and Itri 1999). They suggest the routine clinical use of 3 questions to facilitate both the assessment of fatigue and its impact on the individual over time:

1. Are you experiencing any fatigue?
2. If so, how severe has it been on average during the past week?
3. How does the fatigue interfere with your ability to function?

Asking patients to grade their responses to questions 2 and 3 using a numeric rating scale of 0-10 will give the clinician an understanding of the patient's fatigue experiences (Portenoy and Itri 1999). However, information on patterns, exacerbating and relieving factors, the impact of fatigue on day-to-day activities, and the meaning of the fatigue to the individual, are additional factors that are important to fully appreciate experiences of fatigue (Winningham et al. 1994), and are not addressed in this short clinical assessment of fatigue.

The National Comprehensive Cancer Network in the United States have included a detailed algorithm for clinical assessment of fatigue within each version of their

clinical guideline for cancer-related fatigue involving a brief screening instrument and including screening, primary evaluation and intervention tailored to active treatment, long term follow up, or end of life care (National Comprehensive Cancer Network 2007b). However, no outcomes research has been conducted to determine the effectiveness of the algorithm in clinical practice. This lack of research is likely due to the fact that, while the algorithm is comprehensive and provides an overall framework for clinical practice, it is lengthy (currently spanning 5 pages), which makes its usefulness for daily clinical practice questionable.

As fatigue is a subjective phenomena, self-report measures are the most appropriate method of assessment, and various instruments have been specifically designed to measure cancer-related fatigue. These tools follow one of three formats: incorporating fatigue into tools that measure broader concepts, such as the Symptom Distress Scale (McCorkle and Young 1978), or quality of life scales such as the EORTC QLQ C-30 (Aaronson et al. 1993) and the Rotterdam Symptom Checklist (de Haes et al. 1990); unidimensional instruments that measure a single aspect of the fatigue experience, such as intensity or distress; or multidimensional instruments that capture multiple characteristics and manifestations of fatigue, as well as its impact on function. Examples of the range of available fatigue-specific tools can be found in Table 12.

Table 12: Fatigue assessment tools

Instrument/author	Consists of	Reliability & Validity	Clinical utility
Rhoten Fatigue Scale (Rhoten 1982)	One-item 11 point rating scale to assess current level of fatigue.	Reliability has not been assessed. Validity: patients' ratings are correlated with investigators' based on observation and interviews.	Short and simple to complete. Developed for post-operative fatigue. Cannot be evaluated for many forms of statistical reliability. Does not describe fatigue experiences multidimensionally
Multidimensional fatigue Inventory (MFI) (Smets et al 1995)	20 item, 7 point scale. Measures: general, physical and mental fatigue as well as reduced motivation and activity.	Reliability: Reasonable to good internal consistency (0.65-0.80). Construct validity: significant differences were found between known groups that suggest that these differences were related to circumstances or activity levels. Convergent validity: significant correlation between Visual Analogue Scale - Fatigue findings and MFI in radiotherapy patients ($0.22 < r < 0.78$).	Multidimensional measure o fatigue, groups with/without cancer compared in different circumstances and activity levels. No reporting of test-retest reliability, instrument development was based on researcher's perspective.

Instrument/author	Consists of	Reliability & Validity	Clinical utility
<p>Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (Yellen et al 1997)</p>	<p>41 item 5 point Likert self-report scale ranging from 0-4 consisting of 28 FACT-General and 13 item fatigue subscales. Assesses quality of life across the domains of physical, social, family, emotional and functional well being, relations with physician and fatigue</p>	<p>Reliability: FACT-F showed good internal consistency (alpha 0.95) on initial and retest administration; good stability (test-retest $r=0.87$) over a 3-7 day window. Fatigue subscales independently showed good internal consistency (alpha 0.93-0.95) and test-retest reliability ($r=0.90$).</p> <p>Convergent/divergent validity: both the FACT-F and fatigue subscales showed a significant negative relationship with POMS-F and PFS and a positive relationship with PIMS-V. Non-significant findings were noted with Marlowe-Crowne Social Desirability Scale (MC-20).</p> <p>Discriminant validity: both the FACT-F and fatigue subscale were significantly correlated with haemoglobin with greatest effect in differentiating the very low haemoglobin group from the highest.</p>	<p>High internal consistency and test-retest reliability.</p> <p>Length of entire questionnaire could burden fatigued patients, however fatigue subscale is brief and easy to use.</p> <p>Designed for patients in treatment which may be a limitation depending on the population under investigation. Items generated from patients' perspective.</p>

Instrument/author	Consists of	Reliability & Validity	Clinical utility
Revised Piper Fatigue Scale (Piper et al 1998)	22 item, 0-10 numerical self-report scale and 5 open ended questions to measure 4 dimensions: behavioural/severity, affective meaning, sensory and cognitive/mood	<p>Reliability: internal consistency alphas ranged from 0.92-0.96 for 4 sub-scales, standardised alpha for entire scale – 0.97</p> <p>Construct validity: four factor solutions.</p>	<p>Shorter and easier than previous Piper Fatigue scale, multidimensional assessment of fatigue with theoretical foundation. Comprehensive tool for research purposes but may be burdensome for use in clinical practice. Complex scaling system.</p> <p>Questions apply only to those experiencing fatigue so must screen for fatigue before using.</p>
Brief Fatigue Inventory (BFI) (Mendoza et al 1999)	9 item, 0-10 numeric rating scale to assess severity and impact of fatigue.	<p>Reliability: internal consistency alpha – 0.96.</p> <p>Construct validity: factor loadings 0.81-0.92 show that a single factor accounted for 75% variability.</p> <p>Concurrent validity: BFI significantly correlated with FACT ($r=-0.88$) and Profile Of Mood States (0.84) fatigue subscales.</p>	Short and easy to use. Good for clinical practice. Single dimension of fatigue. Tool was not developed from patients' perspective.

Instrument/author	Consists of	Reliability & Validity	Clinical utility
Schwartz Cancer Fatigue Scale (Schwartz 1998)	28 item, 5 point scale from 1 (not at all) to 5 (extremely). Measures 4 dimensions of fatigue: physical, emotional, cognitive and temporal.	<p>Reliability: alpha internal consistency 0.96 for total scale and 0.82-0.93 for subscales.</p> <p>Content validity: supported by item evaluation by both patients with cancer and oncology nurse experts.</p> <p>Construct validity: factor analysis resulted in 4 factor solution for 70% of variance, preliminary construct validity was supported by differences in fatigue between those receiving treatment and those who had completed treatment and by VAS fatigue scales.</p>	Long but simply worded multidimensional assessment of fatigue. Majority of validation population had completed cancer treatment so further validation required.

Instrument/author	Consists of	Reliability & Validity	Clinical utility
<p>Revised Schwartz Cancer Fatigue Scale (Schwartz and Meek 1999)</p>	<p>6 item 5 point scale. Measures 2 dimensions of fatigue: physical and perceptual.</p>	<p>Reliability: Good internal consistency of alpha – 0.90 for total scale, 0.88 for physical subscale, 0.81 for perceptual subscale.</p> <p>Construct validity: was supported by Lisrel Goodness of Fit Index >0.98 and adjusted GFI > 0.94.</p> <p>Discriminant validity: subjects receiving treatment scores significantly higher (p<0.001) on all items and both subscales and total subscales than those who had completed treatment. Significant differences were found for each item, subscale, total score and time since last treatment (p<0.001).</p>	<p>Brief, simple, tested by advanced statistical techniques. Shortest multidimensional assessment for cancer-related fatigue. First instrument to measure perceptual aspects of fatigue.</p>

Instrument/author	Consists of	Reliability & Validity	Clinical utility
Cancer-Related Fatigue Distress Scale (Holley 2000)	20 item 0-10 numeric rating scale assessing fatigue distress in relation to physical, social, psychological, cognitive and spiritual components.	<p>Reliability: Good internal consistency, alpha 0.9788 for the total 20 item scale.</p> <p>Content validity: content validity indices ranged from 0.6-1.0 with a mean of 0.91.</p> <p>Construct validity: Factor analysis confirmed that all items were loaded on only one factors >0.70.</p>	<p>Short, requires no training and easy to read therefore clinically useful.</p> <p>Psychometrically sound for measurement of distress associated with cancer-related fatigue.</p> <p>Only captures single dimension of fatigue distress rather than whole picture of fatigue experiences.</p>

Instrument/author	Consists of	Reliability & Validity	Clinical utility
Cancer Fatigue Scale (Okuyama et al 2000)	15 item 5 point numeric rating scale measuring 3 dimensions of fatigue: physical, affective and cognitive.	<p>Reliability: good internal consistency alphas were 0.89 for physical, 0.79 for cognitive and 0.88 for the total scale. Test-retest correlations of each factor and total score between first and second sessions all exceeded 0.50.</p> <p>Construct validity: a 3 factor solution was confirmed by repeating factor analysis.</p> <p>Convergent validity: confirmed by correlations between CFS and VAS for fatigue: each factor significantly correlated with VAS score (average $r=0.49$ $p<0.001$).</p> <p>Intersubscale correlation: significant correlations noted for all pairs of subscales, mean value of the intersubscale correlation were 0.37.</p>	Simple and easy to complete. Designed to assess multidimensional cancer-related fatigue. Was conducted in Japanese patient population and did not consider cross-cultural validity. Not developed from patients' perspective.

While gaining insight into the multidimensional fatigue experience provides by far the richest information, this method should be balanced with avoiding burdening patients who are already fatigued with lengthy and complex questionnaires.

Although further psychometric testing of some of these instruments within cancer populations is desirable (Varricchio 2000; Wu and McSweeney 2001), Table 12 shows that, while there are no gold standard assessment instruments at this time, there are a range of available assessment instruments that are more or less appropriate for a variety of purposes. For example, tools such as the Revised Piper Fatigue Scale (Piper et al. 1998) meet the in-depth, exploratory needs of researchers seeking to understand the multi-dimensional fatigue experience or evaluate the impact of specific interventions on various dimensions of patients' fatigue experiences, while the shorter Cancer Fatigue Scale revised version (Schwartz and Meek 1999) allows patients, in just 6 questions, to provide clinicians with a multidimensional picture of their fatigue experiences. Thus, the current measures to assess fatigue, although not perfect and requiring further development and evaluation, are of a standard that allows an understanding of fatigue experiences, or the impact of an intervention on fatigue, to be obtained in clinical practice.

However, it is important at this stage to highlight factors, other than the quality of the assessment instrument, that can impact on the assessment of fatigue. Firstly, social value systems can promote the idea that fatigue is experienced by everybody, not just if you have cancer or are having cancer treatment. If these views are perceived by people with cancer experiencing fatigue they may choose to stop reporting the symptom because they have been made to feel that their fatigue is not important or that it is just part of life (Stone et al. 2003).

The second factor that complicates fatigue assessment is the misbelief that fatigue is an indicator of depression. While a comparison of the multidimensional fatigue construct and depression shows a strong overlap of symptoms (Reuter and Harter 2004) which most probably accounts for the confusion between the two symptoms, fatigue and depression represent two distinct phenomena in people with cancer (Visser and Smets 1998) and can co-exist (Aas et al. 1997; Aktchi et al. 1999). While it is possible that people experiencing cancer-related fatigue can be saddened by it, to date there is no evidence of a cause and effect relationship between fatigue and depression in people with cancer. This is supported by studies of antidepressants and their lack of positive effects on fatigue (Morrow et al. 2003; Roscoe et al. 2005).

Thirdly, discrepancies have been shown to exist between patients, carers and health professionals in relation to cancer-related fatigue. Two large studies compared patients'; carers' and health professionals' perceptions of cancer-related fatigue and reported differences in perceptions of fatigue incidence (Vogelzang et al. 1997; Stone et al. 2003). For example, in Vogelzang's study of 419 patients with cancer, 200 caregivers and 197 oncologists (unrelated to the patients): 78% of patients reported that they experienced fatigue, 86% of caregivers thought that the patients they cared for experienced fatigue while oncologists perceived that 76% of their patients experienced fatigue (Vogelzang et al. 1997). In a similar multicentre study, Stone and colleagues involved 576 patients, 454 caregivers and 368 healthcare professionals (oncologists, nurses, radiographers and haematologists). They found that while 56% of patients reported that fatigue had affected them in the previous month, 71% of carers felt that the patient had been fatigued in the previous month and 65% of health professionals felt that most or nearly all patients had felt fatigued

in the previous month (Stone et al. 2003). These different perceptions of incidence were not the only discrepancies between the groups. In the study by Vogelzang, patients reported that fatigue negatively affected their lives more than pain (61% versus 19%), while oncologists believed that pain had a greater negative effect on patients' lives, compared with fatigue (61% versus 37%) (Vogelzang et al. 1997). Moreover, 50% of patients did not discuss fatigue with their doctor (Vogelzang et al. 1997). In Stone's study, although most health professionals reported that they recommended or prescribed treatment for fatigue for over half of their patients, only 14% of patients reported receiving such treatment. These large multicentre studies both demonstrate the discrepancies between perceptions of fatigue, as well as the outcomes of patient/healthcare professional communications, both of which are likely to complicate the assessment of fatigue.

Response shift is the final factor that can complicate fatigue assessment, or indeed any symptom. This relatively novel concept has received little consideration, but describes the process by which a person's point of reference shifts with time and experience so that, in relation to cancer-related fatigue, their previous definition of extreme fatigue is now what they would consider as moderate, and a previously unknown level of fatigue now occupies the position of extreme fatigue (Breetvelt and van Dam 1991; Visser et al. 2000). This shift acts to minimise the differences that can be observed in the severity of fatigue experienced by people with cancer compared with healthy control groups and, although a shift in internalised standards can be functional for patients, it is troublesome for both clinicians and researchers as it may render assessments made over time incomparable. Further research, both quantitative and qualitative, is required to explore whether the concept is helpful to further our understanding of adaptation in chronic illness.

However, as already highlighted there are a range of assessment instruments for assessing fatigue and these, along with being mindful of the factors that can complicate such assessments, provide sufficient opportunities to develop an understanding of fatigue experiences and evaluate management techniques.

4.5 Current management techniques for cancer-related fatigue

While the most effective approach to symptom management is to identify the cause of the distress and correct it if possible, it is unfortunate, as shown earlier, that at present there is no clear understanding of the causative factors for cancer-related fatigue. This lack of understanding prevents the development of targeted interventions and the approach taken to fatigue management is a general one. Indeed, one of the previous reasons for the lack of interest in fatigue as a topic of research has been the lack of any effective interventions to improve it (Stone et al. 1998). Interventions, as with nausea in chapter 3, can be considered pharmacological or non-pharmacological.

4.5.1 Pharmacological management of fatigue

4.5.1.1 Correction of anaemia

As already highlighted, anaemia has been identified as a potential cause of fatigue. The traditional method of treating anaemia via a blood transfusion, although effective, is associated with risks and is subject to limitations in blood supply. Erythropoietin-alpha therapy, the subcutaneous administration of a growth factor to stimulate the production of red blood cells, is an effective alternative to blood transfusions. Three large community-based non-randomised studies have evaluated

the impact of this therapy on quality of life (Glaspy et al. 1997; Demetri et al. 1998; Gabrilove et al. 2001). In samples ranging from 2,370-3,012, these 3 studies demonstrated that erythropoietin-alpha therapy is effective in reducing fatigue and improving functional status and quality of life in anaemic patients with cancer receiving chemotherapy, as well as increasing haemoglobin level and decreasing transfusion requirements (Glaspy et al. 1997; Demetri et al. 1998; Gabrilove et al. 2001). These results have been supported by 2 double blind randomised controlled trials involving patients (n=349, n=375) suffering from anaemia receiving chemotherapy (Littlewood et al. 2001; Osterborg et al. 2002). While fatigue was assessed within a quality of life questionnaire rather than as an independent symptom, there is clear support from these larger studies that administration of erythropoietin-alpha therapy to reduce anaemia subsequently improves fatigue levels. Published guidelines also support the use of erythropoietin-alpha therapy in clinical practice for the management of anaemia (Turner et al. 2001; National Comprehensive Cancer Network 2007b). However, overall, better quality evidence is needed that explores the impact of erythropoietin-alpha therapy specifically on fatigue, rather than anaemia and quality of life, before the use of such a therapy can be unequivocally supported solely as an intervention to improve experiences of fatigue, as regular measurement of quality of life outwith a clinical trial has been shown to result in improved quality of life (Velikova et al. 2004).

4.5.1.2 Paroxetine

Paroxetine is an antidepressant and its effects on cancer-related fatigue have been explored in 4 studies with mixed results. Two small trials have shown a trend towards a possible benefit for paroxetine in treating general, emotional and mental

fatigue in women with breast cancer experiencing hot flushes (n=13) and in patients receiving interferon-alpha (n=18) (Weitzner et al. 2002; Capuron et al. 2002). However, two large multicentre randomised controlled double blinded placebo controlled trials involving more than 400 patients with solid tumours receiving chemotherapy (Morrow et al. 2003) and 94 patients with breast cancer receiving at least 4 cycles of chemotherapy (Roscoe et al. 2005) have shown that 20g of paroxetine orally on a daily basis had no effect on fatigue experiences, although improvements in mood and depression were noted in the paroxetine treatment groups. Thus, the level of evidence required to draw conclusions about the effectiveness or otherwise of paroxetine in the management of cancer-related fatigue is currently unavailable and further research is required.

4.5.2 Non-pharmacological management of fatigue

4.5.2.1 Exercise

Two meta-analyses and 6 systematic reviews support the benefits of exercise in the management of fatigue, both during and after cancer treatment in patients with breast cancer and solid tumours, as well as those undergoing haematopoietic stem cell transplantation (Courneya and Friedenreich 1999; Stevinson et al. 2004; Oldervoll et al. 2004; Stricker et al. 2004; Galvao and Newton 2005; Knols et al. 2005; Schmitz et al. 2005; Luctkar-Flude et al. 2007; Conn et al. 2006; Cramp and Daniel 2008). The growth seen in the volume of research in this field is most likely because health professionals have become more familiar with the concept of exercise as intervention for fatigue and because the safety and benefits have been demonstrated. The most recent of these reviews (Cramp and Daniel 2008) noted that the majority of studies exploring fatigue and exercise involved individuals

diagnosed with breast cancer and reported 16 studies involving 1172 individuals with breast cancer, highlighting the relevance of exercise to the population of the SNA↔P study.

However, it is reasonable to question whether the specific beneficial effects of physical exercise vary depending on the stage of disease, the nature of the treatment patients receive and their current lifestyle. Consequently, more research is required that systematically assesses the tailoring of type, intensity and frequency of exercise to specific diagnoses, stage of disease and treatments. While many individual studies suffer from methodological shortcomings (such as small samples (MacVicar and Winningham 1986; Mock et al. 1994; Schwartz 1999; Mock et al. 2001; Schwartz et al. 2001), problems with adherence to or monitoring adherence to exercise programmes (Mock et al. 1994; Schwartz 1999; Mock et al. 2001; Schwartz et al. 2001; Mock et al. 2002), and combination effects of interventions (Mock et al. 1994)), there is a sufficient quality of evidence both from large systematic reviews and meta-analyses that include a range of cancer diagnoses to recommend exercise as an intervention for improving experiences of fatigue.

4.5.2.2 Education and information provision

As with exercise, there is a growing body of evidence that supports the implementation of education and information provision for people with cancer in alleviating fatigue experiences. Given this body of evidence and the focus of this thesis, only those studies that include women with breast cancer receiving chemotherapy will be evaluated. These studies are presented in Table 13.

Table 13: Summary of studies exploring effects of education and information on experiences of fatigue

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Given et al (2002)	To evaluate a supportive intervention delivered by nurses tailored to managing fatigue and pain during chemotherapy	RCT	113 patients with a range of diagnoses (26% with breast cancer)	Intervention included teaching, counselling, support, co-ordination and communication. Conducted over an 18 week period with 10 contacts with each patient. Fatigue measured using the Symptom Experience Scale	Reduced fatigue and pain in the intervention group as well as improvements in physical and social functioning at 20 weeks	Symptom Experience Scale measures presence or absence of fatigue.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Jacobsen et al (2002)	To establish and compare the benefits or otherwise of professional or patient administered stress management training	RCT	411 patients about to start chemotherapy (58% with breast cancer)	Patients randomised to receive either usual psychosocial care, professionally administered stress management training or patient self-administered stress management training. QoL assessments were performed before randomisation and before 2 nd , 3 rd and 4 th chemotherapy treatments.	Better physical functioning and increased vitality and mental health in the self-administered training compared with the professional administered stress management training	Fatigue was measured as 'vitality' within the SF36 questionnaire

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Ream and Richardson (2002)	To test feasibility of a fatigue management programme, examine patients' responses and refine the intervention	Pilot evaluation study	8 patients receiving chemotherapy (5 had a diagnosis of breast cancer)	Patients received the 'Beating Fatigue' nursing intervention which is comprised of 4 components: assessment/monitoring of fatigue, education, coaching self-care, provision of emotional support. Evaluation included a daily fatigue diary, HADS, SF36, Brief COPE and interview.	Self-reported fatigue reduced and patients were reported to appreciate the support they received. Patients enjoyed being able to talk to someone about their fatigue.	Involved a large volume of assessment for already fatigued individuals to complete.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Barsevick et al (2004)	To evaluate the impact of 3 telephone sessions to educate patients and develop an energy conservation plan	RCT	396 patients receiving either chemotherapy , radiotherapy or concurrent therapy (n=282, 71% had breast cancer)	Patients in each group participated in 3 telephone sessions with an oncology nurse during the first 5 weeks of treatment to discuss energy conservation and activity management (intervention group). Data on fatigue were obtained before treatment and at 2 points of high fatigue for each type of treatment. Fatigue was evaluated using the POMS, Schwartz Cancer fatigue Scale and the General Fatigue Scale.	The intervention group receiving telephone support and education experienced a greater reduction in fatigue over time compared with the control group.	The control group received education about nutrition which may have impacted on their fatigue experiences.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Williams and Schreirer (2005)	To examine the effect of informal audiotapes on patients' self-care behaviours to manage chemotherapy-related symptoms	RCT	71 women with breast cancer undergoing chemotherapy	33 women received audiotapes on self-care that addressed exercise and relaxation to manage anxiety, fatigue and sleep problems. Three telephone interviews were conducted.	Women that received education demonstrated more and a wider range of self-care behaviours, increased their self-care behaviours over time and reported less anxiety. A higher percentage of women in the control group reported fatigue and the severity ratings increased between the first and second recordings. Patients were appreciative of the telephone calls.	Lack of control over how much information patients were given at their treatment times.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Yates et al (2005)	To evaluate an individualised fatigue education and support programme	RCT	109 women commencing adjuvant chemotherapy for stages I or II breast cancer	Nurses delivered a tailored psychoeducational intervention to improve knowledge and skills relative to self-care behaviours for fatigue in clinic and by phone in 4 weekly sessions. Evaluation involved: a numeric rating scale assessing confidence in managing fatigue; an 11 point numeric scale measuring fatigue at best, worst and average; the Functional Assessment of Cancer Therapy – Fatigue scale; the Piper Fatigue Scale; the Cancer Self-Efficacy Scale; the EORTC QLQ C-30 and the Hospital Anxiety and Depression Scale.	Women who received the intervention experienced significantly less fatigue and less interference from fatigue over the treatment cycle when evaluated one to two weeks after the intervention. The reduction in fatigue and fatigue interference was not sustained at 6 and 10 week follow up.	Battery of evaluation instruments

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Ream et al (2006)	To evaluate the impact of the 'Beating Fatigue' nursing intervention	RCT	103 patients about to start chemotherapy (21% had breast cancer)	Conducted over 3 months and included a patient information pack, a fatigue diary that patients completed for one week following each chemotherapy and a monthly visit from a support nurse at home to assess fatigue, provide psychological support and coach patients in self-care. Fatigue measured using 4 visual analogue scales evaluating: quantification of fatigue; associated distress; effects on work and effects on hobbies.	Intervention group reported significantly less fatigue, lower associated distress and less impact of fatigue on valued pastimes than the control group. They also reported less anxiety and depression than the control group and displayed more adaptive coping	Lack of blinding for both researchers and participants which may have resulted in a placebo effect as well as a lack of control over the information available to both the intervention and control groups

Table 13 shows that 6 randomised controlled trials and 1 non randomised pilot study have demonstrated the positive impact of education and information on women's experiences of fatigue during chemotherapy for breast cancer. Furthermore, patients have been shown to welcome the additional support and contact associated with such interventions (Ream et al. 2002; Williams and Schreier 2005; Ream et al. 2006) and apply the skills they learn in their daily lives to improve their fatigue experiences (Ream et al. 2002; Barsevick et al. 2004; Williams and Schreier 2005; Yates et al. 2005; Ream et al. 2006). Indeed, it is not solely this evidence base that supports the use of educational strategies: the National Comprehensive Cancer Network guidelines for the management of cancer-related fatigue recommend that patients with cancer and their families are provided with preparatory guidance about patterns of fatigue and recommendations for self-care (National Comprehensive Cancer Network 2007b). Consequently, it can be concluded that the use of education and information is an intervention that is likely to be effective in the management of cancer-related fatigue.

4.5.2.3 Measures to optimise sleep

Five studies: 2 feasibility (Berger et al. 2002; Berger et al. 2003), 2 small (n=14 (Davidson et al. 2001) and n=10 (Quesnel et al. 2003) and 1 randomised controlled trial (n=57) (Savard et al. 2005), have provided preliminary evidence that a multicomponent cognitive-behavioural intervention designed to optimise sleep quality also may improve fatigue. These studies are presented in Table 14.

Table 14: Summary of studies to evaluate optimising sleep on experiences of fatigue

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Davidson et al (2001)	To evaluate a sleep therapy programme on sleep, fatigue and QoL.	Descriptive	12 cancer survivors, mixed diagnoses	The six-session group programme included stimulus control therapy, relaxation training, and other strategies aimed at consolidating sleep and reducing cognitive-emotional arousal. Participants kept sleep diaries and rated their sleep quality, mood and functioning at baseline, week 4 and week 8 using EORTC QLQ C-30.	Significant improvement over baseline was observed at weeks 4 and 8 in the number of awakenings, time awake after sleep onset, sleep efficiency, sleep quality ratings, and scores on European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 role functioning and insomnia. Total sleep time and fatigue were significantly improved at week 8.	Small sample size. Preliminary evidence only for the effectiveness of the programme. Fatigue measured using subscale within QoL questionnaire.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Berger et al (2002)	To evaluate the feasibility of an intervention designed to promote sleep and modify fatigue	Prospective, repeated measures, quasi-experimental study	25 women aged 40-65 with stage I-II breast cancer receiving doxorubicin chemotherapy	Each woman developed, reinforced and revised an individualised sleep promotion plan including sleep hygiene, relaxation, stimulus control and sleep restriction techniques. Assessment included a daily diary, Pittsburgh Sleep Quality Index, wrist actigraph, and the Piper Fatigue Scale – completed 2 days before and 7 days after each chemotherapy.	Intervention was feasible . fatigue was stable 2 days after each chemotherapy and mean daily fatigue intensity was lower at chemotherapy 3 than at 1 but rebounded at chemotherapy 4.	Small sample size, recruitment problems meant it was difficult to implement the intervention before the first cycle of chemotherapy. Conflicting information between actigraph and diary in some cases. Adherence issues to the various components of the programme.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Berger et al (2003)	To evaluate outcomes of an intervention designed to promote sleep and modify fatigue after adjuvant chemotherapy for breast cancer	Prospective, repeated measures, quasi-experimental, feasibility study	21 women with stage I-II breast cancer following 4 cycles of doxorubicin chemotherapy	Each woman continued to revise her individualised sleep promotion plan developed during her first cycle of chemotherapy that included sleep hygiene, relaxation, stimulus control and sleep restriction techniques. Assessment included a daily diary, Pittsburgh Sleep Quality Index, wrist actigraph, and the Piper Fatigue Scale – completed for 7 days 30, 60 and 90 days after the last chemotherapy treatment and one year after the first chemotherapy treatment.	Adherence rates were high for most components of the intervention. Sleep and wake patterns were within normal limits except for the number and duration of night time awakenings. Fatigue remained low: 2.9-3.5 on a 0-10 scale.	Small sample size, lack of control group. Conflicting data between diary reports and actigraph. Reduced adherence to stimulus control component of the intervention.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Quesnel et al (2003)	To evaluate the efficacy of a multimodal cognitive-behavioural intervention	Pilot intervention time series design	8 women with insomnia caused or aggravated by breast cancer	Treatment administered during 8 weekly group sessions of 90 minutes that included behavioural, cognitive and educational strategies. Multiple objective and subjective measures undertaken: interviews, sleep diary, polysomnography, ISI, BDI, STAI, MFI, QLQ-C30.	Reduced total wake time and increased sleep efficiency (assessed subjectively and objectively) as well as improved mood, fatigue and quality of life.	Self-selection of patients and small sample size. Unable to determine which aspects of the intervention, if any, were responsible for the therapeutic gains reported.

Author	Aim	Design	Sample	Procedure/Instruments	Findings	Limitations
Savard et al (2005)	To assess the efficacy of cognitive behavioural therapy for insomnia secondary to breast cancer	RCT	57 women with insomnia caused or aggravated by breast cancer	Women randomised to therapy or control group. Treatment consisted of 8 weekly sessions administered in a group and combined the use of stimulus control, sleep restriction, cognitive therapy, sleep hygiene and fatigue management. Evaluations were performed at 3, 6 and 12 months post-treatment. Fatigue was assessed using the Multidimensional Fatigue Inventory.	Women in the intervention group showed greater improvement in sleep and these improvements were maintained in some cases up to 12 months. The treatment of insomnia was associated with decreased anxiety and depression and improved global quality of life.	Although specific fatigue data collected this was not reported. Patients recruited through advertisement therefore highly motivated.

In general, the cognitive-behavioural intervention generally included relaxation training in tandem with sleep consolidation strategies, such as: avoidance of long or late naps and limiting time in bed to actual sleep time; stimulus control therapies, such as only going to bed when tired; using the bedroom for sleep or sexual reasons only; going to bed and getting up at consistent times; avoiding caffeine and stimulating activity in the evenings; strategies to reduce cognitive-emotional arousal, such as relaxing for one hour before going to bed; and setting a pre-sleep routine to be used every night. The results support the feasibility of this intervention being delivered either individually (Berger et al. 2002; Berger et al. 2003) or in a group setting (Davidson et al. 2001; Quesnel et al 2003; Savard et al. 2005) to women either receiving or having received chemotherapy for breast cancer. Given the level of this evidence base it is likely that interventions that optimise sleep do have a positive effect on fatigue experiences. However, further research utilising randomised controlled trial approach are required to establish which of these strategies and techniques are most effective, at what times in the treatment trajectory and for what populations they should be used before the intervention can be conclusively recommended to patients.

4.5.2.4 Energy conservation

Energy conservation is the deliberate planned management of one's personal energy resources to prevent their depletion and involves strategies such as delegation, priority setting, pacing, and planning high-energy-use activities at times of peak energy. A pilot study of 80 patients receiving chemotherapy or radiotherapy used a single group pre-test/post-test design to examine the feasibility of energy conservation and activity management (Barsevick et al. 2002). Three telephone

sessions were used to educate patients about energy conservation and activity management. Using a non-equivalent control group, the authors demonstrated that energy conservation potentially offered a successful means of managing cancer-related fatigue. Following this study, a larger multicentre RCT study (n=396) by the same researchers explored this nurse-delivered intervention (Barsevick et al. 2004). They concluded that energy conservation had a modest but significant effect on patients' fatigue experiences (71% of whom had breast cancer) (Barsevick et al. 2004). Given these initially positive results, it is reasonable to propose that energy conservation may have a role in managing fatigue. However, at this time there is not a sufficient amount of high quality evidence to draw definite conclusions.

4.5.3 Summary of current management techniques for fatigue

There is a range of potential interventions for cancer-related fatigue, however, the level of evidence for each of these varies. At present, while there is some support for the use of pharmacological techniques, that is erythropoietin-alpha therapy or paroxetine, for cancer-related fatigue, there remains insufficient high level evidence that focuses solely on fatigue to unequivocally recommend these in practice. The impact of several non-pharmacological techniques has been evaluated. Of these, and based on current available evidence, exercise has a sufficient amount of high level evidence to support its implementation in practice. The provision of education and information, and measures to optimise sleep and energy conservation, are likely to be positive interventions and there is no evidence that any of these interventions would cause harm. Consequently, while further research is required before unreservedly implementing these interventions in practice, they provide patients and health professionals with additional techniques that may improve fatigue

experiences. Thus, there is a range of techniques that health professionals can suggest and that patients can try to ameliorate fatigue experiences. Indeed, as fatigue is experienced multidimensionally, it is likely that a combination of techniques that influence different components would be most effective in fatigue's management (Ream et al 2006).

However, as these potentially effective interventions have been evaluated within research settings, one can question whether they can be implemented or have such efficacious results in the real world. The following section presents patients' experiences of fatigue and reflects on whether the interventions described above can have an impact on preventing or alleviating this symptom in the real world of clinical practice.

4.6 Patients' experiences of cancer- and chemotherapy-related fatigue

Fatigue has been shown to be a highly prevalent condition among patients with cancer (Stone et al. 1998; Portenoy and Itri 1999), with prevalence rates between 70% to 100% (Watson and Mock 2004). Differences in prevalence rates between studies are likely attributable to the variety of study methods and patient populations. Methods and characteristics most likely to result in different prevalence rates are the inclusion of patients receiving different cancer treatments, at differing stages of disease and different cancer diagnoses, the use of various different definitions of fatigue and the array of measurement instruments, for example, individual items versus lengthy multidimensional fatigue instruments (Cella et al. 1998). Moreover, as already highlighted, patients' and health

professionals' perceptions of cancer-related fatigue differ (Vogelzang et al. 1997; Stone et al. 2003). Thus, subjective indicators are likely to be key in understanding the fatigue experience (Piper et al. 1987; National Comprehensive Cancer Network 2007b). There are a few studies that have solely sought patients' perspectives of fatigue experiences as a result of chemotherapy using either survey or qualitative methods.

Survey methods have consistently shown fatigue during chemotherapy to be an unpleasant symptom that interferes with patients' ability to lead a normal life (Curt et al. 2000; Donovan and Ward 2005; Byar et al. 2006; de Jong et al. 2006). In a range of patient populations either receiving chemotherapy at the time of the survey $n=27$ (Donovan and Ward 2005) and $n=157$ (de Jong et al. 2006), or who had already completed chemotherapy treatment $n=379$ (Curt et al. 2000) and $n=25$ (Byar et al. 2006), chemotherapy-related fatigue is described as: causing alterations in daily routine (Curt et al. 2000; de Jong et al. 2006); distressing and uncontrollable (Donovan and Ward 2005); directly correlated with a reduction in quality of life (Byar et al. 2006) and responsible for changes in employment (Curt et al. 2000). However, these studies utilised a number of tools to reach their conclusions: the Symptom Representation Questionnaire (Donovan and Ward 2005), the Piper Fatigue Scale (Byar et al. 2006; de Jong et al. 2006), the Hospital Anxiety and Depression Scale, SF36 (Byar et al. 2006), and the Multidimensional Fatigue Inventory (de Jong et al. 2006). Such diversity in assessment tools prevents the evidence from these relatively small surveys being amalgamated to increase confidence in the results. Moreover, patients in two studies (Donovan and Ward 2005; de Jong et al. 2006) had received both chemotherapy and radiotherapy, making it impossible to tease out which dimensions of fatigue are particularly

relevant to chemotherapy. Indeed, the work of Byar et al (2006) was part of a pilot study that explored an intervention for sleep that may have affected respondents' perceptions of fatigue. Such secondary data analysis is a feature of the qualitative research that has sought to explore fatigue experiences.

Just a few qualitative studies have explored fatigue experiences. The two largest n=910 (Ferrell et al. 1996) and n=127 (Hilfinger Messias et al. 1997) were based on secondary analysis of data gathered either from several studies of quality of life (Ferrell et al. 1996) or a single study that sought to test the efficacy of an intervention on self-care behaviours (Hilfinger Messias et al. 1997), which explains the unusually large number of participants for qualitative studies. Nevertheless, these two studies have demonstrated the overwhelming effects of fatigue on patients' well-being and daily activities that negatively impact on all dimensions of quality of life. Both studies provided rich and striking quotes from patients describing their experiences using metaphors and similes such as: 'it is wet cement', 'it's like rubber knees', 'I'm tired to the bone' (Ferrell et al. 1996) and descriptions such as: 'wiped out', 'drained', 'slumpish' and 'blah' (Hilfinger Messias et al. 1997). Three other studies have used original data involving small patient numbers, n=15 (Magnusson et al. 1999), n=17 (Holley 2000a), and n=10 (Wu and McSweeney 2007) to explore experiences of fatigue during chemotherapy. All these studies confirmed the negative effects of fatigue on all dimensions of quality of life. Holley (2000) described the distress associated with cancer-related fatigue (her sample included patients who had received radiotherapy, chemotherapy, surgery and biotherapy, making it difficult to know with certainty the relationship between fatigue distress and chemotherapy). Nevertheless, the distress and suffering reported by patients in relation to their fatigue was evident in all aspects of their

lives: physical, social, cognitive, psychological and spiritual (Holley 2000a). Indeed, the most recent study continued to provide rich descriptions of patients' experiences: 'I was just drained, just listless, like a wet fish flopped out, just like a rag doll', demonstrating that patients described fatigue of an unexpected kind and degree that was much more than just being tired and that their inability to anticipate and appreciate the scope of fatigue, in tandem with their lack of awareness of interventions to combat it, caused distress (Wu and McSweeney 2007).

Thus, irrespective of the techniques implemented to explore patients' own experiences of fatigue the results are consistent: fatigue is an unpleasant symptom that negatively impacts on all dimensions of quality of life. Moreover, the fatigue of cancer and cancer-treatment is all encompassing and of a kind and degree that patients cannot anticipate.

4.7 Conclusion

This chapter has defined cancer-related fatigue and briefly described its potential aetiologies. It has shown that, despite considerable efforts, current understanding of the causes of cancer-related fatigue is less than optimal. However, this lack of understanding has not prevented the development of a range of assessment tools with which to assess fatigue from both clinical and research perspectives. An evaluation of these tools demonstrated that, while there is no gold standard assessment tool, and although further refinement and evaluation of most tools is necessary, current available tools are sufficient for developing our understanding of the fatigue experience and evaluating the relative impact of interventions.

Interventions themselves and the available evidence for their support have also been considered. Further research is necessary before pharmacological interventions for fatigue can be unequivocally recommended, although erythropoietin-alpha therapy has potential for improving fatigue experiences. Exercise, education and information, measures to optimise sleep, and energy conservation have varying levels of research support and, at this time, exercise has sufficient high level evidence to recommend it in practice. Both education and optimising sleep are likely to improve experiences of fatigue, while more evidence is required before energy conservation can be unreservedly presented to patients as an effective intervention for improving fatigue experiences.

Patients' experiences of fatigue have also been considered. Exploring the results of those studies whose primary aim was to describe the symptom experience, fatigue has been shown to be an all-encompassing, unpleasant symptom that affects all dimensions of patients' quality of life..

Chapters 2, 3 and 4 have shown that both nausea and fatigue are symptoms of concern for patients with cancer receiving chemotherapy that, despite efforts relating to symptom assessment and management, have a deleterious effect on patients' quality of life. The focus of this thesis is the evaluation of a nurse-led intervention (SNA↔P) aimed at improving patients' experiences of nausea and fatigue. Chapter 5 will briefly summarise the main points from chapters 2, 3 and 4, providing justification for the SNA↔P study before the methods and intervention for SNA↔P are presented in chapters 6 and 7, respectively.

5 CHAPTER 5 – SUMMARY OF LITERATURE REVIEW AND RATIONALE FOR THE SNA↔P STUDY

5.1 Introduction

The last three chapters have presented a review of the literature concerning chemotherapy-related symptoms in general and nausea and fatigue specifically. This chapter will, firstly, briefly summarise the salient points of this literature review before going onto present a short rationale for the SNA↔P study.

5.2 Summary of the literature review

Symptoms are a subjective experience perceived and verified only by the individual experiencing the phenomenon. A significant amount of research has explored the symptoms experienced by patients during chemotherapy which has shown that patients experience a broad range of physical, psychological and social symptoms. Further analysis of this evidence revealed, that not only were nausea and fatigue the most frequently reported symptoms, but they were also consistently ranked within patients' top four symptoms. Both nausea and fatigue are non-observable symptoms, which is a complicating factor in their assessment and management.

Indeed, the assessment of nausea and fatigue is not straightforward. The assessment of nausea is complicated by its close association with vomiting and lack of multidimensional assessment tools that specifically address nausea. In contrast, despite a lack of understanding of the aetiology of fatigue, a plethora of fatigue assessment tools have been developed. However, many of the assessment tools for

nausea (and vomiting) and fatigue are lengthy and research-focused, making them unsuitable for day-to-day use in the clinical situation. This lack of structured assessment makes the choice and evaluation of appropriate management techniques difficult.

There is currently no gold standard pharmacological intervention for the management of nausea, and, while non-pharmacological techniques may be helpful in alleviating patients' nausea experiences, further research is required before unequivocally recommending their use in clinical practice. Furthermore, their translation from research settings into clinical practice is complicated by factors such as health professionals' unfamiliarity with the techniques, their lack of education, as well as the necessary time taken to implement the interventions, and the costs associated with their implementation. The aetiology of fatigue is poorly understood and there are currently no pharmacological interventions that are supported by sufficient evidence to recommend their use in clinical practice. Non-pharmacological interventions, such as exercise and education, presently offer the most improvement in fatigue experiences.

However, the limitations of the many existing intervention studies for nausea and fatigue should be identified. The majority of studies reported within chapters 3 and 4 that sought to evaluate the impact of particular interventions had a variety of design flaws. In the main, studies were small scale, often involving fewer than 50 patients (and so underpowered) and included heterogeneous populations. Moreover, many did not account for the potential of a Hawthorne effect, that is the phenomenon by which subjects in behavioural studies change their performance in response to being observed, by including an attentional control group in their design

and CONSORT (Consolidated Standards of Reporting Trials) guidelines (Moher et al 2001, Boutron et al 2008) were rarely followed in the presentation of their results. Furthermore, the majority of studies tended to focus on the impact of a single intervention on a symptom, rather than the potential for complementary effects of multiple interventions and were conducted over a short time frame, for example, one or two cycles of chemotherapy.

Despite some positive interventions, irrespective of the approach taken to exploring patients' experiences, nausea and fatigue have been consistently shown to be unpleasant symptoms that have a deleterious effect on patients' quality of life. However, despite this fact and the wealth of research that has been invested in developing assessment and management techniques, there is relatively little research evidence that focuses solely on patients' experiences of these symptoms, what they mean to them and the impact they have on their daily lives.

5.3 Rationale for the SNA↔P study

Given the problems associated with assessing nausea and fatigue and the range of management techniques that may or may not be effective, alongside the knowledge that both nausea and fatigue have a negative impact on patients' quality of life, it was appropriate to conduct a study to promote structured assessment and practice in the real world of clinical practice that would address nausea and fatigue and improve patients' experiences. The SNA↔P study aimed to minimise the limitations of previous research studies not only through the design of the study but also within the intervention itself. Firstly it utilised a longitudinal time series design encompassing longitudinal data collection not only across multiple cycles of

chemotherapy (cycles 1-8) but within each cycle of chemotherapy (days 1-14). This provided a thorough understanding and description of symptoms over time while also accounting for the fact that the intervention may take a period of time to ‘work’ or that establishing the most appropriate or effective intervention for an individual may be a lengthy process or indeed that different interventions are more or less appropriate or effective at different times of the treatment journey. The SNA↔P study population was homogenous, women receiving chemotherapy for breast cancer, and also included a control group: a site control group as well as a time control group, as the study was conducted over a lengthy period of time. The SNA↔P study also involved assessment of the total symptom experience (incidence, severity and distress) to ensure that patients’ multidimensional symptom experiences were considered and evaluated, as the intervention may have impacted on differing aspects of the symptom experience at different points in the treatment journey. In relation to the intervention, it is important to note that it was conducted in a real life clinical situation by clinicians as part of their daily practice in an attempt to overcome the potential for a Hawthorne effect. Furthermore, it encapsulated total symptom management, that is assessment and management of symptoms, cyclically over patients’ entire chemotherapy journey rather than the SNA↔P-shot view of previous studies. The evaluation of the intervention was also novel in that it not only considered the statistical significance of the impact of the intervention but also made judgements on the personal significance of the intervention.

While clinical guidelines provide a method of promoting evidence for clinical practice, they are often unwieldy for day-to-day use (see chapter 7). Given the problems associated with their implementation, and the fact that the SNA↔P study

was being conducted within the real world of clinical practice, the study had to involve more than simply introducing clinical guidelines to promote improved assessment and practice in relation to nausea and fatigue. There is some evidence that patients who receive a standard treatment as part of a clinical trial have more positive outcomes than those receiving the same treatment outwith the clinical trial, possibly due to regular structured contact with health professionals (Braunholtz et al. 2001). Indeed, exploring patients' experiences of early clinical trials have shown that patients value the structure and continuity of care and assessment (Cox 1999) while routine quality of life assessment has been shown to result in better quality of life and emotional functioning (Velikova et al. 2004). Consequently, ensuring that the SNA↔P study involved a structured cyclical process of assessment that used the assessment outcomes to initiate interventions in practice was necessary if the intervention was to have an impact on patients' experiences.

Chemotherapy nurses have regular contact with patients throughout their course of chemotherapy, and an integral part of their role is symptom assessment and management. Indeed, they spend a considerable period of time with patients' during the intravenous administration of each cycle of chemotherapy, making chemotherapy nurses the most appropriate group of health professionals on which to focus the SNA↔P intervention.

5.4 Conclusion

This chapter has briefly summarised the literature review of the previous 3 chapters showing that the SNA↔P study responded to a need within clinical practice for

structured symptom assessment and practice. The following chapters present the SNA↔P study in detail.

6 CHAPTER 6 – METHOD

6.1 Introduction

The following chapter describes the methods used in the SNA↔P (Structured Nursing Assessment into Practice) study which evaluated the impact of a nursing intervention on patients' experiences of chemotherapy-related nausea and fatigue. The SNA↔P study arose from my involvement in the WISECARE+ study, and as such, it inevitably draws on, and at times is constrained by, the design and methods of WISECARE+. Such instances will be highlighted in the relevant sections within this chapter.

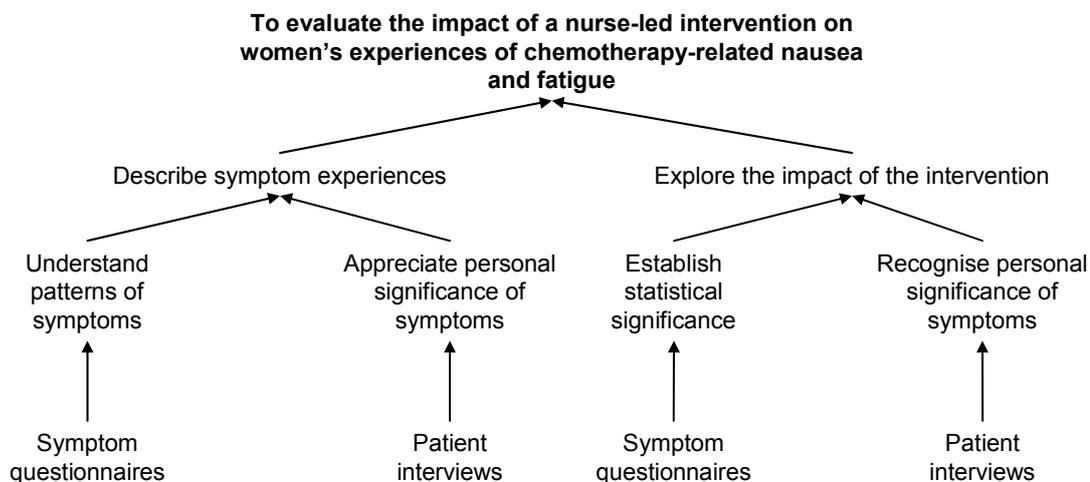
6.2 SNA↔P study design

The SNA↔P study aimed to evaluate the impact of a nurse-led intervention incorporating structured nursing assessment and practice (SNA↔P) on women's experiences of chemotherapy-related nausea and fatigue during a course of chemotherapy for breast cancer. This evaluation involved 2 distinct aims:

1. To describe and explore the patterns and experiences of chemotherapy-related nausea and fatigue.
2. To explore the impact of the intervention on experiences of chemotherapy-related nausea and fatigue.

Both quantitative (structured questionnaires) and qualitative (semi-structured interviews) methods were used to address these aims (see Figure 4).

Figure 4: SNA↔P study aims



Combining research methods in this way is not uncommon in health care research (Sale et al. 2002). The term ‘mixed methods’ is summarised as research designs using qualitative and quantitative data collection and analysis techniques either in parallel or sequential phases (Tashakkori and Teddlie 2003). Research methods, however, are based on specific paradigms: a patterned set of assumptions concerning reality; knowledge of that reality; and particular ways of knowing in that reality (Guba 1990). The quantitative paradigm is based on positivism and seeks to measure and analyse causal relationships between variables in a value-free framework (Denzin and Lincoln 1994). Sample sizes are larger in quantitative research and techniques used include randomisation, blinding, highly structured protocols, and written or orally administered questionnaires with limited responses. In contrast, the qualitative paradigm is based on interpretivism and constructivism where there are multiple realities or truths based on one’s construction of reality (Sale et al. 2002). The emphasis of this type of research is on process and meaning with samples not meant to represent large populations (Sale et al. 2002). Within the

SNA↔P study, structured symptom questionnaire represent the positivist paradigm while semi-structured interviews represent the interpretivist paradigm.

While research has moved beyond the quantitative/qualitative debate, just because methods can be combined does not mean that it is always appropriate to do so, and mixing research methods should not be used to bolster the weaknesses of one method with the strengths of another. Within the SNA↔P study, mixed methods were used in a complementary fashion to produce an additive effect: the information from structured symptom questionnaire facilitating the exploration of the personal significance of nausea and fatigue in interviews, while in turn, interview data was used to give insight into the actual personal significance of the intervention when it was statistically evaluated. While each of these components is integral to the final evaluation of the intervention, for ease of description, qualitative and quantitative components of the SNA↔P study will be described separately in the following sections. The analysis plan will be presented thereafter to demonstrate the complementarity of the quantitative and qualitative data.

6.3 Quantitative component of the SNA↔P study

6.3.1 Design

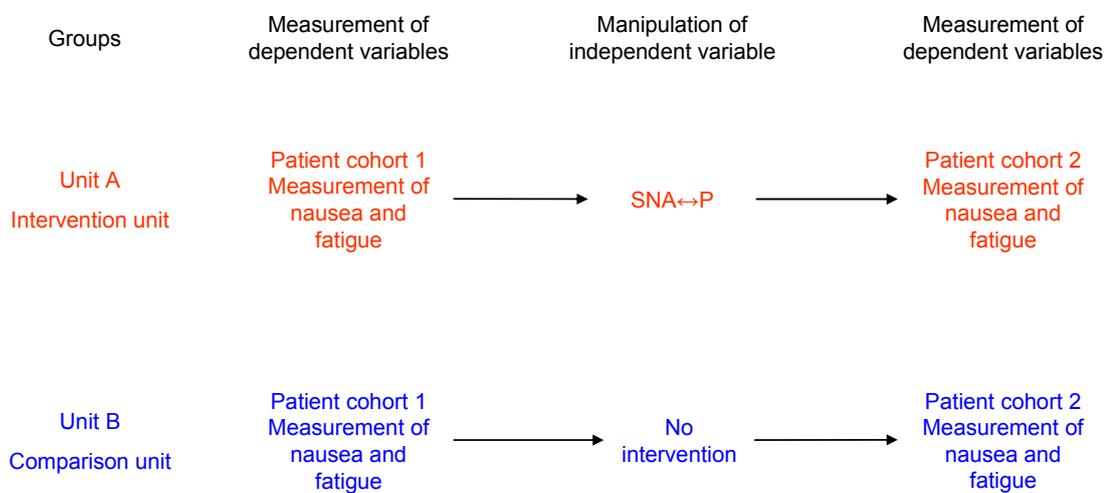
The quantitative component of the SNA↔P study followed a quasi-experimental interrupted time-series design with a control group. The time series design allowed a stable baseline to be established before the introduction of the SNA↔P intervention, (structured nursing assessment into practice), so that any change in the dependent variable (patients' nausea and fatigue) would be due to the intervention and not other environmental events (Burns and Grove 2005). The design of the

SNA↔P study differed from that of the WISECARE+ study as it incorporated a control group. The addition of this control group strengthens the validity of any findings as it allows examination of differences in trends between groups after the intervention (Burns and Grove 2005). There were 4 patient groups in the SNA↔P study:

- Unit A cohort 1 (time control group)
- Unit A cohort 2 (intervention group)
- Unit B cohort 1
- Unit B cohort 2 (site control group)

The SNA↔P study design is shown in Figure 5.

Figure 5: Design of SNA↔P study



6.3.2 Aims

The quantitative component of the SNA↔P study had two aims:

1. To describe patterns of chemotherapy-related nausea and fatigue during a course of chemotherapy for breast cancer.

2. To explore (statistically) the impact of the SNA↔P intervention on chemotherapy-related nausea and fatigue.

6.3.3 Setting

The SNA↔P study was conducted within two typical chemotherapy out-patient Units (Unit A – the intervention site and Unit B – the control site) in the West of Scotland. Although these Units were located in different hospitals they were part of the same hospital trust, and as such, operated to the same policies and procedures. Both Units were responsible for the delivery of out-patient chemotherapy to patients with a range of cancer diagnoses, as well as necessary supportive care, such as blood transfusions. The Units were nurse-led, that is, the organisation and delivery of patient care was led by a team of nurses and supported by medical, pharmacy, allied health professionals and secretarial staff. Although they were identical with respect to policy, protocols and practice (whilst acknowledging the inherent individuality in clinical practice), there was no routine movement of staff between each of the Units.

6.3.4 Sample

Women receiving chemotherapy for breast cancer were recruited from Units A and B. A consecutive sample of eligible patients ensured that the greatest cohort of patients would be recruited in the time allocated to recruitment (14 months) and also aimed to exclude selection bias, conscious or otherwise. All patient included in the SNA↔P study received antiemetic therapy as per hospital policy (identical in Units A and B). Patients were eligible for the study if they met the criteria set in Table 15.

Table 15: Patient eligibility criteria for the SNA↔P study

Inclusion criteria	Exclusion criteria
Aware of their diagnosis of breast cancer	Deemed by any member of the clinical team as being physically or psychologically unfit to participate in the study
Chemotherapy naïve	Previously received a course of chemotherapy
Able to read/write English	Unable to give informed consent
Able to give informed consent	

The WISECARE+ study recruited patients with a range of cancer diagnoses that reflected the patient populations of the clinical sites involved. However, such heterogeneity is likely to be problematic for the analysis in a study that focuses on symptom outcomes, as these may differ according to diagnosis and chemotherapy. In contrast, the SNA↔P study involved only women with breast cancer. This homogenous population was chosen for a number of reasons, as already highlighted in the preface to this thesis: breast cancer represented the largest patient population in the study sites, so giving access to the greatest number of patients during data collection thereby increasing the power of the study; recruiting a homogenous population excluded the potential for differences in symptom experiences associated with varying cancer diagnosis; and breast cancer was of interest to the researcher (hereafter referred to as MM) based on her previous clinical experience.

To ensure maximum homogeneity within the sample, it was initially planned to recruit patients receiving the same chemotherapy regime, however, review of the patient lists in both sites prior to the start of data collection showed there were insufficient numbers of patients receiving any one chemotherapy regime to allow

recruitment of a sufficient sample size within the designated timeframe. Thus, patients were recruited on the basis of their breast cancer diagnosis regardless of the chemotherapy regime they received. The decision to exclude patients who had previously received chemotherapy was based on the evidence that past experiences of symptoms impact on current symptoms (Watson et al. 1998; Montgomery and Bovbjerg 2001; Montgomery and Bovbjerg 2003). As the main aim of the study was to evaluate the impact of the evidence-based intervention on symptom experiences, it was felt that patients who had previously received treatment may perceive and experience their symptoms differently to patients who were chemotherapeutically naïve. Patients were required to be aged 18 years or over to be included in the study, however, there was no upper age limit set, as this study aimed to explore the impact of the intervention with as many patients as possible. While patients were not discouraged from discussing their symptoms with family/friends while they completed the symptom questionnaires, they were encouraged to complete these themselves, and as such, were required to be able to read/write English.

6.3.5 Measures

Two groups of measures were involved in the quantitative component of the SNA↔P study: socio-demographic and symptom measures.

6.3.5.1 Socio-demographic measures

Socio-demographic data was collected not only to characterise and describe those participating in the SNA↔P study, but also to allow comparison between patient groups (Units A and B, cohorts 1 and 2). The demographic details collected about each participant were: age; level of deprivation using the Carstairs deprivation score

(McLoone 2004); and chemotherapy treatment intent, since research has shown that each of these characteristics may affect symptom experiences (Stone et al. 2000a; Macleod et al. 2000b; Macleod et al. 2000a; Simpson and Rosenzweig 2002; Macleod et al. 2004; Goodwin 2007).

6.3.5.2 Symptom measurement

It is in the aspect of quantitative symptom measurement that the SNA↔P study was most constrained by the methods of the WISECARE+ study. This limitation was because the patients participating in Unit A (the intervention site) were also taking part in the WISECARE+ study, and so the process of symptom data collection necessarily followed that of the WISECARE+ study. Consequently, many of the decisions concerning symptom assessment were taken by the WISECARE+ Steering Group (MM was an integral member of this Group, but final decisions were not her responsibility).

6.3.5.2.1 Choice of symptom assessment tool

Given the non-observable nature and subjectivity of both nausea and fatigue, the Steering Group unanimously agreed on the importance of a patient self-report tool for assessing symptoms. A pan-European study had found that patients complained of questionnaire fatigue in response to a battery of questionnaires (Sermeus et al. 2000). Consequently, a symptom questionnaire that was patient-focused and short was required. However, it was also recognised that this should be multidimensional in order to fully capture the total symptom experience (as highlighted in chapters 3 and 4).

MM reviewed available assessment tools and found no assessment tool that met exactly the needs of the WISECARE+ study: a patient focused, short, multidimensional tool that assessed nausea, vomiting, fatigue and oral problems. However, the Chemotherapy Symptom Assessment Scale (Brown et al. 2001) was identified in the search for a clinically usable and patient-focused tool. This is a 24-item multidimensional assessment scale, whose development had strong patient involvement, was multidimensional in that it evaluated incidence, severity and associated symptom distress, and had been developed to be short enough for routinely used in clinical practice. The content validity of the C-SAS was established through the comprehensive 6-stage approach to item generation (Brown et al. 2001), however, although further reliability and validity data were promised, none have been subsequently reported. The use of an assessment tool with such limited validity data and without any reliability data is unconventional and is an area in which the SNAP study is compromised because of its association with the WISECARE+ study. However, the Steering Group agreed that the advantages of patient involvement in the development of the tool, as well as its clinical usability, outweighed the disadvantages of lack of reliability and validity data.

Permission was granted by the authors to adapt the tool, removing all symptoms except nausea, vomiting, fatigue and oral problems, substantially shortening the questionnaire and focusing it only on the symptoms of concern within the WISECARE+ study. As each of the 24 questions within the C-SAS addressed a single symptom, modifying it in this way should not affect the tool's reliability or validity. Each question was comprised of 3 discrete sections evaluating incidence, severity and distress (see Figure 6). The full questionnaire can be found in Appendix B.

Figure 6: Questionnaire presentation

Nausea ...

Have you experienced this today? Yes No

If yes, how severe was this?

Mild Moderate Severe

How much did it bother you?

Not at all A little Quite a bit Very much

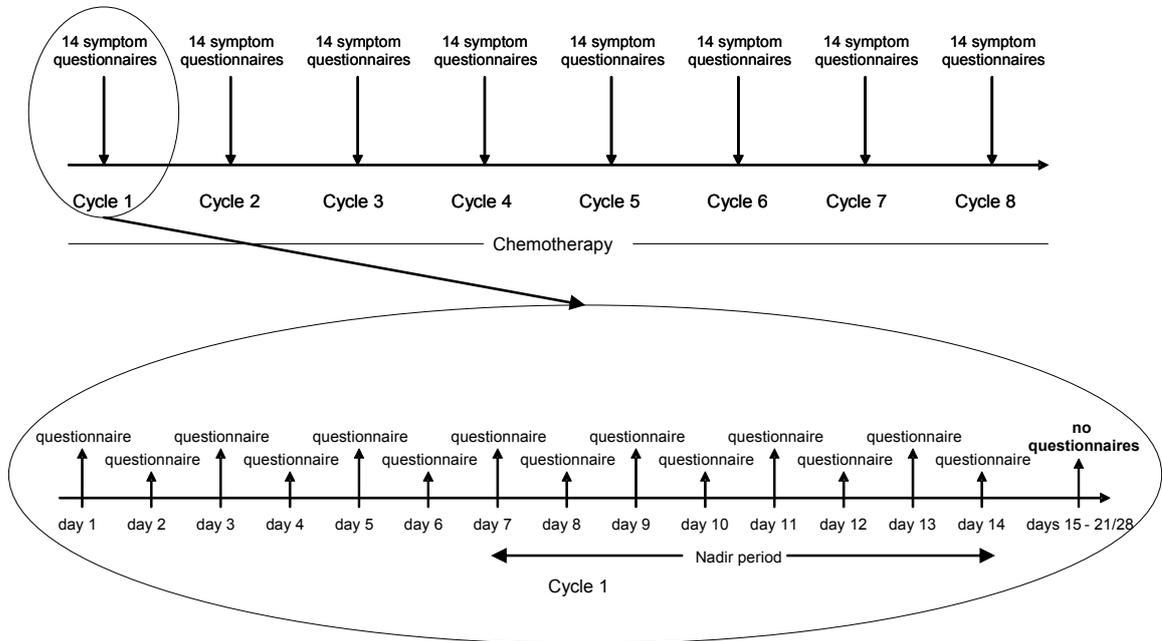
6.3.5.2.2 *Frequency of symptom assessment*

Given that the SNA↔P study sought to describe patterns of nausea and fatigue over a course of chemotherapy, longitudinal assessment of symptoms was necessary.

Moreover, this longitudinal assessment necessarily took place both within each cycle of chemotherapy and across a course of chemotherapy. The frequency with which patients were asked to complete the questionnaire was taken by the WISECARE+ Steering Group and was based not only on their previous experience of symptom assessment showing that patients continued to experience symptoms more than 10 days following chemotherapy administration (Sermeus et al. 2000), but also the current evidence concerning patterns of chemotherapy-related symptoms - short-lived symptoms such as nausea that occur in the first few days following chemotherapy (Kris et al. 1994; Jordan et al. 2005), and those more constant symptoms that continue to be felt for days or weeks following chemotherapy, such as fatigue (Berger 1998; Schwartz 2000; Molassiotis and Chan 2001; Miller et al. 2007). Moreover, extending the duration of data collection would

allow the symptom data to be collected over the nadir period. This is the time during a cycle of chemotherapy, usually between 7-14 days, at which the patient's blood count drops to its lowest and has been associated with greater levels of symptoms, especially fatigue (Pickard-Holley 1991; Irvine et al. 1994; Richardson and Ream 1996; Boehmke and Brown 2005). Being mindful of the potential for questionnaire fatigue, it was decided that patients would be asked to complete this short symptom questionnaire for 14 days following each chemotherapy administration. This schedule gave patients between 7-14 days between completing their questionnaires and returning for their next cycle of chemotherapy. The frequency of symptom questionnaire completion is shown in Figure 7.

Figure 7: Frequency of questionnaire completion



6.3.6 Procedures

6.3.6.1 Pilot study

A pilot study was conducted to test the adapted version of the patient symptom questionnaire in relation to comprehension, usability and compliance during a single cycle of chemotherapy. This pilot study was conducted for the SNA↔P study; however the WISECARE+ study, which had already begun data collection in a number of other clinical sites, benefitted from the minor changes that were made to the patient symptom questionnaire (described later).

6.3.6.1.1 Design

The pilot study was descriptive and exploratory.

6.3.6.1.2 Setting

The pilot test was conducted within two typical chemotherapy out-patient Units (Unit A and Unit B) within the same hospital trust that were to be involved in the main study.

6.3.6.1.3 Sample

Five patients (2 from Unit A and 3 from Unit B) who met the eligibility criteria of the main study (page 134), and who were receiving their first or second cycle of chemotherapy for breast cancer, participated in this pilot study.

6.3.6.1.4 Measures

Comprehension and usability of the patient symptom questionnaire were explored through an informal discussion between MM and each individual patient, the schedule for which is presented in Figure 8.

Figure 8: Interview schedule for questionnaire pilot

How did you find completing these questionnaires (easy, difficult, straightforward, tiresome, worthwhile)?

Did you understand the written instructions on the front cover of the questionnaires?

Were these instructions useful? How often did you look at them?

Was there anything in those instructions that wasn't clear to you or didn't make sense?

Did you have any problems or difficulties completing the questionnaires themselves?

Were any questions in the questionnaire unclear to you?

Did you find the questions relevant to your experiences?

Could you understand the responses that you had to choose from?

Was it clear what you had to do with the questionnaires when you had completed them all?

Have you any other comments about the questionnaires?

Compliance with completing the questionnaire was evaluated by assessing the amount of missing data in the returned questionnaires. Compliance with returning the questionnaires was evaluated by comparing the numbers of questionnaires actually returned with those expected to be returned.

6.3.6.1.5 Procedure

Ethical approval for the pilot study was obtained within the main submission for ethical approval detailed in section 6.3.6.2 ethical considerations and approval, page 144.

The patient's chemotherapy nurse briefly explained the SNA↔P study to them and asked whether they would consider piloting the patient symptom questionnaire that would be used. It was explained that this would involve completing the questionnaire for 14 consecutive days following their chemotherapy and returning all 14 completed questionnaires by post in a stamped addressed envelope to MM. They were also asked if they would be willing to meet with MM at their next

chemotherapy appointment to discuss their perceptions of and experiences of completing the questionnaire.

All 5 patients approached agreed to participate and they were subsequently given the pack of 14 questionnaires, a stamped addressed envelope and verbal instructions (based on the written instructions on the front of the questionnaire) about questionnaire completion. They were asked to complete the questionnaires according to the written instructions on the front of each questionnaire for 14 consecutive days following their chemotherapy and then to return them, in the stamped addressed envelope, to MM.

All patients met with MM to discuss their perceptions of the questionnaire on return for their subsequent chemotherapy treatment.

6.3.6.1.6 Analysis plan

The discussions with patients were guided by a brief set of questions to ensure that all aspects of the evaluation were covered (see Figure 8). MM took notes during each discussion and, at the end of the discussion, went over these with the patient to ensure all their points were recorded. The returned questionnaires were checked for missing data. The number of questionnaires returned by each patient was also noted.

6.3.6.1.7 Pilot study outcomes

All five patients responded positively about their experiences in this pilot study. They found the written instructions on the front cover of each questionnaire a useful reminder about how and when to complete the questionnaire, although all reported that they became familiar with the process after just a few days. No patients

reported any difficulties with completing the questionnaires, nor problems associated with understanding or responding to each question. Patients found the questions relevant at some time during the 14 days following chemotherapy administration, but were unsure about how useful (for MM) it would be to complete the questionnaire if they were not experiencing any symptoms. All patients fully completed and returned all 14 questionnaires.

One change was made to the written instructions on the front cover of the questionnaire as a result of the pilot study. It now read that patients' responses to the questionnaire were valuable whether they were experiencing symptoms or not. No changes were made to the questionnaire itself.

6.3.6.2 Ethical considerations and approval

The patients involved in the quantitative component of the SNA↔P study were facing a particularly stressful period in their lives. Not only had they received a diagnosis of breast cancer (primary or recurrent) within the last three months, but those patients receiving adjuvant chemotherapy (n=79, 75.2% of the total sample) had also undergone breast surgery as first line treatment for their diagnosis. Both surgery and chemotherapy are associated with a period of physical and psychological adjustment (Wainstock 1991; Steginga et al. 1998; Lehto and Cimprich 1999; Landmark et al. 2001). Participating in the SNA↔P study could potentially have added to the stress they were already experiencing.

Asking patients to reflect and report on their symptom experiences by completing a daily questionnaire for 2 weeks following each cycle of chemotherapy may be considered excessive. One could argue that in doing so, some patients would be

constantly reminded of their diagnosis and treatment and potentially focus too much on their symptoms. Alternatively, spending a short time each day reflecting on symptom experiences and completing the questionnaire may be helpful to some patients when they attend for subsequent chemotherapy. They would be more able to explain the symptoms they experienced to the clinicians caring for them and, as such, effective symptom interventions could be initiated. The former was not the intention of the SNA↔P study, and patients' willingness to participate and continue in the study were repeatedly assessed to ensure that this was not detrimental to the patient. To reduce the burden of participation, the questionnaire was designed to be as short as possible while gathering clinically meaningful information and being relevant to patients' symptom experiences.

Ethical approval for the study within Unit A was granted by the Multicentre Research Ethics Committee as part of the ethics application for the multicentre WISECARE+ study. Local Research Ethics Committee approval was granted for Unit B from the hospital Trust in which the research took place.

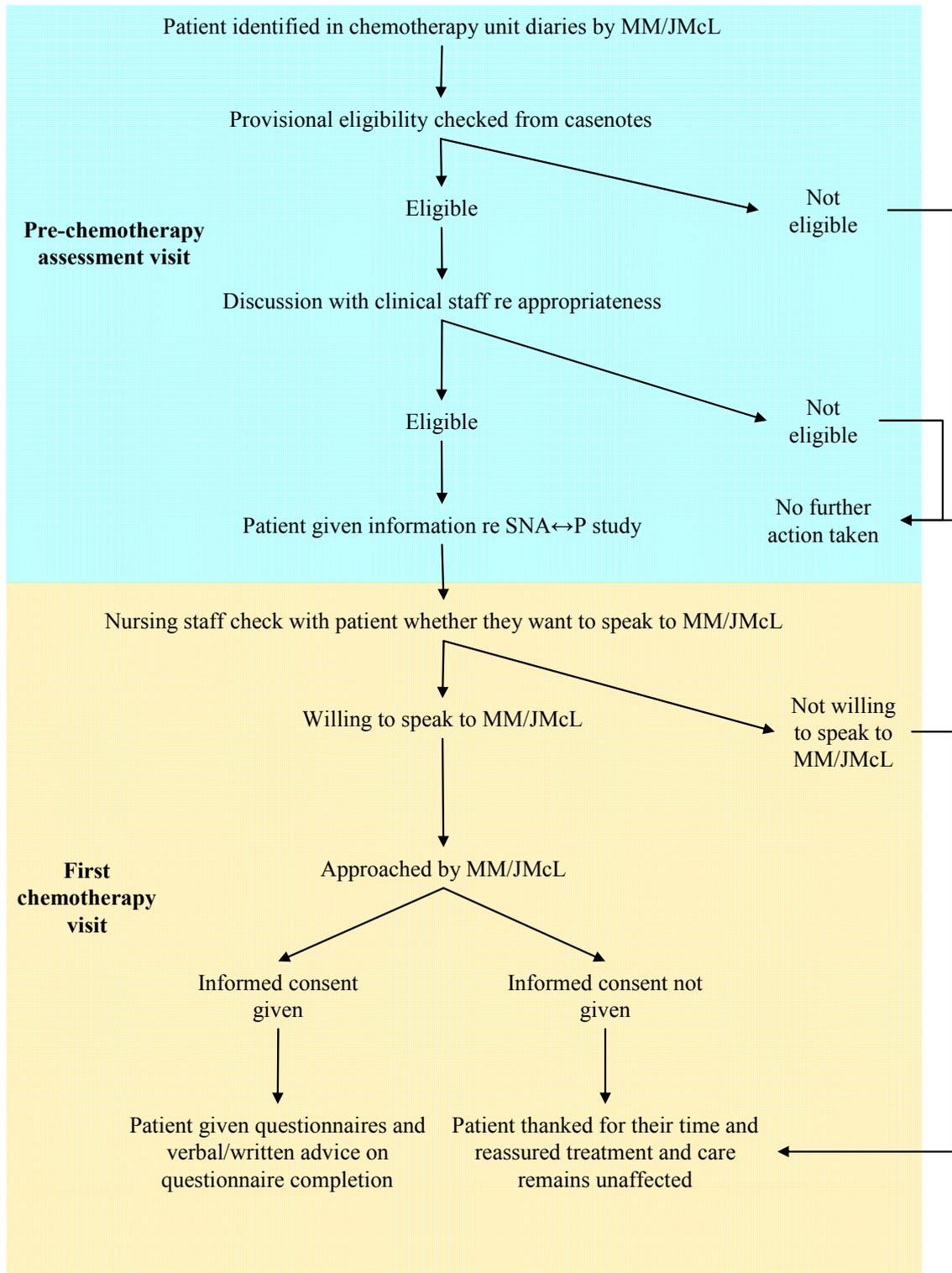
6.3.6.3 Recruitment and consent

Recruitment and patient consent in Unit A was undertaken by a research support nurse (hereafter known as JMcL) who was a senior member of the cancer nursing staff within the hospital. Her extensive cancer nursing experience as well as being known to, and respected by, the nursing staff of Unit A eased these processes.

Recruitment and consent in Unit B was undertaken by MM.

An identical two stage process of recruitment and consent was followed in both Units as described in Figure 9.

Figure 9: Process of patient recruitment



This two-stage process ensured that patients had the opportunity to consider their participation in the SNA↔P study and ask the researcher (either MM or JMCL, depending on the Unit) questions before making a decision. Standard patient

information sheets (see Appendices C (Unit A) and D (Unit B)) were given to each eligible patient during their pre-chemotherapy assessment visit and they were followed up when they returned for their first cycle of chemotherapy, usually about one week later. Patients were reassured that they could withdraw from the study at any time without affecting their treatment and care and without providing a reason for doing so. On agreeing to participate in the SNA↔P study, patients signed a consent form: they kept one copy, a second copy was filed in their casenotes and a third was kept by either MM or JMcL. This third copy was stored in a secure filing cabinet until the end of the study whereupon it was securely archived and will be destroyed, as per University of Stirling regulations, in 2012.

6.3.6.4 Data collection

A short demographic data collection sheet was developed to ensure standardised data collection in both Units and was completed by MM or JMcL as each patient was recruited (see Appendix E). These demographic details were subsequently analysed to compare the patient groups and establish the impact of these potentially confounding demographic variables on the results of the SNA↔P intervention. Demographic data collection sheets were stored securely in a locked filing cabinet in both Units until the end of the study and were subsequently securely archived. They will be destroyed, as per University of Stirling regulations, in 2012.

Following recruitment to the study, patients were taught about how and when to complete the questionnaire, and when and where to return it, by either MM or JMcL, depending on the Unit. A patient education schedule (appendix F) was used by both researchers to ensure the patient education, instruction and information about their involvement and questionnaire completion was standardised across both

Units. Patients were actively encouraged to ask any questions they had about completing the questionnaires at this initial teaching session. Key issues from the teaching schedule were repeated on the front sheet of each questionnaire.

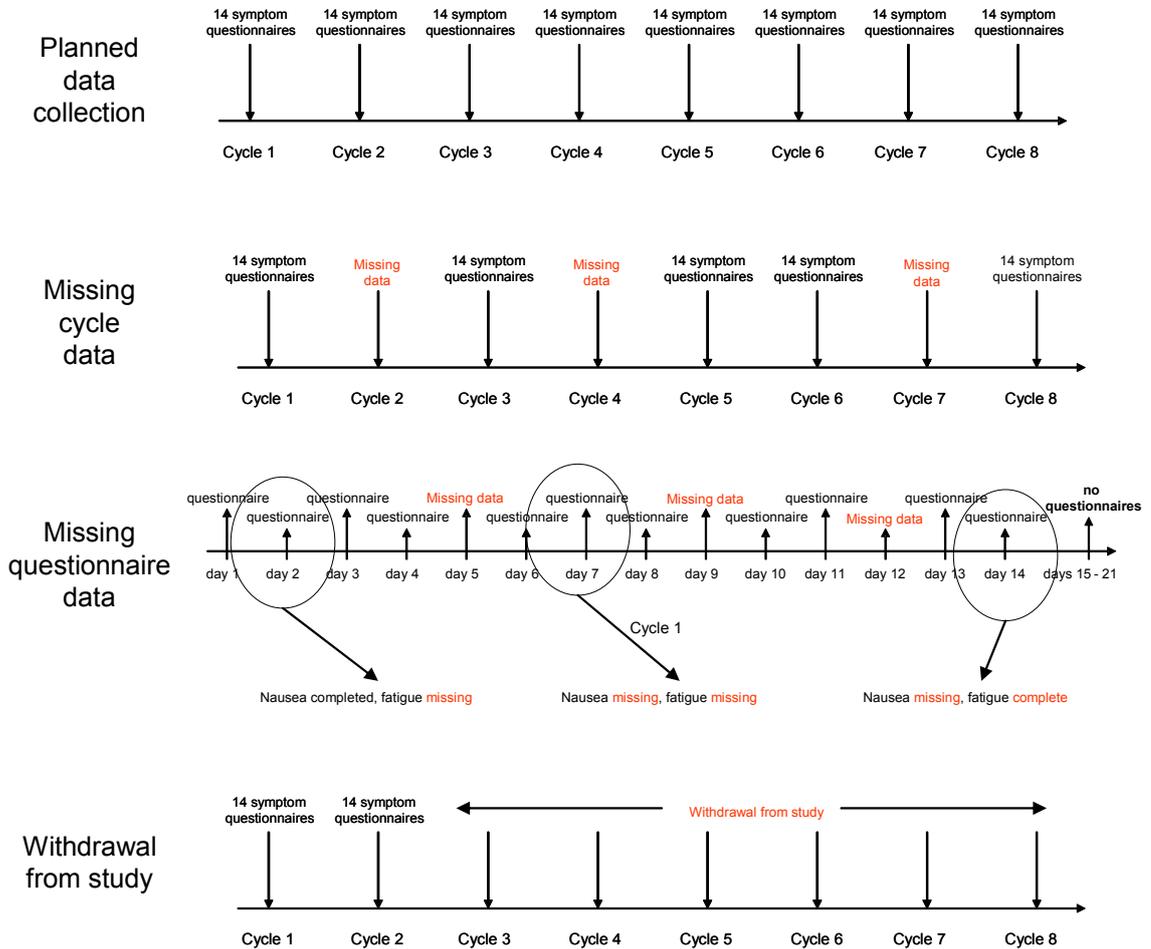
It was intended that MM (Unit B) or JMCL (Unit A) would meet with each patient every time they attended for chemotherapy to check they were still happy to be involved in the study, as well as answering any questions they had about the study or completing the questionnaires, and giving patients their next set of 14 questionnaires. This procedure was possible and worked well in Unit A where JMCL was based, however, existing work commitments, travel time to Unit B, and logistical problems of patients' appointment times being changed due to deferral of treatment or chemotherapy symptoms, meant that it was impossible for MM to be present every time each patient returned for chemotherapy. Consequently, on recruitment, patients in Unit B were given 8 sets of questionnaires and stamped addressed envelopes (one for each cycle of their chemotherapy) and were advised to complete a new set of questionnaires each time they began a new cycle of chemotherapy. They were also encouraged to contact MM if they had any questions or problems about their involvement in the study and their chemotherapy nurse undertook to check at each visit for chemotherapy that their involvement in the study was not having a detrimental effect on them. Patients were advised to return their unused sets of questionnaires to the chemotherapy Unit if they decided to stop participating in the study. While these arrangements worked well, if MM was in Unit B to recruit a new patient when an existing patient was attending for chemotherapy she made every effort to meet with them herself, and informally chat about their involvement in the study.

Patients returned their completed questionnaires to either MM (Unit B) or JMcL (Unit A) who then entered this symptom data into the WISETool, an electronic patient record/database that was developed specifically for the WISECARE+ study. The WISETool stored individual patient's symptom data and transferred this to a secure data warehouse, as well as providing nurses with information about the symptom associated with the chemotherapy regime the patient received, the actual symptoms the patient reported, and the most appropriate nursing interventions for the patient's reported symptoms. More detailed information about the role of the WISETool in the SNA↔P study is provided in chapter 7 – The SNA↔P Intervention. Although MM did not require the variety of WISETool functions for patients participating in Unit B (the control site), entering data to the WISETool meant it was accessible in the same format as Unit A, and facilitated data analysis. Patient questionnaires were stored locally in locked filing cabinets. Following data entry and quality assurance checks, these have now been securely archived and will be destroyed in 2012, as per University of Stirling regulations.

6.3.6.5 Quantitative data management

All questionnaires that were returned either in full or in part were included in the analysis. This process of data management made full use of all the data returned by patients and recognised that any symptom reported was of value. Data was considered 'missing' if the patient subsequently returned symptom questionnaires later in their course of chemotherapy (see Figure 10 for examples of missing data and withdrawal from study). An analysis of missing data was conducted within SPSS. Data from all the patient interviews was used for the analysis.

Figure 10: Example of missing data/withdrawal from study



6.3.6.6 Statistical analysis of quantitative data

The quantitative data generated within the SNA↔P study was used to both:

- describe and explore patterns of chemotherapy-related nausea and fatigue
- and
- explore the impact of the SNA↔P intervention on these symptom experiences.

Using all data received from every patient mean symptom scores were generated for each day (days 1-14) within each cycle of chemotherapy (cycles 1-8) and these were plotted graphically to describe and explore longitudinally patterns of patients' experiences of nausea and fatigue.

Exploring the impact of the intervention involved both primary and secondary hypotheses.

The primary hypothesis was that:

Unit A cohort 2 would have statistically significantly less nausea and fatigue than Unit A cohort 1

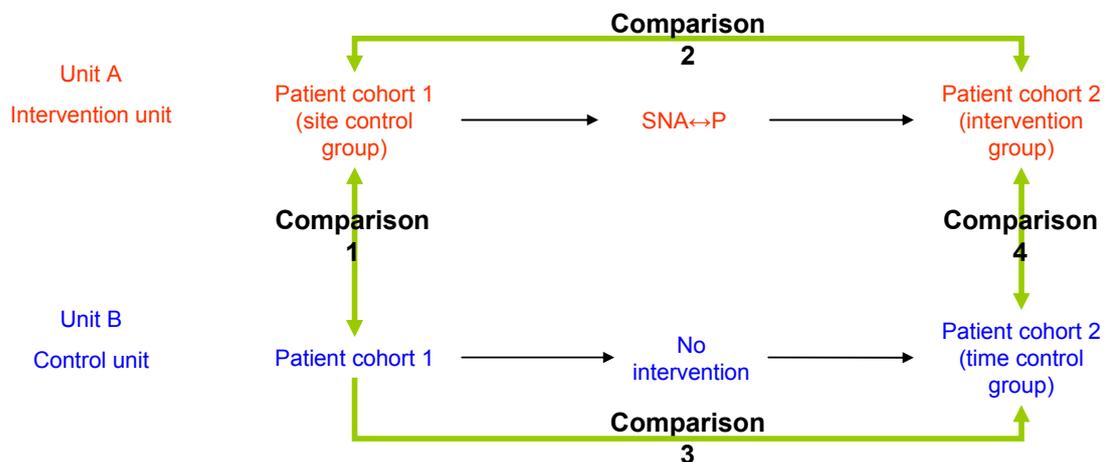
The secondary hypothesis was that:

Unit A cohort 2 would have statistically significantly less nausea and fatigue than Unit B cohort 2.

Given the volume of data generated as a consequence of this longitudinal data collection, mean scores were used to respond to both hypotheses. For each patient, a mean symptom score was generated for total nausea and for total fatigue. Mean nausea scores were generated using the data from the first 3 days following each cycle of chemotherapy (as patterns of nausea demonstrated that the greatest degree of nausea was experienced during the first 3 days of each cycle of chemotherapy) while mean fatigue scores were based on the fatigue scores reported throughout the entire 14 days of data collection following each cycle of chemotherapy. This meant that for each patient (n=105) their responses were condensed into a single mean score for nausea and a single mean score for fatigue.

To ensure the appropriate statistical tests were applied, the distribution of these scores was tested using boxplots. If the data for each patient group were normally distributed, parametric tests (an ANOVA) would be applied to explore whether there were significant differences between the mean scores within each patient group. If the data for each patient group were not normally distributed, the appropriate nonparametric test would be applied (Kruskal-Wallis test), again to establish whether there were statistically significant differences between the mean scores of each patient group. Given that mean scores were being compared between multiple groups, see Figure 11, it was important that the statistical test compared groups simultaneously rather than carrying out multiple tests to compare each patient group as the latter process would greatly increase the chance that a significant difference would falsely be found.

Figure 11: Statistical evaluation of the impact of the SNA↔P intervention



A mean score for nausea and fatigue was also generated for each patient group (based on each patient's mean score within each group) to illustrate the level of difference in mean total symptom scores between each patient group.

Given the level of patient attrition within the SNA↔P study, the analysis that explored the impact of the intervention was carried out firstly using the full data set and then repeated using data from the first 4 cycles of chemotherapy only, which incorporates at least two thirds of each patient group from the total sample.

6.4 Qualitative component of the SNA↔P study

6.4.1 Design

The qualitative component of the SNA↔P study followed a descriptive and exploratory design using semi-structured interviews.

6.4.2 Aims

The qualitative component of the SNA↔P study had 2 aims:

1. To describe chemotherapy-related nausea and fatigue during a course of chemotherapy for breast cancer.
2. To explore the impact of the SNA↔P intervention on chemotherapy-related nausea and fatigue, specifically exploring patients' ability to perceive differences between different symptom scores and what these mean to patients.

6.4.3 Setting

The semi-structured interviews took place in the two typical chemotherapy Units that were involved in the quantitative component of the SNA↔P study (Unit A –

the intervention site and Unit B – the control site). These Units are described in full in section 6.3.3 page 133.

6.4.4 Sample

A purposive sample of women (representative of the total sample with respect to age, deprivation and treatment intent as far as possible) receiving chemotherapy for breast cancer in Units A and B who were already participating in the quantitative component of the SNA↔P study, and who had reported nausea and fatigue within their symptom questionnaires, were recruited. Patients were considered eligible for this component of the SNA↔P study if they met the criteria set out in Table 16.

Table 16: Patient eligibility criteria for the qualitative component of the SNA↔P study

Inclusion criteria	Exclusion criteria
Completed at least one set of symptom questionnaires as part of the SNA↔P study	Deemed by any member of the clinical team as being physically or psychologically unfit to participate in a semi-structured interview
Reporting symptom scores of at least 2 for nausea and/or fatigue within their most recent set of symptom questionnaires	Unable to give informed consent

6.4.5 Measures

Two measures were involved in the qualitative component of the SNA↔P study: socio-demographic, and symptom experience data.

6.4.5.1 Socio-demographic data

Socio-demographic data were collected to characterise those participating in the semi-structured interviews. As before, socio-demographic data collected were: age, level of deprivation, and treatment intent.

6.4.5.2 Symptom experience data

Given the individual and subjective nature of chemotherapy-related nausea and fatigue, developing an understanding of patients' perspectives required a method that facilitated open discussion with patients on an individual level, giving them the opportunity to describe their symptom experiences. One-off semi-structured interviews following a cycle of chemotherapy were conducted with a convenience sub sample (n=9) of the total SNA↔P sample to develop an appreciation of patients' experiences of nausea and fatigue. A prompt, in the form of the patient's symptom graphs generated by the WISETool of their last cycle of chemotherapy, was used throughout the interview. This presented a clear picture, both to the patient and MM of the scores of nausea and fatigue that the patient had reported during the previous cycle of chemotherapy. This helped jog patients' memories of their symptom experiences and was used throughout the entire interview to focus the patient on their symptom experiences. They were also used to facilitate potentially complex discussions concerning the differences between symptom scores, that is, the differences between a symptom score of 1 and 4, or 3 and 5, and what these differences actually meant to patients.

Face-to-face interviews were chosen, as they facilitate the discussion of complex topics, so giving patients the opportunity to explain and describe their symptom

experiences in great depth and clarify any areas of uncertainty, so avoiding misinterpretation. Although each patient's symptom profile was personal to them, an interview schedule was developed and used in each interview (see Figure 12 page 161). This was in keeping with the symptom experience component of the Symptom Management Model (Larson et al. 1994; Dodd et al. 2001a), described in chapter 2, as it focused on patients' experiences of symptoms in relation to their perceptions, evaluation of the symptoms and responses. Using a schedule ensured that all interviews followed the same direction and focused on the crucial issues under study (Burns 2000). The interview schedule was identical for both Units A and B, as this component of the SNA↔P study did not aim to compare symptom experiences between groups of patients.

6.4.6 Procedures

6.4.6.1 Ethical considerations and approval

As in the quantitative component of the SNA↔P study, patients participating in interviews were facing a stressful period in their lives. Taking part in this one-off interview was not intended to add to any stress they were already experiencing. Indeed, that they had already agreed to take part in the SNA↔P study showed their willingness to participate in this type of research. Nevertheless, MM checked first with the nursing staff caring for the patient before approaching them and inviting them to take part in a short informal interview about their symptom experiences during their previous cycle of chemotherapy.

As this qualitative component was not part of the WISECARE+ study, additional ethical approval was sought and received from the Local Research Ethics

Committee of Unit A. Ethical approval for a sub-sample of semi-structured patient interviews had already been granted in the original submission to the ethics committee for Unit B.

6.4.6.2 Recruitment and consent

Eligible patients from both Units A and B were identified by MM before their return for their next cycle of chemotherapy. As the focus of the interview was symptom experiences, it was important that the patient had reported at least some nausea and fatigue in their symptom questionnaires. Patients were also purposively identified on the basis of their demographics to ensure that this sub-sample was as representative of the total sample with respect to age, deprivation and treatment intent as possible.

On identifying a patient, MM checked with the nursing staff to ensure that there was no reason that the patient should not be approached on the day they returned for chemotherapy. During their initial recruitment to the SNA↔P study, patients were informed of the interview aspect of the study but were aware that they may or may not be asked to participate in this. On approaching eligible patients, MM reminded them of this aspect of the study and asked whether they would consider speaking to her about their symptom experiences during their previous cycle of chemotherapy. As well as this verbal information, patients were given a written information sheet that described this component of the SNA↔P study in more detail and were reassured that they could stop the interview at any time without giving a reason. If the patient agreed to participate, they signed a consent form. One copy of this was given to the patient, a second was filed in their casenotes and a third copy was kept by MM. This third copy was stored in a secure filing cabinet until the end of the

study whereupon it was securely archived and will be destroyed, as per University of Stirling regulations, in 2012.

6.4.6.3 Data collection

Patients were able to participate in an interview at any stage during their course of chemotherapy. While symptom experiences may vary across cycles of chemotherapy, interviewing patients at various stages of their course of chemotherapy would not impact on the outcome of this component of the SNA↔P study, as the aim was to understand, in more depth, the individual experience, meaning and significance of chemotherapy-related nausea and fatigue scores. Indeed, it was hoped that including patients at various stages in their course of chemotherapy would incorporate an even greater breadth of symptom experiences.

Purposive sampling ensured that ‘information-rich’ cases were identified. Every effort was made to conduct the interviews in a quiet area within each chemotherapy Unit to ensure that patients felt able to discuss their symptoms and experiences without being overheard. All interviews were tape recorded (with the patients’ permission) to allow MM to concentrate on what was being said without simultaneously taking notes. Patients were reassured that the tape recordings would be destroyed at the end of the study (although transcripts of the interview would be securely archived for 5 years, in line with good clinical research practice).

Following informed consent, and immediately prior to the start of the interview, patients were reassured that they could stop the interview at any time if they felt uncomfortable or upset by the discussion. As each patient was interviewed only once, it was important patients felt at ease so that they engaged in more than a

question/answer session. MM was relatively unknown to patients (especially those of Unit A who were recruited by JMCL), so following informed consent, some time was spent chatting informally to patients prior to the interview proper in an effort to put patients at ease (Green and Thorogood 2004). A few very general questions were asked at the start of the interview to let the patient relax and become less conscious of the tape recorder. Thereafter a structured interview schedule (see Figure 11), using open questions was used, so that, as far as possible, each patient was asked the same questions in the same sequence in a similar manner, while allowing patients to give a full account of their symptom experiences in ways that were comfortable to them (Green and Thorogood 2004). Figure 12 (page 161) shows that the interview was entirely framed around the patient's symptom report and scores. Patients were asked to describe their experiences of symptoms across the range of scores they had reported and to describe what each symptom meant to them. They were also asked to describe the differences that they noticed between symptom scores physically, psychologically, and socially. Patients were asked to only reflect on their experiences of the previous cycle to ensure that they were commenting on symptom experiences that were fresh in their memories. Each interview was divided into discrete sections addressing firstly nausea, and then fatigue, and into individual questions about each symptom. This format aimed to keep the interview clear for patients with regards to the symptom being discussed and the specific issue about that symptom. Throughout each interview, MM tried whenever possible to avoid the 'why' question as it has been suggested that asking 'why' may imply that a person's response was somehow inadequate and may suggest that the researcher is doubtful that a feeling was justified (Patton 1990). Thus, less aggressive wording such as 'can you tell me more about that' was used to

probe deeper into patients' symptom experiences. At the end of the discussion of each individual symptom, patients were asked if there was anything they wanted to say about their experience of that symptom that had not been covered in the interview so far. At the end of the interview the patients were again asked if there was anything they wanted to add that had not been addressed. Following these questions, the patient was thanked for their contribution and time, the interview was concluded, and the tape recorder was switched off.

Figure 12: Patient interview schedule

Introduction and aims of the interview

Some general questions about the patient's story, moving into treatment and symptom experiences

Nausea

Lets look at this picture [showing the patient the symptom graph], can you describe your experiences of nausea during this last cycle of chemotherapy?

What did the nausea mean to you when it was at this score [score X]? Can you tell me a bit more about that?

How did you feel that day when you scored your nausea at [score X]?

How did that impact on your daily life?

Was there anything that you felt unable for that day because of the way you were feeling? (physically, psychologically, socially)

How does nausea at that score compare with nausea at these other scores? (using the symptom graph as a prompt)

In your opinion, what score of nausea is manageable or acceptable to you? Can you tell me a bit more about that?

Is there anything else that you want to say about your experiences of nausea that we haven't covered in what we've talked about so far?

Fatigue

Lets look at this picture [showing the patient the symptom graph], can you describe your experiences of fatigue during this last cycle of chemotherapy?

What did the fatigue mean to you when it was at this score [score X]? Can you tell me a bit more about that?

How did you feel that day when you scored your fatigue at [score X]?

How did that impact on your daily life?

Was there anything that you felt unable for that day because of the way you were feeling? (physically, psychologically, socially)

How does fatigue at that score compare with fatigue at these other scores? (using the symptom graph as a prompt)

In your opinion, what score of fatigue is manageable or acceptable to you? Can you tell me a bit more about that?

Is there anything else that you want to say about your experiences of fatigue that we haven't covered in what we've talked about so far?

Is there anything else that you want to add about your nausea or fatigue that we haven't talked about yet?

Interview conclusion and thanks

6.4.6.4 Qualitative data management

The tape recorded interview data was transcribed by MM. Transcribing audiotaped conversations is a translation process in itself, with choices of punctuation and detail affecting how it is read by those analysing it (Green and Thorogood 2004).

While transcribing is a time-consuming and laborious task, it provided MM with the opportunity to immerse herself in the data (Green and Thorogood 2004).

Furthermore, it allowed MM to produce transcripts that included additional non-verbal information such as pauses, sighing and laughing.

A number of dedicated software packages have been developed to help manage qualitative analysis. Such packages have both advantages (thorough and systematic analysis) and drawbacks (time consuming coding of data and formatting requirements) (Green and Thorogood 2004). However, given that the SNA↔P study involved only 9 structured interviews, such software would have most likely been cumbersome and time consuming to use. Instead, as the interviews were structured, framework analysis was used to analyse the interviews. Framework analysis is facilitated through the introduction of specific issues and themes into the interview which are subsequently sought out and identified in the analysis. As such, framework analysis provides a structured approach to the complex task of organising, analysing and presenting qualitative data (Huberman and Miles 2002).

6.5 Data analysis

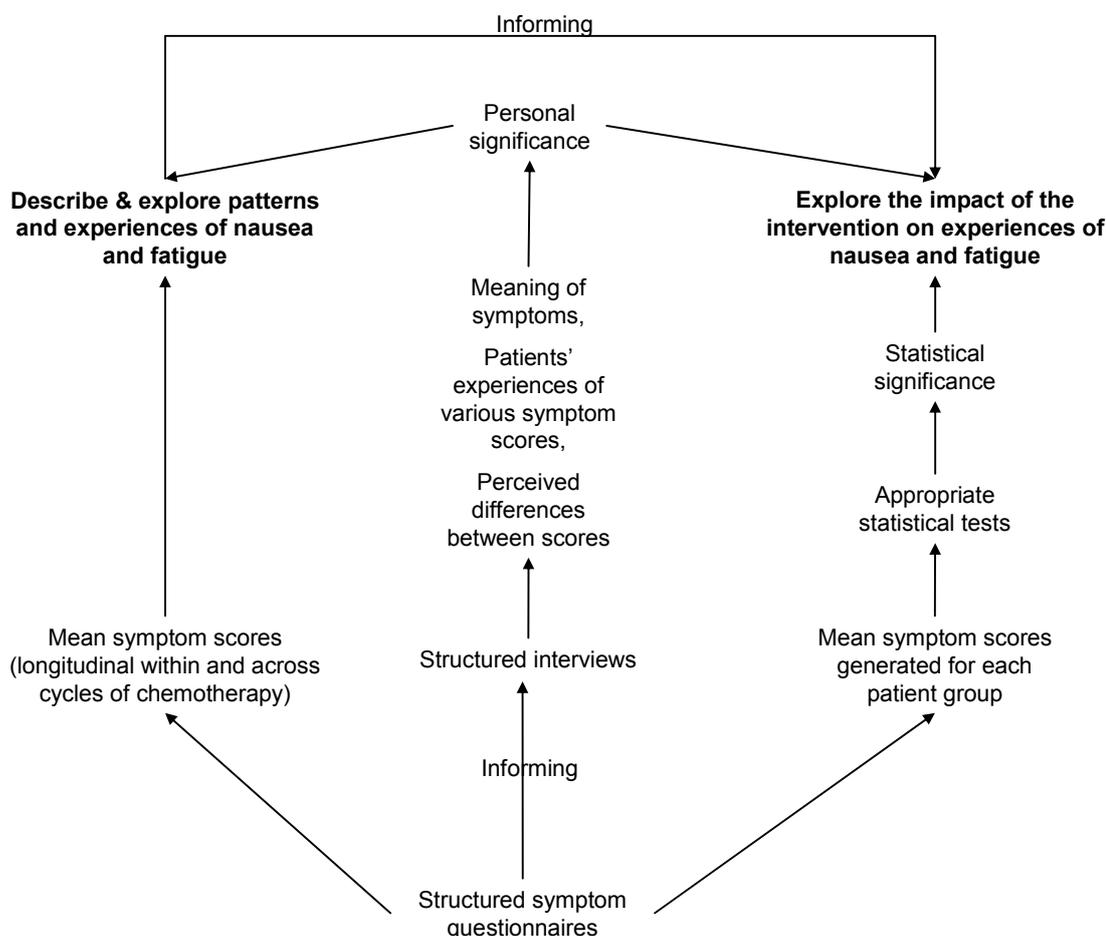
6.5.1 Analysis of confounding variables

Confounding variables for the total sample (age, deprivation and treatment intent) were compared between each of the four patient groups using the appropriate statistical techniques: ANOVA, Kruskal-Wallis and Chi-square tests. No analysis of confounding variables of the qualitative sample was undertaken, as this component of the study did not aim to compare between patient groups.

6.5.2 Analysis of quantitative and qualitative data

Figure 13 demonstrates how the quantitative and qualitative data were drawn together to answer the two distinct research aims: to describe and explore patterns and experiences of nausea and fatigue, and to explore the impact of the intervention on experiences of chemotherapy-related nausea and fatigue.

Figure 13: Complementarity of quantitative and qualitative data



6.5.2.1 Describing and exploring patterns and experiences of symptoms

To describe patterns of symptoms, the average of each symptom score for each day and each cycle of chemotherapy was calculated for all patients participating in the study. These mean scores were then plotted graphically for each day across all cycles of chemotherapy and patterns of both nausea and fatigue identified. These graphs highlighted the difference in patterns between nausea and fatigue and provided important information to enhance the statistical exploration of the SNA↔P intervention. During the interviews, the descriptions that patients gave of the meaning of symptoms and the impact that symptoms had on their lives were used to enrich the description of patterns and experiences of symptoms

6.5.2.2 *Exploring the statistical impact of the intervention*

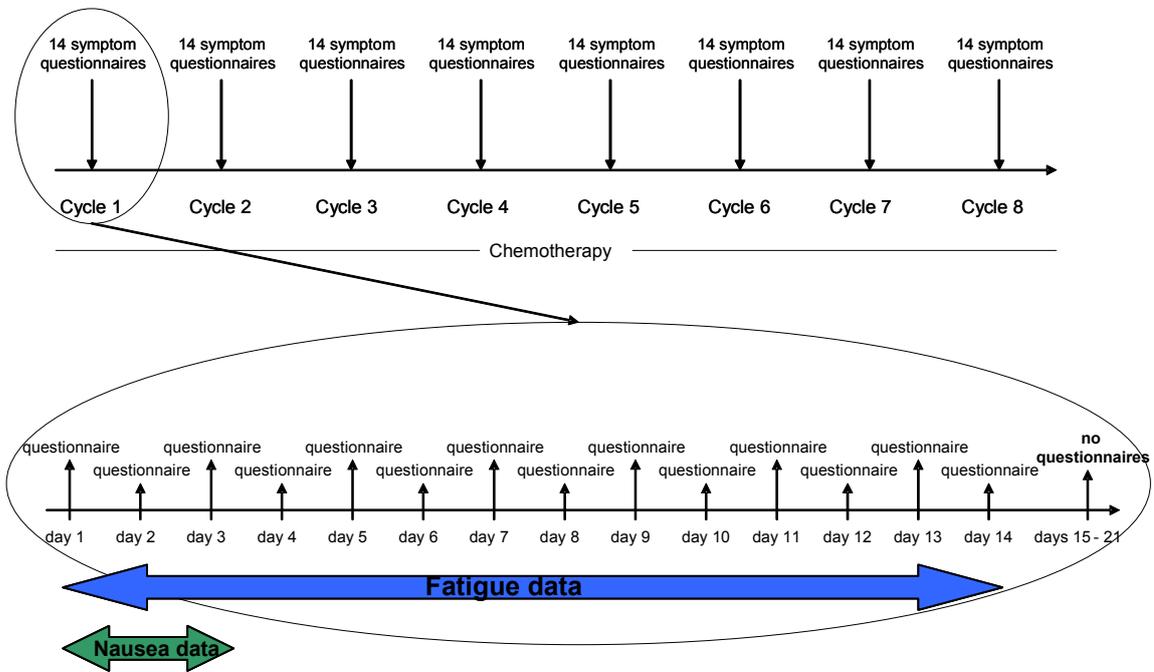
It was hypothesised that patients in cohort 2 of Unit A, that is, following the introduction of the SNA↔P intervention, would have statistically significantly lower symptom scores, thereby demonstrating the effectiveness of the intervention. To conduct this evaluation, a single summary statistic was generated for nausea and for fatigue for each individual patient participating in the SNA↔P study. The summary statistic chosen was the mean (the sum of all the values in the group divided by the number of values in the group) of the **total** symptom score (that is, including severity and distress). This value was chosen as it gives a typical or average symptom score. These summary statistics were then compared between the 4 patient groups:

- Unit A, cohort 1 (time control group)
- Unit A, cohort 2 (intervention group)
- Unit B, cohort 1
- Unit B, cohort 2 (site control group)

However, it is most appropriate to evaluate the impact of an intervention on a symptom at the time when the symptom is experienced most. Consequently, mean symptom scores were calculated following the identification of symptom patterns (see chapter 8 , Description of chemotherapy-related nausea and fatigue, page 213), thereby ensuring they were reflective of the times at which nausea or fatigue were experienced most. Consequently, the impact of the SNA↔P intervention on nausea was evaluated using data from days 1-3 only, while data from all 14 days was used

to evaluate the impact of the intervention on fatigue. Figure 14 demonstrates the use of specific data for quantitative analysis.

Figure 14: Selection of data for quantitative analysis



The frequencies of patients' mean symptom scores (range 0-6) across their course of chemotherapy was presented graphically, and chi-square analysis used to evaluate whether differences existed between patient groups in relation to the presence/absence of nausea and fatigue. Descriptive analysis using boxplots within SPSS examined the underlying distributions of the mean symptom scores within each of the 4 patient groups for each of the symptoms. Given that the data for all groups of patients for nausea were not normally distributed, the non-parametric Kruskal-Wallis test was used to explore differences between patient groups. Given the borderline level of significance from this test, an ANOVA was performed as it may have been more sensitive to differences in grades of nausea. The fatigue data for all patient groups was relatively normally distributed and an ANOVA was

conducted to compare mean fatigue scores between patient groups. The results of this statistical test were confirmed using the non-parametric Kruskal-Wallis test.

The personal significance of the intervention was evaluated using patients' interview data, in which they described their experiences of different symptom scores, that is, how did a fatigue score of 1 compare with a 2 or a 3 or no fatigue? This technique allowed a rounded evaluation of the intervention to be conducted; drawing conclusions that were not only based on statistical evaluations, but that also took account of patients' personal experiences of symptoms and the differences in symptom scores that are perceptible to patients. Such analysis meant that even if a statistically significant difference was established in mean symptom scores before and after the intervention, for example a mean score of 4 before compared with a mean score of 3 after, if patients could not personally differentiate between these scores in relation to their abilities or functioning, this difference would not be considered 'significant'.

6.6 Conclusion

This chapter has presented the methods used to evaluate the impact of the SNA↔P intervention on women's experiences of chemotherapy-related nausea and fatigue during a course of chemotherapy for breast cancer. It has shown that both quantitative and qualitative techniques have been used in a complementary fashion to evaluate the impact of the intervention, statistical and personal perspectives. Reference has been made throughout this chapter to the SNA↔P intervention and this is fully described in the following chapter.

7 CHAPTER 7 – THE SNA↔P INTERVENTION

7.1 Introduction

The aim of the SNA↔P study was to evaluate the impact of a nurse-led intervention incorporating structured nursing assessment and practice (SNA↔P) on women's experiences of chemotherapy-related nausea and fatigue during a course of chemotherapy for breast cancer. The intervention, implemented in Unit A, sought to influence the nursing management of chemotherapy-related nausea and fatigue, and so improve these symptoms. This chapter will provide full details of the aim of the intervention, its content, and implementation in clinical practice.

7.2 The aim of the SNA↔P intervention

The SNA↔P intervention provided a structured process for nursing staff to follow in their assessment of chemotherapy-related nausea and fatigue, as well as providing them with a framework of evidence-based interventions tailored to a range of symptom grades generated through the assessment process to support effective clinical practice. This continuous and structured process of assessment and intervention was implemented cyclically, and continued throughout each patient's course of chemotherapy.

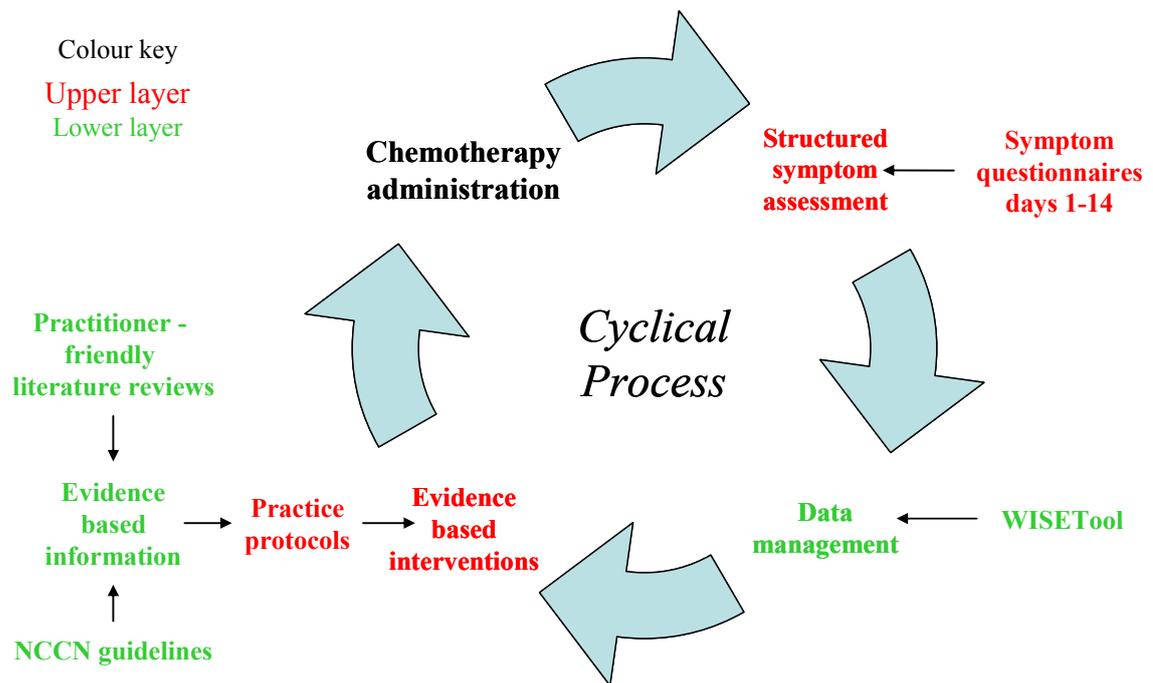
7.3 The component parts of the SNA↔P intervention

The SNA↔P intervention can be viewed as two distinct layers: an upper layer comprising structured patient assessment and evidence-based interventions, and a lower layer supporting these two components in relation to symptom data

management (the WISETool) and the provision of evidence-based information.

Figure 15 depicts the inter-relationships between the component parts of the SNA↔P intervention. The following sections describe the purpose and development of each of the component parts, as well as explaining their relationship to the other components of the intervention.

Figure 15: The inter-relationship of the component parts of the SNA↔P intervention



7.3.1 The upper layer of the SNA↔P intervention

The upper layer of the SNA↔P intervention consisted of structured symptom assessment and evidence-based interventions.

7.3.1.1 Structured longitudinal symptom assessment

Chapters 3 and 4 demonstrated the importance of symptom assessment, not only to gain an understanding of the symptoms experienced by an individual, but also to

evaluate the impact of an intervention on them. However, symptom assessment within routine clinical practice is beset by problems. The reasons for these problems are far reaching, including: the lack of patient-focused clinically useable symptom assessment tools, as shown in chapters 3 and 4; poor patient recall of symptoms over time; patients' reluctance to report symptoms (Stone et al. 2003); as well as the time pressures for clinicians (Davies et al. 2007). Consequently, patients' symptoms go unrecognised and untreated, ultimately reducing the patient's quality of life and potentially leading to the need for urgent medical care or hospitalisation (Du et al. 2002; Polednak 2004; Chen-Hardee et al. 2006; Kuderer et al. 2006).

The structured symptom assessment of the SNA↔P intervention differed from 'traditional' symptom assessment in its longitudinal nature. Previous research has considered longitudinal symptom assessment as: longitudinal during a single cycle of chemotherapy (Richardson et al. 1998); over cycles 1 and 2 of chemotherapy (Dibble et al. 2003; Lee et al. 2005); over cycles 1-3 of chemotherapy (Berger 1998; Schwartz 2000); baseline, 3 months into chemotherapy and at 6 months (Payne 2002); before chemotherapy, on completion of chemotherapy and six months post chemotherapy (Hurria et al. 2006); or longitudinally over multiple cycles but for a shorter period within cycles, for example 48 hours (Rhodes et al. 1987; Rhodes et al. 1988). However, these timeframes are based on arbitrary decisions and provide limited insight into the true longitudinal symptom experience. In contrast, the longitudinal symptom assessment of the SNA↔P study was not only longitudinal within each cycle of chemotherapy, spanning days 1-14, it was also longitudinal across a course of chemotherapy, with patients asked to participate for the entire duration of their chemotherapy treatment. Such assessment of symptoms had value, not only for the exploration of symptom patterns over time, but also because the

intervention may have required time to build up before having a measurable impact on patients' symptom scores.

The SNA↔P intervention sought to overcome the many problems of symptom assessment in clinical practice. Understanding the gold-standard of self-assessment of symptoms as well as the need for multidimensional symptom assessment at the time of symptom experience, symptom assessment within the SNA↔P intervention involved a structured symptom questionnaire that was completed by patients in the evening of each day for 14 days following each cycle of chemotherapy (see Appendix B). This method of data collection provided nursing staff with longitudinal symptom information both within each cycle of chemotherapy and across each patient's course of chemotherapy. As shown in chapter 6 – Method, the symptom questionnaire presented patients with a range of options to describe their symptoms and, according to the patient's response, a score was assigned (see Figure 16).

Figure 16: Symptom scores

Nausea ...

Have you experienced this today? Yes No

If yes, how severe was this?

Mild **1** Moderate **2** Severe **3**

How much did it bother you?

Not at all **0** A little **1** Quite a bit **2** Very much **3**

Thus, patients could have a symptom score ranging from 0-6 for each symptom. However, the interventions were tailored to symptom grades based on these symptom scores. This decision was taken because it was unlikely that there would be a substantial difference in the interventions required for, for example, a nausea score of 1 or 2, or a fatigue score of 3 or 4. Consequently, the symptom scores generated from symptom questionnaires were graded mild, moderate or severe, implementing the same process as the NCCN, whereby fatigue scores (0-10) were assigned to a fatigue grade (none, mild, moderate, severe) (National Comprehensive Cancer Network 2007b). Table 17 shows the symptom descriptors that could comprise each score and the subsequent grade given to that score.

Table 17: SNA↔P intervention: symptom descriptors, scores and grades

Descriptors		Symptom score	Symptom grade
Severity	Distress		
---	---	0	No nausea/fatigue
Mild	Not at all	1	Mild nausea or fatigue
Mild Moderate	A little Not at all	2	
Mild Moderate	Quite a bit A little	3	Moderate nausea or fatigue
Mild Moderate Severe	Very much Quite a bit A little	4	
Moderate Severe	Very much Quite a bit	5	Severe nausea or fatigue
Severe	Very much	6	

The symptom scores and subsequent grade of symptom were used within the second component of the upper layer of the SNA↔P intervention: evidence-based interventions.

7.3.1.2 Evidence-based interventions

Practice protocols for nausea and fatigue recommending evidence-based interventions, and structured around the symptom assessment and grading systems detailed above, were developed by MM. Given that the practice protocols were to be used in daily clinical practice, they were succinct and comprised mainly of flow

diagrams and figures to make them user-friendly and easy to follow (see Appendices G and H).

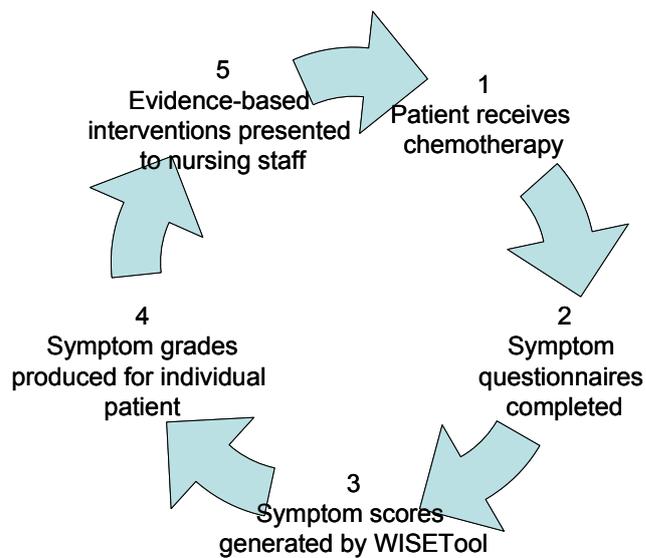
The practice protocols were developed following an extensive review of the literature concerning chemotherapy-related nausea and fatigue. The protocols presented a summary of the baseline assessment required for nausea or fatigue (using the structured symptom questionnaire) and then outlined both assessment and interventions for the various grades of symptoms. Finally, they presented a figure outlining the process of reassessment and interventions intended to continue throughout the patient's course of chemotherapy. Both practice protocols also included an appendix section comprised of additional, but brief, information that nurses might find useful in managing symptoms, for example factors to aid sleep in relation to fatigue, or a script for guided imagery in the management of nausea.

Following their development, each of the practice protocols was evaluated by three expert cancer nurses in the field (of nausea or fatigue) who were asked to comment on their content and presentation, and three clinical cancer nurses from Unit A who were asked to consider, not only the content of the protocols, but also the feasibility of implementing them in practice. The feedback from both expert and clinical cancer nurses was positive with respect to content and presentation, and no further recommendations were made. However the clinical nurses raised concerns about the practicalities of implementing some of the recommended non-pharmacological interventions, such as relaxation and guided imagery, explaining that the nurses in Unit A had neither the time nor expertise to successfully carry out these interventions. MM worked with the nurses to enable them to see that, although the intervention was nurse-led, contributions from other members of the

multidisciplinary team were essential. Consequently, the nurses approached the clinical psychologist for the area, who produced relaxation and guided imagery audiotapes for nurses to give to patients for use both in hospital and at home.

Thus, the upper layer of the SNA↔P study intervention (seen in Figure 17) utilised symptom grades (based on patient's symptom questionnaires) to recommend evidence-based assessment and interventions (contained in the practice protocols). This process was implemented for every patient involved in the intervention site of the SNA↔P study.

Figure 17: Upper layer of SNA↔P intervention



7.3.2 The lower layer of the SNA↔P intervention

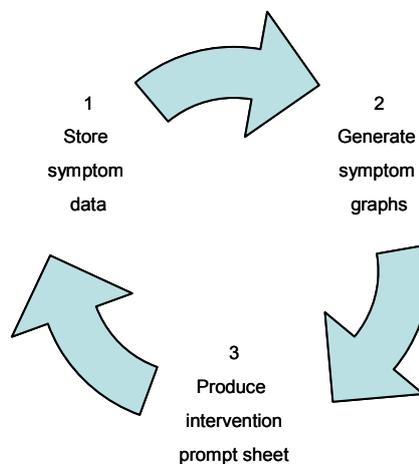
The lower layer of the SNA↔P intervention consisted of the WISETool and evidence-based information. While the intervention could be implemented by practitioners without using the WISETool by manually calculating symptom scores and grades or referring to the evidence-based information, both these components

added value to the intervention. The WISETool enhanced the intervention by visually presenting both symptom and intervention information in a way that enhanced communication and prompted use of the practice protocols, while the evidence-based information ensured that the background information was available to support the interventions recommended within the practice protocols.

7.3.2.1 *The WISETool*

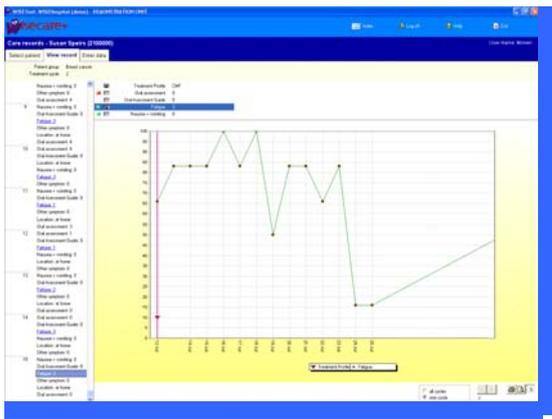
The WISETool was an electronic patient record/database, that could be uploaded to any PC, that was originally developed for use within the WISECARE+ study. It had three key related functions that were important to the SNA↔P intervention (see Figure 18).

Figure 18: Key WISETool functions

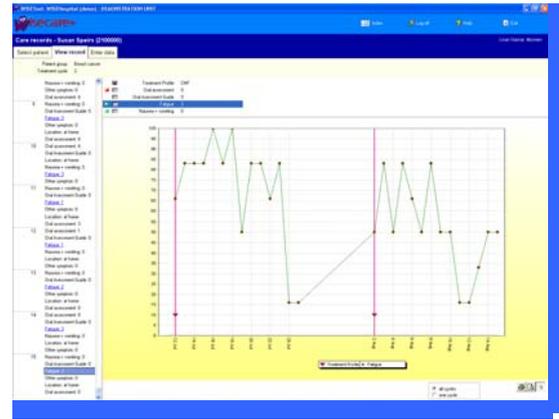


Firstly the WISETool recorded and stored each patient's symptom experiences from their symptom questionnaires. Based on the data entered, it then provided symptom graphs of each patient's symptom scores/experiences for each cycle of chemotherapy, as well as across all cycles of chemotherapy (see Figure 19).

Figure 19: WISETool symptom graphs



One symptom over one cycle of chemotherapy



One symptom over two cycles of chemotherapy

Finally, based on these symptom scores, it supplied an intervention prompt sheet, shown in Figure 20, that summarised, in colour, the patient's symptom experiences for their most recent cycle of chemotherapy, and provided recommendations for interventions appropriate to the symptom score reported by the patient. These recommendations linked directly to the practice protocols.

Figure 20: SNA↔P intervention prompt sheet

Patient Name:	Joe Bloggs
Diagnosis:	Breast cancer
Chemotherapy:	EPI/CMF
Worst symptom scores this treatment cycle (6)	
Nausea – 2 (Mild/moderate)	
Fatigue – 5 (Severe)	
Recommended nursing interventions	
Nausea	
Re-evaluate anti-emetic therapy	
Evaluate compliance with anti-emetics	
Provide education and counselling	
Provide information about foods to eat and avoid	
Encourage use of coping strategies	
Consider non-pharmacological methods of management	
Fatigue	
Check for anaemia	
Education re causes of fatigue	
Give advice on coping strategies	
Suggest distraction and exercise	
Provide stress management techniques	
Give advice re sleep patterns	
Give advice re adequate nutrition/refer to dietician	

While the WISETool was developed by a software expert (Derek Hoy, see preface), MM contributed substantially to the design of the tool, ensuring it could perform the three functions detailed above, was easy to use, and produced outputs that were clinically meaningful. MM also worked with the nursing staff involved in the SNA↔P study to ensure their views on the tool were taken into consideration. Their major concern was the time taken for data entry to the WISETool. Consequently, all

patient symptom questionnaires were barcoded and a barcode reader used to enter patients' symptom data. This process of data entry not only substantially reduced data entry time, but also reduced the potential for error in the data entry process.

The symptom graphs and intervention prompt sheets were printable directly from the WISETool. They were routinely printed and clipped to the front of the patient's casenotes for review by their chemotherapy nurse when they returned for their next cycle of chemotherapy. This procedure meant that it did not need to be the same nurse to enter the data and see the patient at their next cycle of chemotherapy.

7.3.2.2 Evidence-based information

Practitioner-friendly literature reviews on chemotherapy-related nausea and fatigue were developed as part of the SNA↔P intervention. While evidence from the healthcare literature should be integral to clinical decision-making (Lewis 2007), it is all too easy for current best available evidence to pass clinicians by (Lewis 2007; Davies et al. 2007). Indeed, clinicians often lack the time, motivation and appropriate skills required to find, critically appraise, and synthesise information, all of which are necessary if best available evidence is to be integrated in current practice (Davies et al. 2007). Literature reviews, however, provide clinicians with the opportunity to interpret and apply research evidence in practice.

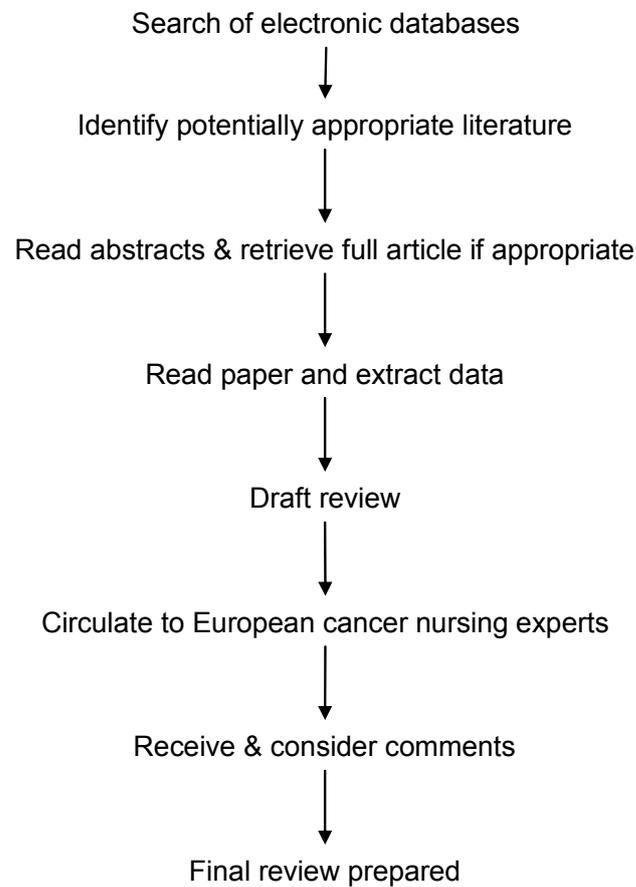
Although systematic reviews that include only evidence from randomised controlled trials are considered the gold-standard for evaluating healthcare interventions, such reviews of the literature were not undertaken in the SNA↔P study, as randomised controlled trials are rarely used within the field of cancer nursing because they are not always the best or only way to explore nursing issues. Thus, excluding non-

randomised controlled trials would have resulted in an extremely small sample size and potentially failed to draw meaningful conclusions about the evidence for practice.

The aim of the practitioner-friendly literature reviews was to provide clinicians with a broad description of nausea and fatigue, as well as an evaluation of assessment and management opportunities. These literature reviews provided support for the evidence-based interventions contained within the practice protocols and allowed practitioners to easily identify the evidence that supported the practice protocols. It was hoped that by presenting the evidence in this way, any potential criticisms of the protocols would be overcome, such as those levied at guidelines, describing them as cookbook medicine and resenting their prescriptive nature (Graham et al. 2000; Timmermans and Mauck 2005). In recognition of the pitfalls of descriptive and uncritical reviews and to minimise error and bias, principles of systematic review were used to guide the review, namely systematic, explicit, thorough, and rigorous searching.

The process and criteria for the reviews was developed by MM and agreed upon by the WISECARE+ Steering Group. MM conducted the literature reviews and implemented the same structured process for both nausea and fatigue. This process involved identifying the questions for the literature reviews, sampling the literature to be reviewed, representing the characteristics of the studies and their findings, analysing findings, interpreting results and reporting the review (Ganong 1987). The process for the development of the literature reviews is presented in Figure 21.

Figure 21: Process of developing literature reviews



The inclusion/exclusion criteria for the literature that would be included in each review is presented in Table 18. Limiting the literature to that published between 1980 and the time of the review (2002) ensured that all relevant evidence was included. Extending the type of literature that could be included in the review to include letters and reports extended the range of evidence included in the review.

Table 18: Inclusion/exclusion criteria for literature reviews

Inclusion criteria	Exclusion criteria
Published between 1980-present time (2002) (inclusive)	Papers addressing symptoms and management within the paediatric setting
Primary research, literature reviews or other documents, such as letters, reports or commentaries relating to the symptom	

The electronic database search was based on keywords and search terms found in Appendix I. Keywords were initially generated by MM and circulated to the WISECARE+ Steering Group for additions, of which there were few. The databases searched were: CINAHL, MEDLINE, PsychLit, British Nursing Index and Embase. Searching these varied databases ensured that literature was identified from a range of disciplines, thereby ensuring the review presented as complete a perspective of each symptom as possible. As shown in Figure 20 above, abstracts of potentially appropriate papers were read, and if they met the inclusion criteria, the full article was retrieved. The reference lists of retrieved papers were examined and further relevant articles were identified. Reading and data extraction continued until each review was constructed. A copy of each draft review was sent to a cancer nursing expert in that field (either nausea or fatigue) within Europe. These individuals were asked to comment on the review with respect to content, presentation and any omissions noted with regards to key papers. This process identified a small number of additional papers. The final reviews (see Appendices K and L) were comprehensive and presented extensive evidence to guide practice.

Given that nurses in Unit A would have limited time in which to read the extensive literature reviews, a summary of each was prepared by MM. These summaries (see Appendices L and M) followed the same outline as the full reviews, but were considerably shorter and provided summarised evidence to support the interventions recommended within the practice protocols.

In tandem with the literature reviews and their summaries, established guidelines for nausea and fatigue were also included in the evidence-based information received by the nursing staff in Unit A. The guidelines chosen for dissemination were developed by the National Comprehensive Cancer Network (NCCN), an alliance of 19 of the world's leading cancer centres, which develops, updates and disseminates a library of clinical practice guidelines that have become the most widely used in clinical practice (www.nccn.org). Permission was sought and granted from the NCCN to include the guidelines for antiemesis and fatigue (see appendices N and O) within the WISECARE+ and SNA↔P interventions. However, although these guidelines meet the criteria for excellence in their development and composition, they are lengthy and cumbersome, and as such, were compromised in their usefulness within the realities of a busy clinical setting. Ultimately, they were used in the SNA↔P intervention as a valuable source of information, supporting both the literature reviews and practice protocols.

Thus, the SNA↔P intervention was comprised of a number of inter-related components: structured symptom assessment; evidence-based interventions; the WISETool; and evidence-based information, each of which played a greater or lesser role in the implementation of the intervention. The following section

describes the range of techniques and approaches undertaken to implement the SNA↔P intervention in clinical practice.

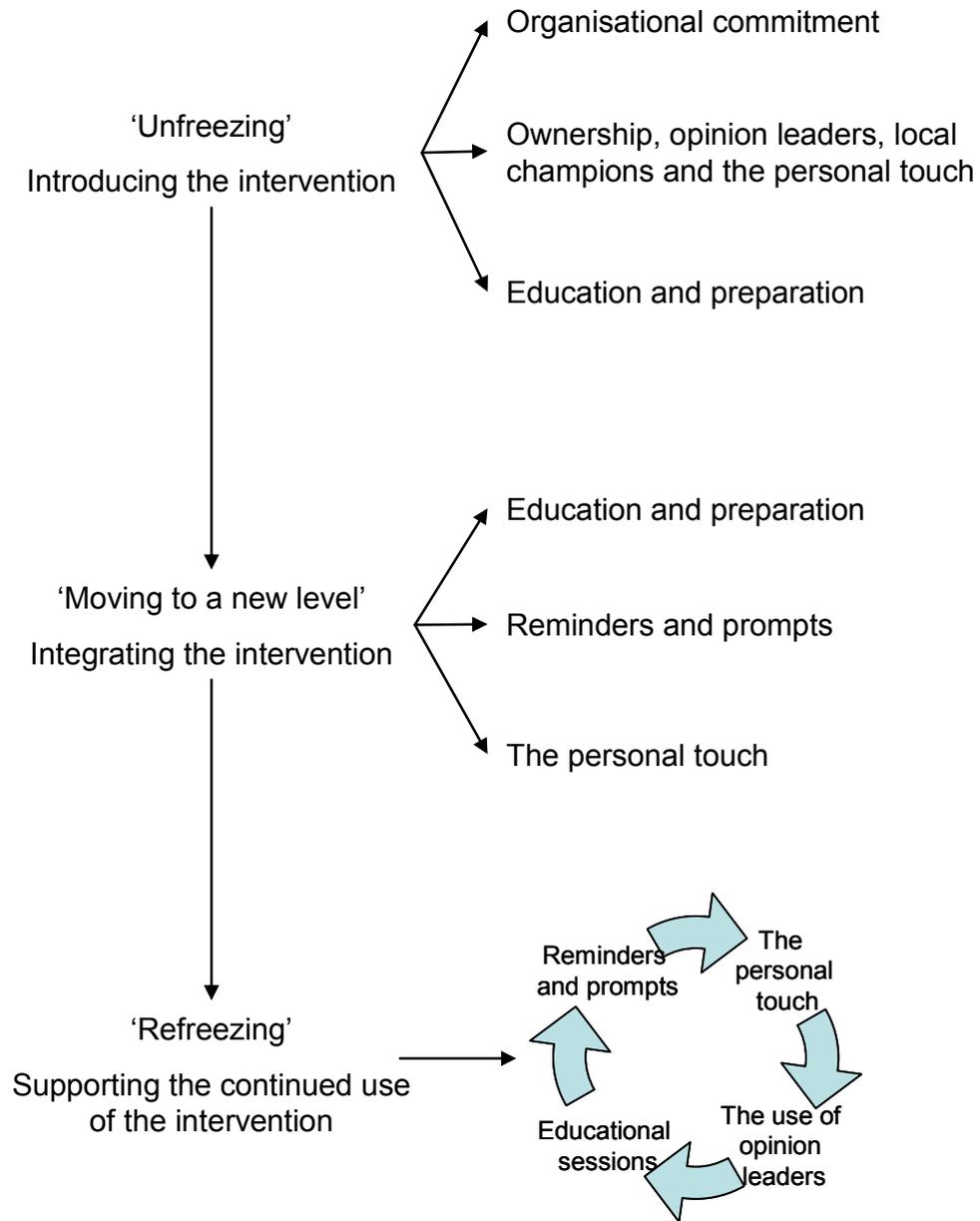
7.4 Implementing the SNA↔P intervention

Lewin, one of the original theorists to study the process of change and its impact on individuals, departments or organisations, identified three distinct phases through which individuals progress when presented with change: unfreezing; moving to a new level; and refreezing (Lewin 1951). These three phases were useful to describe the process through which nursing staff passed during the implementation of the SNA↔P intervention. Unfreezing, a process which occurs when a change is first introduced and which can leave the individual feeling threatened, uncomfortable and anxious, related to the introduction of the SNA↔P intervention to the nursing staff. The SNA↔P intervention meant they had to modify their current process for assessing and managing two common symptoms associated with chemotherapy. Moving to a new level begins when the change is incorporated into the normal process for an organisation, department or individual, and represents the phase where the SNA↔P intervention was integrated into the practice of the nursing staff from Unit A. During this stage the individual feels more comfortable and in control of the situation. Finally, refreezing occurs when the change is permanently incorporated into normal daily operations. At this stage in the process, if the change was taken away, individuals would resist, as it has become part of their identity.

While this theory of change was helpful in providing insight to the various phases involved in implementing the SNA↔P intervention and the perceptions of the nursing staff as they moved through these different phases, it did not provide

specific pointers as to appropriate techniques to facilitate this change. Although not a guideline per se, the SNA↔P intervention did provide a structured process for nursing staff to follow in their assessment and management of nausea and fatigue. Thus, the literature concerning the implementation and utilisation of clinical guidelines was a valuable source of information to guide the implementation of the SNA↔P intervention in practice. Key techniques for the successful implementation of guidelines have been identified as: organisational commitment; raised awareness of the rationale for the changes among those on whom the guideline will impact; dissemination, education and preparation of staff about the nature and content of the guideline; support of practitioners, including outreach work such as provision of information and feedback; leadership, the use of local opinion leaders and the personal touch to champion the guideline; reminders, and the audit and feedback of the results (Duff et al 1996). Each of these techniques was appropriate for at least one of the phases of implementing the SNA↔P intervention into clinical practice as shown in Figure 22.

Figure 22: Implementing the intervention - processes and techniques



Each of these key phases will now be considered.

7.4.1 Introducing the SNA↔P intervention to clinical practice

Introducing the SNA↔P intervention required organisational commitment, creating a sense of ownership using opinion leaders and local champions, and education and preparation.

7.4.1.1 Organisational commitment

The support of the organisation is essential for a change in practice to be implemented as organisational resources must be committed to any necessary support systems that result as a consequence (Ockene and Zapka 2000).

Furthermore, micromanagement may also be necessary by a core team who should be available to troubleshoot on a daily basis (Katterhagen 1996).

MM met with the senior nursing staff responsible for Unit A on several occasions before its involvement in the SNA↔P study was agreed. During these meetings she explained the aims of the study, the role of nursing staff within it, and the benefits of being involved in the study, while answering the questions and concerns of senior management. Following senior management approval, a smaller group of nursing staff who would have day-to-day responsibility for the SNA↔P study was convened. This included MM, JMCL (the research support nurse based in Unit A), the ward sister, and two senior staff nurses from Unit A. MM gave them all a full explanation of the aims and processes of the SNA↔P study and the intervention, and answered their concerns, which focused primarily on the time involved in participating in the SNA↔P study.

7.4.1.2 Ownership – using opinion leaders, local champions

It was important that the nursing staff of Unit A felt a sense of ownership and contribution to the SNA↔P intervention that would encourage them to implement it in their practice. The process used to engender this sense of ownership was ‘localisation’ of the intervention, which involves accommodating any particular requirements of the local area in which it is to be implemented (Duff et al. 1996),

while ensuring that this fine-tuning process does not reduce the validity of the intervention (Mead 2000).

As highlighted above, MM worked with the nursing staff during the initial introductory phase to overcome their concerns about guided imagery and relaxation. Developing links with the Unit psychologist not only accommodated the requirements of the Unit, but also encouraged new ways of multidisciplinary working. Furthermore, MM acknowledged the nurses' concerns about the time consuming nature of data entry to the WISETool and developed a barcoding system that both reduced the time and potential for errors associated with the data entry process.

Much of this work was conducted within the micromanagement team who were respected, senior members of the nursing staff in Unit A. Their involvement was important as the use of opinion leaders or local champions has been shown to increase the uptake of a change in practice (Battista 1991; Davis and Taylor-Vaisey 1997; Schriefer and Botter 2001). The micromanagement team worked informally during this initial period of introducing the SNA↔P intervention to allay any concerns that more junior members of the nursing staff had, and indeed, it was hoped that these nurses would find it reassuring that the senior staff of the Unit were integral in the introduction of the intervention.

7.4.1.3 Educational preparation

At a local level, active educational approaches appear to be more effective than printed materials for communicating changing practice (Cheater and Closs 1997; Davis and Taylor-Vaisey 1997; Thomas et al. 1999). Indeed, group discussion or

workshops that facilitate a more interactive approach have been shown to be more effective than the traditional lecture in producing behaviour change (Moulding et al. 1999). The objectives of such education include: improving awareness of the intervention and its supporting evidence; beliefs about appropriateness, effectiveness and feasibility; and ensuring that practitioners have the necessary skills to implement the intervention (Ockene and Zapka 2000).

The educational sessions to introduce the SNA↔P intervention at Unit A were led by MM, supported by JMcL and the micromanagement team. A range of convenient times (usually at the start or end of nursing shifts) were set within a period of one week, and invitations were extended to all the nursing staff of Unit A, as well as the senior nursing management (as it was hoped that the presence of senior management at some or all of these sessions would demonstrate their support for the SNA↔P study). These education sessions were informal and set out to introduce the intervention to the nursing staff. Nurses were encouraged to contribute and comment as they felt appropriate. Each component of the intervention: symptom assessment; evidence-based interventions; the WISETool; and the evidence-based information, was discussed, and its respective role in the intervention described. Each component was also circulated around those present and nurses had the opportunity to test the WISETool. A fictional scenario was used to demonstrate how the intervention would be implemented in practice and a dummy WISETool was installed on the ward PC to allow nurses to familiarise themselves with the processes of data entry, symptom graphs and intervention prompt sheets.

Approximately one week later, giving nursing staff the opportunity to reflect on the intervention and discuss it amongst themselves, a second meeting was held between

the micromanagement team and the nursing staff of Unit A. The aim of this meeting was to gain nurses' perceptions about the intervention and answer any questions that they had about it. Senior nursing management were not invited to this meeting as this may have stifled nurses' comments. Overall, the nurses accepted the intervention and were happy to start the process of integrating it into clinical practice.

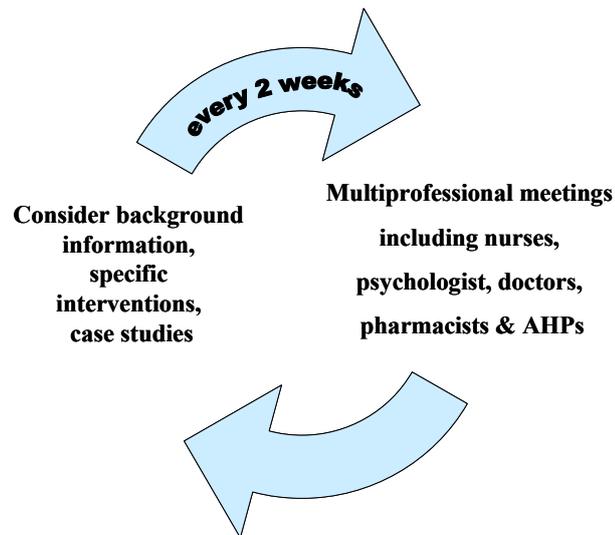
7.4.2 Integrating the SNA↔P intervention into practice

Integrating the SNA↔P intervention into clinical practice involved educational preparation, reminders and prompts, and the personal touch.

7.4.2.1 Educational preparation

MM proposed an educational model to promote the integration of the SNA↔P intervention into clinical practice. This model was discussed during the initial educational sessions with nursing staff and aimed to ensure a sense of ownership in the integration of the intervention into practice. This model of education involved the use of local champions (the two senior staff nurses from the micromanagement team) to lead the integration of the intervention for nausea and for fatigue, shown in the literature to be important in the integration of change (Davis and Taylor-Vaisey 1997; Thomas et al. 1999). Furthermore, the model acknowledged the need for continual education to keep the intervention alive in the minds of the nursing staff and to maintain enthusiasm and motivation for implementing it in practice. The nurses from Unit A were asked to consider the proposed educational model and, if they wished, to develop a model of their own. The nurses, however, willingly accepted the model developed and presented by MM (see Figure 23).

Figure 23: Educational model



This model ensured that on a two-weekly basis there was a meeting of nursing staff led by a member of the multidisciplinary team who would present an educational session on an aspect of nausea or fatigue, such as background information, specific interventions or a case study of a particular patient. It was believed that to make these session any more frequent would have resulted in fewer staff attending, and making them any less frequent would have allowed the SNA↔P intervention to fade into the minutiae of daily clinical practice. The two senior staff nurses (from the micromanagement team) leading either nausea or fatigue were respected members of the multidisciplinary team and had a particular interest in nausea and fatigue. Their initial education session involved repeating the intervention for each symptom and, thereafter, they were supported by MM and JMcL to develop a programme of educational sessions that presented the multiprofessional perspective of the assessment and management of both nausea and fatigue.

7.4.2.2 Reminders and prompts

Reminders, such as posters and laminated pocket sized cards or reminder sheets, have been shown to be effective in augmenting the uptake of a new intervention in practice (Davis and Taylor-Vaisey 1997). Harnessing new technology and generating computerised prompts is becoming an increasingly frequent and effective strategy (Thomas et al. 1999; Duff and Casey 1999). The use of computer prompts has also been highlighted in an effort to increase the clinical use of an intervention (Feder et al. 1999).

A range of reminders and prompts were used within the SNA↔P study to integrate the intervention in clinical practice. The lack of funding meant that the use of costly reminders such as mugs, pens and post-it notes were not possible. However, brightly coloured stickers were made for patients' medical and nursing casenotes alerting health professionals to the fact that the patient was participating in the SNA↔P study. The practice protocols were colourful and so were easy to identify in the nursing folders located outside each of the 4 bedded chemotherapy bays. Coloured posters just above the nurses' desk outside each chemotherapy bay also reminded staff of the SNA↔P study.

Electronic intervention prompt sheets were generated when patients' symptom data was entered to the WISETool. This colour-coded electronic prompt provided information, not only concerning the patient's grades of symptoms, but also the most appropriate interventions for those symptom grades. This prompt could be printed directly from the WISETool, and nurses entering patient data were encouraged to do this, clipping it to the front of each patient's casenotes to guide

appropriate symptom management when the patient attended for their next cycle of chemotherapy.

Carefully considered placement of the practice protocols around Unit A also acted as a reminder for nursing staff. A copy of each practice protocol was stored alongside frequently used local nursing guidelines and policies for symptom management, such as the policies for pain and constipation, in each of the chemotherapy bays. It was felt that storing the practice protocols there would be useful, as nurses regularly referred to these policies in their daily planning of patient care, and so would be reminded of their use for practice. As well as locating the practice protocols in chemotherapy bays, both the practice protocols and the evidence-based information were placed, along with the literature concerning symptom management, in the ward sister's office. It was appropriate to locate the evidence-based information here, as this was the literature that the nursing staff used to obtain further information about symptoms and their management. The summary literature reviews were also located with the professional literature found in the nurses' staff room in the chemotherapy Unit. It was envisaged that this careful placement of the various components of the SNA↔P intervention would subtly remind nursing staff of the SNA↔P study and the intervention, so facilitating its integration into the nursing practice of Unit A.

7.4.2.3 The personal touch

Personal contact in conjunction with other dissemination methods is important in the implementation of a change in practice (Grol 2001). As the SNA↔P intervention was taking place in a single chemotherapy Unit, face-to-face contact between the micromanagement team and the nursing staff was possible.

As researcher for the SNA↔P study, MM was removed from the clinical setting. However, her presence at the education session, both during the introduction of the intervention, as well as occasional informal visits to the Unit and visits to conduct patient interviews, meant that she was often on hand to discuss the study and address any queries that nursing staff had about various aspects of the SNA↔P study. Also, as she had previously worked clinically in the hospital of Unit A (although not Unit A itself) she knew, and was known to, a number of the nursing staff. This eased the process of communication in both directions.

JMcL was a respected member of the senior nursing staff who had worked in cancer care for a number of years. She had a constant presence in Unit A as she was responsible for patient recruitment and local co-ordination. This meant she was on site to ensure the smooth day-to-day management of the study and troubleshoot, if necessary. Minor problems, such as computer or printing problems that could have impacted on the conduct of the study, were always promptly resolved. This gave nursing staff confidence in the day-to-day conduct of the SNA↔P study and encouraged their involvement.

The involvement of the senior staff nurses, who also led each of the symptom education sessions, lent further credibility to the SNA↔P study and its intervention. As they, too, were a constant presence within Unit A, they were available to nursing staff if issues arose with the intervention that staff were unsure about. Their involvement in implementing the study in their clinical practice meant they also fulfilled a role model function for the intervention's integration into practice.

Thus, while educational preparation, reminders and prompts and the personal touch all ensured that the intervention was successfully integrated into practice, maintaining this change in practice required moving the nurses to the third phase of Lewin's process of change: refreezing – where the change is permanently incorporated into normal daily operations (Lewin 1951).

7.4.3 Maintaining the SNA↔P intervention in clinical practice

Local implementation strategies shown to be effective in maintaining change in clinical practice include: educational materials; educational outreach; audit and feedback; reminders; and opinion leaders (individuals identified as influential by their peers) (Cheater and Closs 1997; Moulding et al. 1999). Four specific strategies were put in place during the intervention phase of this study to support the continued use of the intervention in practice in Unit A. These strategies were: the educational sessions; the use of opinion leaders; prompts and reminders; and the personal touch. Detail concerning each strategy is presented below.

7.4.3.1 Educational sessions

Educational session for nausea and fatigue run by the senior staff nurses involved in the micromanagement team continued to take place on a two-weekly basis. These were informal, multidisciplinary sessions during which more information was presented about specific interventions included in the practice protocols. These sessions were led by the most relevant member of the multidisciplinary team, depending on the subject of concern, and aimed to provide more in-depth understanding of the interventions. These sessions were purposefully short (maximum 30 minutes) to encourage attendance, and followed an interactive

format, encouraging questions from those present and discussion of particular instances in which the intervention under discussion could have been, or was, used. When possible, MM was present at these sessions and occasionally gave a short informal summary of recruitment and some descriptive results of symptom patterns. Thus, these sessions not only increased awareness of evidence-based multidisciplinary interventions, but also aimed to encourage and motivate nursing staff in relation to the study in general. It also gave the nursing staff the opportunity to ask MM questions and highlight any issues in relation to implementing the intervention clinically.

7.4.3.2 The use of opinion leaders

Opinion leaders were crucial for sustaining the use of the intervention in practice. The presence of JMcL around Unit A, as well as the senior staff nurses from the micromanagement team was important for maintaining the profile of the intervention; furthermore, they all acted as acting as role models for more junior staff. These nurses were also able to address any problems as they arose.

7.4.3.3 Reminders and prompts

The reminders and prompts of the integration strategy described above continued to be used. Ensuring the practice protocols and intervention prompt sheets were easily accessible and highly visible was important in maintaining their use in practice. The education sessions led by the senior staff nurses also served to remind staff of the study in general, as well as specific interventions.

7.4.3.4 The personal touch

The local opinion leaders lent a personal touch to the SNA↔P study and the intervention. The availability and presence of both JMcL and the senior staff nurses served to keep the intervention in the forefront of nurses' minds. That these senior nurses were involved in the day-to-day use of the intervention gave it credibility and encouraged the nursing staff to continue with their use of it across time. MM's frequent presence in Unit A also demonstrated the researcher's commitment to the study and intervention to the nursing staff there.

7.5 Conclusion

This chapter firstly described the aim of the SNA↔P intervention before demonstrating the significant amount of development work invested by MM in the construction of the intervention. Each component of the intervention was described in detail and their inter-relationships demonstrated. The extensive range of techniques and approaches undertaken by MM and the micromanagement team to introduce, implement and maintain the implementation of the intervention in clinical practice were subsequently presented. It is unfortunate that the SNA↔P study did not evaluate the success of the implementation of the SNA↔P intervention. Neither was such an evaluation undertaken within the WISECARE+ study from which the SNA↔P study arose. This lack of insight complicates the evaluation of the impact of the various components of the intervention. Further discussion of this limitation of the SNA↔P study is found in chapter 9.

However, the implementation of the SNA↔P intervention was not an end in itself. The purpose of implementing the intervention was to improve women's experiences

of nausea and fatigue during a course of chemotherapy for breast cancer. Thus, one can question whether the intervention was successful in achieving this aim. The impact of the intervention on symptom experiences is fully evaluated in the following chapter.

8 CHAPTER 8 – RESULTS OF THE SNA↔P STUDY

8.1 Introduction

This chapter reports on the results of the SNA↔P study which utilised a quasi-experimental interrupted time-series design with a control group. The study hypothesised that the implementation of a nurse-led intervention would improve women's experiences of chemotherapy-related nausea and fatigue during a course of chemotherapy for breast cancer. Both quantitative and qualitative research methods, detailed in Chapter 6, were undertaken to address the 2 distinct aims of the SNA↔P study which were:

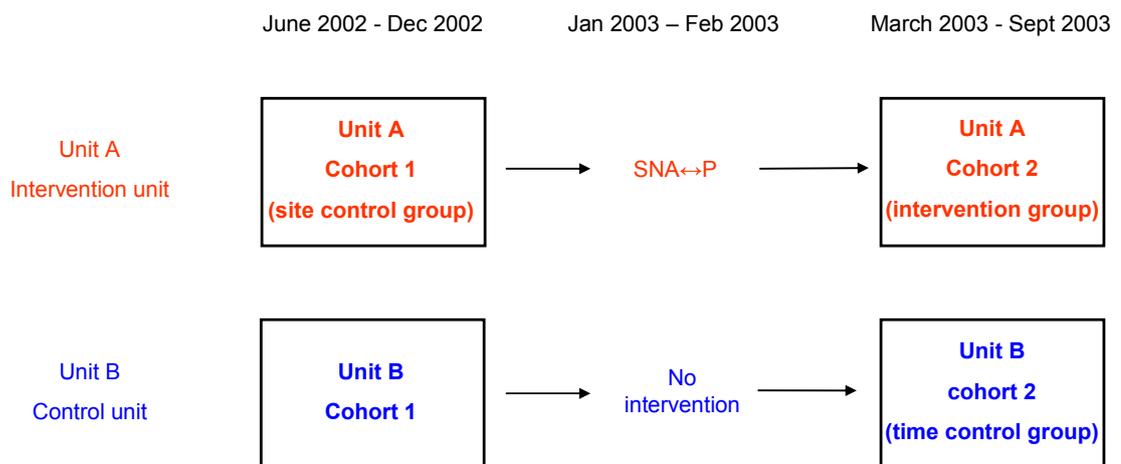
1. To describe and explore the reports and experiences of chemotherapy-related nausea and fatigue.
2. To explore the impact of the intervention on experiences of chemotherapy-related nausea and fatigue.

It is important to describe the sample and consider its characteristics to evaluate whether there are confounding variables within groups of patients that may confound the results of the SNA↔P study. This chapter will present details of the study sample before moving on to address each of the research aims, then draw conclusions on the overarching study aim.

8.2 Sample characteristics

Data collection for this study took place in 2 clinical sites (Units A and B) over 2 time periods – times 1 and 2. Recruitment to each phase was over 7 months. This design resulted in 4 distinct study groups (see Figure 24)

Figure 24: SNA↔P study patient groups



Patients from all study groups completed the symptom questionnaire. A subsample of patients participating in the second cohort of the study participated in a structured interview. Details of each sample are presented below.

8.2.1 Questionnaire sample

8.2.1.1 Recruitment and attrition

Recruitment in Unit A relied on JMcL, the research support nurse who worked alongside MM during the introduction, integration and maintenance of the intervention, as described in chapter 7. Thirty six patients were identified as eligible for participation during cohort 1 with thirty recruited. Four were not approached due to JMcL being on annual leave and the remaining two patients declined to take part due to feeling already too anxious. Twenty two patients were identified as eligible

for participation during cohort 2. Two of those patients were missed by JMCL as a result of miscommunication from ward nursing staff. Thus, twenty patients were recruited.

In Unit B, recruitment was undertaken by MM. Thirty eligible patients were identified during cohort 1 and twenty-five during cohort 2. All agreed to participate.

Therefore, in total, 105 patients about to start chemotherapy for a diagnosis of breast cancer gave their informed consent to participate in the study (see Table 19).

Table 19: Patient recruitment to Units A and B

	Unit A	Unit B
Cohort 1	30	30
Cohort 2	20	25
Total	50	55

Not all patients continued with their participation in the study throughout the duration of their chemotherapy. Table 20 gives detail of the numbers of patients returning their symptom questionnaires for each cycle of chemotherapy within each patient group.

Table 20: Number of patients participating by group and cycle of chemotherapy

Chemotherapy cycle	Unit A Cohort 1 (n=30)	Unit A Cohort 2 (n=20)	Unit B Cohort 1 (n=30)	Unit B Cohort 2 (n=25)	TOTAL
1	30	20	30	25	105
2	26	17	28	19	90
3	26	14	25	18	83
4	24	13	20	18	75
5	16	11	14	18	59
6	13	9	9	18	49
7	10	8	7	14	39
8	7	8	5	13	33

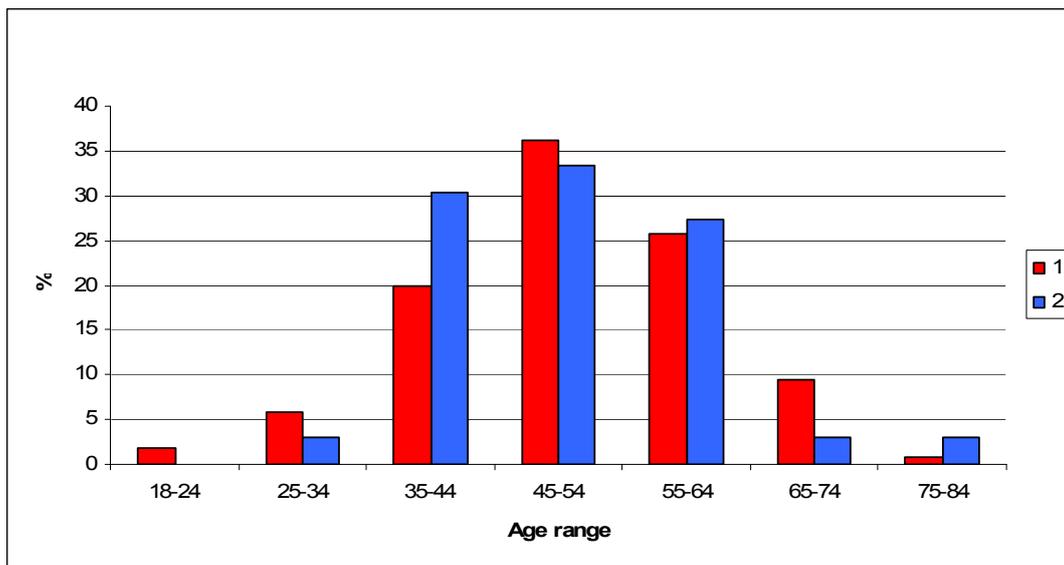
As patients were assured at the start of the study that they could withdraw at any time, without having to give a reason for it, no data was collected as to patients' rationale for discontinuing their participation in the study. There were differences in patient procedures throughout the SNA↔P study between Units A and B. As described in chapter 6, patients in Unit A were met by JMcL at each cycle of chemotherapy and given their next set of patient symptom questionnaires, as well as being assessed for their willingness and ability to continue in the SNA↔P study. Patients in Unit B were given all their symptom questionnaires at the start of their chemotherapy and advised to contact MM should they have any questions, while being assessed on their ability to continue in the study by their chemotherapy nurse at each cycle. Although there were slight differences between Units A and B with respect to levels of patient attrition, overall there was little difference between the

Units with Unit A having 30% of patients completing the questionnaires for the duration of their treatment while 32% of patients in Unit B did so. The characteristics of the sample that started and those who fully completed the study are presented in the following sections.

8.2.1.2 Age

Date of birth was recorded for each patient. Ages have been banded into 10-year groups for ease of reporting. The age range of the total sample at the start of data collection and the age range of those who completed the study to the end is presented in Figure 25.

Figure 25: Age range of questionnaire sample



1 = patients starting SNA↔P study

2 = patients participating in SNA↔P study for total duration of their chemotherapy

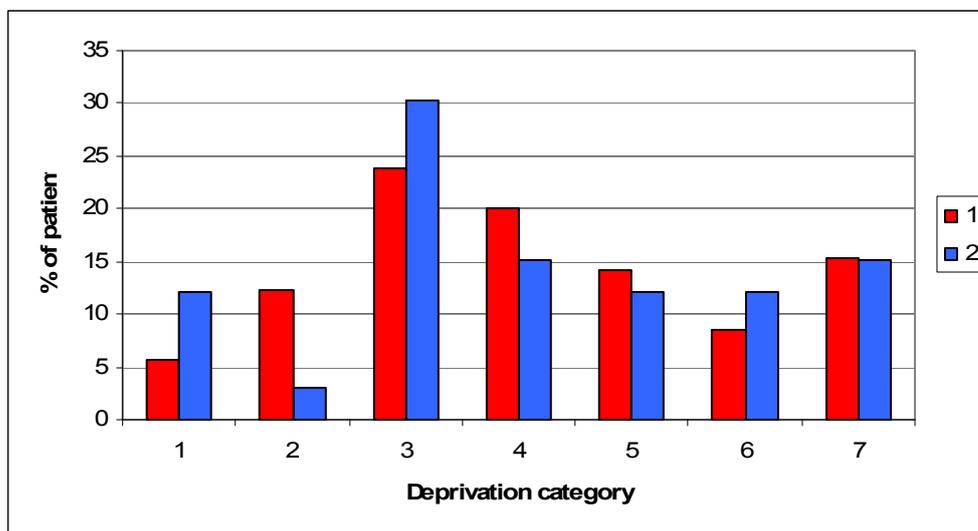
This graph shows that the majority of patients participating in the study (81.9%, n=86) were between 35 years and 64 years of age. While 7.6% (n=8) of the sample

was between 18-34 years of age, 10.6% (n=11) were aged 65 and over. It also demonstrates that the age range of those patients who participated in the SNA↔P study for the total duration of their chemotherapy reflects the total study sample.

8.2.1.3 Social deprivation

The measure of deprivation used in the SNA↔P study was the Carstairs Score, a categorical variable based on postcode ranging from DEPCAT 1 (the most affluent postcode sectors) to 7 (the most deprived) (McLoone 2004). The deprivation scores for the sample (all those starting the study and those who completed the study) are presented below. Figure 26 demonstrates that there was little difference in the level of deprivation experienced by those starting the study and those patients who continued for the full duration of their treatment.

Figure 26: Deprivation score for questionnaire sample

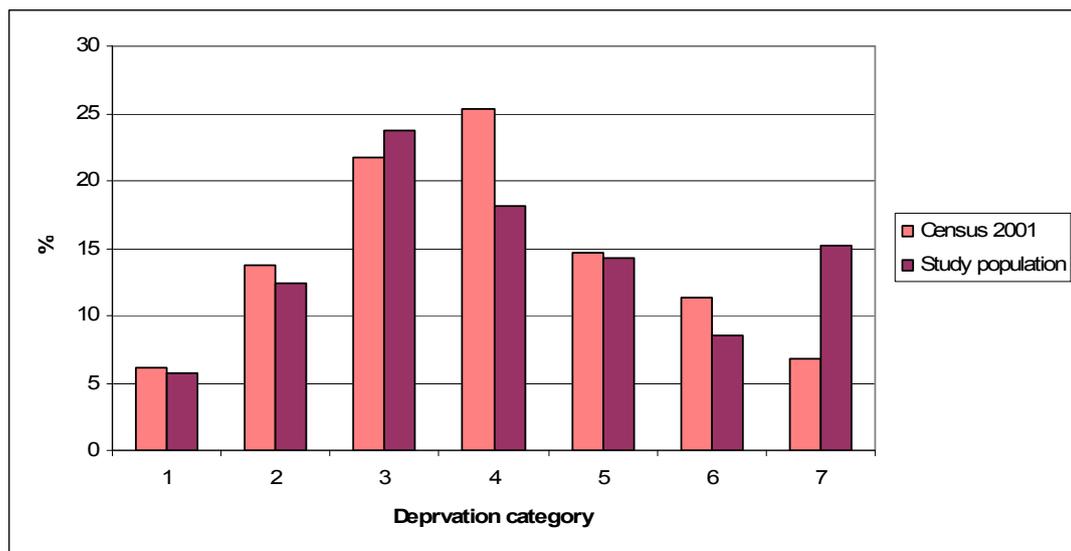


1 = patients starting SNA↔P study

2 = patients participating in SNA↔P study for total duration of their chemotherapy

Figure 27 presents the DEPCAT scores for the total study population and compares these with those of the 2001 Scottish Census (McLoone 2004). This graph shows that the range of deprivation in the study population is not unlike that of the general population.

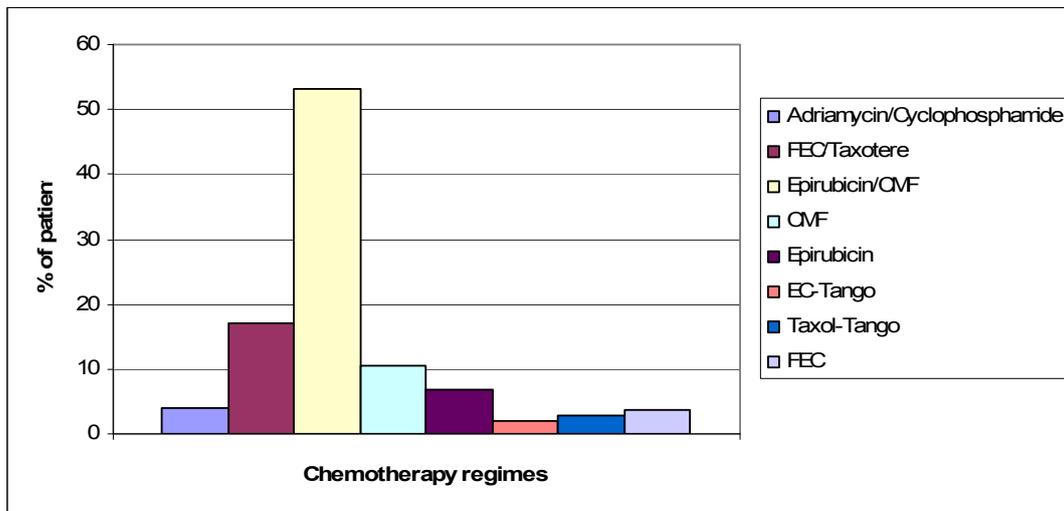
Figure 27: Questionnaire sample compared with national statistics



8.2.1.4 Treatment intent

Eight different chemotherapy regimes were administered to patients participating in the study and information about the symptom profile associated with each regime and its therapeutic use was gathered from the literature as well as through discussions with the Clinical Nurse Specialists (CNSs) working in both the chemotherapy Units. These discussions with CNSs were particularly useful, as they highlighted some idiosyncratic uses of particular chemotherapy regimes in both Units A and B. Figure 28 illustrates the percentage of patients receiving each chemotherapy regime.

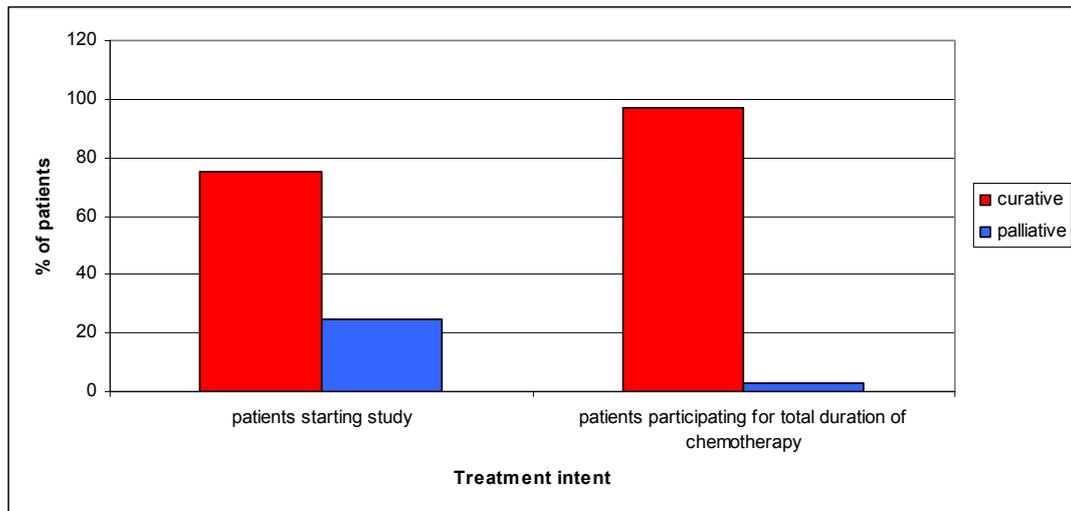
Figure 28: Chemotherapy regimes received by questionnaire sample



These regimes ranged in emetogenicity: some being mildly emetogenic (FEC, FEC/Taxotere, Epirubicin, Taxol-Tango) while others were moderately emetogenic (Adriamycin/cyclophosphamide, CMF, Epirubicin/CMF, EC-Tango). Given the range of chemotherapy regimes, they were classified into two groups on the basis of their intent: curative or palliative. It is important to consider the relative toxicity of curative and palliative treatments, as curative treatments are generally more toxic, that is, they have greater associated symptoms than palliative treatment. However, it may also be the case that those patients receiving palliative chemotherapy are experiencing symptoms associated with advanced cancer.

Figure 29 shows that the majority of patients starting the SNA↔P study were receiving chemotherapy with curative intent (n=79, 75.2%) and it was predominantly patients receiving curative treatment (n=32, 97%) who continued to complete their questionnaires for the total duration of their chemotherapy. Only one patient who was receiving palliative chemotherapy continued to complete questionnaires for the total duration of their chemotherapy.

Figure 29: Treatment intent for questionnaire sample



8.2.2 Interview sample

During time 2 a convenience sample of 9 ‘information-rich’ patients participated in a structured interview: four from the intervention site and five from the control site, representing 20% of the study sample at this time period. Table 21 presents the demographic details of the interview sample.

Table 21: Demographic characteristics of the interview sample

Demographic characteristics of interview sample							
Age range		Deprivation category		Treatment intent		Participating at cycle	
25-34	1	1	0	Curative	6	1	2
35-44	3	2	1	Palliative	3	2	4
45-54	4	3	4			3	1
55-64	1	4	2			5	2
		5	1				
		6	0				
		7	1				

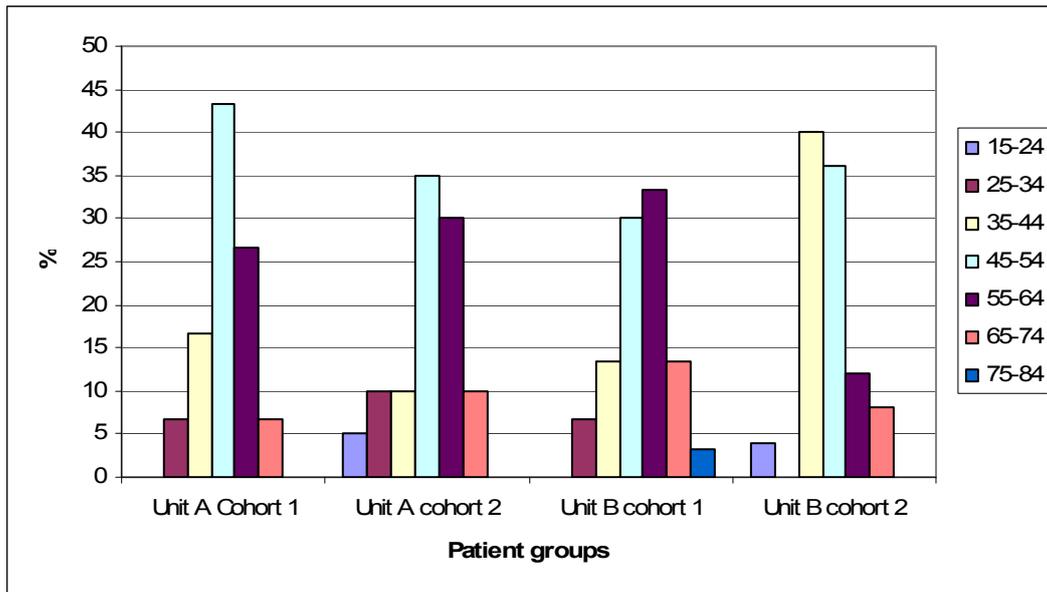
8.2.3 Potentially confounding variables

The potentially confounding variables identified in this study were that of age, social deprivation and treatment intent.

8.2.3.1 Age

The age range of the patient groups was relatively normally distributed and is presented in Figure 30.

Figure 30: Age range of patient groups

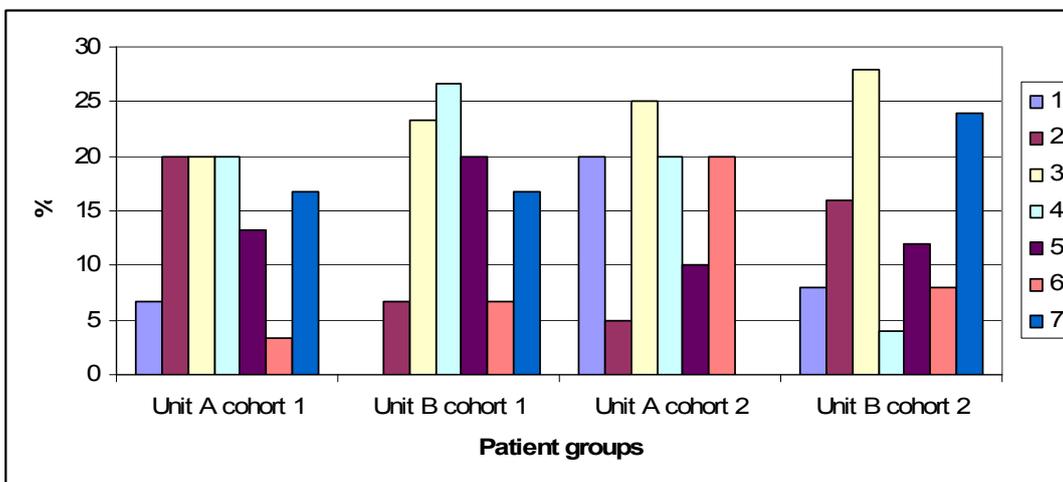


Comparison of the age ranges between the patient groups was carried out using a one-way ANOVA, and showed that the age range of the four groups is not statistically significantly different from one another ($F=1.408$ $df=3$ $p=0.25$).

8.2.3.2 Social deprivation

The level of deprivation of patient groups is presented in Figure 31.

Figure 31: Level of deprivation across patient groups

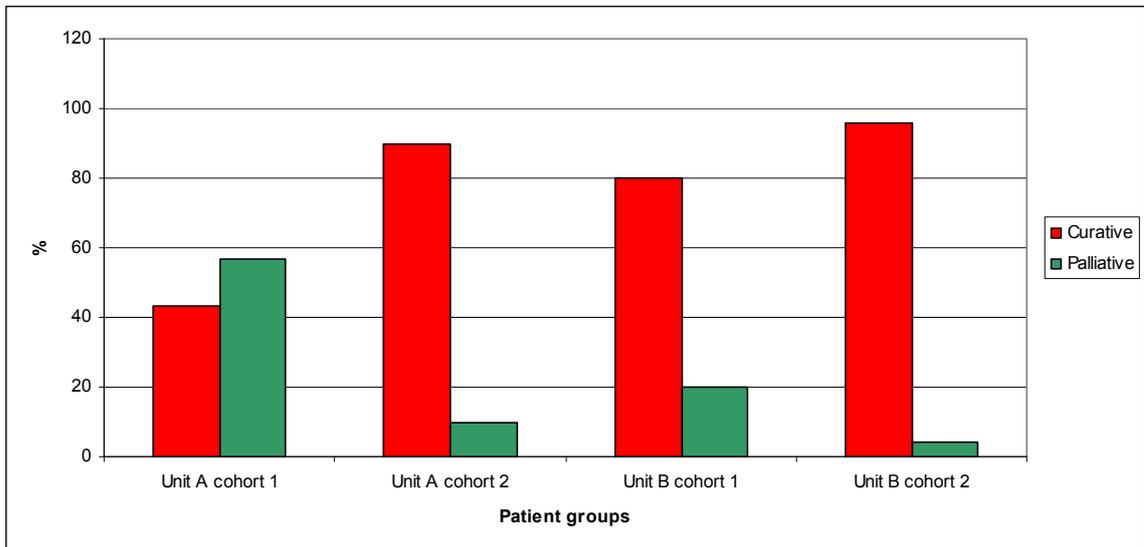


This graph demonstrates that the level of deprivation is not normally distributed. Given such distribution, a Kruskal-Wallis test was conducted showing that the level of deprivation of the four patient groups did not differ significantly (Chi sq. 2.98, df 3, p=0.39).

8.2.3.3 Treatment intent

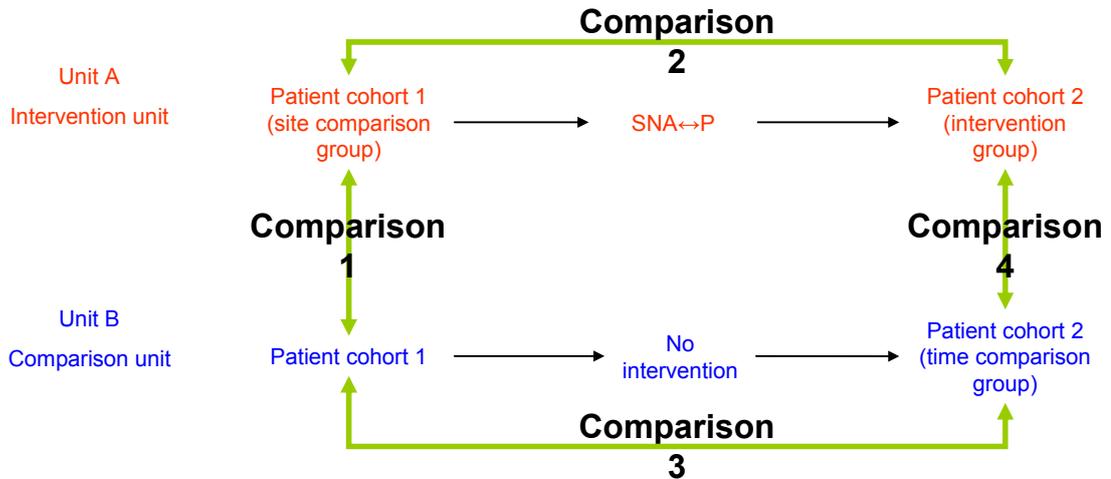
The treatment intent of the 4 patient groups at the start of data collection is presented in Figure 32.

Figure 32: Treatment intent within patient groups



Comparison of the treatment intent between the 4 patient groups at the start of data collection was carried out using a chi square test. Four independent chi square tests were conducted (see Figure 33).

Figure 33: Statistical comparison of treatment intent between patient groups



These test the null hypothesis that there is no difference between population means.

The results of each chi square test are presented below:

Comparison 1: A significant difference in treatment intent between Unit A cohort 1 and Unit B cohort 1 (chi sq 8.53, df 1, p=0.003)

Comparison 2: A significant difference in treatment intent between Unit A cohorts 1 and 2 (chi sq 11.1, df 1, p=0.001)

Comparison 3: No significant difference in treatment intent between Unit B cohorts 1 and 2 (chi sq 3.14, df 1, p=0.76)

Comparison 4: No significant difference in treatment intent between Unit A cohort 2 and Unit B cohort 2 (chi sq 0.64, df 1, p=0.423)

Comparing the symptom scores between those patients receiving curative and palliative chemotherapy gives an indication of whether curative chemotherapy is associated with higher nausea and fatigue scores. This comparison was undertaken using all available symptom data from cycles 1-8. For both nausea and fatigue,

curative chemotherapy is associated with marginally lower mean total scores, as well as lower mean severity and mean distress scores (see Table 22). An ANOVA for each symptom and for all symptom components showed that there were no statistically significant differences between the resulting symptoms from either curative or palliative chemotherapy: total nausea scores ($F=0.783$, $df 1$, $p=0.378$), nausea severity scores ($F=0.536$, $df 1$, $p=0.466$), nausea distress scores ($F=1.107$, $df 1$, $p=0.295$), total fatigue scores ($F=0.032$, $df 1$, $p=0.858$), fatigue severity scores ($F=0.029$, $df 1$, $p=0.865$) and fatigue distress scores ($F=0.031$, $df 1$, $p=0.862$).

Table 22: Comparison of mean nausea and fatigue scores according to treatment intent

		Nausea			Fatigue		
		Minimum	Maximum	Mean	Minimum	Maximum	Mean
Curative	Total	.00	6.00	.9649	.00	5.07	1.3124
	Severity	.00	3.00	.6012	.00	2.64	.8495
	Distress	.00	3.00	.3642	.00	2.43	.4650
Palliative	Total	.00	5.17	1.2134	.00	4.0	1.4764
	Severity	.00	2.75	.7163	.00	2.4	.9126
	Distress	.00	2.42	.4996	.00	1.88	.5655

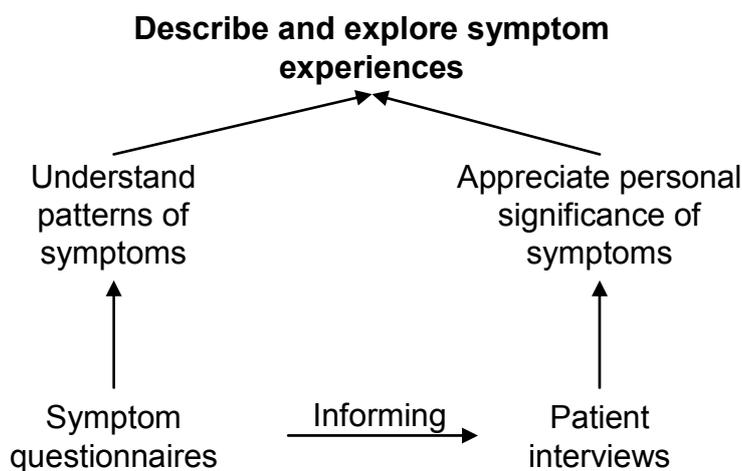
Thus, the analysis of potentially confounding variables has shown that in relation to age and social deprivation, none of the patient groups are statistically significant from one another. However, the groups differ statistically in relation to treatment intent: Unit A cohort 1 differs from cohort 2 of Unit A and cohort 1 of Unit B, who both have a lower proportion of patients receiving chemotherapy with palliative intent. However, there are no statistically significant differences between nausea

and fatigue experienced as a consequence of chemotherapy given with either curative or palliative intent. The remainder of this chapter will address the two distinct aims of the study, before coming to a conclusion about the overarching aim of the study – the evaluation of the impact of the intervention.

8.3 Description of chemotherapy-related nausea and fatigue

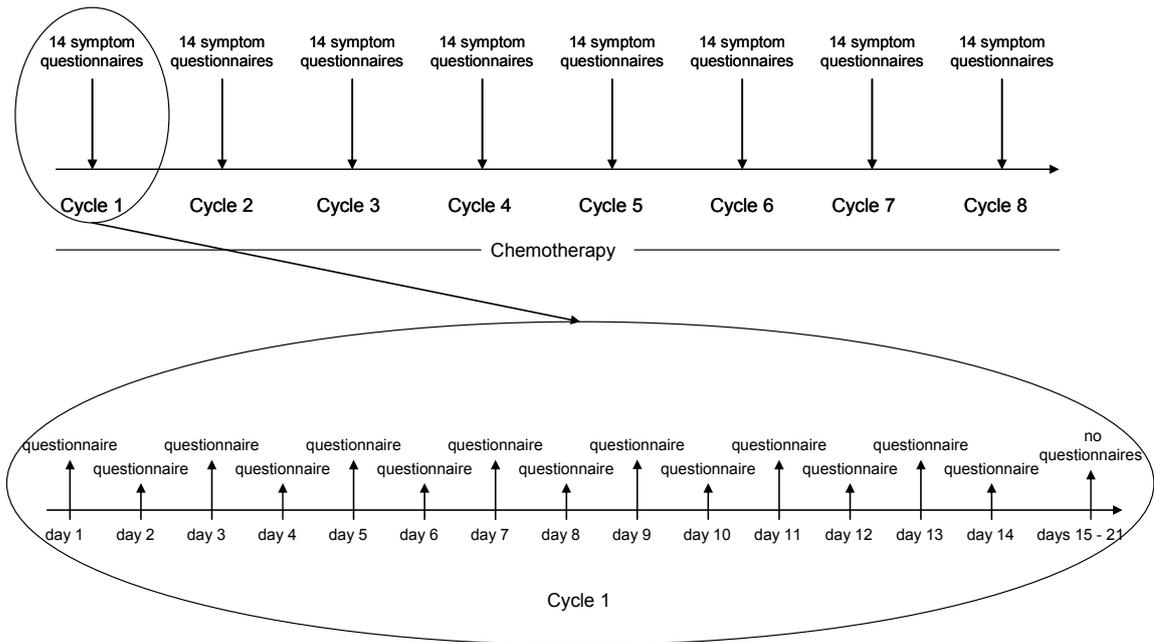
The first aim of this study was to describe and explore the reports of chemotherapy-related nausea and fatigue experienced by women during a course of chemotherapy. Both quantitative data, in the form of symptom scores from symptom questionnaires, and qualitative data, in the form of patients' interviews about their experiences were used to achieve this aim. Figure 34 demonstrates how these two research methods blend to achieve this. This technique was used for both nausea and fatigue experiences. Symptom information from the whole dataset was used, as this exploration and description did not involve group comparisons.

Figure 34: Blending of research techniques to describe symptoms



As intended, a vast amount of quantitative data were generated from the symptom questionnaires. These are presented in Appendix P – summary of quantitative data. These data were longitudinal in nature, both within cycles of chemotherapy (days 1-14), and across cycles of chemotherapy (cycles 1-8), see Figure 35.

Figure 35: Longitudinal data collection process



A missing data value analysis was undertaken within SPSS that not only demonstrated a random pattern of missing data but also confirmed that the missing data represented only 4.3% of the total symptom data. Given this small percentage, missing data was not substituted.

Patterns of nausea and fatigue were explored by generating a mean total, severity, and distress symptom score, for all patients for all days (1-14) across all cycles of chemotherapy (1-8), and plotting these mean scores graphically. The mean was generated on the symptom scores of all patient data for that cycle. Thus, it is important to note that these means were of a reducing group: the number of patients in each cycle being noted above each graph in figures 36 and 38.

Data from the patient interviews during which patients explained their symptom experiences across their range of symptom scores were used to illustrate the personal significance of the mean symptom scores presented in figures 36 and 38. Quotes from patients' interviews are presented throughout and the number in brackets that follows each quote refers to the individual patient's study number.

8.3.1 Nausea

The number of patients reporting nausea (regardless of level of severity or distress) is presented in Table 23 below. As already highlighted above, the number of patients who continued to participate in the SNA↔P study decreased over time. Consequently, the number of patients participating at each cycle is noted below the cycle number. Although the study does have a reducing number of patients participating with each cycle, the final cycle involved 33 patients, which is a reasonable number of patients on which to draw conclusions. The percentages presented in Table 23 are calculated on the number of patients participating in each individual cycle and show that the incidence of nausea reduces over consecutive cycles of chemotherapy during the first few days post-chemotherapy.

Table 23: Percentage of patients experiencing nausea across all cycles of chemotherapy

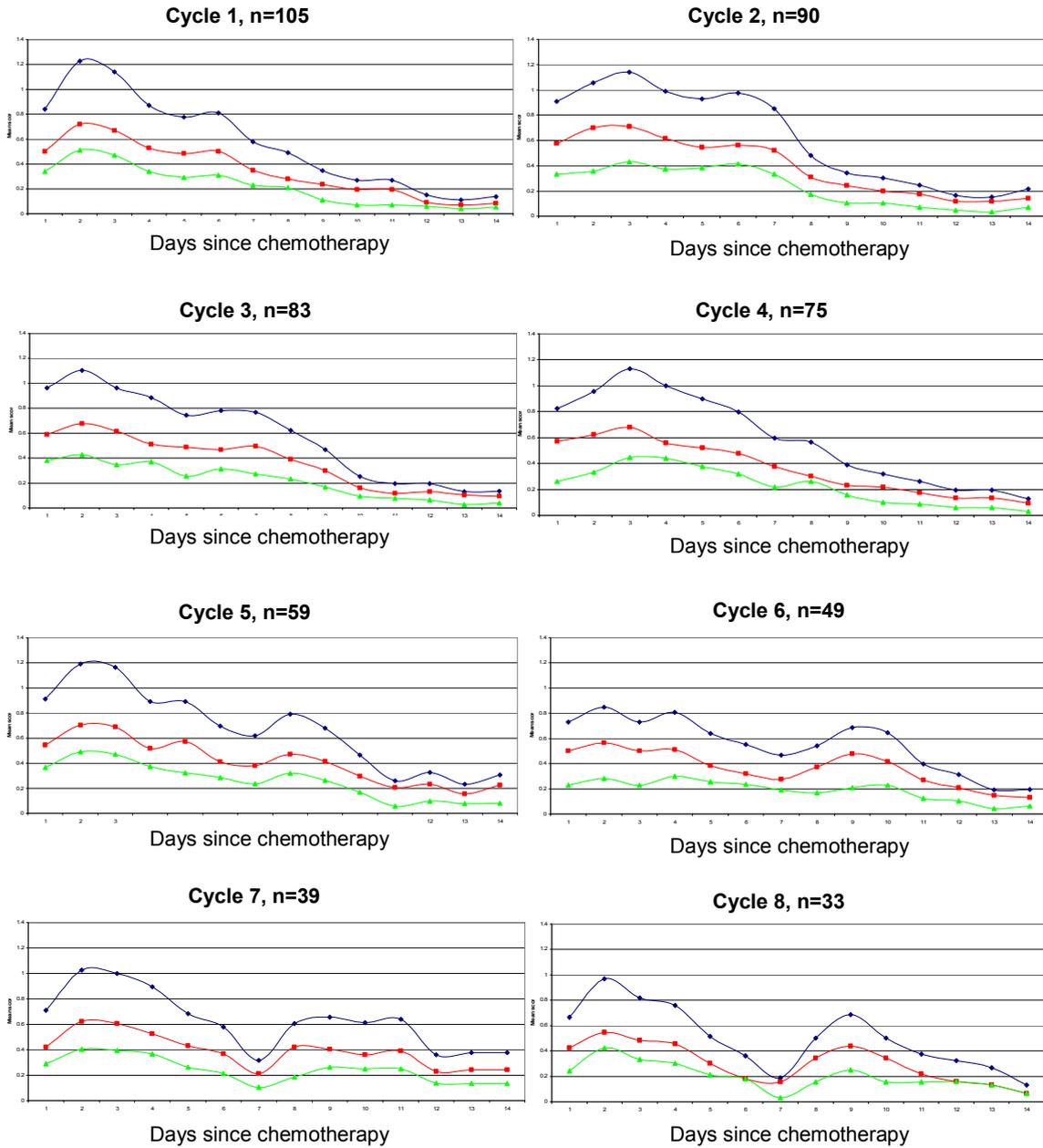
Day	Cycle 1 n=105 % (n=)	Cycle 2 n=90 % (n=)	Cycle 3 n=83 % (n=)	Cycle 4 n=75 % (n=)	Cycle 5 n=59 % (n=)	Cycle 6 n=49 % (n=)	Cycle 7 n=39 % (n=)	Cycle 8 n=33 % (n=)
1	41% (44)	37% (33)	29% (24)	32% (24)	27% (16)	35% (17)	36% (14)	24% (8)
2	47% (49)	44% (40)	41% (34)	32% (24)	37% (22)	35% (17)	36% (14)	30% (10)
3	40% (42)	43% (39)	35% (29)	33% (25)	37% (22)	35% (17)	36% (14)	27% (9)
4	36% (38)	41% (37)	31% (26)	29% (22)	32% (19)	31% (15)	31% (12)	27% (9)
5	29% (30)	34% (31)	31% (26)	25% (19)	32% (19)	24% (12)	28% (11)	21% (7)
6	28% (29)	31% (28)	31% (25)	23% (17)	27% (16)	20% (10)	23% (9)	18% (6)
7	21% (22)	29% (26)	26% (22)	20% (15)	22% (13)	16% (8)	21% (8)	12% (4)
8	20% (21)	21% (19)	23% (19)	20% (15)	25% (15)	24% (12)	31% (12)	21% (7)
9	15% (16)	16% (14)	19% (16)	16% (12)	27% (16)	31% (15)	23% (9)	21% (7)
10	12% (13)	14% (13)	12% (10)	16% (12)	19% (11)	26% (13)	26% (10)	21% (7)
11	7% (7)	11% (10)	8% (7)	15% (11)	15% (9)	18% (9)	26% (10)	15% (5)
12	6% (6)	8% (7)	8% (7)	11% (8)	17% (10)	12% (6)	21% (8)	12% (4)
13	4% (4)	7% (6)	8% (7)	11% (8)	14% (8)	10% (5)	21% (8)	9% (3)
14	6% (6)	8% (7)	8% (7)	8% (6)	12% (7)	10% (5)	18% (7)	6% (2)

Figure 36 demonstrates the patterns of mean nausea scores reported in the symptom questionnaires by all patients participating in each cycle of the study. Mean symptom scores for the total nausea experience (range 0-6) and the individual subscales of severity (range 0-3) and distress (range 0-3) are shown. In general, there is a peak in nausea during the first few days following chemotherapy administration which gradually lessens over time. This pattern changes from cycle 5

onwards where a second peak in nausea is seen around day 8-10 following chemotherapy. This change is likely to be because 45.8% (n=27) of the sample at cycle 5, 53% (n=26) of the sample at cycle 6, 59% (n=23) of the sample at cycle 7 and 60.6% (n=20) of the sample at cycle 8 received the chemotherapy regime EPI/CMF, which entails Epirubicin for cycles 1-4 followed by Cyclophosphamide, Methotrexate and 5-Fluoruracil for cycles 5-8. During cycles 1-4, chemotherapy is administered on day 1 of the cycle while in cycles 5-8 chemotherapy is administered on days 1 and days 8.

Figure 36: Mean nausea scores

Total nausea (range 0-6), Severity (range 0-3), Distress (range 0-3)



Note reducing sample size: n value for each cycle noted above each graph

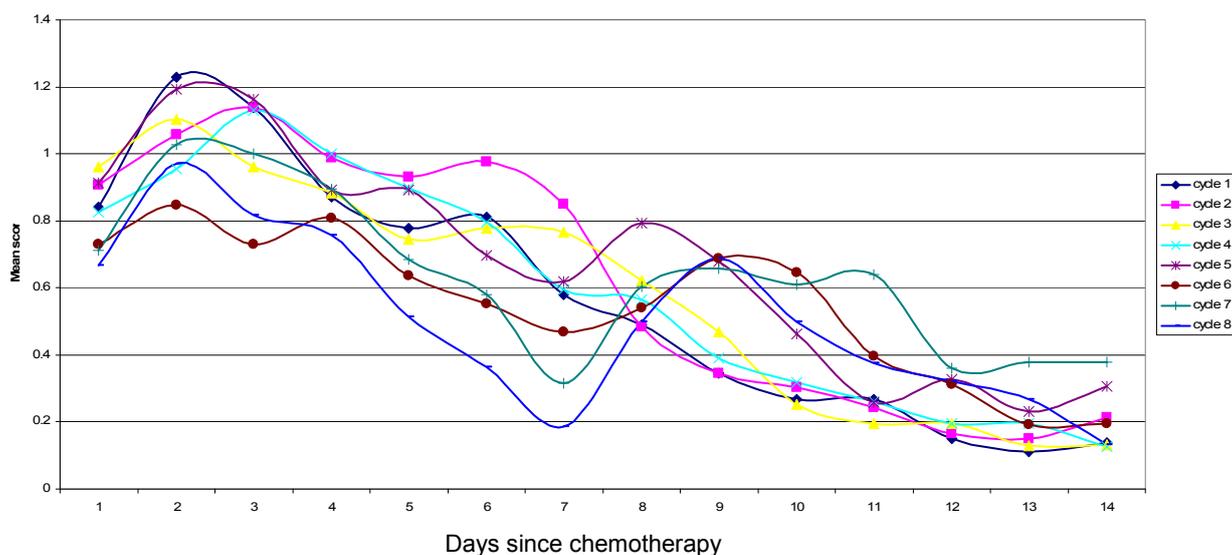
The highest mean score for nausea reported throughout all 8 cycles of chemotherapy was 1.23 (possible range 0-6), seen at day 2 of the first cycle of chemotherapy.

Thereafter, it did not reach above 1.2 although it came close on day 2 of cycle 5,

reaching 1.19. This pattern may again be due to the proportion of patients receiving EPI/CMF, a regime in which drug administration changes at cycle 5. It may be this change in drug that resulted in this increase in experiences of nausea. It can also be seen from Figure 35 that patterns of severity and distress are relatively similar to one another across all cycles of chemotherapy, which suggests that they have a positive correlation, that is, as a symptom becomes increasingly severe, the level of distress associated with it increases. A Pearson Product Moment Correlation Coefficient was calculated to evaluate the degree of the relationship between nausea severity and distress scores. A significant relationship between patients' reports of nausea severity and associated distress was shown ($r\ 0.925$, $N105$, $p<0.01$).

The **total** mean nausea score (incorporating mean severity and distress scores) for each day (1-14) within each cycle (1-8) was plotted and can be seen in Figure 37. This graph shows that there is little variation in total nausea scores between each cycle of chemotherapy (1-8) and again highlights the peak in nausea experiences between days 1-3 and days 8-10. Such similarity in the patterns of mean nausea over each cycle is reassuring, given the reduction in sample size with consecutive cycles, as it indicates that those patients continuing to complete and return their symptom questionnaires were not reporting greatly different nausea experiences from the larger sample at the start of data collection.

Figure 37: Mean total nausea scores within and across cycles of chemotherapy



During each interview, patients were asked a number of questions to describe their experiences of nausea. They were asked to describe how they felt (physically and psychologically) at each of the nausea scores they had reported and the impact that each level of nausea had on their abilities. They were also asked to compare their experiences of nausea between scores, for example, how did a score of 1 compare with a 2 or a 2 with a 4? They were also asked which score of nausea they believed to be acceptable to them, for example, no nausea (score 0), or a score of 1 or 2.

While some patients referred to nausea as ‘feeling sick’,

‘I do feel sick later on in the day.’ (2)

‘I was just constantly feeling sick. It’s very unpleasant.’ (8)

others used different terms to describe their nausea:

‘A bile feeling in your mouth and a watery feeling.’ (3)

‘It felt a bit like travel sickness, as if your head was swimming.’ (5)

'I get a coating in my mouth, a horrible coating.' (7)

'I felt quite squeamish and it kept me awake through the night even though I'd taken my anti-sickness tablets.' (9)

'I'd feel a bit seedy.' (4)

Patients easily articulated the negative impact that nausea had on their daily life, particularly in relation to their functional ability. However, they were less likely to reflect on the psychological impact that nausea had on their life in general. In all cases, patients had to be prompted to consider the psychological impact of their nausea experiences.

Nausea's impact on functional aspects of their daily lives included the following:

'It actually stops me going out and socialising.' (8)

'It stops me driving, I can't drive with it like that.' (4)

'I stay in constantly now, I only go out if I have to.' (8)

'I can't concentrate because that sick feeling sits in your throat.' (5)

'It does stop me doing the things I enjoy for several days.' (4)

'It's constantly there, you wake up with it, you go to bed with it, you're up through the night with it, it's absolutely disgusting.' (8)

While nausea did have a negative psychological impact on some patients,

'It's several days of misery and feeling quite miserable' (4)

'Obviously, you start to get depressed, you can't go anywhere, you can't go out, you can't do anything.' (8)

others seemed to have developed ways of coping with their experiences:

'It doesn't make me feel depressed or anything like that, I just think, it is finite, it will end. I just think, oh God, here we go again.' (5)

'it's not the end of the world.' (2)

Patients spoke easily about the ways they had tried to manage their nausea and there was no discernable differences between patients from Units A or B, despite the fact that patients in Unit A should have been getting tailored symptom advice from their nurses from the SNA↔P practice protocols. There was a sense of trying to keep life as 'normal' as possible in the hope that this would reduce the impact of the nausea.

'I take the anti-sickness, take them all. No point in being a martyr, I take the drugs they give you.' (5)

'I do a lot of reading and stuff like that to try and distract myself from what is going on. I've got people coming in all the time and the house is always busy and that distracts me.' (4)

'I ate a lot of bland food, toast and the like, stuff that wasn't too flavoured.' (2)

'I read and watch TV and try to relax, I tried to think of something else and not let it take over my life. I think it helps to keep a bit of normality in your life.' (7)

'I tried to just be me and do the things I would normally do. I didn't let it take over.'
(3)

Patients were also able to evaluate the effectiveness of their self-care in alleviating their nausea and again, there were no differences in patients' responses between Units A and B.

'I think that the business takes your mind off feeling seedy and you feel OK for a wee while.' (4)

'I take everything they give me and I think the anti-sickness tablets, they do work, they take the edge off it.' (5)

'We had to try to various drug combinations to get that [nausea] under control and certainly with the new stuff [antiemetic] it's not as bad as before.' (8)

'I had felt sick but once I took my tablets again, I was OK.' (3)

'I definitely think it helped to try and not take [eat] anything that was too highly flavoured. I think that did help.' (2)

Thus, in exploring and describing the symptom of chemotherapy-related nausea, this study has shown that nausea peaks around days 1-3 following chemotherapy administration. The second peak seen in cycles 5-8 at days 8-10 in this study is likely to be due to a specific chemotherapy regime (EPI/CMF). No real differences in nausea scores were seen between cycles of chemotherapy. Patients can easily articulate their experiences of nausea and are able to describe it in many ways. They can identify the ways in which it impacts on their functional ability and, with prompting, their psychological response to it. Patients also view their self-care strategies as helpful in managing their experiences of nausea.

8.3.2 Fatigue

The number of patients reporting fatigue (regardless of severity or distress) is presented in Table 24 with the number of patients participating at each cycle noted beneath the cycle number. The percentages presented in Table 24 are calculated on the number of patients participating in each individual cycle. Table 24 shows that there is little fluctuation in percentage of patients reporting fatigue across cycles of chemotherapy, however, the incidence of fatigue is much higher than that of nausea.

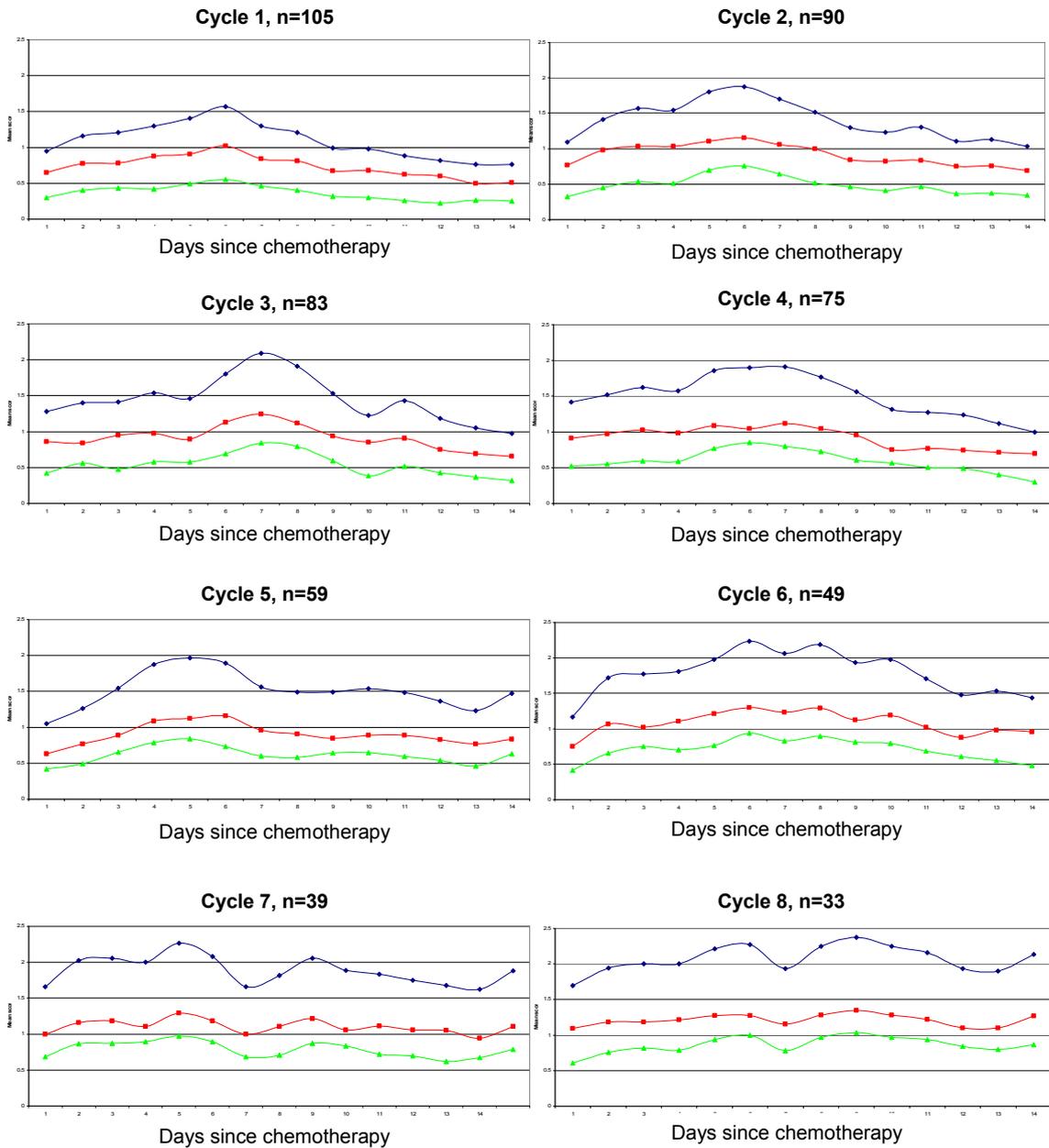
Table 24: Percent and number of patients experiencing fatigue across all cycles of chemotherapy

Day	Cycle 1 n=105	Cycle 2 n=90	Cycle 3 n=83	Cycle 4 n=75	Cycle 5 n=59	Cycle 6 n=49	Cycle 7 n=39	Cycle 8 n=33
1	40% (42)	51% (46)	49% (41)	52% (39)	52% (31)	47% (23)	56% (22)	36% (12)
2	49% (52)	61% (55)	48% (40)	53% (40)	52% (31)	57% (28)	59% (23)	39% (13)
3	50% (53)	61% (55)	55% (46)	56% (42)	61% (36)	57% (28)	59% (23)	42% (14)
4	51% (54)	62% (56)	60% (50)	57% (43)	68% (40)	59% (29)	59% (23)	45% (15)
5	54% (57)	61% (55)	57% (47)	55% (41)	50% (35)	73% (36)	69% (27)	39% (13)
6	57% (60)	60% (54)	63% (52)	60% (45)	66% (39)	71% (35)	59% (23)	36% (12)
7	54% (57)	58% (52)	65% (54)	60% (45)	64% (38)	63% (31)	51% (20)	36% (12)
8	51% (54)	57% (51)	60% (50)	57% (43)	58% (34)	61% (30)	61% (24)	42% (14)
9	40% (42)	51% (46)	57% (47)	59% (44)	52% (31)	59% (29)	61% (24)	42% (14)
10	41% (43)	50% (45)	51% (42)	47% (35)	58% (34)	61% (30)	54% (21)	42% (14)
11	42% (44)	53% (48)	54% (45)	51% (38)	56% (33)	59% (29)	61% (24)	45% (15)
12	39% (41)	44% (40)	49% (41)	49% (37)	51% (30)	57% (28)	56% (22)	42% (14)
13	32% (34)	50% (45)	46% (37)	48% (36)	56% (33)	57% (28)	56% (22)	39% (13)
14	33% (35)	45% (41)	46% (37)	45% (34)	52% (31)	51% (25)	56% (22)	36% (12)

Figure 38 demonstrates the patterns of mean fatigue reported in the symptom questionnaires by all patients participating in the study. Mean symptom scores for the total fatigue experience (range 0-6) and the individual subscales of severity (range 0-3) and distress (range 0-3) are shown. These graphs show a stable pattern of mean fatigue that does not fluctuate within cycles of chemotherapy as did nausea. Total mean fatigue scores and their component parts (severity and distress) appear to have a relatively constant presence within and across cycles of chemotherapy. The highest mean score of fatigue is seen in day 9 of cycle 8 where the mean total fatigue score was 2.375.

Figure 38: Mean fatigue scores

Total (range 0-6), Severity (range 0-3), Distress (range 0-3)



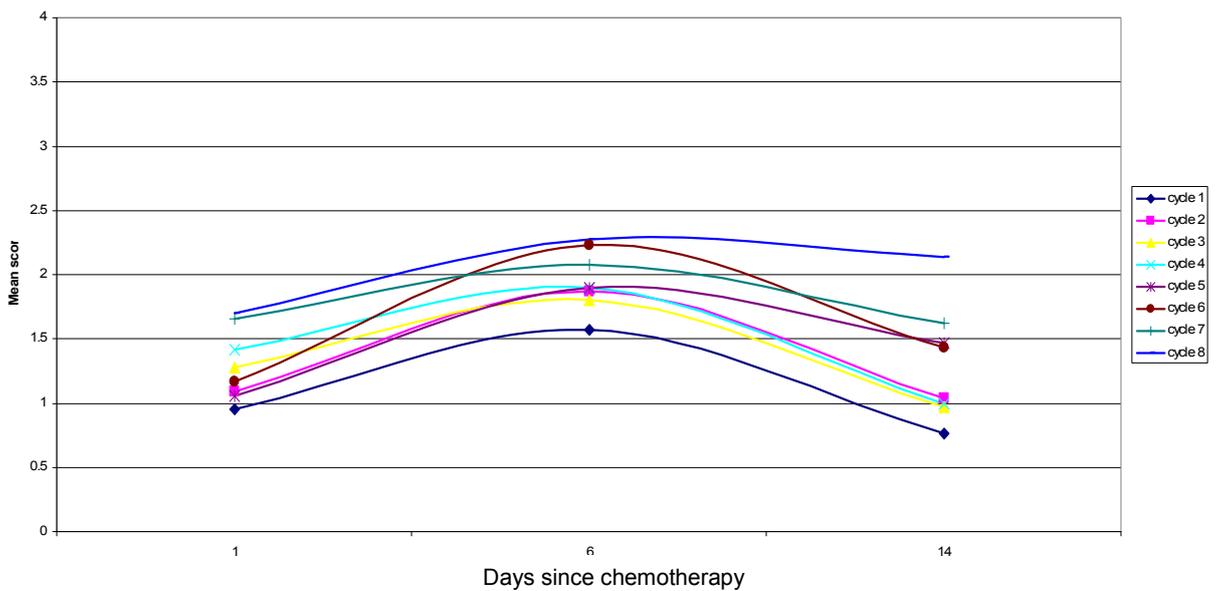
Note reducing sample size: n value for each cycle noted above each graph

As with nausea, Figure 38 shows that patterns of severity and distress are relatively similar to one another across all cycles of chemotherapy, suggesting they have a positive correlation, that is, as fatigue becomes increasingly severe, the level of distress associated with it increases. A Pearson Product Moment Correlation

Coefficient was calculated to evaluate the degree of the relationship between fatigue severity and distress scores. A significant relationship between patients' reports of fatigue severity and associated distress was shown ($r\ 0.865$, $N105$, $p<0.01$).

Looking at the plotted data in Figure 37, there is the suggestion of a slight trend for fatigue to increase up until day 6 following chemotherapy followed by a gradual decrease. To further explore this potential pattern, the data were plotted only to show days 1, 6 and 14 following chemotherapy. This clarifies this trend (see Figure 39).

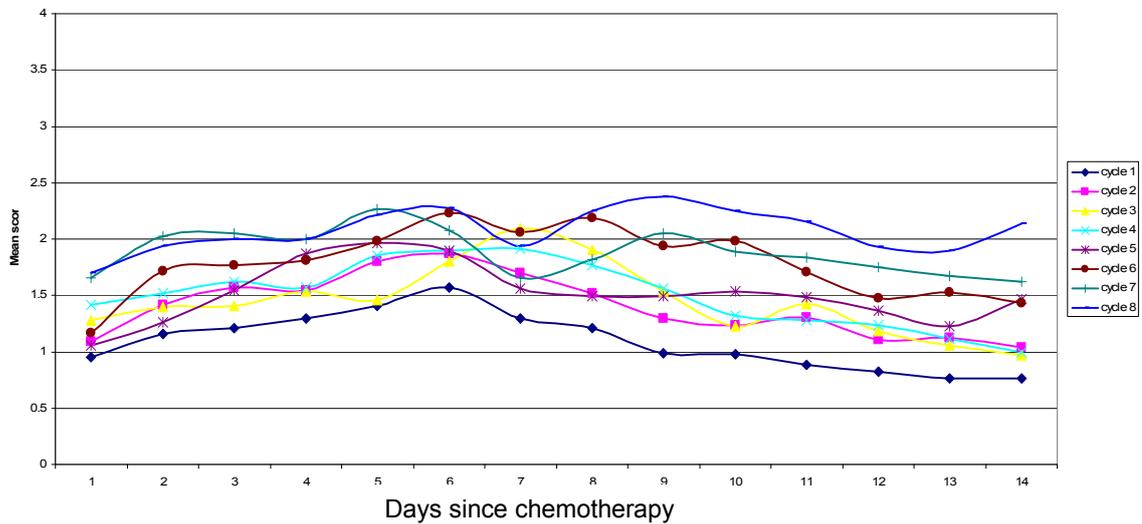
Figure 39: Mean total fatigue scores days 1, 6, 14



The previous plotting of fatigue data (Figures 38 and 39) show that fatigue increases with subsequent cycles of chemotherapy. Plotting the total fatigue scores for each day for all cycles (Figure 40) clearly demonstrates this incremental increase. This graph shows that mean total fatigue scores are almost 3 times greater on day 14 of cycle 8 (2.13) when compared with day 14 of cycle 1 (0.76). Caution is required in

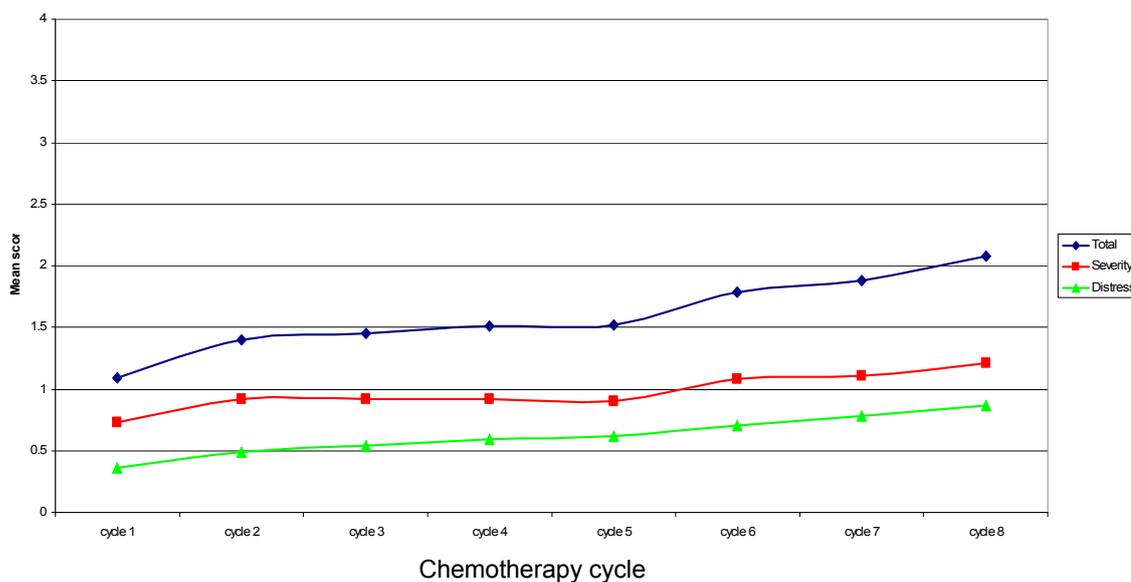
drawing any major conclusions from this result due to the reducing sample on which it is based.

Figure 40: Mean total fatigue scores across 8 cycles of chemotherapy



Given this incremental increase in fatigue with subsequent cycles of chemotherapy, further exploration was undertaken and a fatigue score was generated for each cycle of chemotherapy (the mean total, severity and distress scores for days 1-14 for each cycle of chemotherapy). These scores were then plotted (see Figure 41). This graph continues to demonstrate the incremental increase in total fatigue scores. However, it also shows that the severity scores remained relatively stable during cycles 2, 3, 4 and 5, increasing slightly at cycles 6, 7 and 8. In contrast, the distress scores showed a slight increase with each cycle of chemotherapy. Indeed, while mean total fatigue scores almost doubled between cycles 1 (1.09) and 8 (2.05), mean fatigue distress scores more than doubled between cycle 1 (0.36) and cycle 8 (0.86). Again, caution is required in drawing any major conclusions from this result due to the reducing sample on which it is based.

Figure 41: Mean total, severity and distress fatigue scores for each cycle of chemotherapy



The symptom of fatigue was discussed in patient interviews following their discussion of experiences of nausea. During each interview, patients were asked to describe their fatigue experiences, what feeling fatigued meant to them, their feelings across fatigue scores, their abilities (physical, psychological and social) at various scores and how different scores of fatigue compared with one another. Patients were shown their fatigue graph from the 14 days following their previous cycle of chemotherapy. Patients were often taken aback by this image. This could be seen in their body language rather than what they said, some appeared to physically recoil from what they were being shown, others were shaking their heads while making puffing sounds through their lips. However, immediately following this initial sense of shock, patients acknowledged that their fatigue was entirely different from nausea and that it had been a difficult symptom for them. Without exception, discussions surrounding fatigue were considerably longer than those of nausea.

'Oh, look at that, the tiredness was something else, I can tell you all about those days there [score of 5].' (1)

'Oh aye, I certainly was far more tired [than nauseated].' (7)

Patients found a multitude of ways in which to describe their experiences of fatigue.

General descriptions included:

'You have a horrible feeling in your body.' (1)

'I just couldn't lift my head up.' (3)

'I could have laid down and cried, I felt so tired all over.' (5)

'It was just a feeling that overcame me and I knew I had to go and lie down.' (6)

Other descriptions involved a loss of physical strength and energy:

'I can't walk and I can't drive because I don't have any strength.' (1)

'I usually had stacks of energy but now I feel if I'm doing anything I have to go and sit down for a wee while after.' (3)

'It was an all-over thing, my arms and legs, everything. I just felt I couldn't move. I just wanted to lie in a corner somewhere.' (5)

'I came in from getting the messages [shopping] and just flopped down and when I woke up the messages were still lying there and I thought well they can lie there and defrost because I've no energy to get up and do it.' (8)

'I had no energy. I didn't want to do anything. I didn't want to go anywhere.' (9)

Almost half the patients related their fatigue to a sensation of weakness in their legs:

'I felt my legs wouldn't support me.' (1)

'By the time I get to the top of the stairs my legs are shaking.' (3)

'I went a walk and one of the streets is quite a brae [hill] and by the time I got to the top of it I thought, God Almighty, my legs are sore...right at the top of my legs.'
(3)

'I could virtually hardly move my legs I was so tired...even trying to go into the kitchen and walk up and down the stairs, my legs weren't my own.' (5)

'You lie there and say to yourself, give yourself a shake and get up and do something. You can't though, your legs just won't take you.' (8)

Patients were able to describe the impact of their fatigue both on their functional ability and their psychological status. Two of the nine patients involved were still working, although this was flexible working and they only went to work if they felt able to do so. In relation to their functional ability, it is interesting to note that many of the patients' concerns related to the impact of fatigue on their ability to perform household chores.

'I know that I'll need to rest after today [receiving chemotherapy] so I washed my windows yesterday and my house is all tidied.' (3)

'I wouldn't even attempt the ironing if the score was a 2 because there's no point.'
(5)

'I would maybe Hoover and then have to sit down for an hour before getting up to do something else.' (3)

'I couldn't even do things like the shopping on my own or go into town. I'm just not able to do that. I just wouldn't attempt it.' (6)

'I couldn't Hoover and when he [her husband] offered to do it for me, I said no because I couldn't even bear the sound of it.' (7)

More general aspects of daily life were affected too.

'It's OK up to a [score of] 3 but when it gets to a [score of] 4 or 5, it did interfere with life, probably about 7 or 8 o'clock at night I'd go for a wee lie down instead of watching the telly.' (2)

'He [her husband] can come in from work and be talking to me and the next time he turns around I'm out for the count.' (7)

'I'm still so tired, I've seen me not answer the phone 'cause I can't be bothered moving or talking to anyone.' (8)

'I didn't do very much at all.' (6)

'Sometimes I don't even want to talk.' (1)

'I couldn't really concentrate much, I usually read a lot but I couldn't be bothered.'
(9)

Patients closer to the start of their treatment (those interviewed following cycles 1 and 2) were concerned and unsure about their future fatigue experiences:

'I don't know how it'll be this time because it was really different [worse] this last time from the first time.' (2)

'I just hope it isn't like this the whole way through.' (5)

'Some days it's fine and the next day I fully expect to feel the same but for some reason I'm really tired, I don't understand it.' (7)

However, some of the patients who were further on in their treatment (following cycles 3 and 5) had identified a pattern in their fatigue and were able to use this knowledge to rationalise their fatigue experiences. This did not vary between the intervention or control sites:

'Oh it definitely gets less [the weeks between cycles of treatment], I still have the weakness in my legs although it's not as bad, nothing to the extent it was the first and second weeks after the chemo, because those weeks I don't walk, I shuffle.' (1)

'It gets worse before it gets better. As the weeks go on [between chemotherapy] I feel I have more energy.' (3)

When asked about the impact of their fatigue, some patients acknowledged the negative impact that their fatigue caused:

'Obviously it makes you upset and depressed.' (8)

'It was very frustrating and it got me down that day because I was so tired.' (5)

However, patients seemed reluctant to complain about fatigue, and not all patients perceived their fatigue negatively. They compared it favourably with other potential symptoms.

'I know that it's a side-effect and the way I look at it is at least I'm not being sick.'
(1)

'So I really should feel depressed, but I wouldn't say I was really.' (2)

'I can cope with this better than ulcers and thrush and stuff.' (4)

'I keep saying to myself, if it is only this bad for a few days, then I don't mind.' (7)

'I try not to let it drag me down, try to have a positive attitude.' (6)

Patients had developed a number of self-care strategies to help them manage their fatigue. Despite research-based evidence that advises against 'over-resting', the majority of patients' self-care focused on resting and going to bed. The reason for this self-care action may be because they had not been cautioned against 'over-resting'. Alternatively, it may be because resting when tired is such a common sense strategy. All patients interviewed mentioned at some point that they had no option but to lie down at some point in the days following their chemotherapy.

'I had looked at the website and it said don't fight tiredness, so I just went to bed...if you are tired you need to rest, right?' (1)

'When it comes on you, you have to lie down. You can try to fight it a wee bit but it's hard when it comes so severe, you have to lie down.' (2)

'I decided, that's it, I'm going to sleep, I'm going to lie down I'm that [so] tired.'
(6)

'There were days when I was really really tired and I was in bed most of the day.'
(7)

'When I got up in the morning I felt so terrible that I just had to lie back down again.' (3)

However, some patients had tried to incorporate exercise into their lives and use distraction to alleviate their fatigue. The use of these strategies did not vary between the intervention or control sites.

'I have quite a big garden and sometimes I'd walk to the end of it and have a wee look at the plants and stuff.' (1)

'Well, usually I would try to distract myself, but there [a score of 6] I couldn't do that, I would just go and lie down and not fight it.' (2)

'Even on the days when I'm so tired, I do try to do a bit of walking and stuff like that...even if you don't go far.' (4)

'I have been reading a lot and sitting out and going for runs in the car, that sort of thing.' (7)

'I just take each day as it comes, see how I feel when I wake up.' (3)

Patients were able to evaluate the effectiveness of their self-care. In the main, resting and going to bed was viewed positively.

'It made you feel better, even though I still had that lethargic feeling, I think when you wake up you do feel a bit better.' (1)

'The best thing for it is going to bed, I think it does help if you are really tired, aye it definitely helps.' (2)

'I felt better there [pointing to a lower fatigue score] because I stayed in and rested there [pointing to the four days previously].' (3)

'When you have a sleep you feel better for a wee while, then I still feel tired.' (5)

'Oh yeah, you always do feel better after a sleep.' (7)

'Oh, I'd sleep no bother but I didn't feel any better when I woke up, I'm just as tired.' (8)

Although much less common, distraction and exercise were also viewed positively for their impact on fatigue by a small number of patients

'Yes, getting out helps. It is too easy just to go to your bed or lie on the couch or whatever, you know? You need to get out and get a bit of fresh air, something like that. Even if you don't go far it is just the fact of getting out.' (4)

'Just getting out in the fresh air, even if I'm just sitting or in the car, it makes you feel so much better, like yourself again.' (7)

'If you try to go out a wee bit it helps. If you're sitting in it preys on your mind that you're ill.' (8)

As with nausea, the concept of 'normality' was raised in relation to trying to live with fatigue

'I try and do it every day, go in the shower that is, even if I'm really tired because that's part of your normal routine.' (1)

'It's been better this past week. I've even been back at work this past Tuesday, Wednesday and Thursday, and that makes me feel that I'm just a normal person again.' (5)

'Just the other night we sat out in the garden and I felt fine and we just said, this feels like normal again.' (3)

'When it was a [score of] 2, I could do normal things, just maybe go to bed earlier than normal.' (6)

'I was surprised because I didn't think I could feel like I did, I was just normal.' (6)

'I'm trying to keep my job going, I just work from the house you see, trying to keep it normal but concentrating is hard.' (8)

'I just wasn't myself, wasn't normal. But I've been fine this last week, I've felt more or less like my normal self.' (9)

Thus, exploring and describing chemotherapy-related fatigue has shown that fatigue has a relatively constant presence in the 14 days following chemotherapy administration with a potential to peak around day 6. Fatigue, unlike nausea, increased with each subsequent cycle of chemotherapy with a greater increase in patients' reported distress rather than severity of fatigue although these results should be viewed with caution as they are based on a reducing sample. Patients were keen to describe their fatigue experiences. Their descriptions focused on a loss of strength and energy. When discussing the impact of fatigue on functional ability, patients all focused on their ability to undertake household chores – this is perhaps a consequence of an all-female sample. Some patients who were at the start of their chemotherapy expressed concerns about how they would cope with the fatigue of future cycles, whereas those patients further on in their treatment were better able to predict their patterns of fatigue. Patients did acknowledge the negative impact that fatigue had for them, but tended to compare it favourably with other potential symptoms, despite the fact these were not always symptoms that the patients had actually experienced. Self-care strategies focused on rest and sleep and these were

evaluated positively. Other strategies such as distraction and exercise were also rated positively. As with nausea, patients were keen to keep life as ‘normal’ as possible and the concept of trying to maintain normality in the face of fatigue was frequently raised.

8.3.3 Summary

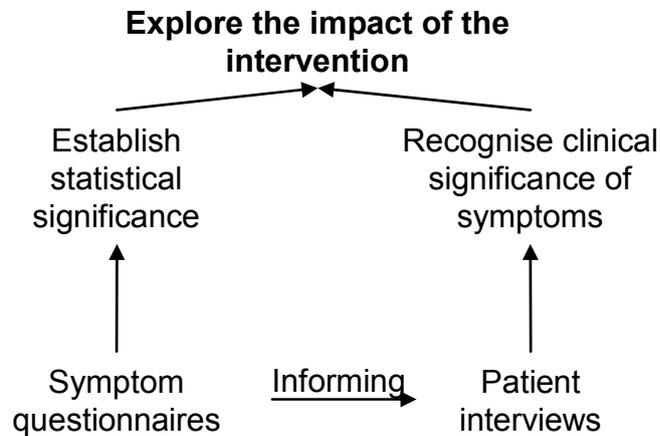
To conclude this section on describing and exploring chemotherapy-related nausea and fatigue, it is clear that both these symptoms have a negative impact on the lives of the patients in this study. However, there the similarities end. Nausea is experienced predominantly in the first 3 days following chemotherapy, whereas fatigue has a more constant presence across all 14 days post-treatment, with a slight peak around day 6. Furthermore, experiences of nausea remain relatively static over cycles of chemotherapy while fatigue shows an incremental increase with each cycle (although based on a reducing sample). The scores assigned to nausea were also, in the main, considerably lower than those of fatigue, although there was a significant correlation between total symptom scores. The results of this exploration will be used to inform the exploration of the study’s intervention in the following section.

8.4 Exploring the intervention

The second aim of this study was to explore the impact of the intervention on experiences of chemotherapy-related nausea and fatigue. Quantitative data, in the form of symptom scores from symptom questionnaires, and qualitative data, in the form of patients’ explanations about their symptom scores, were explored to meet

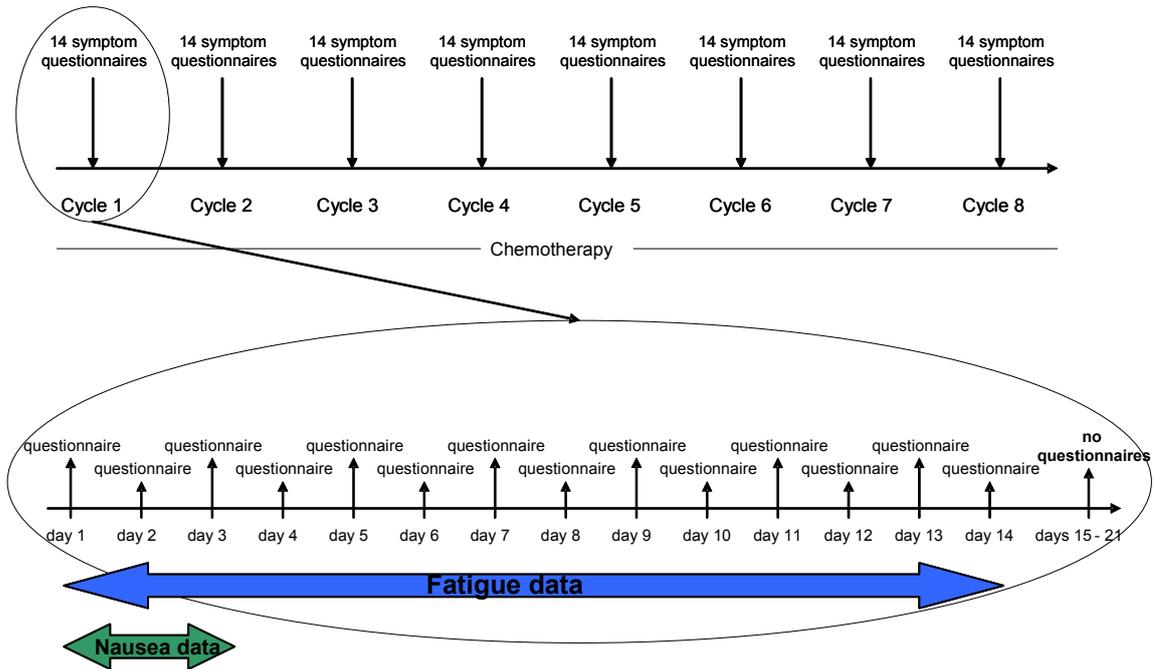
this aim. Figure 42 demonstrates how these two research methods blend to achieve this for both nausea and fatigue.

Figure 42: Blending of techniques to explore the intervention



As highlighted in the previous section, a vast amount of quantitative data was generated from the symptom questionnaires. This data was longitudinal in nature, both within cycles of chemotherapy (days 1-14) and across cycles of chemotherapy (cycles 1-8) and can be found in Appendix P. However, it is most appropriate to explore the impact of an intervention on a symptom at the time when the symptom is experienced most, as this is the time when differences in symptoms are most likely to be seen. The descriptive results above demonstrated that nausea was experienced, in the main, between days 1-3 while fatigue had a relatively constant presence across all 14 days of data collection. Therefore, the quantitative analysis to explore the impact of the intervention utilised nausea data from days 1-3 only and fatigue data spanning all 14 days for all cycles of chemotherapy (see Figure 43).

Figure 43: Selection of data for quantitative analysis



Exploring the impact of the intervention involves comparing symptom outcomes between the 4 patient groups. Given that the aim of this exploration is to conclude whether or not the intervention resulted in a statistically significant improvement in symptom outcomes, a summary statistic was generated for both nausea and fatigue for each individual patient. These summary statistics were then compared between each patient group using an appropriate test. The choice of summary statistic was the mean (the sum of all the values in the group divided by the number of values in the group) of the **total** symptom score as this represents patients' full symptom experience, encapsulating both severity and distress scores. The mean was chosen as it gives the 'average' symptom experience. The mean is sensitive to extreme scores, however, using the mean score was not envisaged to be problematic for this study, because the symptoms were being evaluated at the time they were experienced

most, that is, days 1-3 for nausea, and days 1-14 for fatigue, and consequently, the time when most extreme scores were recorded. Indeed, it would have been inappropriate to explore the impact of the intervention on nausea using data from all 14 days as the data from days 4-14 would have dampened the mean, making it a poor reflection of the true symptom experience. Figure 44 below shows how the data was collated and the way in which a mean score was generated for each patient, dependent on their questionnaire returns.

Figure 44: Data collation and generation of mean scores for nausea and fatigue

	Patient 1	Patient 2	Patient 3
Cycle 1	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,missing data,11,12,13,14
Cycle 2	1,2,3,4,5,6,7,8,9,10,11,12,13,14	Missing data	1,2,3,4,5,6,7,8,9,10,missing data
Cycle 3	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1, missing data,7,8,9,10,11,12,13,14
Cycle 4	1,2,3,4,5,6,7,8,9,10,11,12,13,14	Missing data	1,2,3,4,5,6,7,8,9,10,11,12,13,14
Cycle 5	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,6,7,8,9,10,11,12,13,14	
Cycle 6	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,6,7,8,9,10,11,12,13,14	
Cycle 7	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,6,7,8,9,10,11,12,13,14	
Cycle 8	1,2,3,4,5,6,7,8,9,10,11,12,13,14	1,2,3,4,5,6,7,8,9,10,11,12,13,14	
	↓	↓	↓
	Nausea – mean of 24 responses Fatigue – mean of 112 responses	Nausea – mean of 18 responses Fatigue – mean of 84 responses	Nausea – mean of 10 responses Fatigue – mean of 42 responses

Patient discontinued participation, therefore data not considered missing

The following sections present the results of the exploration of the intervention on patients' experiences of nausea and fatigue.

8.4.1 Nausea

8.4.1.1 Differentiating between levels of nausea

Patients were able to clearly distinguish between the presence and absence of nausea and were consistent in their sense of relief when their nausea was resolved:

'I would get a good day [nausea score of 0] and feel better, able to do everything, and you think oh that's it gone, that's great, and next day you feel that bad again.'

(4)

'...yes, that was it gone [a score of 0], it seemed to be going on longer this time, but that was it gone' (2)

'A couple of days and it settled down [to a score of 0] and I was fine. Thankfully, I didn't experience any more sickness or nausea this time' (5)

'...there, when it went away altogether [a score of 0], I felt great again' (8)

'...you have a good day [a score of 0] and then a couple of bad days, [scores of 1 and 2] and then good days again and it's gone and you feel fine again, til the next time [cycle of chemotherapy].' (9)

They were less able to distinguish between different levels of nausea in terms of how they felt in general:

'It's difficult to explain, it's probably more or less the same [between a score of 1 and 2]' (9)

'Just a stronger feeling than the day before, I don't know how else to describe it [comparing a score of 1 and 2].' (5)

'It just felt worse than it did the day before, yeah, just the same feelings but worse [comparing a score of 2 and 3].' (4)

Patients tried to describe their functional abilities at varying total scores of nausea and explain any differences in their abilities, but found it difficult to distinguish between scores of 1 and 2:

'I have been practically able to do everything I would normally do [at a score of 1], but I'd be feeling a bit seedy.' (4)

'...[nausea at a score of 2] didn't bother me a lot, I could get on with things.' (2)

'You try not to let it get to you, just try to get on with things but it's always there, even when it was a score of one or two, just always there' (5)

Although just two patients reported total nausea scores of 3 and above, they were able to define the impact of nausea at these higher scores in relation to their functional abilities noting,

'It actually stops me going out and socialising.' (8)

'It stops me driving, I can't drive with it like that.' (4).

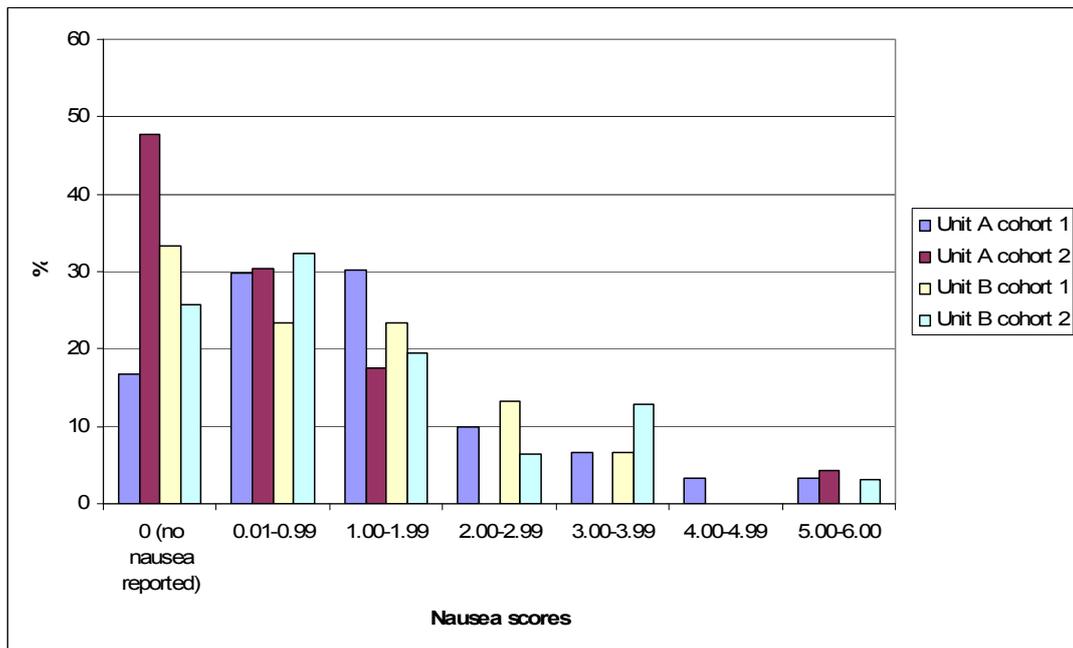
'you can't go out, you can't go anywhere, you can't do anything.' (8)

Thus, while patients found it difficult to distinguish between lower total nausea scores, higher scores (whilst less frequent and still being individually experienced) had a greater impact on function.

8.4.1.2 Exploring the impact of the intervention – cycles 1-8

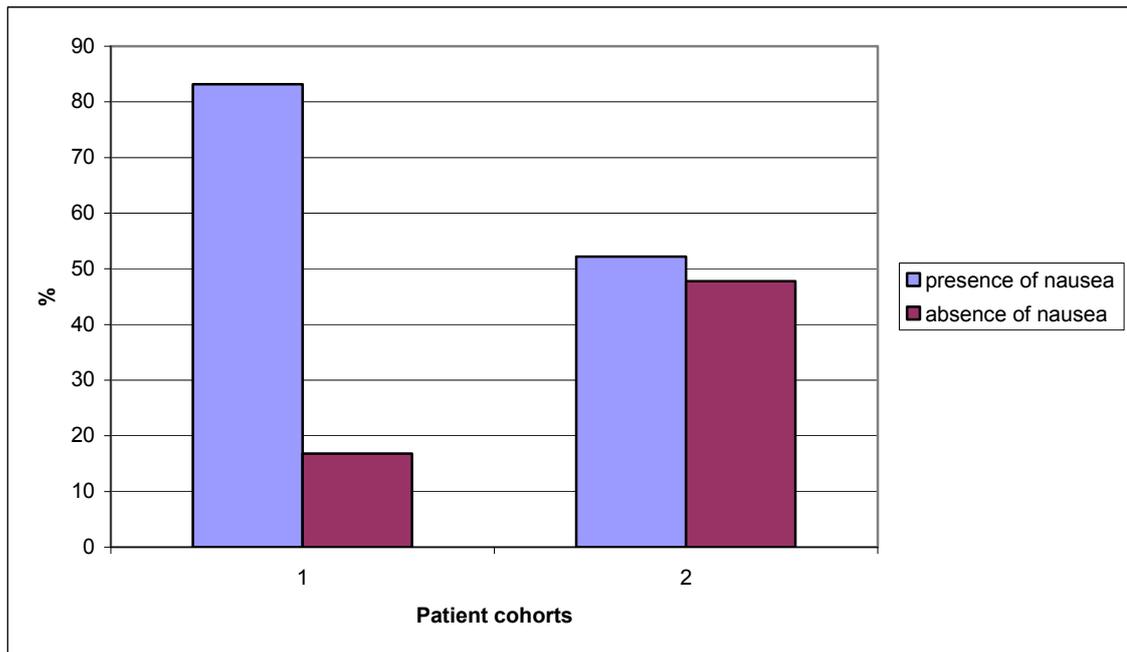
A basic evaluation of the impact of the intervention on nausea can be undertaken by looking at the range of nausea scores between the patient groups. Figure 45 depicts the range of nausea scores in the 4 patient groups.

Figure 45: Range of nausea scores (cycles 1-8)



The most notable aspect of this is the difference in the percentage of patients who did not experience any nausea in Unit A, cohort 2 (following the introduction of the intervention): 47.8% of patients reported no nausea compared with 16.8% before the SNA↔P intervention (see Figure 46).

Figure 46: Unit A - presence and absence of nausea (cycles 1-8)



Chi square analysis demonstrates that this is a statistically significant difference (chi sq 5.998, df 1, $p=0.014$). Separate chi square analysis of those patients receiving chemotherapy with curative and palliative intent did not demonstrate a significant difference (curative intent $p=0.116$, palliative intent $p=0.180$). This analysis suggests that the significant effect is not restricted to either treatment intent group, although this is most likely because of small patient numbers in each group (chemotherapy with curative intent: cohort 1 no nausea $n=3$, nausea $n=11$, cohort 2 no nausea $n=9$, nausea $n=10$, chemotherapy with palliative intent: cohort 1 no nausea $n=2$, nausea $n=13$, cohort 2 no nausea $n=1$, nausea $n=1$). Chi square analysis comparing the presence and absence of nausea between cohorts 1 and 2 of Unit B show no statistically significant difference (chi sq 0.415, df 1, $p=0.519$).

Nausea symptom outcome data were not normally distributed – see boxplots in Figure 47, and mean total nausea scores are presented in Table 25.

Figure 47: Boxplots for mean nausea scores (cycles 1-8)

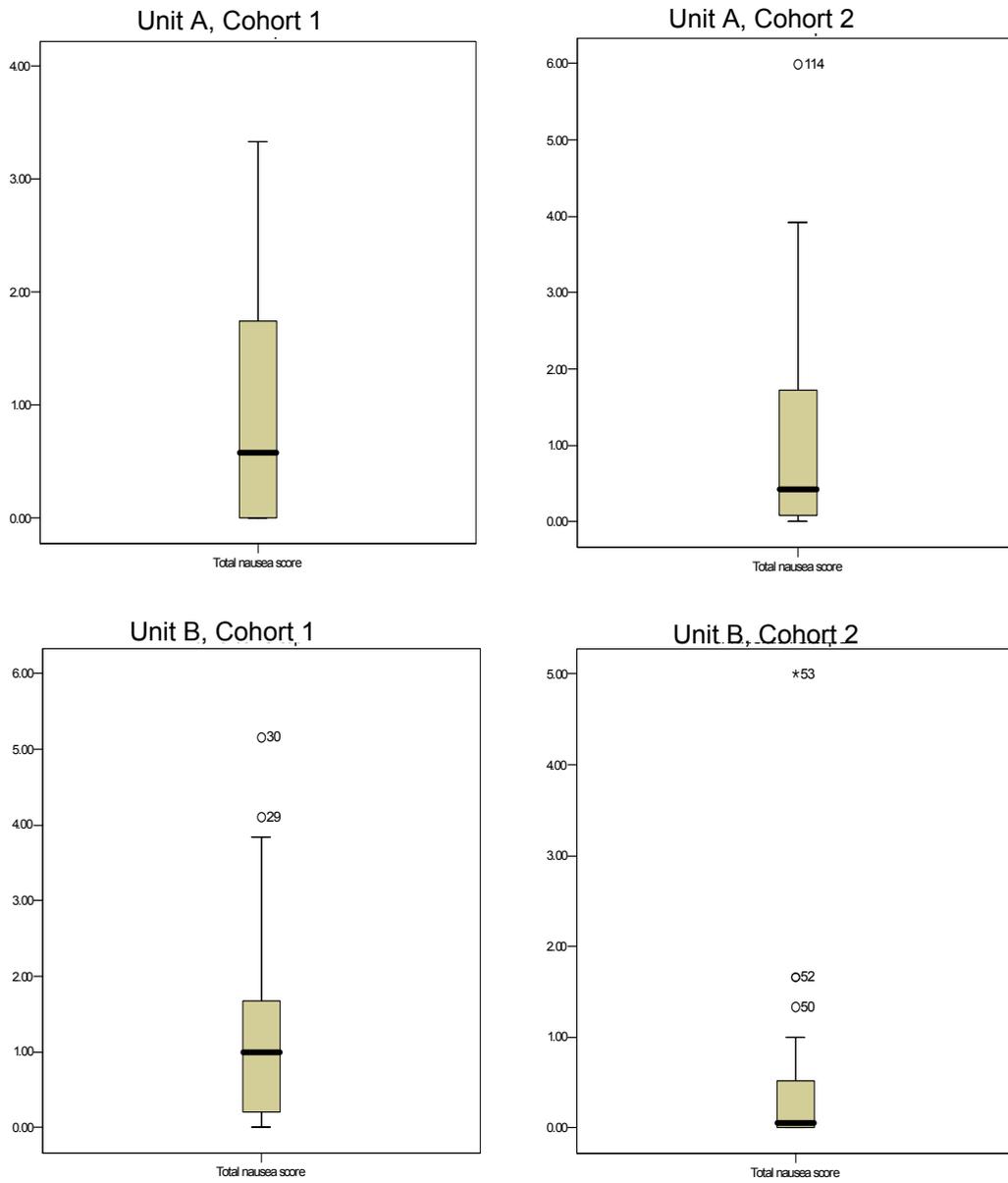


Table 25: Mean total nausea scores (cycles 1-8) (range 0-6)

Unit A Cohort 1	Unit A Cohort 2	Unit B Cohort 1	Unit B Cohort 2
1.27	0.56	0.94	1.17

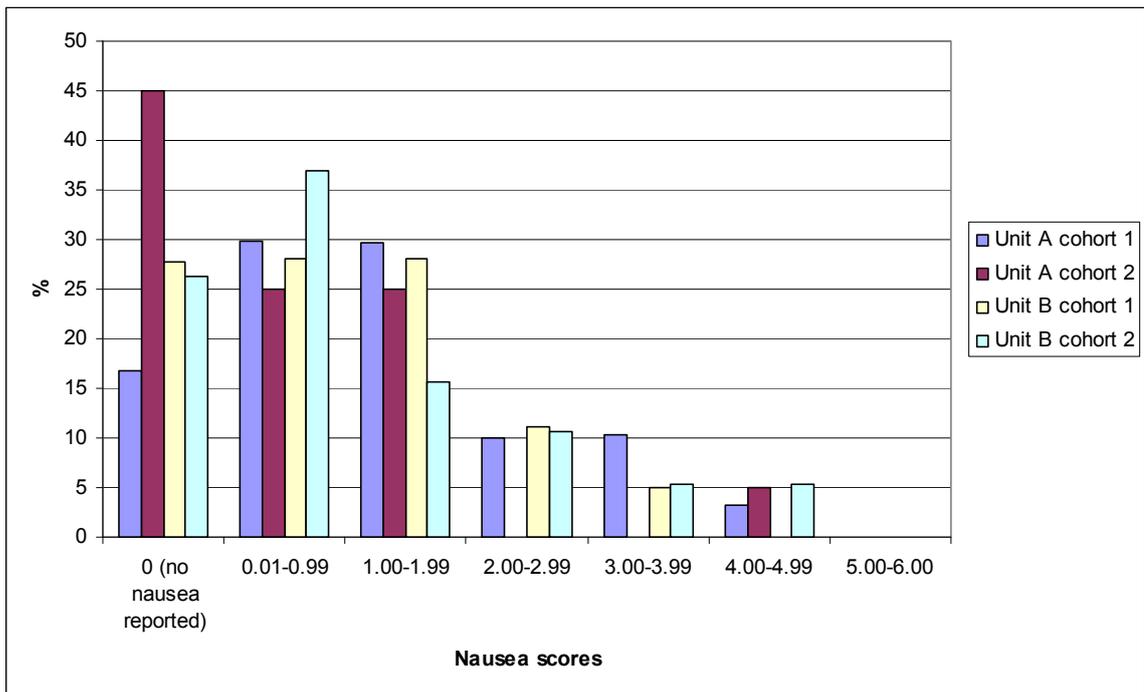
The appropriate approach to compare mean total nausea scores was the non-parametric Kruskal-Wallis test. This test showed no statistically significant differences between patient groups (Chi sq 7.154, df 3, $p=0.067$). Given this borderline level of significance, an ANOVA was performed, as it may have been more sensitive to differences in grades of nausea. This ANOVA confirmed a lack of statistically significant differences in mean total nausea scores between patient groups ($p=0.203$).

This analysis shows that there is a statistically significant intervention effect in relation to the presence and absence of nausea. As patients were able to distinguish between having and not having nausea during interviews, this result also has personal significance. There is no statistical support for an intervention effect on grades of nausea.

8.4.1.3 Exploring the impact of the intervention – cycles 1-4

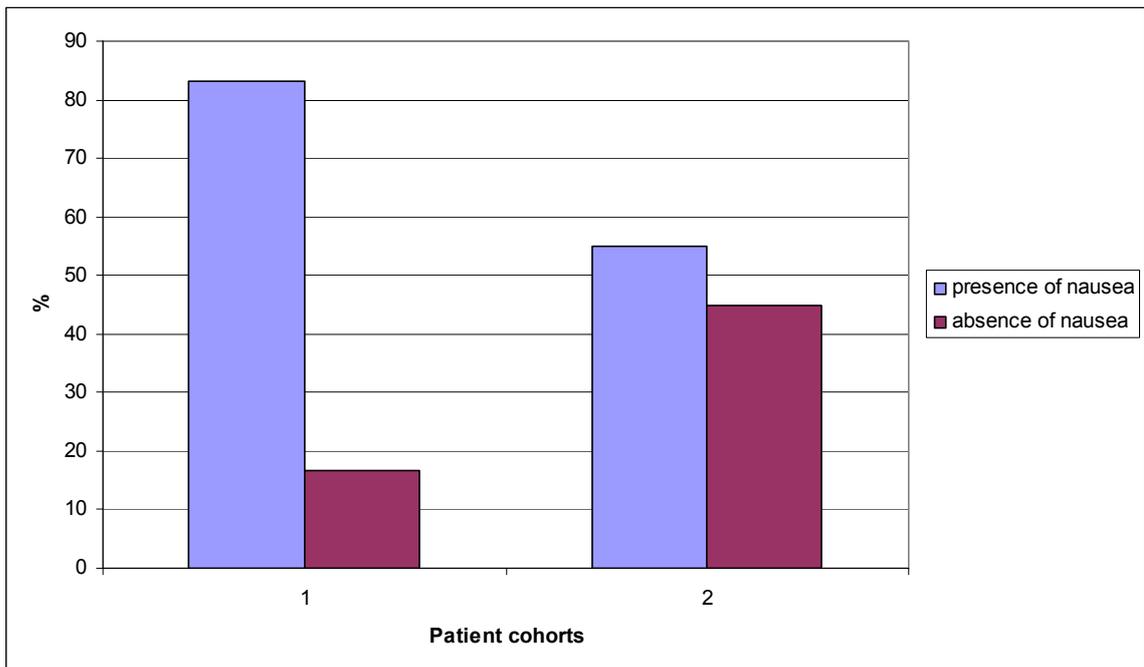
A basic evaluation of the impact of the intervention on nausea during the first 4 cycles of chemotherapy can be undertaken by looking at the range of nausea scores between the patient groups. Figure 48 depicts the range of nausea scores in the 4 patient groups.

Figure 48: Range of nausea scores (cycles 1-4)



The most notable aspect of this is the difference in the percentage of patients who did not experience any nausea in Unit A, cohort 2 (following the introduction of the intervention): 45% of patients reported no nausea compared with 16.8% before the SNA↔P intervention (see Figure 49).

Figure 49: Unit A - presence and absence of nausea (cycles1-4)



Chi square analysis demonstrates that this is a statistically significant difference (chi sq 4.778, df 1, p=0.029). Separate chi square analysis of those patients receiving chemotherapy with curative and palliative intent did not demonstrate a significant difference (curative intent p=0.220, palliative intent p=0.161). This analysis suggests that the significant effect is not restricted to either treatment intent group, although this is most likely because of small patient numbers in each group. Chi square analysis comparing the presence and absence of nausea between cohorts 1 and 2 of Unit B show no statistically significant difference (chi sq 0.013, df 1, p=0.908).

Nausea symptom outcome data were not normally distributed – see boxplots in Figure 50, and mean total nausea scores are presented in Table 26.

Figure 50: Boxplots for mean nausea scores (cycles 1-4)

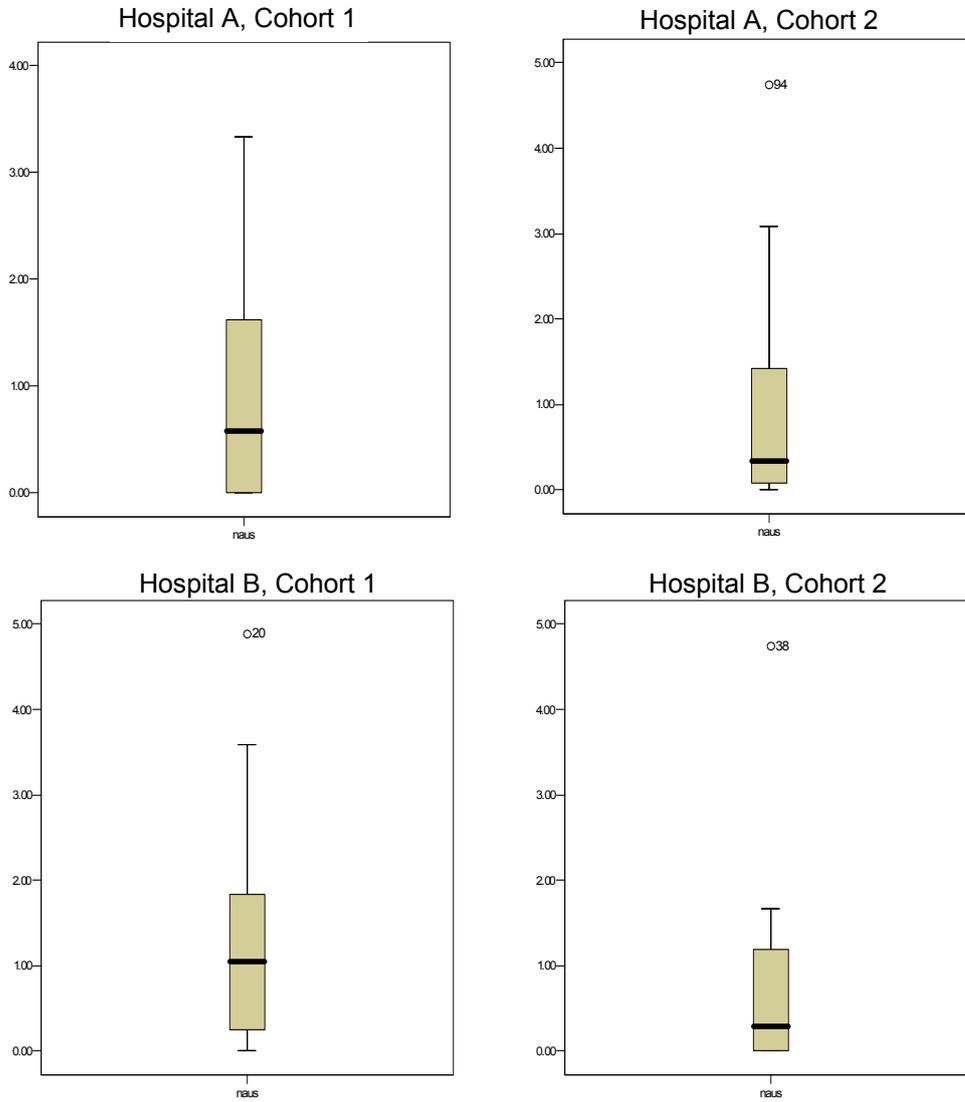


Table 26: Mean total nausea scores (cycles 1-4) (range 0-6)

Unit A Cohort 1	Unit A Cohort 2	Unit B Cohort 1	Unit B Cohort 2
0.91	1.03	1.25	0.72

The appropriate approach to compare mean total nausea scores was the non-parametric Kruskal-Wallis test. This test showed no statistically significant differences between patient groups (Chi sq 4.006, df 3, p=0.261).

This analysis shows that there is a statistically significant intervention effect in relation to the presence and absence of nausea during the first 4 cycles of chemotherapy. As patients were able to distinguish between having and not having nausea during interviews, this result also has personal significance. There is no statistical support for an intervention effect on grades of nausea during the first 4 cycles of chemotherapy.

8.4.2 Fatigue

8.4.2.1 Differentiating between levels of fatigue

Fatigue scores varied between patients. Within each patient's report, fatigue often spanned the full range of scores possible (0-6). Patients were able to appreciate differences in their fatigue experiences at different scores, most often based on functional ability.

A score of 1

'A score of 1 was good. I would be tired but it wouldn't stop me doing things, but I would be tired doing them. I'd just feel like I need a nap, I need a nap.' (5)

'I could live at that level all the time [a score of 1], that would be fine.' (7)

A score of 2

'I wasn't doing the things I'd normally do but I was doing the necessary. I had to make myself move to do anything.' (9)

'It was a relief because you felt you were coming back to normal at a score of 2 [compared with a score of 4].' (8)

A score of 3

'I am able to do less [at a score of 3 compared with 2], I thought, I'd better put that ironing away as I've been in bed all morning. I went upstairs and hung up a couple of things and was exhausted. I had to sit on the bed.' (1)

'I just don't feel that I can do the things that I normally can do.' (4)

'I was feeling weak and didn't want to drive the car and I couldn't walk far, so I didn't go out those days [when the score was 3 or above] I just stayed in nearly every day.' (9)

'I don't go the gym on days like that [score of 3 or above].' (2)

'I couldn't go up and down the stairs those days, that made me stay in.' (3)

A score of 4

'I was definitely more active when the score was 4 than when it was 5.' (7)

A score of 5

'When it was a [score of] 5 I was sleeping till lunchtime. I remember one of the days I woke up and was hungry but I just couldn't be bothered getting out of bed.'
(8)

'It felt much worse [than a score of 4].' (2)

'I was holding onto the [supermarket] trolley, it was a terrible terrible tiredness that I couldn't shake off. It was horrible.' (5)

'All the time the score was a 5 I couldn't get out of bed.' (1)

'The days it was a [score of] 5 was just the pits, I was so so tired, absolutely no energy at all. Even trying to go into the kitchen for a glass of juice was such a chore.' (5)

A score of 6

'I wouldn't say it was twice as bad [a score of 6 compared with a score of 3] but it was definitely worse.' (2)

'I was dead tired, y' know what I mean?...couldn't do a thing.' (6)

'A few days into it and I just feel that I am floored there [pointing to a score of 6]. I am just so tired.' (5)

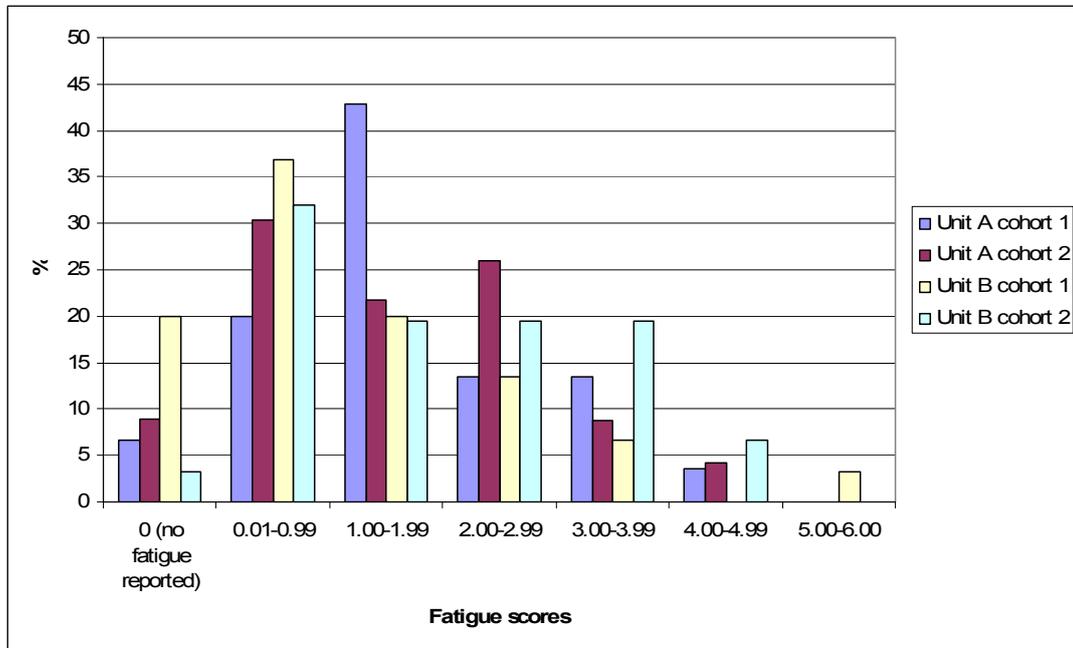
Thus, while patients described their experiences in their own ways, demonstrating the individuality with which the symptom is experienced, there is general agreement that scores of 1 and 2 are manageable, scores of 3 and 4 affect functional abilities while scores of 5 and 6 have significant deleterious effects on their lives.

8.4.2.2 Exploring the impact of the intervention – cycles 1-8

An evaluation of the impact of the intervention on fatigue can be undertaken by looking at the range of fatigue scores between the patient groups - see Figure 51. Chi square analysis demonstrates that there is no statistically significant difference

in the presence or absence of fatigue between cohorts 1 and 2 of either Unit A (chi sq 0.77, df 1, p=0.782) or Unit B (chi sq 3.683, df 1, p=0.06).

Figure 51: Range of fatigue scores (cycles 1-8)



Fatigue total symptom score data were relatively normally distributed (see Figure 52) and the mean total scores are presented in Table 27.

Figure 52: Boxplots for fatigue (cycles 1-8)

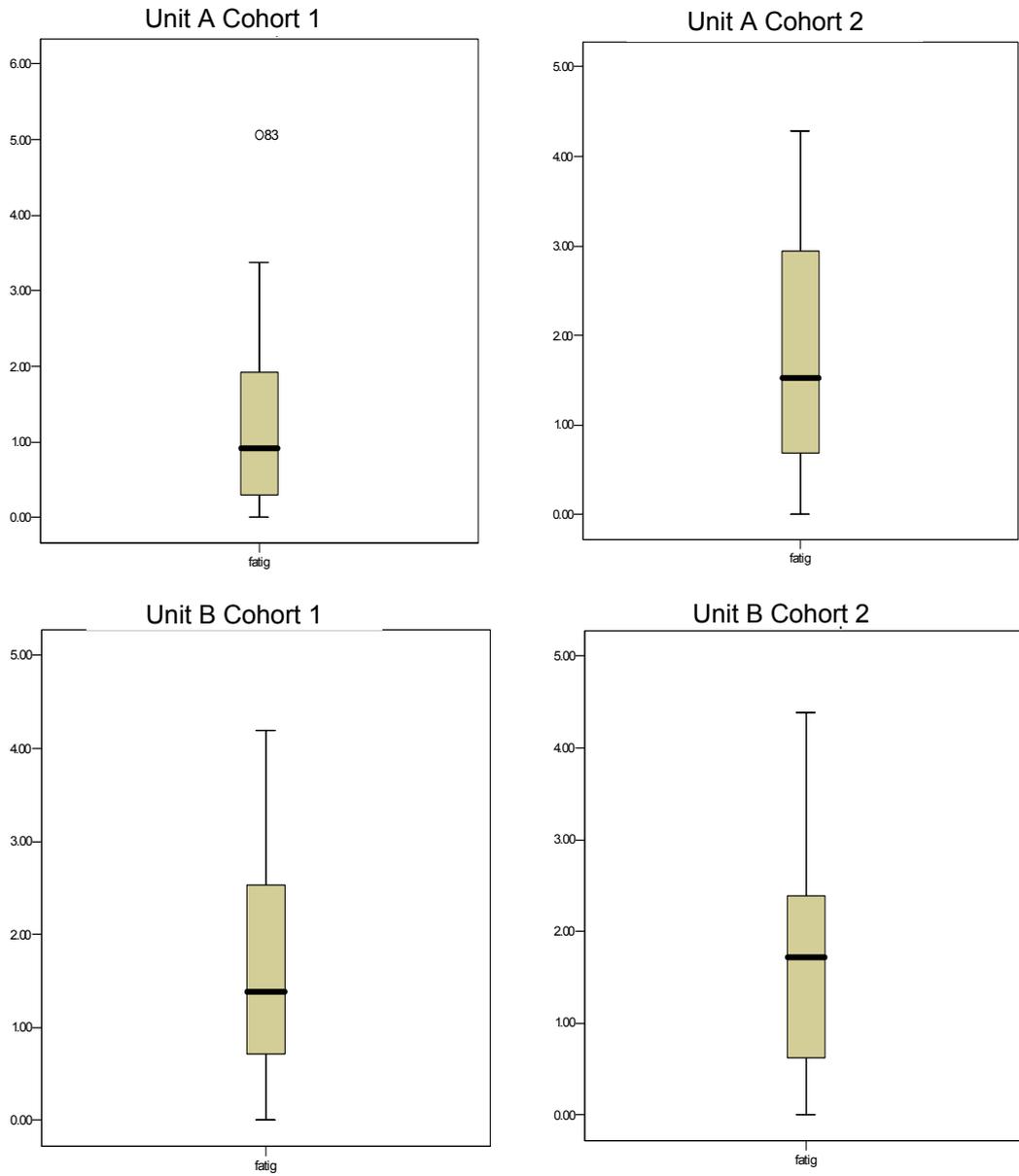


Table 27: Mean total fatigue scores (cycles 1-8) (range 0-6)

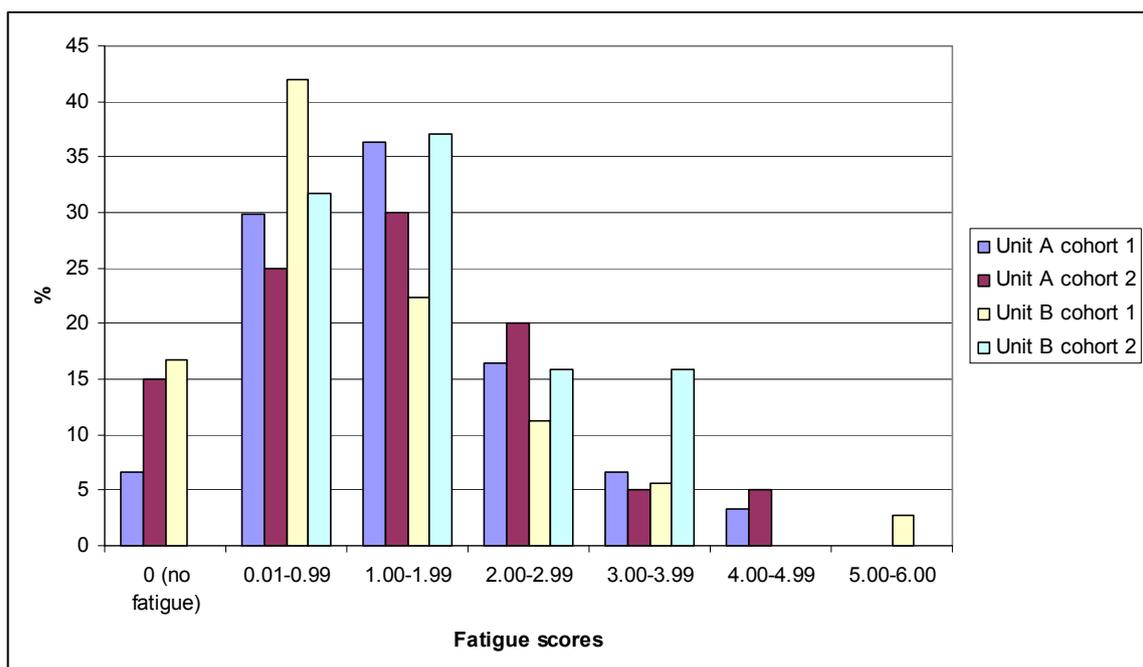
Unit A Cohort 1	Unit A Cohort 2	Unit B Cohort 1	Unit B Cohort 2
1.61	1.63	1.11	1.76

An ANOVA of the 4 patient groups showed that there were no statistically significant differences in mean total fatigue scores ($p=0.196$). This was supported by a Kruskal-Wallis test which also reported no statistically significant differences between mean total fatigue scores (chi sq 6.492, df 3, $p=0.090$). Thus, despite the fact that the majority of patients from all 4 groups reported some level of fatigue during their chemotherapy, no statistically significant results were found to support the impact of the SNA↔P intervention on patients' fatigue experiences.

8.4.2.3 Exploring the impact of the intervention – cycles 1-4

An evaluation of the impact of the intervention on fatigue during the first 4 cycles of chemotherapy can be undertaken by looking at the range of fatigue scores between the patient groups - see Figure 53. Chi square analysis demonstrates that there is no statistically significant difference in the presence or absence of fatigue between cohorts 1 and 2 of either Unit A (chi sq 0.926, df 1, $p=0.336$) or Unit B (chi sq 3.554, df 1, $p=0.06$).

Figure 53: Range of fatigue scores (cycles 1-4)



Fatigue total symptom score data were relatively normally distributed during the first 4 cycles of chemotherapy (see Figure 54) and the mean total scores are presented in Table 28.

Figure 54: Boxplots for fatigue (cycles 1-4)

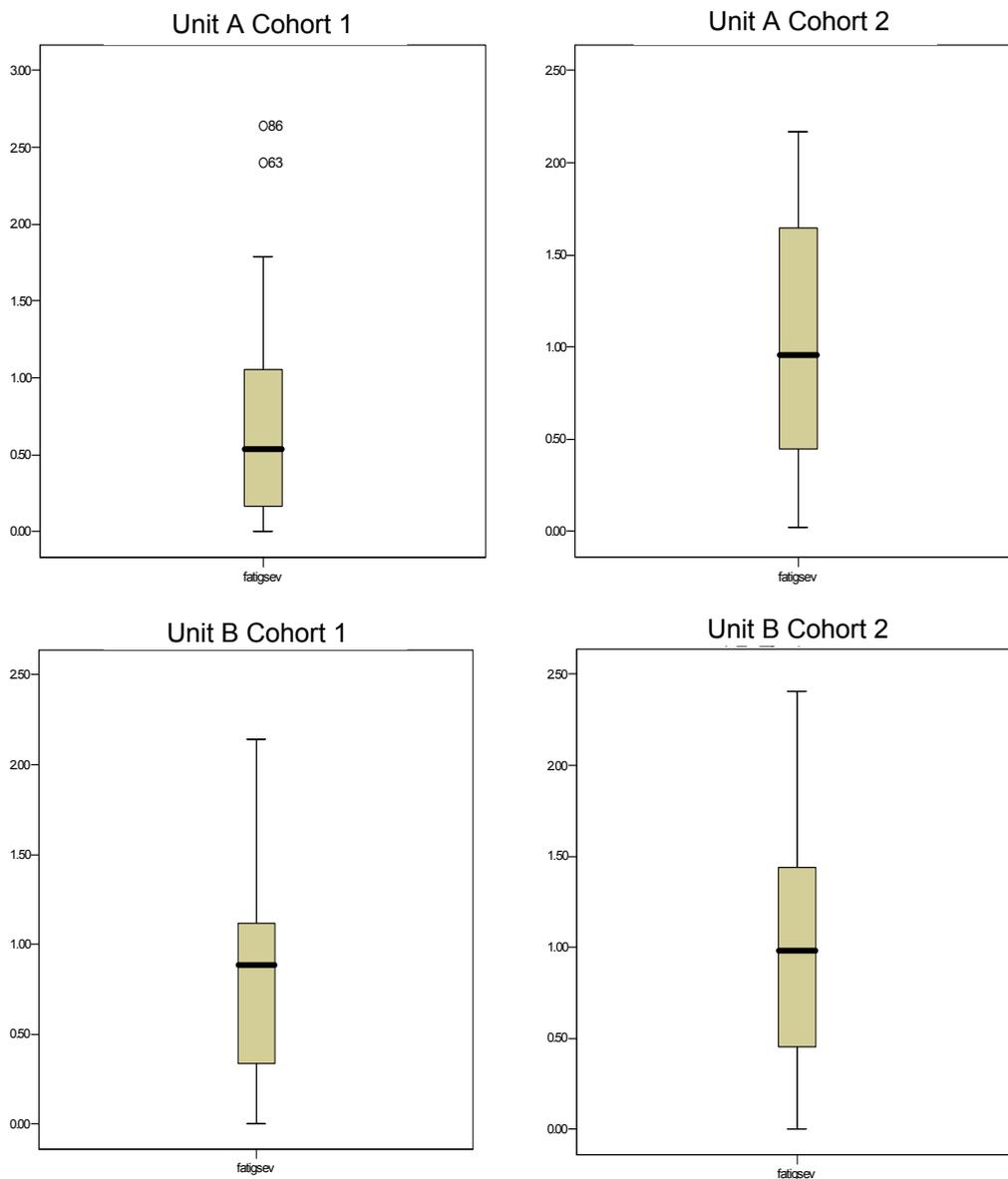


Table 28: Mean total fatigue scores (cycles 1-4) (range 0-6)

Unit A Cohort 1	Unit A Cohort 2	Unit B Cohort 1	Unit B Cohort 2
1.10	1.49	1.47	1.51

An ANOVA of the 4 patient groups showed that there were no statistically significant differences in mean total fatigue scores ($p=0.441$). This was supported by a Kruskal-Wallis test which also reported no statistically significant differences between mean total fatigue scores (chi sq 4.319, df 3, $p=0.229$). Thus, despite the fact that the majority of patients from all 4 groups reported some level of fatigue during their first 4 cycles of chemotherapy, no statistically significant results were found to support the impact of the SNA↔P intervention on patients' fatigue experiences.

8.4.3 Summary

The SNA↔P intervention did have a significant effect on the presence and absence of patients' experiences of nausea in the intervention site which was further supported by clinical significance data from patients' interviews. However, this positive effect was not demonstrated in the analysis of levels of nausea experiences. No statistically significant differences in total fatigue scores were identified in relation to not only the presence and absence of fatigue, but also levels of fatigue between the 4 patient groups.

8.5 Evaluating the impact of the intervention

The overarching aim of this study was to evaluate the impact of the implementation of a nurse-led intervention, incorporating structured nursing assessment and practice, on the symptoms of nausea and fatigue experienced by women receiving chemotherapy for breast cancer. Figure 55 illustrates how through exploring and describing symptoms, in tandem with exploring the intervention, informed conclusions about the impact of the intervention can be drawn.

Figure 55: Evaluation of the intervention

Key aspects that should be considered in this final evaluation are:

1. How were nausea and fatigue experienced by patients? What did nausea and fatigue mean to them?
2. Was there any reduction in the percentage of patients actually experiencing either nausea or fatigue as a consequence of the intervention?
3. Was there a reduction in the mean levels of either nausea or fatigue as a consequence of the intervention?

Both nausea and fatigue were experienced by patients and distinct patterns for both symptoms were identified. While nausea was, in the main, mild and short-lived following chemotherapy administration (whether that was on day 1 or 8 of a chemotherapy cycle), fatigue was persistent, scored higher than nausea and experienced across all 14 days of data collection. This incidence was reflected in the patient interviews – patients tended to accept nausea as a symptom to be tolerated

and that would abate, while fatigue appeared to have an increased and sustained impact on patients' functional abilities and psychological well-being.

The evaluation of the SNA↔P intervention resulted in a statistically significant difference in the percentage of patients experiencing nausea, with significantly fewer patients experiencing nausea in cohort 2 of Unit A compared with cohort 1. Information from patient interviews demonstrates that this difference is not only statistically but also personally significant.

While patients' descriptions of fatigue were undoubtedly individual, there was general agreement about the impact that various grades of fatigue had on their lives. No statistically significant differences were seen between patient groups in relation to the presence and absence of fatigue, nor levels of fatigue.

8.6 Conclusion

This chapter has presented the full results of the SNA↔P study. It has described symptoms of chemotherapy-related nausea and fatigue, showing patterns of symptoms and providing rich descriptions of the meaning and impact of nausea and fatigue experiences for patients. It has also evaluated the intervention in relation to the presence and absence of nausea and fatigue between patient groups as well as the mean total symptom scores while considering potentially confounding variables. Finally, it has drawn conclusions about the overarching aim of the study – the evaluation of the impact of the SNA↔P intervention, proposing that, although the intervention had a positive effect on chemotherapy-related nausea (in relation to its presence and absence), a similar impact was not seen in relation to chemotherapy-related fatigue. These findings will be discussed in the following chapter.

9 CHAPTER 9 – DISCUSSION

9.1 Introduction

This chapter gives a brief overview of the results of the SNA↔P study before considering both its key aspects, and its limitations. Based on these aspects, conclusions are then drawn on the contribution of the SNA↔P study and its implications for clinical practice and research are considered.

9.2 Overview of the results of the SNA↔P study

The SNA↔P study evaluated the impact of a nurse-led intervention based on structured assessment and practice on patients' experiences of chemotherapy-related nausea and fatigue. Using complementary quantitative and qualitative methods, the SNA↔P study had 3 key outcomes.

Firstly, distinct patterns of chemotherapy-related nausea and fatigue were demonstrated. Nausea was relatively short-lived, peaking during the first 3 days following chemotherapy, whereas fatigue had a more constant presence over the 14 days following chemotherapy administration. These patterns were enriched by patients' descriptions of their symptom experiences. Patients' descriptions of nausea reveal that this is an unpleasant symptom, although usually mild. While it does impact on patients' functional abilities, they have difficulty in differentiating between shades of nausea. Experiences of fatigue differ considerably from those of nausea. Patients were overwhelmed by their experiences of fatigue and were able to clearly differentiate between levels of fatigue and the impact each had on their functional abilities.

Secondly, the SNA↔P intervention had a significant positive effect on patients' experiences of nausea. Statistically fewer patients reported nausea following the implementation of the intervention. This result is supported in terms of personal significance as, during interviews, patients were clearly able to distinguish between experiencing nausea or not. The SNA↔P intervention did not impact on patients' experiences of fatigue. There were no statistically significant differences in patients' experiences of fatigue between any of the patient groups involved in the SNA↔P study.

Thirdly, the SNA↔P study demonstrated that an evidence-based intervention focusing on structured symptom assessment and management can be implemented in routine clinical practice.

9.3 Key aspects of the SNA↔P study

The following sections will describe the significant nature of specific components of the SNA↔P study.

9.3.1 *The intervention*

The SNA↔P intervention sought to influence the assessment and subsequent management of chemotherapy-related nausea and fatigue. It ensured structured longitudinal, multidimensional symptom assessment, as well as providing a method of identifying appropriate interventions for the symptoms reported through the structured assessment for each cycle of chemotherapy. While the same intervention was used in tandem as part of the WISECARE+ study, this was developed solely by MM (researcher and author of this thesis).

9.3.1.1 Fundamental aspects of the SNA↔P intervention

9.3.1.1.1 The relationship between symptom assessment and interventions

The SNA↔P intervention incorporated both symptom assessment and management, whereas previous research has focused on either the development of structured assessment tools for nausea (Rhodes et al. 1984; Morrow 1992; Lindley et al. 1992; Borjeson et al. 1997; Rhodes and McDaniel 1999) or fatigue (Rhoten 1982; Smets et al. 1995; Yellen et al. 1997; Schwartz 1998; Piper et al. 1998; Mendoza et al. 1999; Holley 2000b), or the implementation and evaluation of specific interventions, such as progressive muscle relaxation training (Arakawa 1995; Arakawa 1997; Molassiotis 2000; Molassiotis et al. 2002b; Yoo et al. 2005; de Carvalho et al. 2007) or psychoeducational support and information (Gaston-Johansson et al. 2000; Williams and Schreier 2004). The SNA↔P study took this link between symptom assessment and management a step further, not only implementing and evaluating them simultaneously, but also tailoring the recommended symptom management to the specific level of symptoms reported by patients within their assessment. Thus the generic ‘one size fits all’ approach to symptom management that requires patients to ‘fit’ symptom management information to their individual experiences was avoided.

9.3.1.1.2 Concurrent use of multiple interventions

A major feature of the SNA↔P intervention was in that it promoted the simultaneous use of a range of symptom management techniques, both pharmacological and non-pharmacological. Thus, while the intervention literature to date has sought to evaluate the benefits of single interventions such as antiemetic

drug therapies (Morrow et al. 1995; Roscoe et al. 2000), progressive muscle relaxation training (Arakawa 1995; Arakawa 1997; Molassiotis 2000; Molassiotis et al. 2002b; Yoo et al. 2005; de Carvalho et al. 2007), psychoeducational support and information (Gaston-Johansson et al. 2000; Williams and Schreier 2004), or music therapy (Standley 1992; Ezzone et al. 1998; Sahler et al. 2003) for the relief of nausea (and vomiting), none have drawn these therapies together and evaluated their simultaneous implementation. Likewise, the management of fatigue has tended to focus on individual interventions, such as exercise (MacVicar and Winningham 1986; Mock et al. 1994; Schwartz 1999; Mock et al. 2001; Schwartz et al. 2001; Mock et al. 2002; Courneya et al. 2007; Schneider et al. 2007), education and information (Given et al. 2002; Jacobsen et al. 2002; Barsevick et al. 2004; Yates et al. 2005), and measures to optimise sleep (Davidson et al. 2001; Berger et al. 2002; Berger et al. 2003; Quesnel et al. 2003; Savard et al. 2005), with multiple interventions, such as music therapy and relaxation for nausea (Sahler et al. 2003) or support and education for fatigue (Ream et al. 2006), being employed much more rarely.

9.3.1.2 Positive aspects of the SNA↔P intervention

9.3.1.2.1 Research-based

The SNA↔P intervention was evidence-based: the structured assessment, recommended interventions and methods of integrating and implementing the intervention in practice were all based on rigorous reviews of the literature. The multidimensional symptom assessment incorporated severity and distress assessment in recognition of the fact that the most intense symptom experiences are not consistently the most distressing for patients (Rhodes et al. 1984), and took into

account: the need for succinct clinical assessment rather than lengthy, potentially arduous assessments (Morrow 1992; Lindley et al. 1992; Rhodes and McDaniel 1999); addressing nausea as an entity in its own right, rather than as a component in nausea and vomiting as with many current assessment tools (Morrow 1992; Lindley et al. 1992; Rhodes and McDaniel 1999); the importance of self-assessment, rather than that of health professionals (Eisenberg et al. 2003; Grunberg et al. 2004; Liau et al. 2005). However, the use of an assessment tool with no evidence of reliability and limited validity, while a consequence of the SNA↔P study's association with the WISECARE+ study, can be criticised.

The interventions were research-based and, although many of these have not been evaluated in routine clinical practice (Standley 1992; Arakawa 1997; Ezzone et al. 1998; Molassiotis 2000; Dibble et al. 2000; Molassiotis et al. 2002b; Roscoe et al. 2003; Sahler et al. 2003; Yoo et al. 2005; de Carvalho et al. 2007; Molassiotis et al. 2007), the nurses of Unit A were supported by MM to develop ways of integrating some of the more unfamiliar and anxiety-provoking interventions, such as guided imagery and relaxation, using techniques previously shown to be successful for example, the use of tape recordings (Gaston-Johansson et al. 2000; Williams and Schreier 2004).

The processes of introducing, integrating and maintaining the intervention in clinical practice were carefully developed and implemented (see chapter 7).

Evidence utilisation is particularly challenging, as it requires investment at both the organisational and practitioner level (Pearson 2006). The SNA↔P study worked with nursing management and senior nurses, as well as those nurses involved in providing patient care, to ensure commitment at all levels. A recent systematic

review of interventions aimed at increasing research use in nursing identified educational sessions led by local opinion leaders and the formation of multidisciplinary committees as effective (Thompson et al. 2006), both of which had been implemented in the SNA↔P study. It is likely that incorporating multiple processes in the introduction and maintenance of the SNA↔P intervention was responsible for the lack of opposition to the SNA↔P intervention by the nursing staff of Unit A. Indeed, the nurses appeared to welcome the structured and prescriptive design that directed their implementation of interventions tailored to specific levels of symptoms as well as the necessary structured patient symptom assessment to facilitate their evaluation.

9.3.1.2 Cyclical implementation of the intervention

The SNA↔P intervention was implemented cyclically over each patients' course of chemotherapy. This cyclical approach allowed for the fact that the effectiveness of the intervention may build up over a period of time, rather than occurring instantly, or that it may take a number of cycles of chemotherapy to establish the most effective intervention or combination of interventions for specific patients. This process is particularly relevant for fatigue, as it has already been shown that identifying the most effective interventions for individual patients can take time and occur across a number of cycles of chemotherapy (Ream et al 2006). While this may also be the case for nausea, there is currently no evidence to support or refute this theory, as existing studies have consistently evaluated interventions over shorter timeframes (Arakawa 1995; Arakawa 1997; Dibble et al. 2000; Molassiotis et al. 2002b; Roscoe et al. 2003; Williams and Schreier 2004; Yoo et al. 2005; Molassiotis et al. 2007)

9.3.1.2.3 A real-world research environment

The logistics of implementing the intervention in practice were considered throughout the intervention period and efforts were made to make the intervention as straightforward and as time efficient as possible. Nurses' concerns over the time-consuming nature of data collection were overcome by the use of barcoding within the questionnaires that not only considerably decreased the time required for data entry, but also reduced the potential for errors during data entry. The intervention prompt sheet generated by the WISETool addressed the fact that different nurses may have entered the patient's symptom data to the WISETool than then saw the patient when they attended for chemotherapy. The intervention prompt sheet provided a summary of the patient's symptoms during their previous cycle of chemotherapy, as well as an overview of the recommended nursing intervention for those symptom scores that could be used by any nurse caring for the patient. These interventions reflected those within the practice protocols that were strategically located throughout Unit A.

While the intervention was nurse-led, it also required support from the multidisciplinary team. Multidisciplinary management of oncology patients receiving treatment has been shown to result in improved patient outcomes (Thomas et al. 2000; Whitmer et al. 2006; Rummans et al. 2006; Wright et al. 2007), and a recent research study has demonstrated the key role that nurses can play in co-ordinating and managing the multidisciplinary team (McEvoy et al. 2007). Within the SNA↔P study, although the symptom assessment and many of the interventions were within the remit of the nursing staff, a multidisciplinary approach was taken throughout the study involving all members of the multidisciplinary team

(clinicians, nurses, psychologist, dieticians, physiotherapists, occupational therapists and pharmacists) that acknowledged their individual contributions to the implementation of the intervention. All members of the multidisciplinary team were encouraged to be involved in the education sessions that took place in Unit A during the integration and maintenance phases of the SNA↔P study, which encouraged sharing of expertise for the benefits of patient care. However, no formal evaluation of the attendance at these meetings was conducted, nor were the multi-disciplinary team's perceptions of the value of such meetings obtained. Thus, their usefulness and contribution to the success of the intervention remains unknown.

9.3.1.2.4 Positive perspectives of the nursing staff

Clinicians have been shown to be opposed to, and reluctant to, engage with quality improvement initiatives, such as the use of guidelines or protocols, resenting the lack of autonomy this gives them (Graham et al. 2000; Timmermans and Mauck 2005). Lack of time and resources, limited knowledge and understanding of methods of quality improvement, differing perceptions about what constitutes quality care, and the widespread belief that quality care is already being provided, have all been proposed to explain clinician's opposition to quality improvement initiatives, such as guideline implementation (Davies et al. 2007). Indeed, clinicians have been shown to have a general sense of indifference towards research-based evidence (Lewis 2007). However, contrary to the evidence above that would suggest otherwise, the nursing staff involved with the SNA↔P study welcomed the prescriptive, structured processes involved in symptom assessment and intervention recommendations, and appreciated the simplicity of the SNA↔P intervention. In instances where they did have concerns about the implementation of the

intervention concerning, for example, their lack of training or the practicalities associated with specific interventions, MM worked with them to overcome these initial concerns and develop alternative methods, such as tape recordings of guided imagery sessions by the Unit psychologist, to ensure that the interventions recommended within the study could be implemented in routine clinical practice. Anecdotal reports of nursing staff saying that they ‘didn’t know what they would do when the intervention was taken away’ at the end of the study can be seen as Lewin’s process of ‘refreezing’ referred to in chapter 7 (Lewin 1951). This suggests that the change brought about by the SNA↔P intervention had been permanently incorporated into nurses’ daily practice.

9.3.1.3 Problems associated with the SNA↔P intervention

9.3.1.3.1 Identifying the most effective components

The SNA↔P intervention was complex, involving not only multidimensional symptom assessment, but also the simultaneous use of multiple interventions. Thus, it was not possible to establish which components of the intervention were the most useful for nursing staff and patients, or which components were most responsible for the positive impact on patients’ experiences of nausea. Moreover, it may have been that some nurses engaged more than others with the SNA↔P intervention, and there is no way of knowing who those nurses were, or the reasons why they engaged more successfully with the intervention.

9.3.1.3.2 Lack of patient involvement

In the United Kingdom, the promotion of the involvement of people with cancer in their own care is part of a paradigm shift regarding the relationship between

patients, carers and healthcare practitioners (Department of Health 2001; Department of Health 2006). Such policy reflects recent moves towards a culture where greater patient involvement in healthcare generally, and decision-making and management in their own care specifically, are considered essential in meeting patients' healthcare needs, replacing the traditional top-down 'doctor knows best' model of care (Coulter 1997). Consequently, it was a failing of the SNA↔P intervention that patients were not involved in the development of the practice protocols (part of the evidence-based intervention) to obtain their perspective of the appropriateness and practicalities of undertaking the symptom management techniques recommended therein. This level of patient involvement in future studies would ensure that any self-care interventions that patients are advised to undertake are patient friendly and so, more likely to be performed.

9.3.2 *Methods of evaluating the effectiveness of the intervention*

9.3.2.1 *Key aspects and their benefits*

9.3.2.1.1 *The study design*

The SNA↔P study employed a rigorous time series design involving a control group, homogenous sample, and innovative longitudinal symptom data collection, both within and across cycles of chemotherapy. Each component of this design will be discussed in turn.

Before-and-after designs are made stronger with the addition of a control group that receives the same measurement but not the intervention (Burns and Grove 2005).

The addition of a control group to the SNA↔P study strengthened the validity of the findings, as it allowed examination of differences in trends between patient

groups after the intervention (Burns and Grove 2005). Consequently, this design increases the strength of the confidence that any improvement observed in symptoms during cohort 2 was due to the SNA↔P intervention, rather than other variables, such as a change in policy, between the two timepoints.

Given that the SNA↔P study focused on patients' symptoms and involved a homogenous population (women having chemotherapy for breast cancer), excludes the potential that changes in symptoms before and after the intervention were a consequence of patients' differing diagnoses, rather than the intervention itself. While it is not novel to research the experiences of women receiving chemotherapy for breast cancer, indeed, they are one of the most frequently researched patient groups, it was new to explore the impact of the intervention on a homogenous group since the WISECARE+ study, from which the SNA↔P study arose, involved an extremely heterogeneous population of 7 diagnostic groups.

The data used to evaluate the impact of the SNA↔P intervention was longitudinal, both within cycles of chemotherapy (for 14 days following each administration of chemotherapy), and across cycles of chemotherapy (up to 8 cycles depending on how long patients participated in the study), and so encompassed patients' whole experience during chemotherapy. Testing the impact of the intervention on such longitudinal data allowed for the fact that the intervention may require time to 'build up', as well as the fact that it may take a period of time for the 'right' intervention or combination of interventions to be established for each symptom and each patient (Ream et al. 2006). Indeed, although the evaluation of the impact of the intervention on nausea experiences was eventually based on patients' reports of nausea over the first 3 days following chemotherapy (and so excluded nausea

reported for days 4-14), this was an informed decision based on a full understanding of patients' experiences over time.

9.3.2.1.2 The combination and complementarity of quantitative and qualitative data

Data collected to evaluate the SNA↔P intervention was both quantitative from structured symptom questionnaires, and qualitative, from structured interviews involving a sub-sample of the population.

Data from patients' structured symptom questionnaires provided information regarding patients' longitudinal, multidimensional symptom experiences, incorporating symptom incidence, severity and distress. Statistical analysis of this data allowed the exploration of symptom patterns that, although interesting and informative in their own right, ultimately informed the evaluation of the impact of the intervention. It was then possible to draw conclusions with regards to the statistical significance of the intervention.

While traditionally, research has relied on statistical approaches using hypothesis or probability testing to determine the statistical significance of findings (Estabrooks and Hodgins 1996), the first misinterpretation of the test of significance is the confusion of statistical significance with practical significance (Slakter et al. 1991). While significance testing is important and goes some way towards determining the likelihood of a true treatment effect (Whitney 2002), tests of statistical significance do not provide any information about the importance or meaningfulness of research findings (LeFort 1993). Structured patient interviews complemented the longitudinal, multidimensional symptom questionnaire data, as they were guided by

patients' symptom graphs and focused on discussing symptom scores, the meaning and impact of symptoms at specific scores, and comparing symptom experiences between scores. This approach provided insight into the symptom experiences that patients had described using structured questionnaires, and allowed the evaluation of the personal significance of the intervention: showing that patients were clearly able to distinguish between the presence and absence of nausea but less able to differentiate between shades of nausea, while there was a general consensus of the overwhelming nature of fatigue and its impact on their daily lives at various scores.

Combining quantitative and qualitative approaches to develop understanding of the personal significance of symptom experiences facilitated an important evaluation of the SNA↔P intervention that was used alongside traditional statistical techniques and allowed a more rounded evaluation of the impact of the intervention. For example, the statistically significant difference between the presence and absence of nausea before and after the intervention was supported by personal significance in that patients could easily differentiate between the presence and absence of nausea, allowing confident conclusions to be drawn concerning the effectiveness of the SNA↔P intervention on experiences of nausea.

9.3.2.1.3 Undertaken in the 'real-world'

Exploring and testing symptom management interventions is routinely performed within research studies that often fail to consider the practical implications of implementing their interventions within the real world of clinical practice (Standley 1992; Troesch et al. 1993; Mock et al. 1994; Arakawa 1995; Arakawa 1997; Schwartz 1999; Molassiotis 2000; Mock et al. 2001; Schwartz et al. 2001; Mock et al. 2002; Molassiotis et al. 2002b; Sahler et al. 2003; Yoo et al. 2005; Billhult et al.

2007; de Carvalho et al. 2007). However, the SNA↔P study was undertaken in the real world of clinical practice, and the intervention and data collection was performed by regular nursing staff during their day-to-day practice. Evaluating the intervention in the real world of clinical practice ultimately demonstrated its applicability and usability.

9.3.2.2 Problems and difficulties associated with evaluating the intervention

There were, however, a number of issues that complicated the evaluation of the intervention. These issues focus on the study sample, the lack of patients' perspective in the evaluation of the intervention, and difficulty establishing the most effective components of the intervention.

9.3.2.2.1 The SNA↔P sample

It was not difficult to recruit patients to the SNA↔P study, however, retaining them was problematic. Just 33 patients (31.4%) of the original 105 patients recruited continued to return their completed symptom questionnaires throughout their entire course of chemotherapy. This attrition is not likely due to the procedures of administering questionnaires that differed between Units A and B, as there was little overall difference in attrition rates between the 2 Units. Comparing SNA↔P study attrition rates with other longitudinal research studies is complicated by the fact that no other longitudinal studies follow the longitudinal pattern of the SNA↔P study: data collection within and across cycles of chemotherapy. For example, the 'longitudinal' nature of a study has previously referred to measures conducted: at baseline, 3 months into chemotherapy and at 6 months (Payne 2002); before chemotherapy, on completion of chemotherapy and six months post chemotherapy

(Hurria et al. 2006); or measures conducted over a 2 month period (Dibble et al. 2003; Lee et al. 2005). While it would have been helpful to compare the patient attrition of the SNA↔P study with that of the WISECARE+ study, from which it arose, such data is unavailable.

The problem of sample attrition in longitudinal studies is not simply deterioration of the sample in terms of size, although a decrease in the sample size can be problematic in that it lowers a study's power (Huck 2004). The main issue that makes sample attrition detrimental to research is when those who drop out have unique characteristics such that the remaining sample ceases to be representative of the original sample (Boys et al. 2003; Dodds et al. 1989) which may lead to the potential bias of the final result. In the case of the SNA↔P study however, analysis showed that the characteristics of those patients continuing to complete and return their symptom questionnaires were similar to that of the overall sample (see chapter 8, px-x). Thus, one can conclude that the results are representative of the total sample.

The SNA↔P sample was sizable (n=105) although this number reduced over time, and consequently, the numbers of patients within each patient group grew smaller. While the sample size could have been increased by extending the duration of data collection, data collection, including the time of the intervention, had spanned 16 months and extending this may have resulted in adding confounding variables as changes in symptom protocols and policies. Moreover, it was constrained by the WISECARE+ study data collection schedule. Recruiting patients with breast cancer from other clinical sites, although increasing the sample size, would have further complicated the study, as these areas would not have been operating to the same

policies and procedures as Units A and B of the SNA↔P study, adding a further variable to the comparison of symptom experiences. The reducing sample size also contributed to the problems associated with confounding variables and comparing symptom experiences between patient groups. The lack of a matched control group complicated comparisons and affects the conclusions that can be drawn.

Furthermore, while homogeneity of the sample (women receiving chemotherapy for breast cancer) was the aim of sample selection, this sample was not homogenous enough, as it included women receiving chemotherapy with both curative and palliative intent. Future research would be well advised to recruit a matched control group.

The power of the SNA↔P study should also be considered. The power of a study refers to its ability to detect differences if the research hypothesis is true. As the SNA↔P study sample for Unit A was based on patients recruited to the WISECARE+ study who also met the criteria for the SNA↔P study, MM had little influence over the numbers of patients recruited or the recruitment timeframe. However, efforts were made to recruit similar numbers of patients from Unit B during times 1 and 2, although they were not matched in relation to potentially confounding variables. The main issue is that the non-significant results of the SNA↔P study may have been due to low power, meaning that a larger sample with power calculations based on the results of the SNA↔P study is required to determine this. However, while results from the WISECARE+ study were based on a larger sample size, and as such, had greater power, they also demonstrated a lack of statistically significant improvement in fatigue experiences as a consequence of the intervention.

9.3.2.2.2 Lack of patients' perspectives

Patients' viewpoints on the effectiveness of the intervention were not sought. Given the drive to involve patients in their care highlighted above (Coulter 1997; Department of Health 2001; Department of Health 2006), and, as many of the interventions, such as relaxation and dietary modification for nausea or exercise and distraction for fatigue, relied on patients undertaking these while at home without the direct supervision or advice from specialist health professionals, exploring patients' perspectives of the relative effectiveness of interventions would have provided additional insight into the effectiveness of the intervention in general. Indeed, while patients did reflect on the ways in which they managed their symptoms during the structured interviews, this issue was not the focus of the interviews and, as such, was not specifically assessed.

9.3.2.2.3 Establishing the use of, and the most effective, components of, the intervention

As already identified, the complex nature of the SNA↔P intervention complicated its evaluation, as it was not possible to establish which components of the intervention were most clinically effective, useful and usable. Addressing this issue in future research, including both health professionals' and patients' perspectives, would provide added insight and facilitate the future development of complex interventions.

As the SNA↔P study was undertaken in the real world of clinical practice it was not possible, without constant observation, which would have been logistically impossible and may indeed have resulted in altered nursing practice, to know

whether the nursing staff in Unit A adhered to the intervention. While the nursing staff were not openly hostile to the SNA↔P study and its intervention and appeared to welcome the simplicity of the system, no patients from Unit A (the intervention site) behaved as though they had previously seen their symptom graphs, or referred to the nursing staff making any of the specific recommendations included in the practice protocols, during their interviews.

9.3.3 *The effectiveness of the intervention*

In exploring the effectiveness of the intervention, it is important to consider the key aspects as well as problem areas of the various components that make up the SNA↔P study. These are: the sample; data collection; symptom patterns; the analyses; and the results.

9.3.3.1 *The sample*

The SNA↔P study was conducted in two chemotherapy Units within a single NHS Trust which ensured that the policies and procedures between the two Units were identical. The use of a control group strengthened the design of the study and its subsequent conclusions. However, while the sample involved a relatively homogenous group of patients: women receiving chemotherapy for breast cancer, it can be criticised, as it involved women receiving a range of chemotherapy regimes with either curative or palliative intent. While analysis conducted within the SNA↔P study demonstrated no statistically significant differences in nausea and fatigue between chemotherapy given with either curative or palliative intent, a matched control group would have increased confidence in the results.

Consecutive recruitment to the study ensured that the sample was representative of the general population of women with breast cancer, and it also reflected the general population according to 2001 Scottish census data (McLoone 2004). Analysis of potentially confounding variables also showed that the four individual patient groups within the sample were not statistically significantly different in relation to age or social deprivation however, there were significantly more patients receiving chemotherapy with palliative intent in Unit A cohort 1 than any other patient group. The sample was sizable (n=105 starting the study and n=33 continuing throughout their entire chemotherapy treatment), indeed, conclusions concerning symptom management are frequently drawn within studies of much smaller sample sizes (Arakawa 1995; Dibble et al. 2000; Mock et al. 2001; Schwartz et al. 2001; Molassiotis et al. 2002b; Berger et al. 2003; Williams and Schreier 2004; Savard et al. 2005; Molassiotis et al. 2007). However, given the level of patient attrition experienced, the numbers of patients in each of the four patient groups were small, especially for analyses comparing confounding variables. A larger sample size would have afforded the study greater power to detect differences in symptom experiences where they existed.

9.3.3.2 Data collection

The longitudinal design of symptom data collection undertaken in the SNA↔P study provided a fundamental change in the way in which symptoms are explored. Symptom data was collected by means of a multidimensional symptom assessment questionnaire longitudinally within each cycle of chemotherapy and across multiple cycles of chemotherapy. Although no complaints were received about this

longitudinal data collection, one should consider the level of patient attrition highlighted above before judging the acceptability of this method of data collection.

Previous research has taken a more limited view to ‘longitudinal’ data collection, collecting data: during a single cycle of chemotherapy (Richardson et al. 1998); at cycles 1 and 2 of chemotherapy (Dibble et al. 2003; Lee et al. 2005); at cycles 1-3 of chemotherapy (Berger 1998; Schwartz 2000); at baseline, 3 months into chemotherapy and at 6 months (Payne 2002); before chemotherapy, on completion of chemotherapy and six months post chemotherapy (Hurria et al. 2006); or longitudinally over multiple cycles but for a shorter period within cycles, for example 48 hours (Rhodes et al. 1987; Rhodes et al. 1988). These approaches, based on arbitrary decisions about when to collect symptom data, fail to provide insight into patients’ total experiences during chemotherapy. Consequently, conclusions or recommendations based on such evidence are as limited as the evidence itself.

The longitudinal data collection of the SNA↔P study is an improvement on these more limited, snapshot views as it collected patients’ entire symptom experience, during a course of chemotherapy, both within and across cycles, to describe and better understand patients’ symptom patterns, as well as to evaluate whether these change over time was a consequence of intervention techniques. Although the evaluation of nausea was eventually based on patients’ nausea experiences during the first 3 days following chemotherapy, this was an informed decision based on a full understanding of patients’ experiences.

However, it is also important to note that the SNA↔P study did not include patients’ entire symptom experiences of nausea and fatigue, as data collection

spanned just days 1-14 of a 21- or 28-day cycle of chemotherapy. This is, again, a constraint as a result of its association with the WISECARE+ study. Consequently, data was not collected for either 7 or 14 days of each cycle of chemotherapy. This decision was based on current evidence concerning patterns of chemotherapy-related symptoms (short lived symptoms such as nausea that occur in the first few days following chemotherapy (Kris et al. 1994; Jordan et al. 2005), and those more constant symptoms that continue to be felt for days or weeks following chemotherapy, such as fatigue (Berger 1998; Schwartz 2000; Molassiotis and Chan 2001; Miller et al. 2007), as well as the potential for questionnaire fatigue. Indeed, completing a questionnaire for 14 consecutive days across multiple cycles of chemotherapy requires considerable commitment from patients and may have contributed to the level of attrition within the study. Consequently, one can appreciate the need for balance between gleaning as much symptom information as possible without over-burdening patients. While there is no evidence to suggest that patients experience significant symptoms between days 15-21 or 15-28 of a cycle of chemotherapy, it is possible that important information regarding patients' symptom experiences may have been lost, especially that information concerning anticipatory nausea that can occur in the days immediately prior to subsequent chemotherapy administrations (Hickok et al. 2001; Figueroa-Moseley et al. 2007) and that have been shown to affect up to one third of patients receiving chemotherapy (Hickok et al. 2001).

The longitudinal data collection of symptom data also encompassed the total symptom experience as it involved not only multidimensional quantitative symptom data of incidence, severity and distress from the symptom questionnaire, but also involved an innovative method of establishing an in-depth understanding of

patients' symptom experiences at various symptom scores through focused discussion facilitated by patients' symptom graphs during structured interviews. The importance of appreciating the component parts of the symptom experience was highlighted in the SNA↔P data that showed, although in general, there was a significant correlation between symptom severity and distress for both nausea and fatigue, as well as between total nausea and fatigue, during chemotherapy cycles 2-5 there was a slight increase in distress associated with fatigue despite relatively stable fatigue severity scores. Appreciating the factors that contribute to patients' total symptom experiences can facilitate the selection of the most appropriate interventions. However, while this is an interesting finding, it is based on a reducing sample and should be confirmed using a larger sample before focusing too much on it.

9.3.3.3 *Symptom patterns*

Establishing the patterns of symptoms over multiple cycles of chemotherapy spanning patients' entire courses of chemotherapy, produced illuminating results because, as already highlighted, much 'longitudinal' research is based on arbitrary decisions about the duration of longitudinal data collection. The longitudinal data collection of the SNA↔P study, however, allowed comparison of symptom patterns over multiple cycles of chemotherapy, establishing that while there were no differences in the nausea reported by patients over time, patients' experiences of fatigue increased with each cycle of chemotherapy to the point that mean total fatigue on day 14 of cycle 8 was almost 3 times greater than that on day 14 of cycle 1, and mean fatigue distress scores more than doubled between cycles 1 and 8.

However, caution should be applied before drawing major conclusions from these results due to the reducing sample size on which they are based.

Again, it is important to highlight the missing symptom data from days 15-21 or -28, as this may have continued to provide illuminating information about patients' experiences during this time. Evaluating the balance between increasing the available symptom data and of over-burdening patients applies here, too.

9.3.3.4 The analyses

Understanding the patterns of symptoms over time within each cycle of chemotherapy, as well as across cycles of chemotherapy allowed informed decisions to be made about the data used in the evaluation of the intervention. It is most appropriate to evaluate the impact of an intervention at the time of greatest symptom experience, as this is the time when differences in symptoms are most likely to be seen. In addition, the qualitative data from patient interviews confirmed that patients' experiences of nausea were focused during the first few days following chemotherapy, while their experiences of fatigue spanned the 14 days of data collection. Consequently, informed decisions based on both quantitative and qualitative data were made to use data from days 1-3 of each cycle of chemotherapy for nausea, and data from days 1-14 for all cycles of chemotherapy for fatigue.

Utilising both quantitative and qualitative methods to explore symptom experiences facilitated a thorough evaluation of the impact of the intervention. While traditional statistical techniques were used to evaluate the statistical significance of the SNA↔P intervention, this was complemented by qualitative data from structured interviews that focused on patients' symptom graphs and explored the meaning and

impact of symptoms at the various scores patients had reported, as well as encouraging them to compare their experiences of differing symptom scores. These interviews allowed insight into the personal significance of patients' symptom experiences. This method of evaluating the impact of the intervention allowed conclusions to be drawn that were not only statistically sound, but also considered the personal significance of symptom experiences.

9.3.3.5 *The results*

Patients were able to complete a multidimensional assessment tool to report their experiences of nausea that demonstrated distinct patterns of nausea within and across cycles of chemotherapy. The general patterns of nausea (total, severity and distress) from the SNA↔P study illustrated a peak during the first 3 days following chemotherapy, followed by a marked, then gradual, decrease over the remaining data collection period. These patterns are supported by a small evidence base: the peak in nausea in the days immediately following chemotherapy (Rhodes et al. 1987; Rhodes et al. 1988; Dibble et al. 2003; Lee et al. 2005), followed by a decrease over time (Dibble et al. 2003; Lee et al. 2005). It is unfortunate that, although the early work was longitudinal across 6 cycles of chemotherapy, it involved only the first 48 hours following chemotherapy (Rhodes et al. 1987; Rhodes et al. 1988), while the later evidence, although longitudinal within a cycle of chemotherapy measuring nausea for 11 consecutive days following chemotherapy, only explored nausea during the first 2 cycles of chemotherapy (Dibble et al. 2003; Lee et al. 2005).

The SNA↔P study was successful in improving patients' experiences of nausea with statistically significantly fewer patients reporting nausea following the

implementation of the intervention than before. This statistically significant result is supported by data from the structured interviews during which patients' could clearly distinguish between the presence and absence of nausea, making this positive outcome both statistically and personally significant. The difference in mean total nausea scores before and after the intervention was not statistically significant (a reduction of 0.71). Moreover, as patients found it difficult to differentiate between shades of nausea, for example between a score of 1 and 2 during their interviews, it is unlikely that they would have been able to perceive a reduction in their nausea of 0.71. Thus, the intervention had neither a statistically or personally significant impact on patients' experiences of grades of nausea. While one can question whether the intervention can be deemed a success on the basis of these results as indicated, during the interviews, patients clearly preferred to have no nausea as opposed to even minimal nausea so, one could argue, would ultimately prefer to have their nausea eradicated rather than somewhat reduced. Consequently, the SNA↔P intervention can be deemed successful.

Patients were able to complete a structured multidimensional assessment tool for fatigue that showed fatigue had a relatively constant presence in the 14 days following chemotherapy with gentle peaks and troughs seen throughout all cycles of chemotherapy. Mean scores for all components of the symptom experience (total, severity and distress) increased with each subsequent cycle of chemotherapy. These trends replicate the patterns of fatigue identified in the WISECARE+ study (Miller et al. 2007), the study from which the SNA↔P study arose. The undulating picture is also supported by the 'rollercoaster' pattern of fatigue reported within 2 studies of women (n=72, n=27) during their first 3 cycles of chemotherapy for breast cancer (Berger 1998; Schwartz 2000). However, the peak in fatigue immediately following

chemotherapy that has been identified by patients in a number of studies (Berger 1998; Richardson et al. 1998; Schwartz 2000; Wu et al. 2007) was not reported by patients in the SNA↔P study.

No statistically significant differences in relation to experiences of fatigue were seen between patient groups before and after the SNA↔P intervention, either in relation to the presence and absence of fatigue, or in levels of fatigue scores. During interviews, however, patients were able to differentiate between different fatigue scores and although each had their own ways of describing their individual experiences of various fatigue scores, there was general agreement about the experience of various scores of fatigue and the impact that these had on their lives. This finding suggests that the assessment tool was sensitive enough to detect changes over time, had they been experienced. Thus, it is important to consider the interventions that were recommended within the SNA↔P intervention for fatigue that were supported by the literature review and NCCN fatigue guideline (National Comprehensive Cancer Network 2007b). Chapter 4 demonstrated that while physiological and biochemical factors, psychosocial factors and demographic factors most probably all have a role in the development of fatigue, the necessary level of evidence to allow firm conclusions to be drawn about the exact aetiology of fatigue is not currently available. Consequently, one can question whether current interventions, although the best to date, have the ability to significantly reduce patients' fatigue experiences. Indeed, it is likely that as our understanding of the aetiology of fatigue becomes clearer and more specific, so will our interventions. Furthermore, the sustainability of interventions for fatigue should be considered. Many studies of interventions have chosen to evaluate their impact over apparently arbitrary time periods, for example, over 10 weeks (MacVicar and Winningham

1986), across cycles 1-3 (Schwartz et al. 2001), over 18 weeks (Given et al. 2002), and during cycles 2-4 (Jacobsen et al. 2002). Indeed, cases evaluating the sustainability of fatigue interventions have not shown positive results, for example an education and support programme that proved initially successful after 1-2 weeks was unable to sustain this positive effect at 6- and 10-week follow up (Yates et al. 2005). Thus, it could be any positive effects of the interventions employed within the SNA↔P study were short lived and, as such, were not statistically identifiable.

9.3.4 Additional findings of the SNA↔P study

Patients in the SNA↔P study were overwhelmed by their experiences of fatigue and spoke passionately and at great length about this. They were able to describe their abilities and feelings, both physical and psychological, at various fatigue scores. Patients often felt unable to fight their fatigue, and without exception, resorted to going to bed and sleeping: *'I felt so terrible that I just had to lie back down again'*, despite evidence to show that this is counterproductive and can increase feelings of fatigue (Winningham 1991; Winningham et al. 1994), a fact that some patients in the SNA↔P study recognised: *'I'd sleep no bother, but I didn't feel any better when I woke up, I'm just as tired'*. Their fatigue clearly impacted on their quality of life, ability to work, care for their family and home, as well as their ability to participate in social activities. In themselves, these are not new findings: numerous studies, both qualitative and quantitative, have already shown fatigue to be a very troublesome symptom, for example, the studies explored within chapter 2 and those of Ferrell et al (1996), Hilfinger Messias et al (1997), Magnusson et al (1999), Holley (2000) and Wu and McSweeney (2007). The SNA↔P study can add to these findings as it not only allowed patients to describe their overwhelming

experiences, but was also able to quantify these through the use of symptom scores from patients' structured symptom questionnaires. What is important though, is the lack of improvement in this situation during the last decade, raising questions concerning fatigue education, assessment and interventions.

While patients' expectations of symptoms were not a focus of the SNAP study, patients' expressiveness during discussions of their experiences suggested that the levels of fatigue they experienced and its impact on their lives were not expected. This unexpectedness supports the findings of Wu and McSweeney (2007,) who highlighted patients' lack of preparedness for the level of tiredness they experience. Given the richness of earlier research that has shown how patients experience fatigue (Ferrell et al. 1996; Hilfinger Messias et al. 1997; Magnusson et al. 1999), as well as the plethora of studies showing that patients receiving chemotherapy identify fatigue as one of the most troubling symptoms (Coates et al. 1983; Love et al. 1989; Tierney et al. 1991; Tierney et al. 1992; Cooper and Georgiou 1992; Sitzia et al. 1995; Griffin et al. 1996; Foltz et al. 1996; de Boer-Dennert et al. 1997; Lindley et al. 1999; Carelle et al. 2002), it is important to explore potential reasons for this lack of preparedness.

One explanation could be that chemotherapy nurses are unaware of the impact of fatigue on a patient's quality of life and simply do not emphasise fatigue as a key symptom during their patient education. Alternatively, it could be that nurses do appreciate the significance of fatigue for patients but feel at a loss for effective interventions. Consequently, due to their feelings of helplessness, they gloss over fatigue during patient education. Finally, it may also be that the terminology used within patient education, that is, 'tiredness', does not adequately describe the level

of fatigue that patients are likely to experience. Because ‘tiredness’ is a feeling that people are familiar with in their daily lives, patients may fail to appreciate the extent of the tiredness associated with chemotherapy that health professionals and other sources of information, such as the internet, try to convey. Patients may assume that their experiences of tiredness will be of a level that they are familiar with and that everyday commonsense methods to alleviate it, such as rest or sleep, that have been effective in the past, will be effective. However, from the literature and from the SNA↔P study, the most tired one has ever felt does not compare with the level of tiredness associated with cancer and cancer treatment (Irvine et al. 1994; Glaus et al. 1996; Holley 2000a; Johnston and Coward 2001).

Given the extent of fatigue patients reported, one can consider the appropriateness of lengthy assessment tools. Chapter 4 presented a range of fatigue assessment tools that were more or less appropriate for a variety of settings, proposing that scales, such as the Revised Piper Fatigue Scale (Piper et al. 1998), were appropriate for the in-depth multidimensional evaluation of fatigue required for research purposes, while the shorter Cancer Fatigue Scale revised version (Schwartz and Meek 1999) allowed patients, in just 6 questions, to provide clinicians with a multidimensional picture of their fatigue experiences. The suitability of currently available fatigue assessment tools for potentially fatigued individuals should be considered before utilising them for research or practice purposes, and clinicians should be mindful of the somewhat under-explored concept of response shift bias (Breetvelt and van Dam 1991; Visser et al. 2000) identified in chapter 4, when measuring patients’ symptom experiences over time.

Finally, one can question how realistic some of the fatigue interventions are in real life. For example, taking a short walk to reduce fatigue would have been utterly impossible for patients in Wu and McSweeney's study (2007), whose fatigue was so significant that they were unable to walk to the bathroom in the next room, and for patients in the SNA↔P study who, '*could virtually hardly move my legs, I was so tired...even trying to go into the kitchen and walk up and down the stairs, my legs weren't my own*'. It may also be unrealistic to expect patients experiencing anything other than mild fatigue to have the concentration to read information leaflets or participate in educational interventions. Being unable to participate in an intervention, regardless of its appropriateness, could have negative psychological consequences for patients.

9.4 Limitations

The discussions above have alluded to a number of limitations of the SNA↔P study. These relate predominantly to 2 distinct aspects of the study: the sample, and the complex intervention.

9.4.1 The sample

Patient attrition was a major issue with just 31.4% of those starting the study participating for the entire duration of their chemotherapy treatment. As the SNA↔P study failed to follow up patients who dropped out to establish their reasons for doing so, it is difficult to draw definite conclusions about the rationale for the attrition seen within the study. That said, while undoubtedly beneficial in understanding patients' experiences of symptoms, the longitudinal evaluation of the SNA↔P study required considerable and lengthy co-operation from patients over

extended periods of time which may have contributed to the attrition rates seen. Moreover, the patients involved in the SNA↔P study were receiving chemotherapy and as such were experiencing both physical and psychosocial issues/concerns. Indeed, it could have been that the fatigue that patients experienced as a consequence of their chemotherapy (and that was a key focus of the study) was a contributor to their withdrawal. This unfortunately means that the most fatigued patients (and those who may have benefitted most from the intervention) may have been too fatigued to continue their participation in the SNA↔P study. Consequently, the potential impact of the intervention may have been reduced. Although the demographic variables of patients who participated for the duration of their chemotherapy treatment did not differ significantly from those who dropped out, the degree to which the symptom profiles of those who dropped out differed from those patients who continued to participate in the study remains unknown. Although relatively sizable in comparison to existing research studies that explore symptom management, the sample of the SNA↔P study, when split into 4 patient groups for analysis, was fairly small, which created difficulties with regards to the power of the study to detect differences between patient groups as well as considering the issues associated with confounding variables. It is a limitation of the SNA↔P study that a power analysis was not conducted during the planning phase. This failing relates to the SNA↔P study's association with the WISECARE+ study and its subsequent reliance on patients recruited to the WISECARE+ study at Unit A. While it is positive that the number of patients recruited from Unit B was relatively similar to that of Unit A, this does not overcome the fact that the SNA↔P study was underpowered. Indeed, given the number of patients participating in the SNA↔P study, power calculations suggest that the study had an 80% chance of

detecting a large effect (0.8) at a significance of $p=0.05$ (with 26 patients in each patient group) (Faul et al 2007). Indeed, in order to detect a medium effect (0.5), 64 patients would have to have been recruited per patient group while 394 patients per group would have been necessary to detect a small effect (0.2) (Faul et al 2007). It is essential that future studies of this kind undertake such a power analysis to ensure that definite conclusions and recommendations for practice can be made.

Finally, although homogeneity was the aim of sample selection (involving only women receiving chemotherapy for breast cancer), the inclusion of women receiving chemotherapy with either curative or palliative intent added another confounding variable for consideration in the analysis. Future such studies should attempt to achieve greater homogeneity within the sample.

9.4.2 The SNA↔P Intervention

The use of the SNA↔P intervention and its maintenance in clinical practice was not monitored and, given the complexity of the intervention in that it included assessment and multiple interventions over a prolonged time period, this means it is impossible to know which aspects of the intervention were the most effective, used or preferred by nurses and patients. Given the real world environment in which the study was conducted, it was impossible to evaluate nurses' adherence to the intervention and the recommendations for practice therein, as to observe this in practice may have induced a Hawthorne effect with nurses changing their behaviour in response to being observed. It may have been that some nurses engaged more than others with the intervention, however, there is no way of establishing whether this was the case, or if it was, who those nurses were, and the reasons why they engaged more successfully with the intervention. While a questionnaire to nursing

staff may have elicited some ideas with regards to their preferred components of the intervention and its use in practice, this too could have been flawed with nurses giving the responses they believe to be 'expected' or 'correct' rather than reporting actual clinical practice. The use of interviews or focus groups with nursing staff throughout the study and at its end may have provided some valuable insight into the most effective or favoured components of the intervention while a questionnaire to patients about their perceptions and preferences may also have been helpful. Future research of this kind should consider a combination of techniques that would provide a clearer understanding of the various aspects of such a complex intervention in practice.

Given the recent moves towards greater patient involvement in their care and in health care generally, a lack of patient involvement is also a limitation of the intervention in relation to its development and evaluation. There was no patient involvement in the development of the practice protocols, nor did patients have the opportunity to comment on the appropriateness or usefulness of the self-care interventions that nursing staff should have recommended they undertake whilst at home.

Finally, it is important to highlight that although longitudinal, the SNA↔P data did not include all patients' experiences of nausea and fatigue, as no data was collected between days 15-21/28 of 21 or 28 day chemotherapy cycles (again, a constraint from the WISECARE+ study). Although this design may have resulted in a loss of symptom data, especially relating to anticipatory nausea, the decision to limit the data collection period was based on ensuring a balance between over-burdening patients and obtaining meaningful symptom data. Indeed, relieving anticipatory

nausea was not an aim of the study, as it requires significantly different management approaches to that of post-chemotherapy nausea (Morrow and Roscoe 1998; Morrow et al. 1998).

9.4.3 Lessons learnt from the SNA↔P study

Given the limitations highlighted above, there are a numbers of ways in which such a study could be improved were it to be repeated in the future. Firstly, in relation to the sample a power calculation and subsequently larger sample would ensure more definite conclusions could be drawn about the impact of such an intervention while a matched control group would overcome issues associated with confounding variables. Likewise, greater homogeneity would ease the complexity associated with confounding variables. A structured approach to exploring reasons for patient attrition would also be beneficial.

Secondly, while the complementary use of structured questionnaires and interviews allowed a rounded evaluation of the intervention, longitudinal interviews would provide illuminating information to evaluate the symptom experience over time as well as potentially exploring patients' perceptions of the most effective or useful interventions. Exploring and comparing whether treatment intent influences symptom experiences may also be possible through such longitudinal qualitative investigation.

Finally, in relation to the intervention itself, future research should make every effort to establish which aspect of the intervention, that is structured assessment or specific interventions, that patients' found most useful or effective. Undertaking

various techniques to explore nurses' perceptions of the intervention and its various components would also be beneficial for future research.

9.5 Conclusions that can be drawn

Considering the design, analyses, results and limitations of the SNA↔P study, one can conclude that the SNA↔P study demonstrates the use of multidimensional symptom assessment to identify, describe and compare patterns of symptoms, and their component parts, over multiple cycles of chemotherapy. It also presents sufficient evidence to argue that an intervention comprised of structured assessment in tandem with specific evidence-based interventions can not only be implemented in routine clinical practice, but also has significant potential to improve patients' experiences of chemotherapy-related nausea. Further testing of the intervention involving a large homogenous sample and a matched control group would ensure the necessary power with which to draw final conclusions.

While the SNA↔P intervention did not positively impact on patients' experiences of fatigue, results from the study that explore and describe patients' experiences of fatigue, both quantitatively and qualitatively, identify a need for improved fatigue education, as well as appropriate assessment tools and intervention techniques.

9.6 Recommendations for practice and further research

A number of recommendations based on the outcomes of the SNA↔P study can be made for both practice and research that focus on symptom management in general, the management of nausea and fatigue specifically, as well as research utilisation.

9.6.1.1 General symptom management

The SNA↔P study demonstrated the feasibility of succinct, longitudinal, multidimensional symptom assessment in clinical practice and illustrated the benefits of this in identifying patterns and comparing these over time to truly understand patients' symptom experiences. While understanding total symptom experiences, more in-depth appreciation of the component parts would allow practitioners to implement interventions that are appropriate to the level of symptom component that is most troubling the patient. For example, exercise may be appropriate for patients experiencing mild fatigue, while energy conservation may be more realistic for patients with severe fatigue. Working with patients to explore their symptom patterns would facilitate patient education regarding symptom management, as well as identifying times of high and low symptom burden that would allow patients to better plan their daily lives and choice of interventions to perform during a course of chemotherapy.

Further research can build on current understanding of symptom patterns. Symptom assessment using sensitive, multidimensional assessment tools within homogenous patient populations will allow the identification of common symptom patterns that can be used, not only to predict periods when patients' lives may be compromised by high levels of symptoms, but also to ensure the implementation of appropriate and timely interventions. While some research began to explore the different symptoms and their patterns related to specific chemotherapy (Buckingham et al. 1997; Sitzia and Dikken 1997; Sitzia and Huggins 1998), these studies can be criticised for their small sample sizes and the use of a lengthy 61- (Sitzia and Huggins 1998) or 75- (Buckingham et al. 1997; Sitzia and Dikken 1997) item

symptom questionnaire. Moreover, although longitudinal in that they assessed symptoms across a course of chemotherapy, symptom assessment was conducted once at the end of each cycle, and so relied on patient recollection of their symptom experiences during the previous 3-4 weeks. Also, as these studies were conducted around a decade ago, they involve chemotherapy regimes that are now obsolete, and research that includes recently developed chemotherapeutic agents is necessary.

Harnessing technology, such as handheld computers or mobile phones to transfer patients' structured symptom experience data to their health professionals has already been shown to be feasible, and has potential for ensuring timely and appropriate interventions (Maguire et al. 2005; Kearney et al. 2006). Extending these exploratory studies to include longitudinal data collection over a course of chemotherapy, rather than cycles 1-2 (Kearney et al. 2006) or 1-4 (Maguire et al. 2005), would ensure patients' entire symptom experiences were understood. Risk modelling provides a powerful mechanism for identifying patterns and predicting what will happen in the future and early work employing such predictive risk modelling techniques has involved women with breast cancer receiving chemotherapy (Cowie et al. 2008). Developing and extending such predictive risk modelling to incorporate a variety of cancer diagnoses and treatments would mean that patients could be provided with information concerning their specific risk of developing certain symptoms and their likely levels throughout a course of cancer treatment.

Exploring patterns of symptoms should now involve whether it is possible to identify relationships between specific symptoms, known as symptom clusters. Symptom clusters are defined as three or more concurrent symptoms that are related

to each other (Dodd et al. 2001b) and, to date, research on symptom clusters in patients with cancer has focused primarily on fatigue, insomnia, pain and depression (Sarna 1993; Gaston-Johansson 1996; Broeckel et al. 1998; Bower et al. 2000; Redeker et al. 2000; Chan et al. 2005; Beck et al. 2005). One could argue that establishing relationships between symptoms would be helpful for symptom management, in that alleviating or ameliorating one symptom could have a ‘knock on’ effect on others. Consequently, exploring symptom patterns in isolation should no longer be an option for health professionals, and research exploring symptom patterns should consider whether some symptoms always occur together or whether the presence of specific symptoms makes others more or less likely to occur.

9.6.1.2 Management of nausea

Patients in the SNA↔P study were able to assess their nausea independent of vomiting. However, many assessment tools include assessment of nausea in tandem with vomiting and are lengthy, and so require considerable patient effort to complete, for example, the Morrow Assessment of Nausea and Emesis (Morrow 1992) has 17 items and the Functional Living Index – Emesis (Lindley et al. 1992) has 18 items. Current clinical practice using the Common Toxicity Criteria (National Cancer Institute 1999; Trotti et al. 2003), although positive as it identifies nausea as distinct from vomiting, grades it unidimensionally mild, moderate or severe, according to patients’ ability to eat. The SNA↔P study has shown that nausea has many more implications for patients over and above impacting on their oral intake. As such, the assessment of nausea in practice should be succinct and multidimensional, and should consider incidence, severity and associated distress.

Given the results of the SNA↔P study that have shown that patients can assess their nausea, independently of vomiting, using a succinct multidimensional longitudinal questionnaire, there is a need for a concentrated body of research that incorporates such assessment in the development and testing of specific nausea-related interventions with the aim of improving patients' experiences. Such assessment would also allow the greater understanding of patients' longitudinal experiences of nausea. Involving patients in both assessment and intervention development will ensure that both are not only manageable, but also effective.

9.6.1.3 Management of fatigue

The appropriateness of fatigue assessment and current management techniques should be considered in practice. Lengthy questionnaires are inappropriate for those patients already fatigued and, like nausea above, fatigue assessment in clinical practice should be longitudinal, succinct, multidimensional and consider incidence, severity and associated distress. Research to develop such tools should involve patients who are, or who have, experienced fatigue, to ensure that they are within patients' abilities to complete longitudinally, as well as including issues that are relevant to patients' experiences.

The suitability of interventions for fatigue, as well as their sustainability, should also be considered in practice. As already highlighted, many interventions for fatigue, such as exercise or education may be difficult, or indeed, impossible, for those already compromised by fatigue to undertake. Recommending such inappropriate interventions may have detrimental effects on patients' psychological well-being, resulting in a downward spiral effect leading to poor communication about fatigue and a lack of understanding of fatigue experiences between patients

and those caring for them. Thus, in practice, the appropriateness of interventions and the patients' level of fatigue, as well as the sustainability of the intervention, should be considered, and interventions that are most appropriate for the patient's level of fatigue recommended, with regular re-assessment.

Patient education in clinical practice is also important to consider, as patients in the SNA↔P study appeared to be surprised by the levels of fatigue they experienced. Earlier in this chapter it was suggested that the terminology that is currently used to describe fatigue, that is 'tiredness', may be responsible for patients' lack of appreciation of the extent, level, and impact of fatigue they experience. Using day-to-day language, such as 'tired', does not adequately portray cancer-related fatigue. Further development of the terminology is required, and working with patients who are, or who have, experienced fatigue as a consequence of cancer or cancer treatments, would be helpful in developing the terminology used to describe this symptom which adequately reflects their experiences.

Continued efforts should be made within research that explore the potential aetiologies of fatigue in relation, not only to cancer, but also to specific cancer treatments. A better understanding of the causes of fatigue will allow the development of specific targeted interventions that would be more likely to be effective in overcoming this overwhelming symptom. Research that develops and tests such interventions within the real world of clinical practice would ensure that they were feasible to implement at the clinical level, while working with patients during their development and testing would also ensure that these were both realistic and manageable for patients.

9.6.1.4 Improving research utilisation

Nurses constitute the largest group of healthcare providers, and their care influences patient outcomes (Blegen et al. 1998; Aiken et al. 2002; Estabrooks et al. 2005b). Indeed, the SNA↔P study demonstrated the positive impact that chemotherapy nurses can have on patients' experiences of nausea. Despite their potential to positively impact on patient outcomes through evidence-based practice, it has been shown that nurses often fail to incorporate research into their practices, preferring to use knowledge gained through personal experience and interaction with co-workers, rather than journal articles or textbooks (Estabrooks et al. 2005a). Evidence utilisation is particularly challenging, as it requires investment at both organisational and practitioner levels, as well as the use of multiple interventions (Pearson 2006), all of which were considered and included within the SNA↔P study. A recent systematic review of interventions aimed at increasing research use in nursing identified educational sessions led by local opinion leaders and the formation of multidisciplinary committees as effective (Thompson et al. 2006), both of which again were implemented in the SNA↔P study.

Nurses should be encouraged to find ways of implementing research in their clinical practice. In so doing, they could demonstrate the impact that they have on patient outcomes and highlight their unique contribution to patient care, as well as evaluating new interventions to improve patients' experiences. There is a growing amount of understanding and expertise concerning research utilisation in nursing aimed at ensuring that research knowledge is reflected in the care that patients receive. The multidimensional Promoting Action on Research Implementation in Health Services (PARIHS) framework suggests that the quality of evidence, context

and facilitation, and the interplay among them, are fundamental ingredients to promote research uptake (Kitson et al. 1998; Rycroft-Malone et al. 2002; Rycroft-Malone 2004). However, a review of barriers to research utilisation identified primary barriers as: lack of time; lack of relevant skills; poor team-working; and aspects of nursing culture, such as ritualistic care, no authority and no incentives (Sitzia 2002). The SNA↔P study demonstrated that these aspects can be overcome, for example, although guided imagery and relaxation were not within the remit of nursing staff in the SNA↔P intervention sites, MM worked with them to overcome their initial reticence and develop alternative methods (tape recordings from the Unit psychologist) to ensure that the intervention was implemented in routine practice. This process is supported by the finding that inter-personal contact improves the likelihood of behaviour change when introducing innovations to health settings (Thompson et al. 2006). Moreover, the multidisciplinary educational sessions as part of the SNA↔P study gave nurses the opportunity to explore evidence-based interventions for specific symptoms and encouraged them to implement these in practice. Initiating and supporting similar sessions within clinical areas would stimulate discussion of research-based evidence between nursing staff, potentially leading to its implementation in clinical practice.

However, the responsibility for ensuring research is implemented in practice does not lie solely with practitioners. Within symptom management, it is important that researchers consider the applicability of the interventions developed, as well as the practicalities of implementing them in the real world of clinical practice. Aspects such as intervention costs, appropriate locations, and staff training, should be included in their evaluation of an intervention before presenting it as a realistic means of improving patients' symptom experiences in clinical practice. One could

argue that research findings are more likely to be adopted by practitioners if they are sensitive to and have considered the limitations and boundaries within which practitioners work.

9.7 Conclusion

The SNA↔P study was a longitudinal study that evaluated the impact of a complex evidence-based intervention incorporating structured multidimensional symptom assessment and multiple symptom management techniques on patients' experiences of nausea and fatigue during a course of chemotherapy for breast cancer. Using complementary quantitative and qualitative research methods allowed a rounded evaluation of the intervention that incorporated both statistical and personal significance. This design provided insight into patients' experiences of nausea and fatigue during chemotherapy, as well as allowing informed and confident conclusions to be drawn on the study outcomes.

The study results have provided understanding of patterns and experiences of nausea and fatigue across a course of chemotherapy. The intervention shows significant potential for improving patients' symptom experiences, and further testing in a large homogenous population with a matched control group is necessary. However, as a research study successfully conducted within the real world of clinical practice, the SNA↔P study has identified a number of implications for practice and research in relation to symptom management generally, the management of nausea and fatigue specifically, as well as promoting research utilisation.

Thus, in conclusion, the SNA↔P study has demonstrated the potential of structured assessment and practice in routine clinical care for improving patients' symptom experiences during chemotherapy. In so doing, it has highlighted a number of significant areas in which clinical practice can be influenced, and research conducted, to further improve patients' symptom experiences.

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Evaluation of a nurse-led intervention (SNA↔P) to
improve patients' experiences of chemotherapy-
related nausea and fatigue

Appendices

APPENDIX A – WISECARE+ STEERING GROUP

Roles & Responsibilities

Nora Kearney Professor of Cancer Care Cancer Care Research Team Department of Nursing and Midwifery University of Stirling Stirling FK9 4LA	Principle Investigator
Dickon Weir-Hughes Chief Nurse & Deputy Chief Executive The Royal Marsden Hospital (London & Surrey) Fulham Road, London SW3 6JJ	Royal Marsden representative & general project advisor
Sara Lister Assistant Chief Nurse/Head of School The Royal Marsden Hospital (London & Surrey) Fulham Road, London SW3 6JJ	Royal Marsden representative & general project advisor
Derek Hoy Research Fellow Department of Nursing and Community Health Glasgow Caledonian University Glasgow G4 0BA	IT development & support, data management
Professor Walter Sermeus Centre for Health Services and Nursing Research School of Public Health Catholic University of Leuven Leuven, Belgium	Data management & analysis
Dr Faith Gibson Lecturer in Children's Nursing Research Great Ormond Street Hospital for Children NHS Trust London	Advice & support, lead for WISECARE+ Teenage Pilot Project

WC1N 3JH

Morven Miller
Research Fellow
Cancer Care Research Team
Department of Nursing and Midwifery
University of Stirling
Stirling
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Clinical site support, general project
management

APPENDIX B - PATIENT SYMPTOM QUESTIONNAIRE



To be completed by nursing staff												
Name												
WISECARE+ number												
Chemotherapy regime												
Cycle number (circle)	1	2	3	4	5	6	7	8				
Reporting on day (circle)	1	2	3	4	5	6	7	8	9	10	11	12
	13	14										

Below you will see a list of symptoms that are sometimes associated with chemotherapy. You may not experience all of these symptoms but it is useful for staff to know which symptoms you have experienced. The information you provide will be used by nursing staff to help plan your care.

You should complete this questionnaire daily for **14** days following each cycle of chemotherapy you receive. It is best completed in the **evening** and when you are completing it, **think of your experiences throughout the day**.

Please answer all the questions. Please answer all the questions. Firstly, tick whether you have experienced a symptom and then if you have experienced the symptom, please tick the boxes that best describe your experience that day.

There is also a list of activities that you **may** or **may not** have tried in relation to any symptoms you have experienced. Please tick 'yes' or 'no' to show whether you have tried these activities that day.

Thank you for completing this questionnaire.

NAUSEA

Have you experienced NAUSEA today? Yes No

If yes,

How severe was this? Mild

 Moderate

 Severe

How much did it bother you? Not at all

 A little

 Quite a bit

 Very much

Self-care activities

I took my anti-sickness tablets regularly Yes No

I ate small, frequent meals Yes No

Today's date is

NAUSEA (feeling sick)

Have you experienced **NAUSEA** today? Yes No

If yes,

How severe was this? Mild

Moderate

Severe

How much did it bother you? Not at all

A little

Quite a bit

Very much

VOMITING (being sick)

Have you experienced **VOMITING** today? Yes No

If yes,

How severe was this? Mild

Moderate

Severe

How much did it bother you? Not at all

A little

Quite a bit

Very much

Please turn over....

Self-care activities for nausea and vomiting

- | | | |
|--|------------------------------|-----------------------------|
| I took my anti-sickness tablets regularly | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| I ate small, frequent meals | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| I tried to relax | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| I tried to distract myself, for example, watching television, talking with friends, listening to music etc | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| I avoided very hot or very cold foods | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| I ate bland tasting foods | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| I contacted the hospital for further advice | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| Other (Please describe) | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

Please turn over....

Feeling unusually tired

Have you experienced **TIREDFNESS** today? Yes No

If yes,

How severe was this? Mild

Moderate

Severe

How much did it bother you? Not at all

A little

Quite a bit

Very much

Self-care activities for tiredness

I rested when I felt tired Yes No

I did some physical activity Yes No

I tried to eat a balanced diet Yes No

I tried to get into a good sleeping routine Yes No

I tried to distract myself, for example,
watched television, reading, gardening
etc Yes No

I contacted the hospital for further advice Yes No

Other (Please describe) Yes No

Please turn over....

Oral problems (problems with your mouth or throat)

Have you experienced **PROBLEMS WITH YOUR MOUTH OR THROAT** today? (e.g. sore or dry mouth/throat, mouth ulcers) Yes No

If yes,

How severe was this? Mild

Moderate

Severe

How much did it bother you? Not at all

A little

Quite a bit

Very much

Self-care activities for oral problems

I used my mouthwash regularly (at least twice a day) Yes No

I brushed my teeth using a soft toothbrush Yes No

I used dental floss Yes No

I removed my dentures Yes No

I avoided very hot or very cold foods Yes No

I avoided smoking Yes No

I avoided drinking alcohol Yes No

I avoided spicy foods Yes No

Other (Please describe) Yes No

Please turn over...

Please complete this questionnaire by ticking the box in the right hand column that best represents how your mouth feels or looks today.

TICK HERE

Voice	Normal	
	Deep or raspy	
	Difficulty talking/painful	
Swallow	Normal swallow	
	Some pain on swallow	
	Unable to swallow	
Lips	Smooth, pink and moist	
	Dry and cracked	
	Ulcerated or bleeding	
Tongue	Pink, moist and papillae present	
	Coated or loss of papillae with shinny appearance with or without redness	
	Blistered or cracked	
Saliva	Watery	
	Thick or ropy	
	Absent	
Mucous membranes (inside skin of lips and cheeks)	Pink and moist	
	Reddened or coated (increased whiteness) without ulceration	
	Ulceration with or without bleeding	
Gingiva (gums)	Pink and stippled and firm	
	Oedematous with or without redness	
	Spontaneous bleeding or bleeding with pressure	
Teeth/dentures	Clean and no debris	
	Plaque or debris in localised area (between teeth if present)	
	Plaque or debris generalised along gumline or denture bearing area	

Please turn over....

Other symptoms

Have you experienced **any other symptoms** today? Yes No

What was it.....

What was it.....

How severe was this? Mild

How severe was this? Mild

Moderate

Moderate

Severe

Severe

How much did it bother you? Not at all

How much did it bother you? Not at all

A little

A little

Quite a bit

Quite a bit

Very much

Very much

Thank you for completing this questionnaire.

If you are in hospital, please return this to your nurse.

If you are at home, please keep this with your other questionnaires and post it back when you have completed all 14 days of questionnaires.

APPENDIX C – STANDARD PATIENT INFORMATION SHEET – UNIT A

‘Hospital/Institution headed paper’

Date

You are invited to take part in the above research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Patients receiving chemotherapy frequently receive it as an out-patient or stay in hospital for a short period of time. As a consequence nurses have less time to spend with patients and patients are more likely to experience symptoms and side-effects when they are at home without the direct care of a health professional.

The purpose of this study is to provide nurses with information that will help them care for their patients and to find out how patients feel about participating in their own self-care. The project will last for 2 years.

You have been invited to take part in the project because you are scheduled to receive chemotherapy and have never received chemotherapy before. Patients from both the United Kingdom and mainland Europe are taking part in the project and it is hoped that over 600 patients will be involved.

Should you choose to take part in the project, your treatment will be no different than if you choose not to participate. If you do take part, you will be asked to complete a short questionnaire for 14 days following each cycle of chemotherapy you receive. This will ask questions about your symptoms of nausea, vomiting, fatigue and any mouth problems you have. It will also ask you what self-care you have been performing. This questionnaire will take about 5-10 minutes to complete. You may or may not be given

some extra information about your self-care. Whether you do or do not receive this additional information will be determined by a completely random process that will be initiated if you decide to join the project. Your nurse will have no control over whether you are allocated to receive this information as this decision will be computer generated. You will not have to visit the hospital more than usual but you will have to visit your GP for a simple blood test 10 days after your chemotherapy. There are no lifestyle restrictions when participating in the project. We hope that the results from your questionnaires will help nursing care to be tailored to your individual needs and help you express the symptoms that you have been experiencing. The extra self-care information you may be given will tell you about some symptoms you may experience and what you can do to help manage these. You may also be asked to complete a short questionnaire about how you found your care.

All the information which is collected about you during the course of the project will be kept strictly confidential. Any information about you will have your name removed so you cannot be recognised from it.

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, of which you will get a copy. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care that you receive. Similarly, should you chose not to take part, your care will not be affected.

For further information, please contact

APPENDIX D – STANDARD PATIENT INFORMATION SHEET – UNIT B

Patient Information Sheet

Study title: An exploration of patients' symptoms and self-care activities following chemotherapy

Invitation

You are being invited to take part in a research project. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you would like to take part.

Thank you for reading this.

What is the purpose of the project?

Patients receiving chemotherapy often experience some side effects associated with the drugs used in their treatment. It is more common now for patients to spend a lot of time not in hospital, but at home, in between their chemotherapy treatments. This means that patients have to deal with their side effects while they are at home, without the direct care of the specialists from the hospital.

This project aims to collect information about patients' symptoms related to their chemotherapy treatment. As well as this, it will collect information about what patients' do at home to help their side-effects. It will also compare these results to those of another similar study.

Why have I been chosen?

The project aims to collect as much information about patients' symptoms as possible and so we want to include as many patients as are willing to take part. You have been

chosen because you and your doctor have agreed that you will have a course of chemotherapy and because you have not had chemotherapy before.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do take part you will be given this information sheet to keep and be asked to sign a consent form. You will also be given a copy of the signed consent form. If you decide to take part, you are still free to withdraw at any time (even once you have started the project) and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care that you receive.

What will happen to me if I take part?

Taking part in this project involves filling out questionnaires about your symptoms and any activities that you have tried to make the symptoms better. The questionnaire does not take long to complete and is very simple. You can see the questionnaire before you decide whether to take part or not. It asks you some questions about your symptoms that day and focuses on nausea (feeling sick), vomiting (being sick), tiredness and mouth problems. These are symptoms that your doctor and nurse will talk to you about. You will be asked to complete this short questionnaire in the evening for 14 days after your chemotherapy. We would like you to complete these questionnaires for each cycle of chemotherapy that you have. Your doctor or nurse will be able to tell you how many cycles of chemotherapy you can expect to have. There are no right or wrong answers in the questionnaire, it is only your experience that we would like to know about. You may also be asked to take part in a short interview about the symptoms that you have reported but you don't have to take part in an interview if you don't want to.

The project will be just over a year long but you will only take part for the length of time that you are having chemotherapy (or until you decide that you want to stop completing the questionnaires).

What do I have to do?

Taking part in the project will not change what you are able to do. You will be able to eat, drink, exercise, drive and take part in any activities that you would normally do. It

also will not affect any medication that you normally take or that your doctor advises for you.

What are the side effects of taking part?

There are no side effects or risks associated with taking part in this project.

What are the possible benefits of taking part?

Your treatment and care will not be affected whether you take part or not in this project. However, answering the questionnaire might make you think more about your symptoms and help you remember certain symptoms more clearly when it comes time to speak to your doctor or nurse at the hospital.

What happens when the project stops?

Because taking part (or not) in this project does not affect the treatment and care that you will receive, there will be no change to your treatment and care when the project stops.

Will my taking part in the project be kept confidential?

If you take part in the project, a nurse researcher from the Nursing and Midwifery School at the University of Glasgow will collect some information about your diagnosis, chemotherapy, age, postcode and gender. **All the information that is collected about you during the course of the project will be kept strictly confidential.** Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Your General Practitioner (GP) will be sent a letter, telling him/her that you are taking part in this project. Your doctor in the hospital will also be sent a similar letter.

What will happen to the results of the project?

The results of the project will be used to build a picture of the common symptoms that patients receiving chemotherapy experience and the activities they try to make these symptoms better. They will also be compared with the results of another similar study. The results of the project are likely to be available in July 2003 and any patient who has

participated in the project will be able to see these results by asking their hospital doctor. No patients will be identified in any reports or publications about the project.

Who is organising the research?

Dr Dunlop at Glasgow Royal Infirmary and Morven Miller, a nurse researcher at the Department of Nursing and Midwifery of the University of Stirling are organising the research project.

Who has reviewed the project?

The Research Ethics Committee of Glasgow Royal Infirmary has reviewed this project.

Contact for further information

Should you have any further questions about the project, please contact either:

Dr Dunlop,
Consultant Oncologist,
Department of Medical Oncology
Glasgow Royal Infirmary,
Telephone: 0141 211 1160

Morven Miller
Research Fellow
Department of Nursing and Midwifery
University of Stirling
Telephone: 01786 466104

You may also ask to speak to someone who is not directly involved with the project for advice.

Thank you for taking the time to read this information sheet.

APPENDIX E – DEMOGRAPHIC DATA COLLECTION SHEET

Patient Registration Form

Date

Patient project number

Patient name

Date of birth

Postcode

Tel no.

Diagnosis	Stage of disease
Breast cancer

Treatment

Therapeutic intent () curative
() palliative

APPENDIX F – PATIENT EDUCATION SCHEDULE

Patient education schedule for questionnaire completion

Have you:	COMPLETED
1. given a demonstration of how to complete the questionnaire	()
2. highlighted the importance of there being no right or wrong answers	()
3. explained the timing of questionnaire completion, i.e. in the evening, reflecting on the symptoms that were experienced throughout that day	()
4. stressed the importance of putting the correct date on the questionnaire	()
5. explained what to do if the questionnaire is forgotten about	()
6. explained that it is important to complete the questionnaire even if they have no symptoms	()
7. given details of how to return the questionnaires once completed	()
8. shown patient where your contact details are (on patient information sheet) and reassured them that they should call if they have any questions or problems with completing the questionnaire	()
9. reassured the patient that they can withdraw at any time, without reason, without their subsequent care and treatment being affected	()

APPENDIX G – NAUSEA PRACTICE PROTOCOL



Chemotherapy-Related Nausea

Practice Protocol

This nursing practice protocol for the management of chemotherapy-related nausea is tailored specifically for the nursing care of patients participating in WISECARE+, namely patients who are chemotherapeutically naïve. The following issues will be considered:

BASELINE ASSESSMENT OF NAUSEA.....	3
AIM	3
CONSIDERATIONS.....	3
METHOD OF ASSESSMENT.....	4
NAUSEA SCORING CHART.....	4
OUTCOMES OF ASSESSMENT.....	5
ASSESSMENT DURING CHEMOTHERAPY.....	6
INTERVENTIONS FOR NO NAUSEA (SCORE 0).....	7
INTERVENTIONS FOR MILD/MODERATE NAUSEA (SCORE 1-4).....	8
INTERVENTIONS FOR SEVERE NAUSEA (SCORE 5-6).....	9
NON-PHARMACOLOGICAL INTERVENTIONS.....	10
PROGRESSIVE MUSCLE RELAXATION TRAINING.....	10
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APPENDIX A – EMETOGENICITY TABLES.....	15
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Nurses are advised to read the National Comprehensive Cancer Network Anti-emesis practice guideline in conjunction with this protocol. This can be obtained from the lead WISECARE+ nurse in your clinical area.

Baseline assessment of nausea

Aim

To assess each individual's risk of developing/experiencing chemotherapy-related nausea and vomiting and so instigate appropriate anti-emetic therapy and nursing actions.

Considerations

1. The specific chemotherapeutic agents being administered
2. The dosage of the chemotherapy administered
3. The schedule and route of chemotherapy administration
4. The efficacy of the anti-emetic regime
5. Individual patient variability and characteristics for example:
 - Age (older people appear to suffer **less** nausea)
 - Gender (females appear to suffer **more** nausea)
 - Positive history of motion sickness (this **increases** their likelihood of experiencing nausea)
 - Previous experience of nausea for example in relation to other illness or pregnancy (this **increases** their likelihood of experiencing nausea)
 - Previous history of chronic alcoholism (this **decreases** experiences of nausea)
 - Patients' expectations of developing nausea (those who **expect** symptoms are more likely to **experience** them)

A full list of the emetogenic potential of the majority of chemotherapy drugs as well as an algorithm for calculating the emetogenic potential of chemotherapy regimes is available in Appendix A. It is important to recognise that different authors have produced different guidelines regarding the emetogenic potential of specific drugs, which are mostly based on consensus rather than 'hard evidence'.

Method of assessment

Clinical assessment should evaluate the presence or absence of nausea, its severity (mild, moderate or severe) and associated distress (not at all, a little, quite a bit, very much). This assessment should be completed prior to the patient starting chemotherapy to assess for anticipatory nausea.

Nausea (feeling sick)

Have you experienced this today? Yes No

If yes,

How severe was this? Mild (1)

Moderate (2)

Severe (3)

How much did it bother you? Not at all (0)

A little (1)

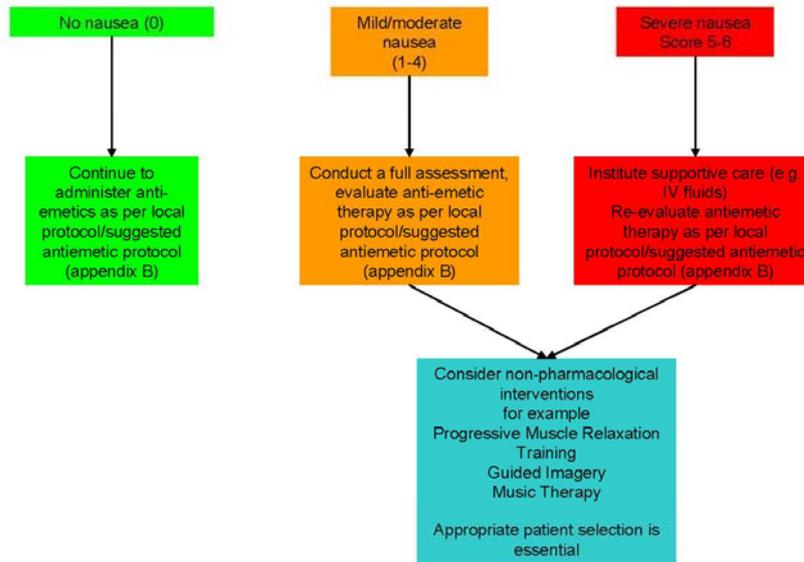
Quite a bit (2)

Very much (3)

Nausea scoring chart

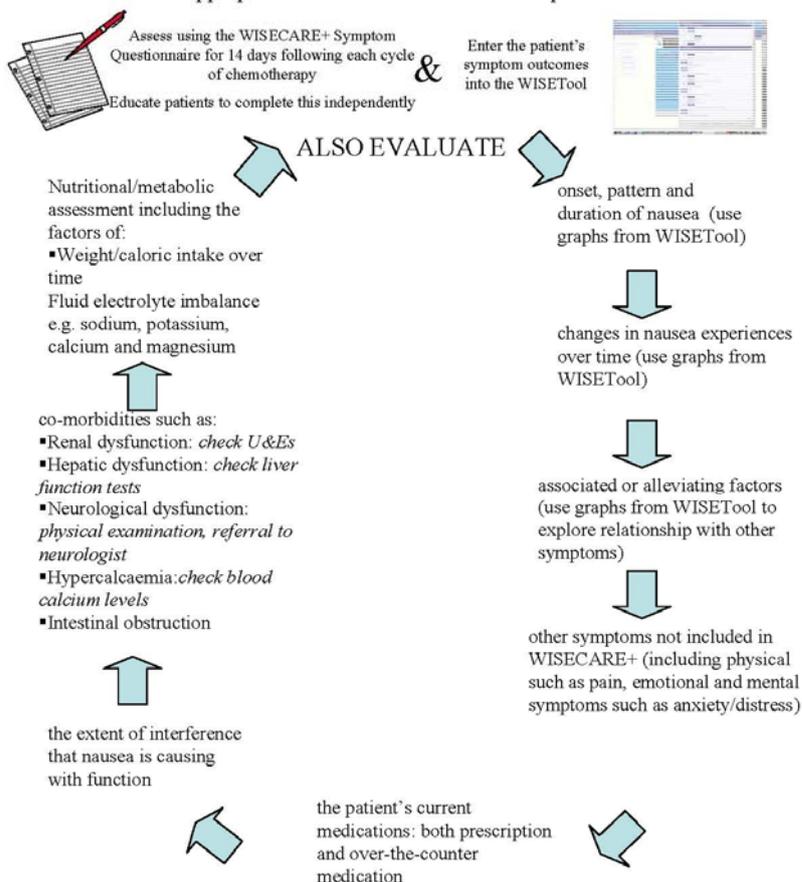
Score	Descriptors		Summary description
	Severity	Distress	
0	---	---	No nausea
1	Mild	Not at all	Mild nausea
2	Mild Moderate	A little Not at all	
3	Mild Moderate	Quite a bit A little	Moderate nausea
4	Mild Moderate Severe	Very much Quite a bit A little	
5	Moderate Severe	Very much Quite a bit	Severe nausea
6	Severe	Very much	

Outcomes of assessment



Assessment during chemotherapy

To ensure optimal management of nausea and provide timely interventions appropriate to the individual's nausea experiences



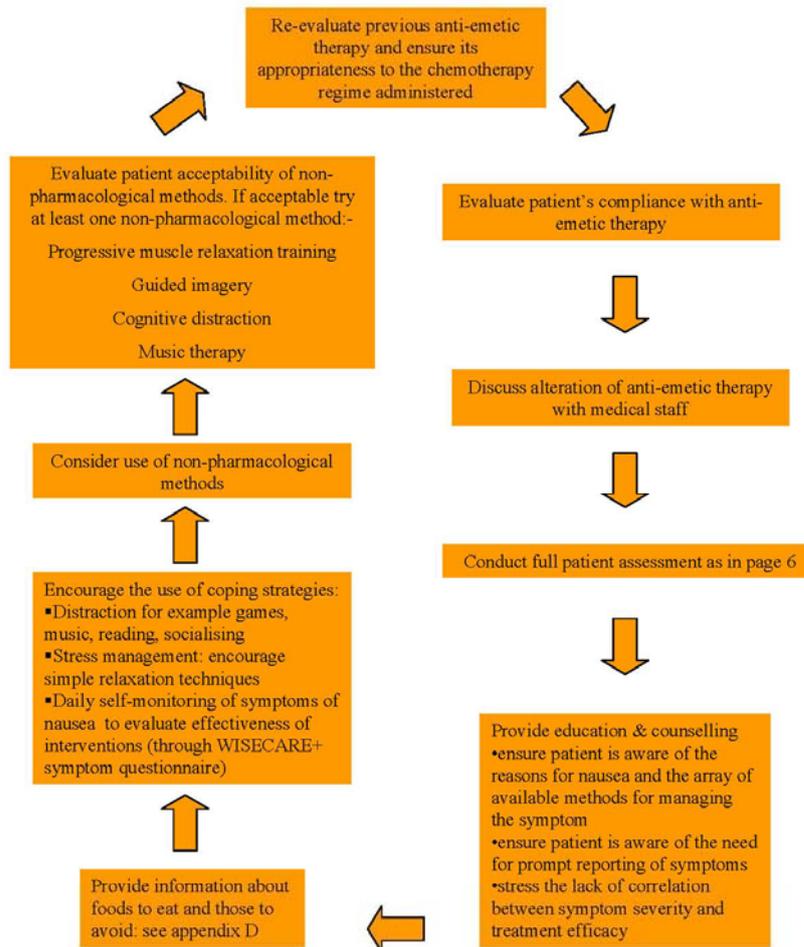
Interventions for no nausea (score 0)

Continue to administer anti-emetics as before, ensuring that the lowest level of anti-emetic cover necessary is the therapy of choice.
Use good practice guidelines (Appendix C)

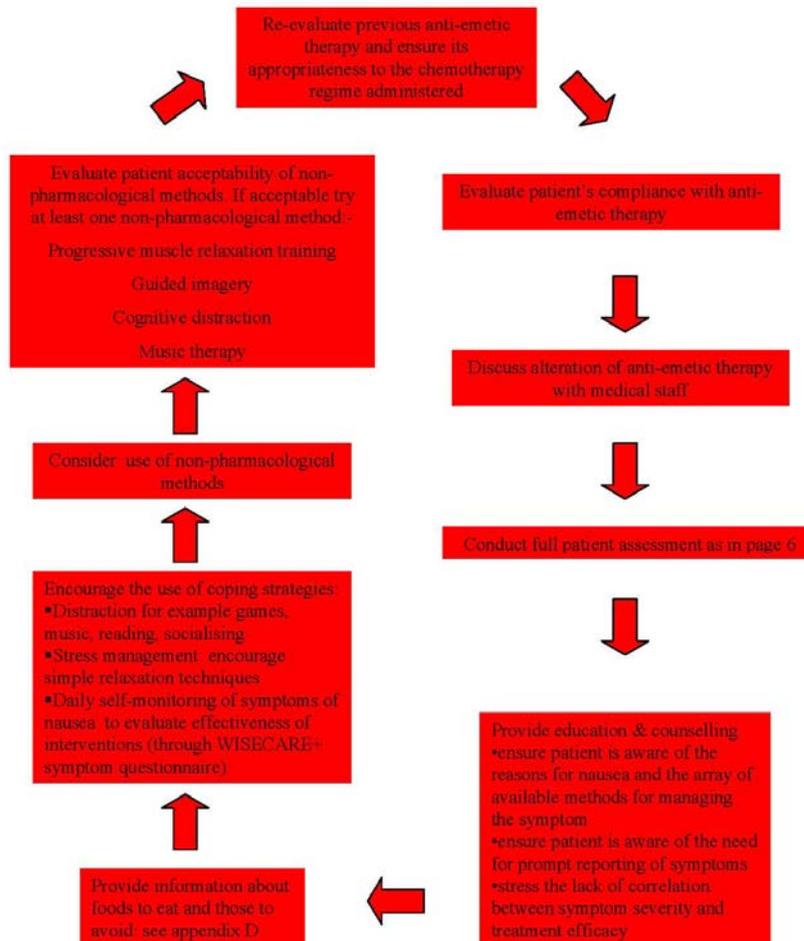


Re-evaluate nausea according to WISECARE+ re-evaluation (p14)

Interventions for mild/moderate nausea (score 1-4)

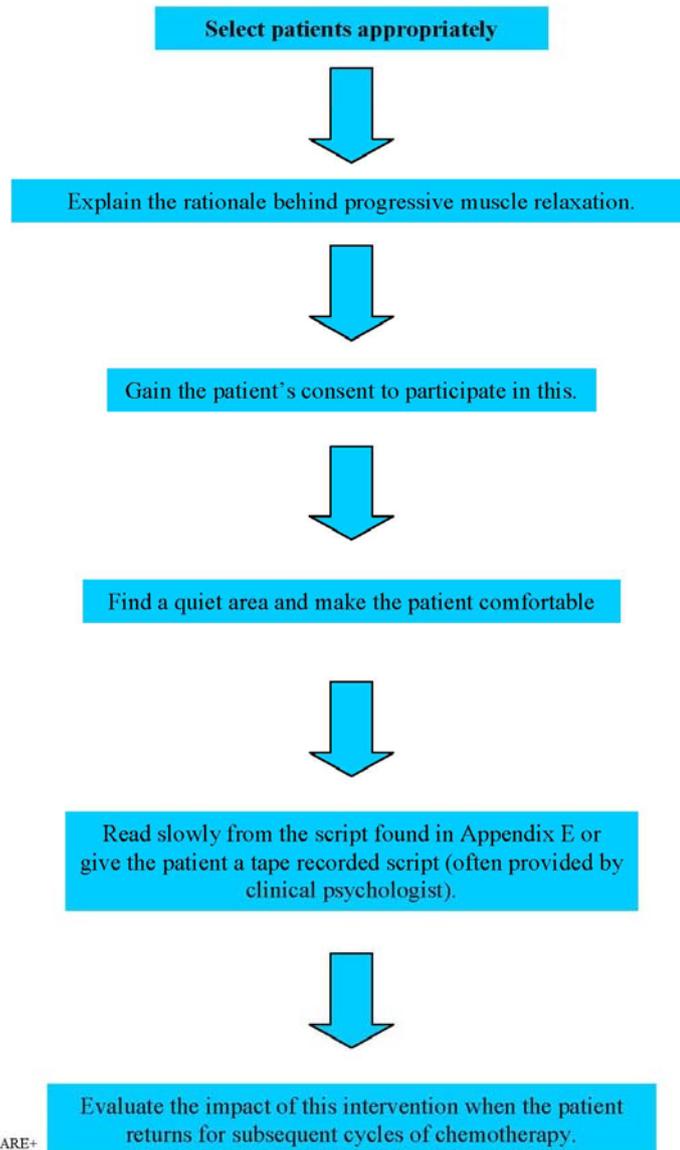


Interventions for severe nausea (score 5-6)



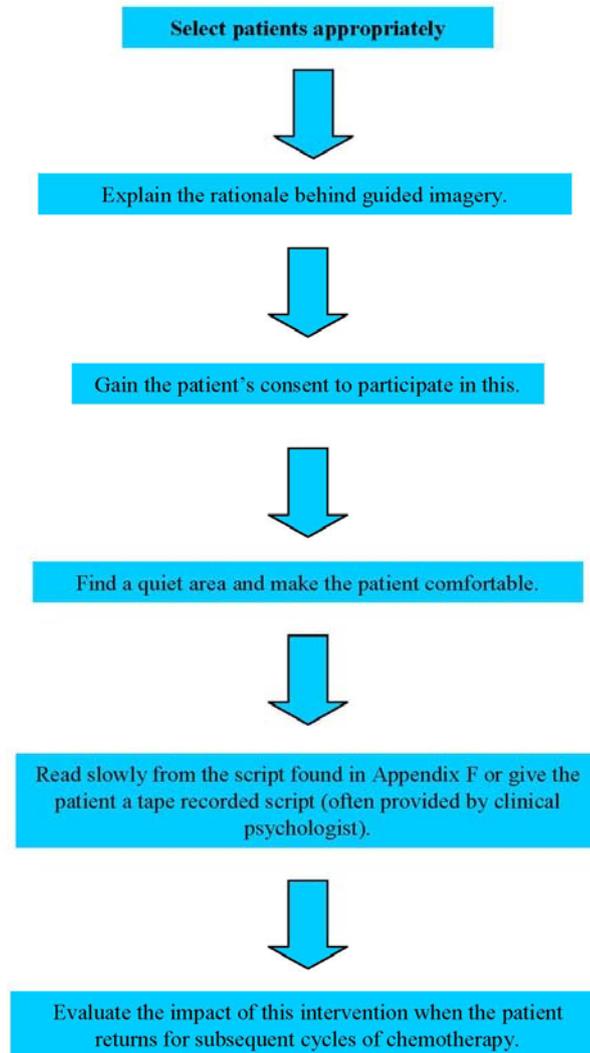
Non-pharmacological Interventions

Progressive muscle relaxation training

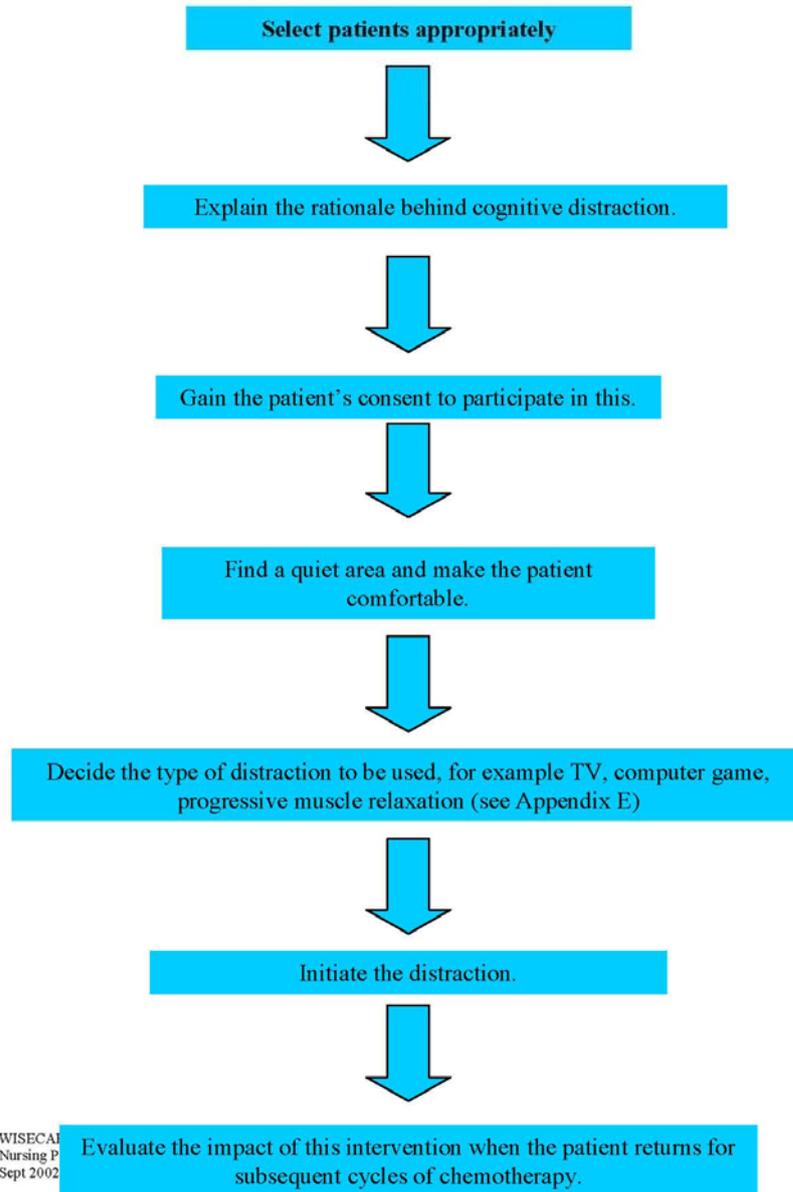


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Guided Imagery

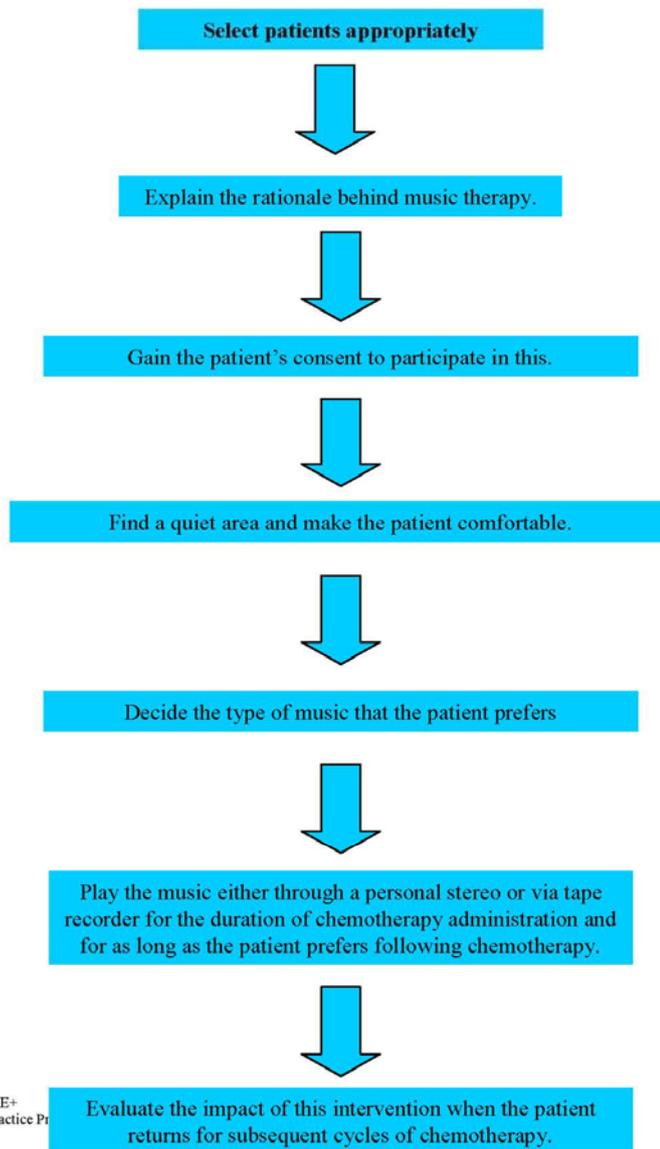


Cognitive distraction



WISECAI
Nursing P
Sept 2002

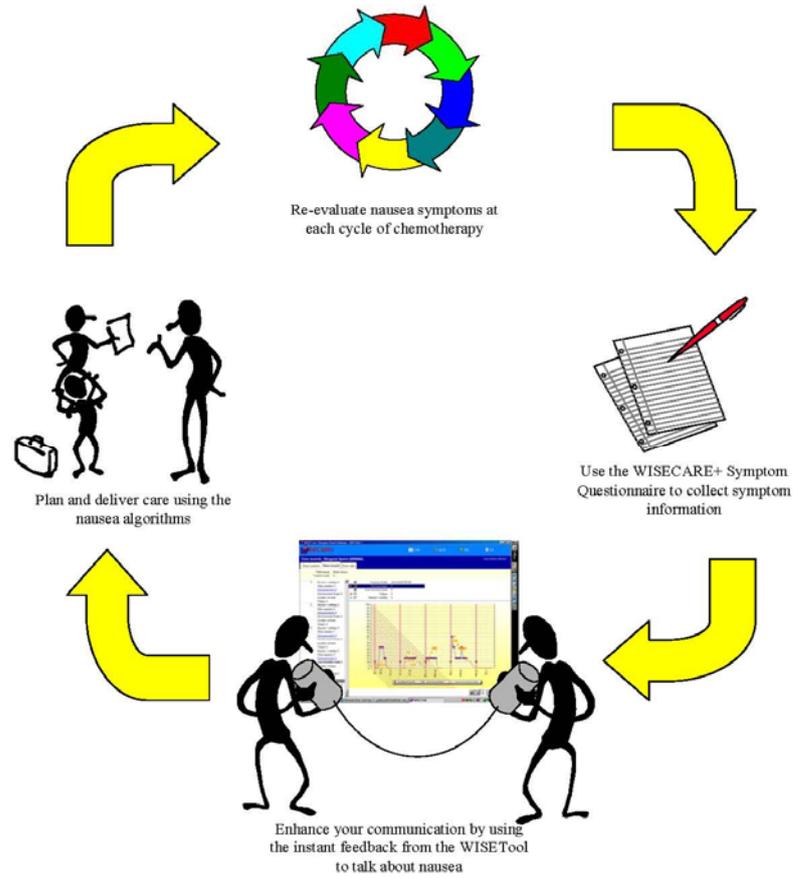
Music Therapy



WISECARE+
Nursing Practice Pr
Sept 2002

Re-evaluation of nausea

To continuously strive to prevent or reduce patients' experiences of nausea



Appendix A – Emetogenicity Tables

Emetogenic potential of chemotherapy agents (Hesketh 1999)		
Level	Frequency of emesis (%) [±]	Agent
5	>90	Carmustine >250mg/m ² Cisplatin >50mg/m ² Cyclophosphamide >150mg/m ² Dacarbazine Meclorethamine Streptozocin
4	60-90	Carboplatin Carmustine <250mg/m ² Cisplatin <50mg/m ² Cyclophosphamide >750 mg/m ² <1500 mg/m ² Cytarabine >1g/m ² Doxorubicin >60mg/m ² Methotrexate >1000mg/m ² Procarbazine (oral)
3	30-60	Cyclophosphamide <750mg/m ² Cyclophosphamide (oral) Doxorubicin 20-60mg/m ² Epirubicin <90mg/m ² Hexamethylmelamine (oral) Idarubicin Ifosfamide Irinotecan Methotrexate 250-1000mg/m ² Mitoxantrone <15mg/m ²
2	10-30	Capecitabine Docetaxel Etoposide 5-Fluorouracil <1000mg/m ² Gemcitabine Methotrexate >50mg/m ² <250mg/m ² Mitomycin Paclitaxel Topotecan
1	<10	Bleomycin Busulfan Chlorambucil (oral) 2-Chlorodeoxyadenosine Fludarabine Hydroxyurea Methotrexate <50mg/m ² L-phenylalanine mustard (oral) Thioguanine (oral) Vinblastine Vincristine Vinorelbine

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²⁵proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

Algorithm for defining the emetogenicity of combination regimes (Hesketh 1999)

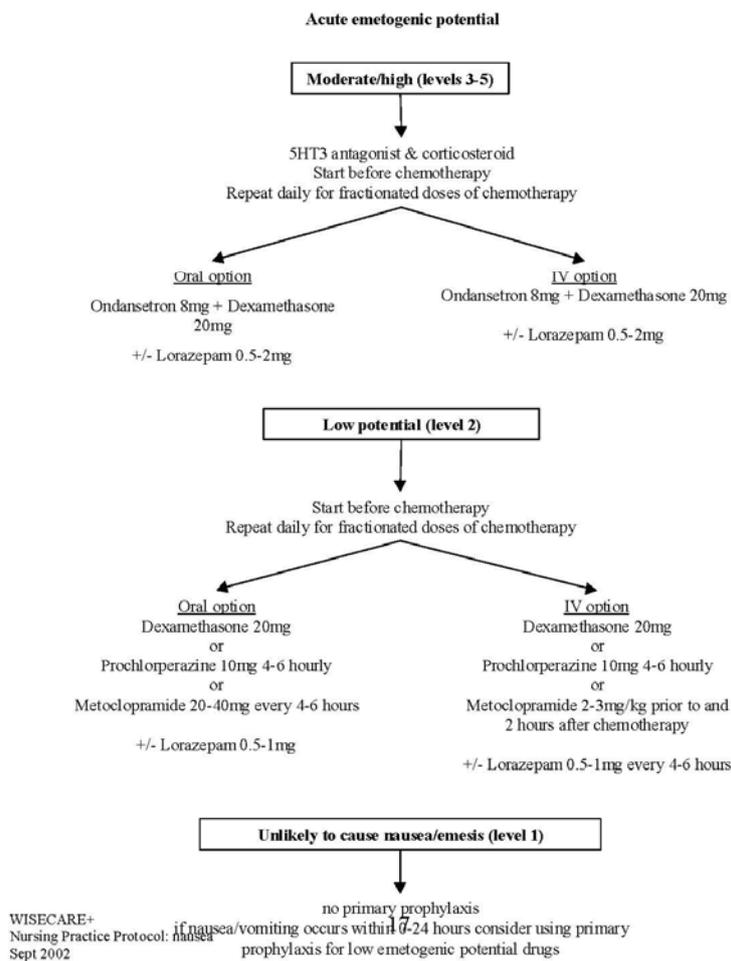
1. Identify the most emetogenic agent in the combination
2. Determine the relative contribution of other agents to the emetogenicity of the combination. When considering other agents, the following rules apply:
 - a. Level 1 agents do not contribute to the emetogenicity of a given regime
 - b. Adding one or more level 2 agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination
 - c. Adding level 3 or 4 agents increases the emetogenicity of the combination by one level per agent

Appendix B – Suggested anti-emetic protocol

This has been developed based on recommendations set out within the following key documents:

National Comprehensive Cancer Network (2001) **Antiemesis: practice guidelines in oncology**.
National Comprehensive Cancer Network

Fausser AA, Fellhauer M, Hoffmann M, Link H, Schlimok G, Gralla RJ (1999) Special Paper:
Guidelines for anti-emetic therapy: acute emesis. **European Journal of Cancer** 35(3): 361-370



Delayed emetogenic potential

Cisplatin >50mg/m²

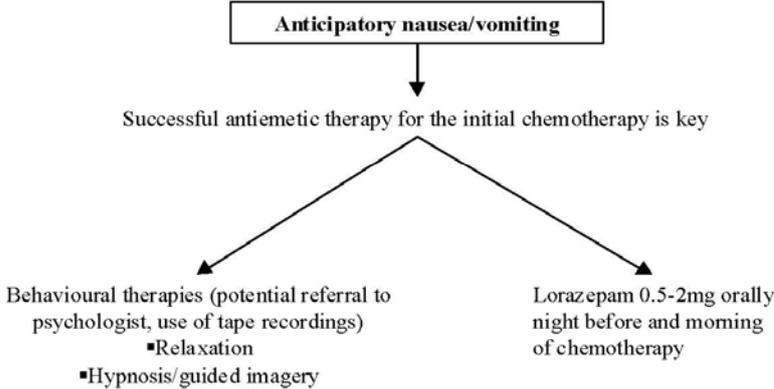
Dexamethasone 8mg twice daily for 3 days
+
Ondansetron 8mg twice daily for 3 days
or
Dexamethasone 8mg twice daily for 3 days
+
Metochlopramide 0.5mg/kg four times daily for 3 days

+/- Lorazepam 0.5-2mg every 6 hours

**Carboplatin >300mg/m², Cyclophosphamide >600-1000mg/m²,
Doxorubicin >50mg/m²**

Dexamethasone 8mg twice daily for 3 days
or
Ondansetron 8mg twice daily for 3 days

+/- Lorazepam 0.5-2mg every 6 hours



Appendix C – Principles of good practice in the administration of anti-emetics

- Prevention of nausea and emesis is the primary goal in the management of chemotherapy-related nausea and/or vomiting.
- Anti-emetics must be initiated prior to commencement of chemotherapy.
- The choice of the anti-emetic should be based on the emetogenic potential of the chemotherapy agents being administered.
- Anti-emetics should be administered for the same length of time as the duration of the emetic activity of the chemotherapy agent being used.
- The lowest, maximally effective dose of an anti-emetic should be used.
- Combination anti-emetic therapy is more effective than single-agent.
- The toxicity of the anti-emetics chosen for use should be considered.
- Drug options may be based on a patients' individual experience.
- Delayed emesis is a major problem and prophylactic therapy is essential.

Appendix D – Foods to eat and avoid when nauseated

Foods to eat	Foods to avoid
Toast and crackers	Large meals
Yoghurt	Too much to drink with meals
Oatmeal	Fatty, greasy, or fried foods
Baked or grilled chicken (without skin)	Sweets, biscuits, or cake
Fruits and vegetables that are soft or bland, such as canned peaches	Foods with strong smells
Chilled drinks sipped slowly, between meals	
Ice chips, ice lollies	
Flat ginger ale, flat cola, fruit juice (no gas)	

Appendix E – Example of script for progressive muscle relaxation training

(Read slowly and clearly)

I will now begin to guide you through different parts of your body, from your feet to the top of your head. With each part of the body, I will ask you to focus on tensing, then relaxing the muscles in that particular part of the body. Follow my instruction, step by step. If a certain area provokes a sharp pain for you, stop tensing it. Instead, tell yourself to relax that body part. For example, if your right arm is painful, just quietly say to yourself "RelaxRelax," while focusing your thoughts on that arm. Continue until I guide you to a different body part. Throughout the series of tensions and relaxations, it is important to take slow, deep breaths. I will remind you to focus on your breathing.

Now close your eyes and focus on your breathing. Your breathing is deep, steady, slow and rhythmic – in and out. Refresh yourself with each inhale, and let go with each exhale. (Pause for 10 seconds)

Let's begin with your right foot. Focus on your right foot. Tense the muscles in that foot. Squeeze your toes closed, and hold them closed for a few moments. Study the tension in your right foot. Now relax your toes and the muscles of your right foot. Notice the difference between tension and relaxation in your right foot. Now tense the muscles in your left foot. Focus on your left foot. Tense the muscles in your left foot. Squeeze your toes closed. Hold for a few moments. Study the tension in your left foot. Now relax your toes and the muscles of your left foot. Notice the difference between tension and relaxation in your left foot. Notice how both feet feel – are they warm or tingling? Take a deep breath. And as you breathe in, imagine your breath going through your body and down to your toes. As you breathe out, let your breath go up and out, from your feet through your body and out your lungs. (Pause)

Now focus on the muscles of your right lower leg. Tense the muscles of your right lower leg. Hold for a few moments. Study the tension in your right calf and shin. Now relax the muscles of your right lower leg. Notice the difference between tension and relaxation in your right lower leg. Now I want you to focus on your left lower leg. Tense the muscles in your left lower leg. Hold for a few moments. Study the tension in your left calf and shin. Now relax the muscles of your left lower leg. Notice the difference between tension and relaxation in your left lower leg.

Now focus on the muscles of your right upper leg. Tense the muscles in your right thigh. Hold for a few moments. Study the tension in your right thigh. Now relax the muscles of your right upper leg. Notice the difference between tension and relaxation in your right thigh. Now I want you to tense the muscles in your left upper leg. Focus on your left upper leg. Tense the muscles in your left thigh. Hold for a few moments. Study the tension in your left thigh. Now relax the muscles of your left upper leg. Remember to breathe. Notice the difference between tension and relaxation in your left upper leg. Now tense the muscles in both thighs together. Hold for a few moments. Study the tension in both your left and right thighs. Now relax your thighs. Notice how both legs feel – are they warm, tingling, heavy or relaxed? Take a deep breath. You're becoming more and more relaxed. As you breathe in, imagine your breath going through your body and down your legs. As you breathe out, let your breath go up and out, from your legs through your body and out of your lungs. (Pause for 10 seconds)

Now focus on the muscles of your buttocks. Squeeze together and tense the muscles in your buttocks. Hold for a few moments. Study the tension in your buttocks. Now relax the muscles of your buttocks. Notice the difference between tension and relaxation. Take a deep breath – in through your nose and out slowly through your mouth.

Now focus on your abdomen. As you take a deep breath in, hold it and tense the muscles of your abdomen for a few moments. Study the tension of the muscles in your abdomen. Now relax the muscles in your abdomen. Notice the difference between tension and relaxation.

Now focus on your chest. As you take a deep breath, hold it and tense the muscles of your chest for a few moments. Study the tension of the muscles of your chest. Now relax the muscles of your chest. Study the difference between tension and relaxation of your chest. The relaxation is growing deeper and still deeper and you are relaxed, drowsy and relaxed. Your breathing is regular and relaxed, and with each breath your relaxation increases. Each time you exhale, you spread relaxation through your body. (Pause for 10 seconds)

Now let's move to your right hand. Focus on your right hand. Tense the muscles in it. Close your fingers and squeeze. Hold for a few moments. Study the tension in your right hand. Now relax your fingers and the muscles of that hand. Notice the difference between tension and relaxation in your right hand. Now I want you to tense the muscles in your left hand. Focus on your left hand. Tense the muscles in your left hand. Close your fingers and squeeze. Hold for a few moments. Study the tension in your left hand. Now relax your fingers and the muscles of your left hand. Notice the difference between tension and relaxation in your left hand. Notice how both of your hands feel – are they warm or tingling? Take a deep breath.

Now focus on the muscles of your right lower arm. Tense the muscles of your right lower arm. Hold for a few moments. Study the tension in your right forearm. Now relax the muscles of your right lower arm. Notice the difference between tension and relaxation in your right forearm. Now I want you to focus on your left lower arm. Tense the muscles in your left lower arm. Hold it for a few moments. Study the tension in your left forearm. Now relax the muscles of your left lower arm. Notice the difference between tension and relaxation in your left forearm.

Now focus on the muscles of your right upper arm. Tense the right biceps and triceps muscles. Hold for a few moments. Study the tension in your right upper arm. Now relax your right biceps and triceps muscles. Note the difference between tension and relaxation in your right upper arm. Now I want you to tense the muscles in your left upper arm. Focus on your left upper arm. Tense the left biceps and triceps muscles. Hold for a few moments. Study the tension in your left upper arm.

Now relax your biceps and triceps muscles. Remember to breathe. Notice the difference between tension and relaxation in your left upper arm. Now I want you to tense the muscles in both arms together. Hold for a few moments. Study the tension in both your left and right arms. Now relax your arms. Notice how both arms feel – are they warm, tingling, heavy or relaxed? Take a deep breath. You're becoming more and more relaxed. As you breathe in, imagine your breath going into your body and down through your arms. As you breathe out, let your breath go up and out, from your arms into your body and out your lungs. (Pause for 10 seconds)

Now bring your attention to your shoulders. Squeeze together and tense the muscles in your shoulders. Hold for a few moments. Study the tension in your shoulders. Now relax the muscles of your shoulders. Notice the difference between tension and relaxation in your shoulders. Take a deep breath – in through your nose and slowly out through your mouth.

Now focus on your neck. Tense the muscles of your neck. Concentrate on the tensions in your neck. Now relax the muscles of your neck. Notice the difference between the tension and relaxation of your neck. Note the pleasant feeling of warmth and heaviness coming into your body. As you continue to relax, you are clearly aware of what I am saying and what you are doing. You are becoming more deeply relaxed.

Now focus on and tense the muscles of your lips. Study the tension in your lips. Now relax your lips. Notice the difference between tension and relaxation of your lips.

Now move your attention to your eyes. Tense the muscles around your eyes. Study the tensions in your eyes. Now relax the muscles of your eyes. And notice the difference between tension and relaxation of your eyes.

Now tense the muscles of your forehead, focus on the tension of the muscles in your forehead. Hold it for a few moments. Now relax your forehead. Notice the difference between tension and relaxation in your forehead.

Now focus on your scalp and the top of your head. Tense the muscles of the top of your head. Hold it for a few moments. And now relax the muscles of your head. Be aware of the difference between tension and relaxation of your head.

Focus on your breathing. Breathe in energy and healing and breathe out tensions and worries. With each breath, let go a little more and let your muscles and all of your body become more and more relaxed.

Appendix F – Example of script for guided imagery

I will guide you to a scene and through a sensory experience to a place that is peaceful and pleasurable to many of us – an uncrowded beach and seashore. And now with your eyes closed, imagine a movie screen on your eyelids where you can paint a vivid and realistic picture.

Bring yourself to a quiet, warm place along the seashore. Connect all of your senses to this place. Hear the sound of the waves slowly rushing upon the shore and drawing back. Also hear the whirr of the cool breeze coming off the water. And perhaps even listen to the sound of sea gulls flying distantly overhead. Bring alive the smells of the shore. Perhaps you notice the salt in the air and the subtle odour of seashore plants. You return to the sound and feeling of the waves as you visualise them washing away all of your tension, washing away anxiety, washing away fear, washing away all of your unwanted sensations, and cleansing your body inside and out.

As these waves are coming in and out, as they wash away your troubles and tensions, as they help you feel peaceful and relaxed, imagine that you can clearly visualise this entire scene. You gradually picture this in your mind's eye. Perhaps you can see the blue of the water, slowly rippling off into the distance, rising as the water approaches the shore to form waves that curl up to form whitecaps. The water then spreads across the shore and fans out onto the beach, and draws back into the ocean. Picture the blue water and its movement in and out. See it vividly in your mind's eye. The water may be a deep blue off in the distance and a lighter whitish blue as it approaches the shore and forms the waves. Now look above the water and the blue sky and picture the quality of that blue. There may also be clouds in the sky, forming contours of white against the blue. Look at the shapes of the clouds. They may be wispy, faint clouds that blur with the blue of the sky, or they may be distinct, puffy white clouds that clearly stand out as separate units floating across the sky. Allow these clouds to float by you slowly, as if reflecting that you have nothing to worry about. Sometimes the clouds pass in front of the sun for a few moments, creating a pleasant, refreshing sense of coolness. Then as the clouds float past and the sun reappears, you can feel its warmth again on your body. It's so pleasant to sit here and watch the clouds as they form and dissolve above you. The sound of the ocean, the waves coming and going, the movement of the clouds forming and dissolving, lulling you deeper and deeper into relaxation. (Pause)

You may now wish to take in other details about the beach. You look down the shore and notice the line created by the meeting of the water with the land. You may see rocks. Remind yourself that you have no place to go and nothing to do but take in the beauty of the colours, shapes, sounds, smells, and feelings of the water... the waves... the sky... the clouds... the breeze... the sun... the sea gulls... the coastline. See the details of the ebb and flow of the water against the land. Imagine your face being warmed by the gentle sun. Feel the cool breezes against your face and through your hair as they come off the breaking waves. As you look out onto the water, see where the horizon meets the sky off in the distance. There may be some sailboats or buoys that break that horizon line. Take a moment to recapture and create those vivid images. You may continue to stay at this beautiful and tranquil beach as long as you like. You are not in a hurry. Just relax and enjoy these pleasant sensations.

APPENDIX H – FATIGUE PRACTICE PROTOCOL



Cancer-related fatigue

Nursing Practice Protocol

‘Cancer-related fatigue is an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning’
 National Comprehensive Cancer Network 2001

This nursing practice protocol for the management of cancer-related fatigue is tailored specifically for the nursing care of patients participating in WISECARE+, namely patients receiving chemotherapy. The following issues will be considered:

BASELINE ASSESSMENT OF FATIGUE	3
AIM	3
METHOD OF BASELINE ASSESSMENT	3
FATIGUE SCORING CHART.....	3
OUTCOMES OF ASSESSMENT	4
ASSESSMENT DURING A COURSE OF CHEMOTHERAPY	5
ASSESSMENT FOR FATIGUE SCORES 1-2 (MILD FATIGUE)	6
ASSESSMENT FOR FATIGUE SCORES 3-6 (MODERATE-SEVERE FATIGUE)	6
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APPENDIX A: FACTORS TO AID SLEEP	11

Nurses are advised to read the National Comprehensive Cancer Network Cancer-Related Fatigue practice guideline in conjunction with this protocol. This can be obtained from the lead WISECARE+ nurse in your clinical area.

Baseline Assessment of Fatigue

Aim

To detect cancer-related fatigue at the earliest opportunity and instigate appropriate nursing action.

Method of baseline assessment

Clinical assessment should evaluate the presence or absence of fatigue, its severity (mild, moderate or severe) and associated distress (not at all, a little, quite a bit, very much). This assessment should be completed prior to the patient starting chemotherapy.

Fatigue (tiredness)

Have you experienced this today? Yes No

If yes,

How severe was this? Mild (1)

 Moderate (2)

 Severe (3)

How much did it bother you? Not at all (0)

 A little (1)

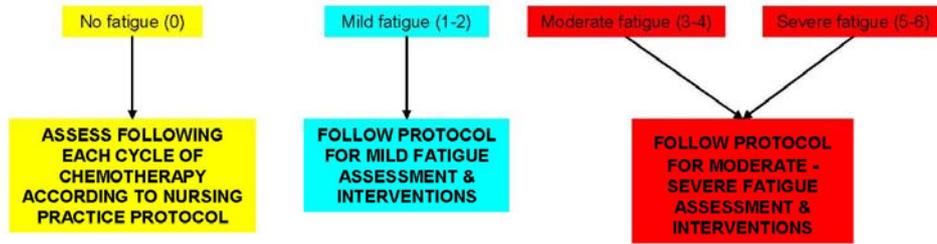
 Quite a bit (2)

 Very much (3)

Fatigue scoring chart

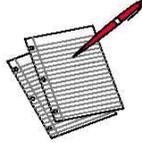
Score	Descriptors		Summary description
	Severity	Distress	
0	---	---	No fatigue
1	Mild	Not at all	Mild fatigue
2	Mild Moderate	A little Not at all	
3	Mild Moderate	Quite a bit A little	Moderate fatigue
4	Mild Moderate Severe	Very much Quite a bit A little	
5	Moderate Severe	Very much Quite a bit	Severe fatigue
6	Severe	Very much	

Outcomes of Assessment



Assessment during a course of chemotherapy

To ensure minimum fatigue and provide timely interventions appropriate to the individual's fatigue experiences

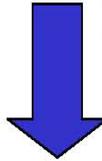


Assess fatigue using the WISECARE+ Symptom Questionnaire that includes incidence, severity and distress (see page 3)

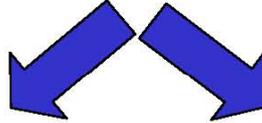
Teach patients how to perform this assessment by themselves for 14 days after each cycle of chemotherapy



Enter the patient's fatigue symptom outcomes and self-care into the WISETool



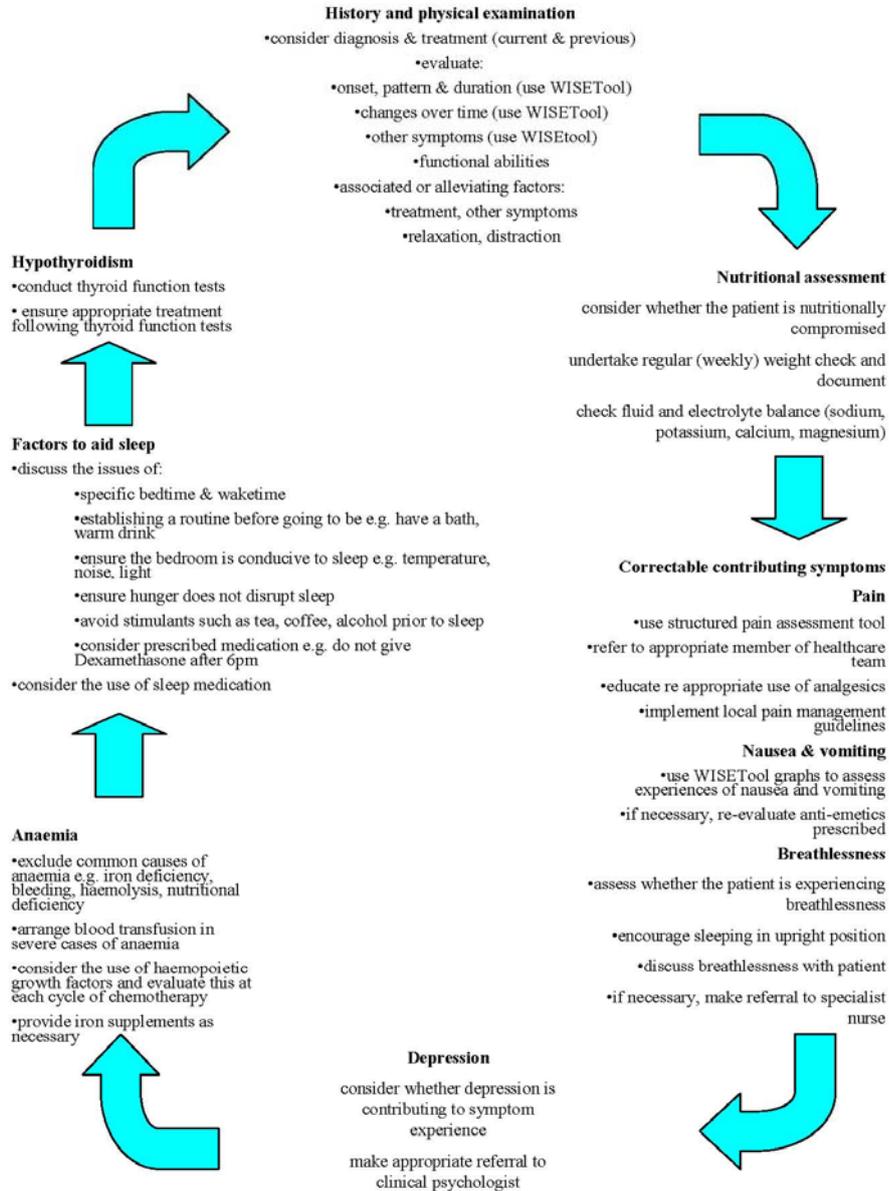
Symptom score generated as seen on page 3



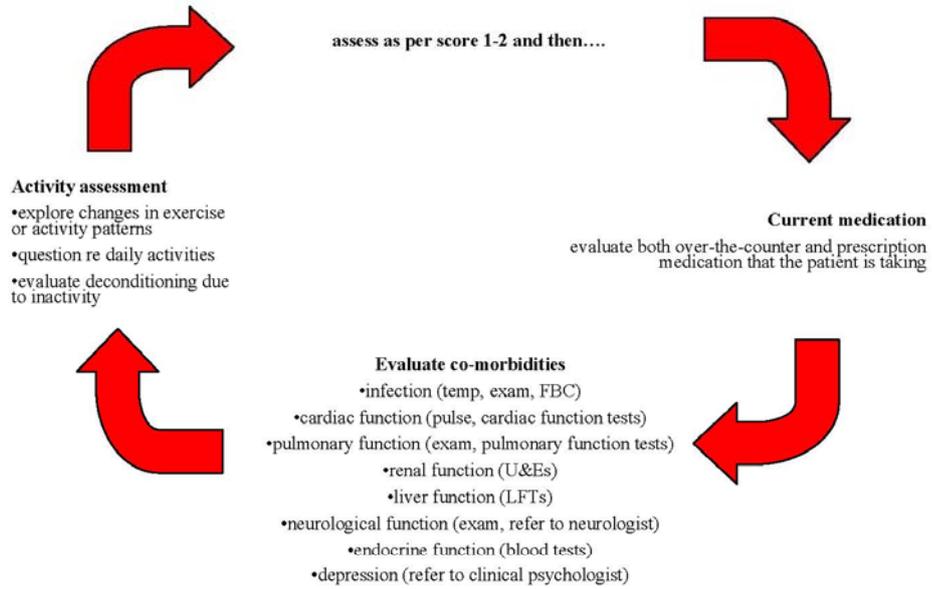
Fatigue score 1-2
FOLLOW ALGORITHM FOR MILD FATIGUE ASSESSMENT & INTERVENTIONS

Fatigue score 3-6
FOLLOW ALGORITHM FOR MODERATE - SEVERE FATIGUE ASSESSMENT & INTERVENTIONS

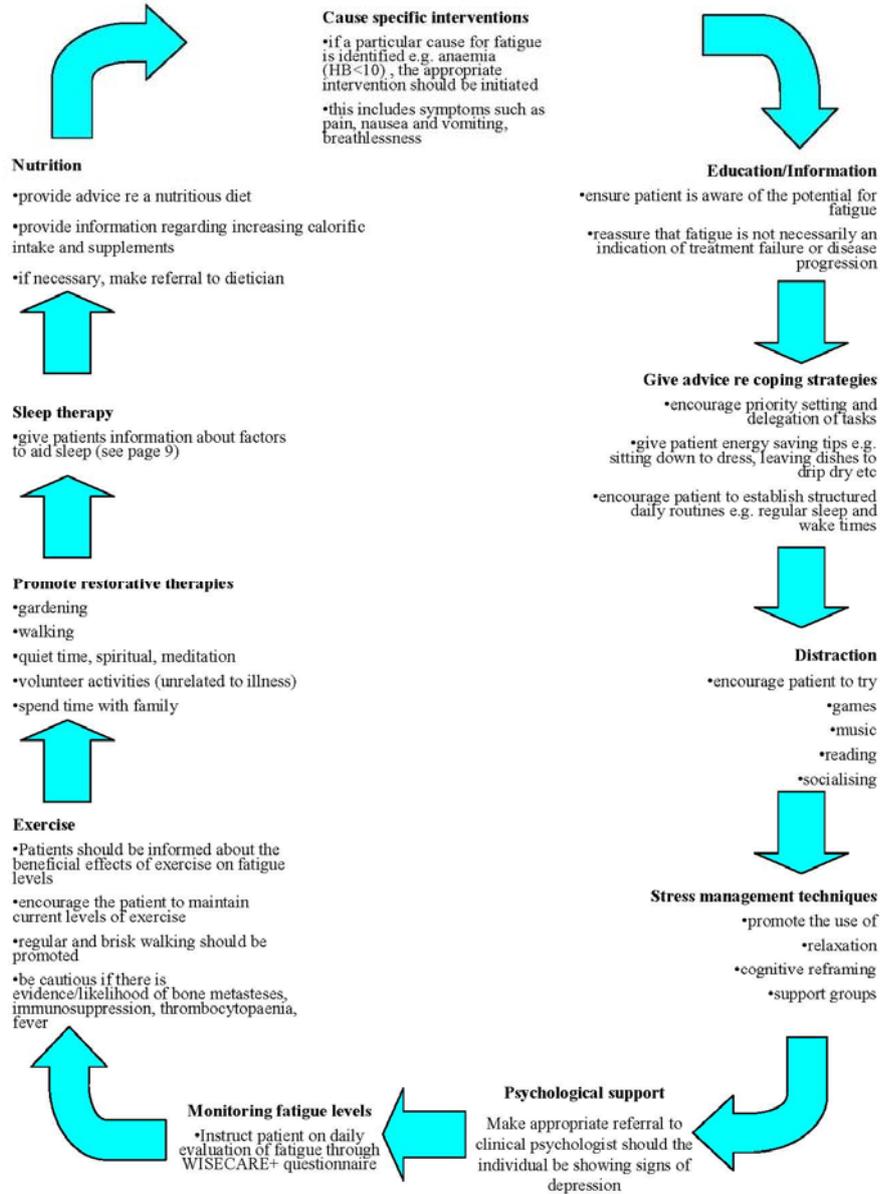
Assessment for fatigue scores 1-2 (mild fatigue)



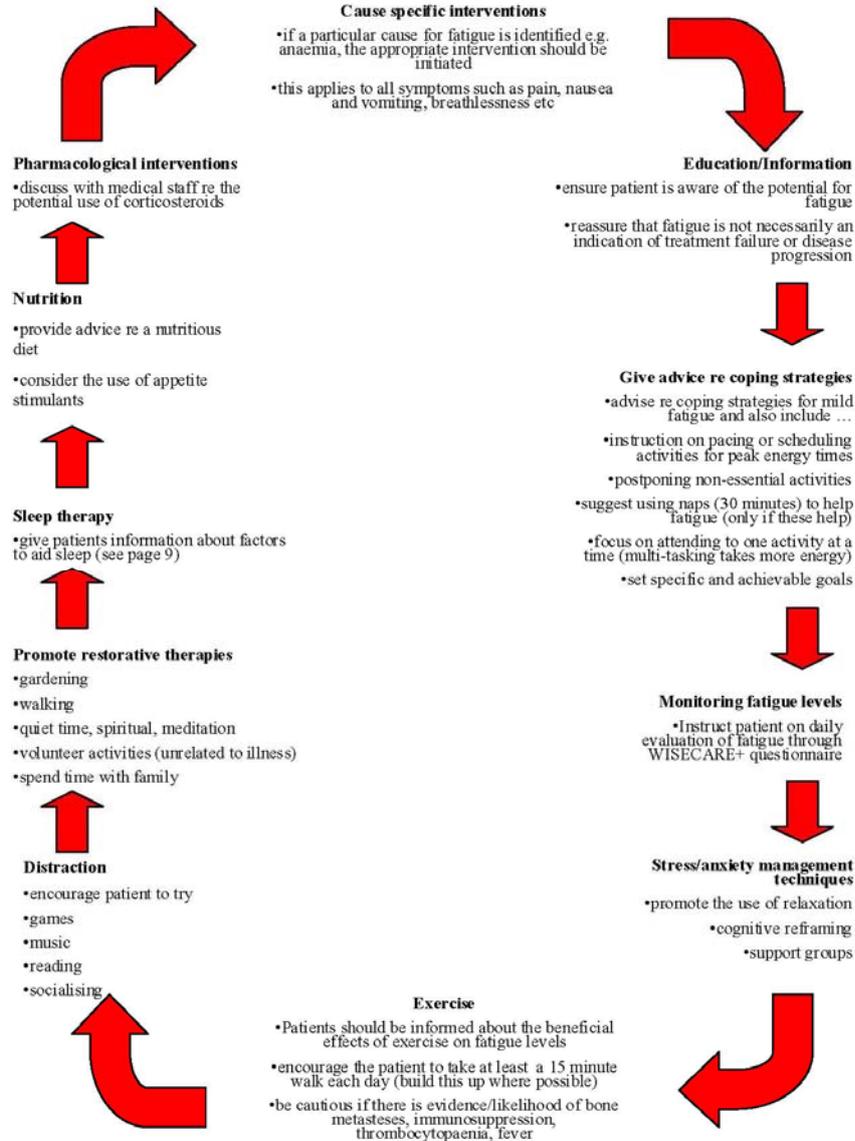
Assessment for fatigue scores 3-6 (moderate-severe fatigue)



Interventions for fatigue score 1-2 (mild fatigue)

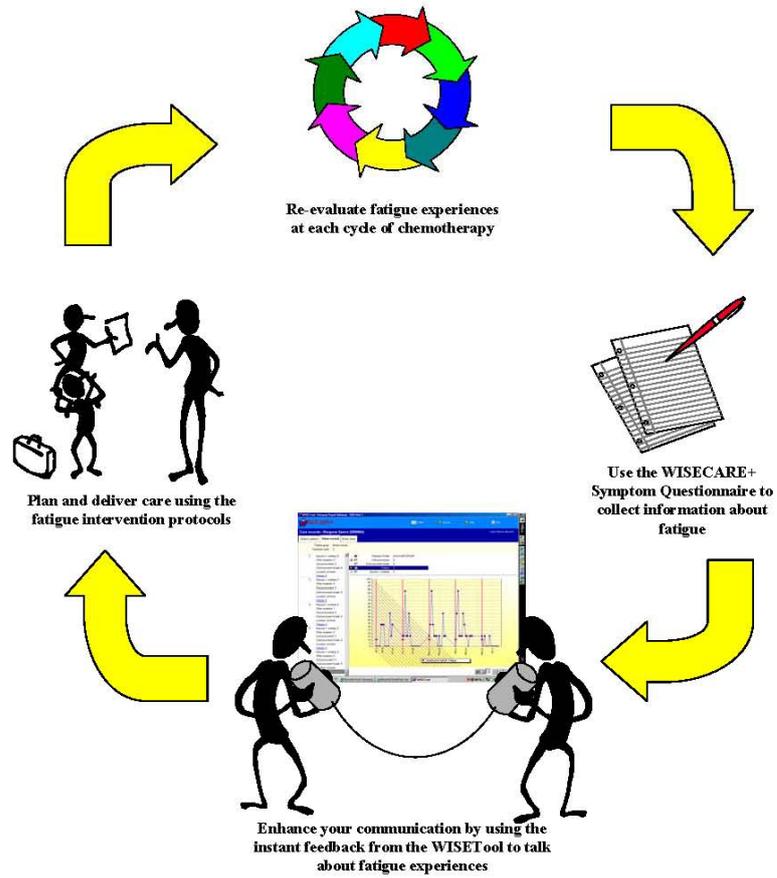


Interventions for fatigue score 3-6 (moderate-severe fatigue)



Re-evaluation of fatigue

To monitor the effectiveness of fatigue interventions, identify the most effective for individuals and continuously strive to reduce patient's symptoms of fatigue



Appendix A: Factors to aid sleep

The following guidelines should be promoted with patients:

- Go to bed and rise at the approximately the same time each day
- Have specific bedtime routines to promote relaxation such as a hot drink or a warm bath
- Ensure that the bedroom/bedclothes are not too warm or cold
- Ensure that the bedroom is not too light
- Close windows to prevent noise from disturbing sleep or have a ticking clock to drown out background noise
- Try not to sleep during the day if this then prevents you sleeping at night
- Do not lie awake in bed if sleep does not come, either read for a short while or have a warm drink, then try again
- Relaxation exercises should be encouraged if sleep is prevented by feelings of anxiety or stress

APPENDIX I – ELECTRONIC KEYWORD DATABASE SEARCH

Key words used in database search of literature reviews

<u>Nausea</u>	<u>Fatigue</u>
Subject headings	Subject headings
Nausea	Fatigue
Keywords	Keywords
Anti-emetics	Activity
Assessment	Assessment
Behavioural interventions	Chemotherapy
Cancer	Distress
Chemotherapy	Exercise
Distress	Guided imagery
Guided imagery	Incidence
Incidence	Interventions
Interventions	Management
Management	Non-pharmacological
Non-pharmacological	Patient attitudes
Patient attitudes	Patient experience
Patient experience	Patient perceptions
Patient perceptions	Pharmacological
Pharmacological	Psychological
Progressive muscle relaxation training	Self-care
Psychological	Severity
Relaxation	Treatment
Self-care	Quality of life
Severity	
Treatment	
Quality of life	

APPENDIX J – NAUSEA LITERATURE REVIEW



Chemotherapy-Related Nausea & Vomiting

Review of the literature

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ISSUES FOR CONSIDERATION ASSOCIATED WITH ANTIEMETIC ADMINISTRATION	12
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Introduction

The purpose of this paper is to review recent and current literature relating to the assessment and management of chemotherapy-induced nausea and vomiting. Inclusion criteria for literature in this review were:

- Relating to nausea or vomiting in adults induced by chemotherapy (not including anticipatory nausea and vomiting)
- Primary research, literature reviews, opinion articles and patient information leaflets/booklets
- Published between 1990-2001

Key databases (Medline and Cinahl) were systematically searched using specific keywords (nausea, vomiting, chemotherapy, neoplasm) all of which were 'exploded' and combined appropriately. Articles were identified, abstracts read (where possible) and a full copy of each article was sought if it met, or was thought to meet, the inclusion criteria. Each article was read, the relevant data extracted and the review constructed. The literature base relating to chemotherapy-induced nausea and vomiting is vast and this review does not purport to have included each and every piece of literature. However, it does address the main areas involved in the assessment and management of chemotherapy-induced nausea and vomiting. Tables of key primary research relating to nausea and vomiting, both pharmacological and non-pharmacological, are also provided.

The clinical significance of nausea and vomiting

It is unquestionable that chemotherapy-induced nausea and vomiting represent a significant problem for patients with cancer. Results demonstrate that although the introduction of 5-HT₃ receptor antagonists have reduced the incidence of vomiting, incidence of nausea has actually risen (Roscoe et al. 2000). Estimates of the prevalence of nausea and vomiting due to chemotherapy vary but have been estimated at between 60-72% (Morrow 1992; King 1997).

Inadequate control of nausea and vomiting reduces patients' quality of life and functional status and jeopardises the delivery of optimal treatment (Ouwerkerk and Keizer 1990; Bregni et al. 1991; Jones et al. 1991; Kaye 1991; Fitch 1992; Fitch 1993; Jenns 1994; Ouwerkerk 1994; Fessele 1996; Grant 1997; Pendergrass 1998; Roscoe et al. 2000; Eremita 2001). Indeed, nausea and vomiting can affect compliance and precipitate physiological complications including fluid and electrolyte imbalance, malnutrition and oesophageal injury (Kaye 1991; Egan et al. 1992; Jenns 1994; Fessele 1996; Grant 1997; Roscoe et al. 2000; Eremita 2001). Such implications ultimately have consequences in relation to both direct and indirect costs. Direct costs of poorly managed nausea and vomiting include increased hospitalisation and the increased medical and nursing costs of managing adverse events (Pendergrass 1998). Indirect costs cover lost or reduced patient/caregiver productivity and income (Pendergrass 1998). With the continued development of new cytotoxic agents and the advent of colony stimulating factors, both of which facilitate more aggressive, and therefore potentially more emetogenic drug therapy, effective management of nausea and vomiting by health professionals is imperative.

Assessing nausea and vomiting

Adequate diagnosis of a symptom is a prerequisite for its management. The nurse's role in assessment begins as soon as the patient is thinking about treatment (Fitch 1992). Assessing patient's risk factors before treatment provides some insight into what type of experiences relating to nausea and vomiting a patient might be expected to experience (Beaulieu 2000). The nurse must have knowledge of the emetogenic potential of the chemotherapy regime that the patient is receiving, as this should be considered in formulating the antiemetic regime. In addition to this, exploring what the patient expects to happen will help clarify any false ideas that they might have, such as believing that experiencing nausea and vomiting means that the treatment is working (Fitch 1992). Indeed, patients' expectations of how severe nausea and vomiting will be has been shown to account for unique variance beyond pharmacologic factors in predicting the frequency and severity of these symptoms (Haut et al. 1991). Key issues that the nurse should consider when assessing patients' characteristics associated with nausea and vomiting include:

- Age: the young are more severely affected than the old (Hogan 1990; Sledge 1990; Fitch 1992; Fitch 1993; Ouwerkerk 1994; Dodd et al. 1996; Goodman 1997; Pendergrass 1998; Beaulieu 2000)
- Gender: women are more affected than men (Sledge 1990; Fitch 1992; Fitch 1993; Goodman 1997; Pendergrass 1998; Beaulieu 2000)
- History of alcohol intake: patients with a history of chronic alcohol ingestion appear to experience less nausea and vomiting (Hogan 1990; Sledge 1990; Fitch 1992; Fitch 1993; Ouwerkerk 1994; Goodman 1997; Pendergrass 1998; Beaulieu 2000)
- History of motion sickness: susceptibility to motion sickness is associated with increased nausea and vomiting following chemotherapy (Sledge 1990; Fitch 1992; Fitch 1993; Beaulieu 2000)
- Emetic response to previous chemotherapy: patients with previous uncontrolled emesis following chemotherapy are more likely to experience severe nausea and vomiting despite aggressive antiemetic coverage (Sledge 1990; Fitch 1992; Fitch 1993; Ouwerkerk 1994; Goodman 1997; Pendergrass 1998; Beaulieu 2000)

The use of assessment scales in daily practice may facilitate the task of improving symptom control. However, accurate assessment is dependent on the clarity of meaning of the symptoms and the use of tools to reflect the patient's experience (Rhodes 1997). Cultural sensitivity should also be considered when assessing symptom of nausea and vomiting (Rhodes 1997). Consequently, the reliability and validity of assessment tools should be carefully considered before utilising them in practice (Jenns 1994). For example, nausea is seldom recognised and assessed as a separate phenomenon (Jenns 1994).

Types of assessment scales

Visual analogue scales

This is a scaling format on which respondents can quantify their symptoms by making a mark on a 10cm line with anchors at each end that indicate the extremes of the symptom under study such as 'no nausea' and 'worst possible nausea'. The anchors at either end require meaningful descriptors with

tested reliability (Rhodes et al. 1995). Visual analogue scales were designed to be used with seated subjects and there has been questions raised as to whether they can reliably be completed by a supine patient (Rhodes et al. 1995). Another potential disadvantage with visual analogue scales is that patients require careful instruction from trained personnel to produce reliable answers (Kaye 1991). One further criticism is that visual analogue scales are unidimensional and as such measure a single aspect such as intensity of nausea, which ultimately questions their applicability for measuring the multidimensional phenomena of nausea and vomiting (Del Favero et al. 1992).

Ordinal Scales

Descriptive ordinal scales ask patients to grade their nausea for example as 'no nausea', 'mild', 'moderate' or 'severe'. While category scales such as this are attractive for use in situations where large groups are being investigated, they may become less sensitive over time than VAS in detecting change due to their bluntness (Borjeson et al 1997). Furthermore, a large number of variables have not been shown to increase the accuracy of the assessment (Jaeschke et al. 1990).

Multidimensional scales

Multidimensional instruments consider a variety of components that make up experiences of nausea, vomiting and retching and the distress that the patient experiences as a consequence of these components. The Rhodes Index of Nausea and Vomiting (INV-2) is one such multidimensional instrument (Rhodes et al. 1984). It contains 8 questions that measure the patients' perceived duration, frequency and distress of nausea, frequency, amount and distress of vomiting and frequency and distress of retching using 5 point Likert scales. The total score of the INV-2 provides the patient's total experience score. Subscale scores for nausea, vomiting and retching can also be derived from the instrument. This tool captures the difference between the actual occurrence of vomiting and the emotional response and distress that the patient associates with that symptom. This type of symptom distress measure is unavailable on other rating scales. It is especially useful in evaluating the effectiveness of nursing interventions designed to decrease symptom occurrence and the associated distress.

Patient diaries, logs and journals

Patient diaries have been shown to provide useful assessment information and have contributed to increased experience in problem solving and improved self-care management (Rhodes 1997). These methods of assessment allow the evaluation of specific pharmacological and non-pharmacological interventions as well as situational or concomitant factors on nausea and vomiting (Goodman 1997, Rhodes 1997). Such reliable self-reporting has been essential in the development of evidence to evaluate interventions for the management of nausea and vomiting.

Indirect measures

Methods of assessment should be both simple and reproducible (Kaye 1991). Assessment techniques should consider not only the occurrence of a symptom but also the distress associated with that

symptom (Rhodes et al. 1995). As already mentioned, the Rhodes Index of Nausea and Vomiting Form 2 measures the individual components of symptoms and their associated distress. The use of indirect measures of nausea and vomiting is valuable as they allow assessment of the impact of nausea and vomiting on other aspects of the patient's functional abilities (Kaye 1991; Jenns 1994). These include evaluating factors such as appetite, elapsed time before resuming eating and drinking, general well-being and preferred antiemetic treatment (Kaye 1991; Jenns 1994).

An objective approach to measuring nausea and vomiting was described by Jenns (Jenns 1994), which consists of evaluating face temperature, blood volume pulse, heart rate and skin pallor which appear to differ significantly from baseline during episodes of nausea and vomiting. Such objective measures may provide an alternative approach to assessing and measuring these patient symptoms.

Deciding on a method of assessment

A number of reported research endeavours have demonstrated that there is no significant advantage of analogue scales over ordinal rating scales (Jaeschke et al. 1990; Kaye 1991; Del Favero et al. 1992; Borjeson et al. 1997). Indeed, the choice of scale should be driven by the needs of the particular situation (Borjeson et al. 1997). Issues that should be considered when making this decision include:

- *Interpretation*: clinicians and researchers often find verbal scales easier to interpret
- *Comprehension*: verbal scales have been shown to be easier to understand (especially for older people)
- *Population*: verbal rating scales are good for assessing symptoms in a large population
- *Sensitivity*: verbal rating scales are less sensitive than visual analogue scales when evaluating changes over time

To give a complete picture of the patient's symptom experience, information is required on other factors such as frequency, duration, distress, alleviating and aggravating factors, medication used and so on. It is also important to consider the time frame of the assessment: ideally assessment should be made during the peak period based on the pharmacokinetics for the drugs in question (providing this makes sense clinically) (Kaye 1991; Jenns 1994). Assessing symptoms retrospectively can result in problems primarily associated with patient recall, resulting in inaccurate information on which to base clinical decisions.

Nausea is a subjective response and as such, self-assessment is appropriate (Jenns 1994). Self-report questionnaires obtain the unique perspective of the patient and are often the best source of information (Rhodes et al. 1995). However, such self-assessment should not be performed too often to prevent patients focussing too frequently on this distressing side-effect (Jenns 1994). Observing patients to establish their experiences of nausea and vomiting is a problematic method of indirect assessment as it requires one-to-one relationship and is limited with respect to the time frame over which such intense observation can be carried out (Jenns 1994; Rhodes et al. 1995). Indeed, while it could be argued that the use of observer-rated measures is an appropriate means for assessing vomiting, its accuracy in nausea is doubtful (Kaye 1991).

Ongoing assessment is the key to successful symptom management as it provides a clear picture of the impact of the symptom on the individual's and the family's quality of life and what interventions are effective (Fitch 1993). Such an assessment should include:

- The nature and character of the nausea and vomiting (onset, frequency, severity)
- Interference with daily activities
- The impact of nausea and vomiting on nutritional status, fluid balance and metabolic homeostasis
- The presence of risk factors such as infection, change in mental status
- The presence of side effects from antiemetic medications

(Fitch 1993)

Managing nausea and vomiting

As there are multiple pathways for the stimulation of the vomiting centre in the brain, it follows that drug combinations are more effective than single agents in controlling nausea and vomiting that occurs as a result of chemotherapy (Aapro 1991; Lane et al. 1991; Budzar et al. 1994; Heron et al. 1994; du Bois et al. 1997; Tsavaris et al. 1999). Consequently, for most patients, the use of various antiemetic drugs forms the basis for emesis control. In addition to multiple drug combinations, behavioural strategies, such as progressive muscle relaxation and guided imagery, have also been tried and tested for their effectiveness in the prevention and control of chemotherapy-induced nausea and vomiting (Dundee and Yang 1990; Brown et al. 1992; Morrow et al. 1992; Troesch et al. 1993; Bauer 1996; King 1997; Shen et al. 2000). Selecting and administering the appropriate antiemetic therapy, be it pharmacological or behavioural, can significantly improve patients' quality of life and functional status, facilitating the effectiveness of potentially life-saving therapy and favourably effecting the overall cost of managing the disease (Del Favero et al. 1992; Fitch 1993; Fessele 1996; Goodman 1997). Consequently, the best management is based on treating the patient as an individual, in conjunction with careful consideration of the drug regimen prescribed, convenience, cost-effectiveness and combination pharmacotherapy.

Pharmacological management

The choice of antiemetics and decision making

Considerable progress has been made in the pharmacological management of nausea and vomiting and prevention of nausea and vomiting before they occur is the key to successful management (Goodman 1997). Several classes of drugs are used to prevent and treat chemotherapy-induced nausea and vomiting. Their activity can be explained by their affinity with certain neurotransmitter receptors (Pendergrass 1998). Treatment with two or more antiemetics may improve their efficacy and/or reduce unwanted side effects. It is crucial that nurses understand the mechanisms of action and aims of various classes of antiemetics as they are in a prime position to recommend antiemetic medication changes should the patient require it. A survey of Oncology Nursing Society members demonstrated the wide variety of antiemetic regimes administered (Rhodes et al. 1995). Indeed, a treatment algorithm centred

around 4 key questions relating to emetogenic potential, patient history and age and the effectiveness of standard antiemetics was developed in response to a quality assessment and improvement programme, (Johnson et al. 1997). Continued assessment following the introduction of this algorithm demonstrated a change in the pattern of antiemetic usage based on the patients' relative risks for nausea and vomiting and resulting in appropriate antiemetic plans for individual patients (Johnson et al. 1997).

The pool of literature addressing the pharmacological management of chemotherapy-related nausea and vomiting is extremely large and it was not feasible to review each and every piece of literature for this review. However, in an attempt to provide some form of evidence-base for practice, a literature search was employed that ensured the inclusion of literature that addressed:

- the key classes of drugs associated with the pharmacological management of chemotherapy-related nausea and vomiting
- important developments in the pharmacological management of nausea and vomiting such as evaluation of drug combinations, drug dosage as well as mode of administration.

When reviewing this literature, the reader should be mindful that the 1990s saw the introduction of 5-HT₃ receptor antagonists (such as Ondansetron and Granisetron), rendering obsolete some of the findings of earlier studies. Table 1 summarises the various classes of antiemetic drugs, their clinical uses and common side-effects in conjunction with nursing considerations. Table 2 presents a summary of research addressing the pharmacological management of chemotherapy-related nausea and vomiting.

Serotonin Receptor Antagonists (for example Ondansetron)

5-HT₃ receptor antagonists have had a profound impact on the clinical management of acute chemotherapy induced nausea and vomiting (Cunningham 1997). They are the most recently approved antiemetic drugs and inhibit the emetic response by preventing serotonin released in the GI mucosa from binding to 5-HT₃ receptors (Aapro 1991; Egan et al. 1992; Rhodes et al. 1995; Pendergrass 1998; Beaulieu 2000). These agents are a mainstay for highly emetogenic therapy (especially acute emesis) and appear to be as effective in both oral and intravenous forms (Bregni et al. 1991; Heron et al. 1994; Crucitt et al. 1996; Pendergrass 1998; Friedman et al. 2000). Intravenous and oral Ondansetron plus Dexamethasone has been shown to be superior in the management of Carboplatin-induced nausea and emesis compared with intravenous oral Metoclopramide plus Dexamethasone (du Bois et al. 1997) and a study evaluating oral Ondansetron versus Prochlorperazine demonstrated that oral Ondansetron was more effective for up to three days in the prevention of emesis (Crucitt et al. 1996). The appropriate dosage of oral Ondansetron has been evaluated, with the same efficacy shown when administered twice daily rather than three times daily (Dicato et al. 1992). Furthermore, oral Ondansetron was associated with more positive health related quality of life measurements (Crucitt, Hyman et al. 1996) and was superior to a Metoclopramide based regimen in the prevention of acute emesis following FAC chemotherapy (Fluorouracil, Doxorubicin and Cyclophosphamide) (Bosnjak et al. 2000) and Cisplatin-based chemotherapy (Heron et al. 1994). The efficacy of oral formulations of 5HT₃ receptor antagonists means that patients can spend increasing amounts of time at home (Dicato et al. 1992;

Ouwerkerk 1994). However, questions about its role in the management of nausea and vomiting associated with moderately emetogenic chemotherapy have been raised. A randomised, controlled double-blind, cross-over comparison of Ondansetron and Dexamethasone for patients receiving moderately emetogenic chemotherapy demonstrated that both drugs offered adequate out-patient control of chemotherapy-induced emesis, indeed, Dexamethasone was shown to have an advantage in the control of delayed nausea (Jones et al. 1991). However, this class of drug has not been shown to be consistently effective in the prevention of delayed nausea and vomiting when administered beyond 48 hours and is therefore not generally recommended for this purpose (Anderson et al. 1994; Cunningham 1997; Goodman 1997).

Side effects associated with 5-HT₃ receptor antagonists are mostly mild and transient and include headache, constipation, fatigue, dry mouth, dizziness and diarrhoea (Sledge 1990; Aapro 1991; Jones et al. 1991; Egan et al. 1992; Rhodes et al. 1995; Crucitt et al. 1996; Cunningham 1997; Goodman 1997; Pendergrass 1998; Beaulieu 2000; Eremita 2001). Elevated liver function tests and fever have been reported, but less frequently (Cunningham 1997).

Phenothiazines (for example Prochlorperazine)

These drugs are useful for mild to moderately emetogenic chemotherapy as well as an adjunctive therapy for delayed and breakthrough emesis (Sledge 1990; Goodman 1997; Beaulieu 2000) and have both tranquillising and antiemetic effects (Goodman 1997). A randomised double blind study to compare the effectiveness of high-dose Prochlorperazine and high-dose Metoclopramide demonstrated that high-dose Prochlorperazine is an active and cost effective antiemetic (Olver et al. 1992). Indeed, their multiple routes of administration mean that they are often used in combination with other agents (Rhodes et al. 1995). Because their mechanism of action differs from that of 5-HT₃ receptor antagonists, they may be added to the combination of a 5-HT₃ receptor antagonist in conjunction with a corticosteroid if necessary (Goodman 1997). Their side effect profile consists of extrapyramidal effects and sedation, which limit their use to an extent (Rhodes et al. 1995; Beaulieu 2000). The risk of these symptoms is greater for patients aged 30 years or younger (Goodman 1997). However, prophylactic Diphenhydramine or Benztropine may be given to prevent extrapyramidal reactions (Goodman 1997). Older patients may experience excessive sedation and fatigue as well as an unsteady gait when administered phenothiazines and dose adjustment for this patient population may be necessary (Goodman 1997).

Butyrophenones (for example Haloperidol)

These drugs are major tranquillisers and their mode of action as antiemetics is poorly understood (Goodman 1997). The most beneficial aspect of their use is their ability to be combined with agents such as 5-HT₃ receptor antagonists (Bregni et al. 1991; Goodman 1997). These drugs may be most useful when anxiety and anticipatory symptoms aggravate the degree and intensity of the nausea and vomiting experienced by patients (Goodman 1997). Adverse effects include akathisia, dystonic reactions and severe extrapyramidal effects (Goodman 1997). It is also important to note that when

butyrophenones are used in combination with other central nervous system depressants, their effects can be additive (Goodman 1997).

Substituted benzamides (for example Metoclopramide)

Until the development of 5-HT₃ receptor antagonists, this class of drug was the drug of choice for the treatment of nausea and vomiting caused by highly emetogenic chemotherapy (Rhodes et al. 1995). This type of drug blocks dopamine receptors in the chemotherapy trigger zone and serotonin receptors when given in large doses (Beaulieu 2000). Achieving optimal antiemetic results is dependent on maintaining an adequate drug plasma level at the time the patient is most likely to experience emesis (Goodman 1997). A comparative study was conducted to explore the possibility of replacing Ondansetron with Metoclopramide in patients receiving mild to moderately emetogenic chemotherapy (Tsavaris et al. 1999). Despite the heterogeneity of the sample and its relatively small size, this study demonstrated that 57% of patients were able to complete chemotherapy being supported with Metoclopramide with the subsequent cost reduction of 44% (Tsavaris et al. 1999). However, while beneficial in managing the effects of low to moderately emetogenic chemotherapy regimes, such drugs are also associated with extreme extrapyramidal side effects (Rhodes et al. 1995; Goodman 1997; Beaulieu 2000), particularly in those aged under 30-35 years of age (Sledge 1990; Aapro 1991). The risk of agitation and dystonic reactions can be minimised by infusing the drug over 30 minutes in conjunction with Diphenhydramine (Goodman 1997). In addition to its antiemetic properties, Metoclopramide also enhances gastric emptying so combating the sense of fullness caused by gastric stasis, heartburn caused by chemotherapy and the slowed colonic transit time caused by 5-HT₃ receptor antagonists (Goodman 1997).

Cannabinoids (for example Dronabinol)

In general, cannabinoids are rarely used as a first line therapy although they may be useful in patients who have a low tolerance or minimal response to other antiemetics (Aapro 1991; Goodman 1997; Pendergrass 1998; Beaulieu 2000). A review of technical reports relating to marijuana use demonstrated that inhaled marijuana was effective in reducing or eliminating nausea and vomiting following chemotherapy (Musty and Rossi 2000) while a systematic review of research literature between 1975-1996 illustrated that cannabinoids were slightly better than conventional antiemetics and that patients preferred them (Tramer et al. 2001). A randomised, double-blind parallel group multicentre study to evaluate the efficacy of Dronabinol and Prochlorperazine for the management of chemotherapy-induced nausea and vomiting concluded that the combination of the two drugs was significantly more effective than either single agent (Lane et al. 1991).

With respect to side-effects, short term use of marijuana has been shown to lead to sedation, a high and smoking intolerance in some patients (Goodman 1997; Beaulieu 2000; Musty and Rossi 2000). However, their combination with Prochlorperazine appeared to decrease these dysphoric effects (Lane, Vogel et al. 1991). Cannabinoids are also reportedly poorly tolerated by older people (Sledge 1990; Jones and Cunningham 1991; Pendergrass 1998). Because central sympathomimetic activity may

increase with the use of cannabinoids, these should be used with caution in patients suffering from hypertension or heart disease as well as those patients already receiving sympathomimetic drugs (Goodman 1997). There is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy et al. 1999).

Corticosteroids (for example Dexamethasone)

Corticosteroid hormones have a well-defined antiemetic history, both as single agents and in combination with other antiemetics (Sledge 1990; Aapro 1991; Bishop, Matthews et al. 1992; Pendergrass 1998), however their method of action is poorly understood (Rhodes et al. 1995; Pendergrass 1998). A meta-analysis of randomised evidence about the efficacy of Dexamethasone against acute and delayed nausea and vomiting following highly or moderately emetogenic chemotherapy illustrated that Dexamethasone is clearly effective in protecting from emesis both in the acute and delayed phases (Ioannidis et al. 2000). Recommendations for future research is directed towards determining whether the delayed phase effect is dependent on the acute phase benefit (Ioannidis et al. 2000). Corticosteroids are the agents most commonly used in combined antiemetic regimens, for example, Dexamethasone and Ondansetron are widely used for both acute and delayed emesis (Rhodes et al. 1995; Goodman 1997; Pendergrass 1998). They have been reported as increasing the efficacy of 5-HT₃ receptor antagonists by up to an additional 20% (Beaulieu 2000) and their combination with 5-HT₃ receptor antagonists has been noted to be the most superior way of managing vomiting associated with highly emetogenic chemotherapy (Goodman 1997).

Side effects associated with short bursts of steroids used in antiemetic therapy are minimal (Sledge 1990). However, because they might cause psychotic reactions and affect glucose metabolism, they should be used with caution in patients with diabetes mellitus and those with certain psychiatric disorders (Pendergrass 1998; Beaulieu 2000). Agitation and insomnia, as well as increased appetite and euphoria, can also be bothersome for patients, especially when corticosteroids are taken over a 4-5 day period (Rhodes et al. 1995; Goodman 1997; Beaulieu 2000). Minor fluid retention and dyspepsia have also been associated with short courses of corticosteroids (Jones and Cunningham 1991). Perirectal burning is commonly felt when Dexamethasone is administered intravenously, but this can be avoided by increasing the length of infusion time to 10 minutes (Goodman 1997).

Benzodiazepines (for example Lorazepam)

Although drugs such as Lorazepam have been used as antiemetics, they have low antiemetic potency and their beneficial effects are mainly related to their sedative, anxiolytic and amnesic properties (Sledge 1990; Rhodes et al. 1995; Goodman 1997; Pendergrass 1998; Beaulieu 2000). Consequently, they are most effective in alleviating anticipatory nausea and vomiting and in reducing anxiety (Goodman 1997; Pendergrass 1998; Beaulieu 2000). Indeed, a randomised controlled trial comparing the effects of Lorazepam and Prochlorperazine demonstrated that although there was no difference in relation to nausea and vomiting, Lorazepam significantly reduced total post-therapy symptom experience by decreasing patients' experience of fatigue and pain (Simms et al. 1993). Indeed, although

statistical significance was not reached, a crossover study to compare the benefits of Lorazepam in combination with Dexamethasone and Promethazine demonstrated that the frequency of all degrees of nausea and vomiting was less with Lorazepam (Budzar et al. 1994). However, as these drugs are capable of producing all levels of CNS depression, they should be used with caution in older patients and those with compromised respiratory status (Rhodes et al. 1995; Goodman 1997) as well as patients with compromised hepatic or renal function (Goodman 1997).

Issues for consideration associated with antiemetic administration

Side-effects

Antiemetic agents have varying degrees of effectiveness, ranging from highly effective to largely ineffective, depending on factors such as chemotherapy regimes and the dosage and administration protocol. Even when pharmacological methods are effective, they can produce unwanted side-effects of their own such as sedation or dystonic reactions or administration demands such as hospitalisation that can limit their acceptance or usefulness for some patients.

The element of 'control'

The element of 'control' was highlighted in a study conducted to evaluate the efficacy of patient-controlled IV anti-emetic administration (Wilder-Smith et al. 1990). Although the intervention was not evaluated in conjunction with a control group, improvements in patients' nausea and vomiting was thought to be due in part to psychological mechanisms such as the feeling of self-control over symptoms (Wilder-Smith et al. 1990). More rigorous research utilising a double blind, quasi-experimental design compared patient-controlled and nurse-controlled antiemetic therapy (Edwards et al. 1991). This study demonstrated that not only was there no difference in nausea scores between the two groups of patients, but also patients in the patient-controlled group consumed significantly less medication than the subjects in the nurse-controlled group (Edwards et al. 1991).

Complementary therapies

Advances in the pharmacological management of nausea and vomiting have given cancer nurses more time to develop practical and behavioural supportive interventions that patients with cancer frequently need. Such non-pharmacological strategies should be within the regular repertoire of nurses' interventions. Indeed, oncology nurses have been shown to use behavioural techniques as effectively as do clinical psychologists and oncologists (Morrow et al. 1992). These interventions are referred to as complementary therapies because they do not replace standard antiemetic therapies, rather they are adjuncts used to maximise quality of life (Bauer 1996). However, it is important to talk with the patient before incorporating these interventions into their plan of care as some patients may be sceptical and uninterested (Bauer 1996).

Four reasons have been proposed to explain why behavioural interventions are likely to be useful:

- They can decrease affective and psychological arousal and reduce general feelings of distress

- They can serve as cognitive distracters, redirecting patients' attention from conditioned stimulus and refocusing it on neutral or relaxing images
- They can promote feelings of control and reduce feelings of helplessness by demonstrating to patients that they can successfully help themselves reduce treatment side effects
- They can easily be administered and learned within the chemotherapy environment and would have few if any side effects

(Burish and Tope 1992; Bauer 1996; King 1997)

While these non-pharmacological techniques offer the advantage of being inexpensive, easy to learn, self-performed and free from side-effects (Fitch 1992), the majority of patients and healthcare providers have not incorporated these interventions into their usual care (Dibble et al. 2000). This may be because there are no clinical guidelines that indicate what method or combination of methods is most effective in specific clinical situations. Table 3 describes the major complementary therapies associated with nausea and vomiting. Table 4 presents a summary of research addressing the non-pharmacological management of chemotherapy-related nausea and vomiting.

Progressive muscle relaxation training

This can be described as the relaxation of skeletal muscles over which one has conscious control and can be extremely beneficial (Ouwerkerk 1994). The individual is taught to recognise tension in various muscle groups, subsequently relax them and so achieve the deepest degree of relaxation possible (King 1997). With practice, the patient should be able to control their level of relaxation and move quickly into a state of deep relaxation (Redd et al. 2001). The patient can then use this technique during negative experiences or when feeling tense or anxious (Redd et al. 2001). It is a low cost and easy to learn technique that can be incorporated into the care of many patients receiving chemotherapy. Indeed, King advocates that if it is taught and used before initial chemotherapy, progressive muscle relaxation training may prevent or at least delay the onset of symptoms and that patients can use the technique following the completion of their treatment (King 1997). A useful script for progressive muscle relaxation training has been developed and published by Bauer (Bauer 1996).

The relationship between anxiety, nausea and relaxation has been explored using a randomised clinical trial approach (Lerman et al. 1990), which suggested that relaxation was effective in reducing anticipatory anxiety in patients who utilised a distraction orientated coping style but not in those patients who employed information-gathering coping styles. A recent study evaluated PMRT in the management of chemotherapy-related nausea and vomiting and found that the duration and intensity of nausea were lower in the experimental group, although the former was at a borderline level of significance (Molassiotis 2000). Duration and intensity of vomiting were also lower in the experimental group (Molassiotis 2000). However, delayed nausea and vomiting were observed in both groups (Molassiotis 2000).

Guided imagery

Guided imagery is a process by which the individual is asked to focus on pleasing images they associate with relaxation (Ouwerkerk 1994; King 1997) and individually tailored imagery is more beneficial to a patient than standardised imagery (Mastenbroek and McGovern 1991). It is proposed that the patient's attention to aversive stimuli is blocked by their attention to these pleasing images (Redd et al. 2001). However, the positive effects of distraction usually last only as long as the patient is actively engaged in the distraction task (Redd et al. 2001).

The impact of this technique was explored in relation to the occurrence and distress associated with nausea, vomiting and retching for patients receiving Cisplatin based chemotherapy (Troesch et al. 1993). It is interesting to note that while no statistical significance could be established with respect to symptom occurrence and distress with the addition of guided imagery to standard antiemetic therapies, patients receiving guided imagery felt significantly more in control, more powerful, more relaxed and more prepared than did the control group (Troesch et al. 1993). While limited in its population, such a study calls for additional experimental studies to evaluate patient coping and decrease the occurrence and distress associated with cancer treatment. A useful script for guided imagery has been developed and published by Bauer (Bauer 1996).

Self-hypnosis

This is a technique whereby individuals learn to evoke a physiological sense of altered consciousness and complete body relaxation (King 1997). However, it has mainly been evaluated in children and adolescents as they are more readily hypnotised than adults and in relation to the development of anticipatory nausea and vomiting rather than post-treatment nausea and vomiting (King 1997).

Acupressure and acupuncture

Acupressure is based on the Eastern concept that the body is activated by *Chi* energy that travels along pathways at differing depths of the body known as meridians (Dibble et al. 2000). In a similar fashion to a river, these meridians can become blocked, slowed or hyperstimulated (Dibble et al. 2000). Applying pressure (acupressure) or inserting a needle (acupuncture) into one or more of these points can relieve the imbalances by either stimulating or easing energy flow (Dibble et al. 2000). Two points have been associated with mitigating nausea:

- The Nei-Guan point (P6) which is located on the pericardium meridian located on the anterior surface of the forearm
- The Three Miles (ST36) which is located on the stomach meridian below the knee and lateral to the tibia

When these points are located correctly, the person may feel a mild charge similar to that of static electricity or it may feel tender like a bruise (Dibble et al. 2000). This mild discomfort caused by the pressure ceases after a few minutes as the point 'releases' (Dibble et al. 2000). This 'release' is thought to rebalance the *Chi* energy, which causes the relief of nausea (Dibble et al. 2000).

A pilot study demonstrated that patients receiving chemotherapy can be taught to use acupressure to ameliorate experiences of nausea and vomiting (Dibble et al. 2000). Indeed, patients in this study found acupressure easy to learn and use (Dibble et al. 2000). However, inferring practice implications at this time for acupressure is perhaps a little too soon and further research is required to compare the effects of P6 and ST36 alone and in combination. The comparison of passive acupressure (Sea-Bands) and active acupressure (finger) is also important as well as the evaluation of both techniques in men and children. Indeed, it has been shown that acupressure in tandem with acupuncture allows the prolongation of the positive effects of acupuncture (Dundee and Yang 1990).

A different technique is that of electroacupuncture. Shen and her colleagues explored the benefits of this technique compared with minimal needling and mock electrical stimulation or antiemetic medications alone in controlling emesis among patients undergoing a highly emetogenic chemotherapy regime (Shen et al. 2000). In a three-arm, parallel group, randomised controlled trial they demonstrated that patients receiving electroacupuncture had fewer episodes of emesis than the other groups for the first 5 days following chemotherapy administration (Shen et al. 2000). However, this effect was of limited duration and differences among the groups were not significant during the 9 day follow up period (Shen et al. 2000).

Just as studies have demonstrated the association between acupuncture or acupressure and relief of nausea and vomiting related to chemotherapy (Dundee and Yang 1990; Dibble et al. 2000; Shen et al. 2000), several studies have documented the suppression of nausea by transcutaneous electrical nerve stimulation (TENS) over the Neiguan point.

One such study aimed to evaluate the efficacy of a miniaturised portable TENS unit (ReliefBand) as an addition to standard antiemetics for controlling nausea and vomiting induced by Cisplatin-based chemotherapy in gynaecologic oncology patients (Pearl et al. 1999). This rather complicated project consisting of two components (a parallel-subjects trial that was randomised, double-blinded and placebo-controlled followed by a follow-up crossover trial) demonstrated that the ReliefBand was effective in controlling nausea and vomiting in conjunction with standard antiemetics (Pearl et al. 1999).

Biofeedback

Biofeedback is a process whereby patients learn to control a specific physiological response by receiving information about moment to moment changes in that response (King 1997). There are 2 frequently used types of biofeedback: electromyographic (EMG) biofeedback, which is intended to induce a deep state of muscle relaxation and skin temperature (ST) feedback, which is to prevent skin temperature changes such as those that precede nausea and vomiting (King 1997).

A random controlled trial explored the impact of biofeedback and progressive muscle relaxation (Burish and Jenkins 1992). Patients who performed relaxation training had less nausea and vomiting

than those who did not whereas patients who performed biofeedback had lowered physiological arousal but not changes in nausea or anxiety levels (Burish and Jenkins 1992). This goes some way to demonstrate that biofeedback alone may not be as effective as relaxation training in decreasing chemotherapy induced nausea and vomiting (Burish and Jenkins 1992).

Cognitive distraction

Cognitive distraction (attentional diversion) is thought to act by focusing patient's attention away from nausea and vomiting (King 1997). Indeed, it has been suggested that simply distracting patients has decreased anticipatory nausea and vomiting (King 1997). The effects of cognitive distraction (using computer games) and progressive muscle relaxation have been evaluated on prechemotherapy levels of nausea in adult patients, showing that both interventions resulted in improved levels of nausea (Vasterling et al. 1993). However, further research is required to evaluate whether the effects of simple distraction can be maintained post-chemotherapy.

Music therapy

Most frequently, music therapy, the use of music to prevent or control nausea and vomiting, has been used in conjunction with other non-pharmacological methods (King 1997). Music should have a slow steady rhythm, low frequency tones and soothing orchestral effects, avoiding high frequencies and sharp notes (Ouwerkerk 1994). Few studies have evaluated music therapy as a therapy in its own right although one small study (n=14) did demonstrate that patient's reports of nausea were less if they had listened to music during their chemotherapy administration (Standley 1992).

Discussion

In general, the pharmacological management of chemotherapy-induced nausea and vomiting has been well explored and the most efficacious antiemetic regimes available to date have been identified. Furthermore, the use of rigorous research methods, primarily the randomised controlled trial, often in combination with blinding of both the investigators and patients, and the recruitment of adequate sample sizes, provides sound evidence to facilitate appropriate clinical decision-making. However, despite this sound evidence-base for practice, a significant proportion of patients receiving chemotherapy still report symptoms of nausea and vomiting. This may be due to poor dissemination of study results in tandem with their lack of adoption into clinical practice. Changing practice is widely acknowledged as a complex process and it could be argued that the focus for future pharmacological research should be the widespread introduction and adoption of pharmacological guidelines in real life clinical situations. Exploration of innovative methods of changing practice should be initiated. One such project that aims to promote the use of evidence-based guidelines for managing patient symptoms (including nausea and vomiting) is WISECARE+. WISECARE+ is a European cancer nursing project that uses knowledge sharing and evidence-based nursing guidelines to both harmonise and direct nursing care. Through measuring patient symptom outcomes over time we hope to be able to demonstrate an improvement, so illustrating the positive impact that evidence-based nursing guidelines

can make to patient outcomes. Economic evaluation of pharmacological methods is also severely lacking from much of the previous research conducted in this area. However, given the cost-conscious era in which we are called to deliver the best care for the least cost, such an omission is unacceptable and should be addressed in future research.

Non-pharmacological methods of managing nausea and vomiting are also of great interest to cancer nurses. However, this review of the literature has shown that the evidence-base to support many of these techniques is, at best, weak. Research is flawed due to small sample sizes as well as being complicated by confounding variables such as stage of disease, the various chemotherapy regimes administered, culture and patients' continued compliance with performing these non-pharmacological techniques. Indeed, the lasting effects (or not) of many non-pharmacological interventions can only be speculated at. While conducting small scale exploratory, descriptive research is undoubtedly necessary, cancer nurses must then use the information gleaned from these smaller studies to build programmes of research that generate an evidence-base strong enough on which to base clinical practice and decisions. The preliminary evidence available today suggests the positive benefits that patients can achieve through the use of non-pharmacological techniques. It would be unacceptable not to use this preliminary information to design larger, more robust studies such as randomised clinical trials to demonstrate beyond doubt to healthcare personnel (many of whom may be sceptical of such methods) the exact benefits to be gained through the widespread introduction of non-pharmacological techniques. As well as addressing benefits to patients, carers and healthcare professionals as well as cultural influences, these studies should also include a strong economic evaluation.

Further issues to highlight include the problems associated with evaluating nausea and vomiting as one symptom when they are most clearly separate, although related, symptoms. Future research should make every effort to ensure that they are treated as such. Finally, distinguishing between acute and delayed symptoms of both nausea and vomiting is also essential and should be incorporated into research designs. Consequently, despite the current wealth of evidence on which to base clinical decisions, it would seem that the evidence base for practice still requires development in a number of key directions.

Conclusion

Reducing the unpleasant side effects of chemotherapy-induced nausea and vomiting will clearly enhance patients' quality of life. Well planned, prophylactic strategies that are tailored to each individual patient's characteristics, personality and chemotherapy treatment are essential to maximise the response to therapies initiated. If at all possible, these therapies should be both pharmacological and non-pharmacological. However, clinical challenges remain and nurses should be involved in further research that addresses the particularities of anticipatory nausea and vomiting, patient's preferences in therapies, pharmacoeconomics and quality of life issues.

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APPENDIX K – FATIGUE LITERATURE REVIEW



Cancer-Related Fatigue

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Introduction

Fatigue is a highly prevalent condition among patients with cancer. Our current understanding and management of fatigue has been likened to that of emesis in the early 1980s: a serious problem with an impact on patients' quality of life that is receiving greater recognition from nurses than medical staff (1). Indeed, fatigue rather than nausea and vomiting is now the primary complaint of people with cancer. A telephone survey of patients with cancer demonstrated that 78% of 419 patients felt fatigue during the course of their disease and treatment, with 32% stating that they experienced it daily (2). More recently, 76% of 379 patients reported that they experienced fatigue while 54% reported nausea, 23% depression and 20% pain (3). Indeed, a recent review of fatigue research to date states that fatigue is an important problem both during active treatment for cancer as well as following cancer treatment (4). As treatment improves and survival rates increase, optimal symptom management becomes increasingly important. Fatigue, its assessment and its management are clearly key concerns for those caring for patients with cancer, however, they are often neglected due to the lack of a clear definition of fatigue.

Definitions of fatigue

The myriad definitions of cancer-related fatigue lack clarity, cohesiveness and consistency (5). Indeed, confusion surrounds the definition and use of the term fatigue (6). As such, fatigue, like pain, is best described by the person experiencing it (7). However, to assess and manage fatigue, one must have first arrived at a definition of the concept. Broad categories of classification such as 'acute' and 'chronic' fatigue have been established. Acute fatigue has been defined as that caused by hard work resulting in loss of efficiency, relieved by rest and serving a protective function (8, 9). Chronic fatigue results from the cumulative effects of a disease or treatment and tends to be unrelieved by sleep or rest (8).

In 1996, as a result of confused and inconsistent definitions of fatigue, Ream and Richardson attempted to clarify the concept, aiming to identify its essential attributes, distinguishing between colloquial and nursing usage (6). Based on this concept analysis, they concluded that fatigue is 'a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with an individuals' ability to function to their normal capacity' (6). Most definitions have conceptualised fatigue simply as a loss of energy or decrease in physical function (9), with several terms used interchangeably to describe fatigue such as weakness, lack of energy and exhaustion (9). A more recent definition comes from Schwartz who conceptualised cancer-related fatigue as a self-perceived experience consisting of physical, emotional, cognitive, temporal aspects (10). However, whatever the definition, the outcome is clearly decreased functional performance and reduced quality of life (9).

Prevalence of fatigue

Fatigue is a highly prevalent condition among patients with cancer (11, 12). The prevalence of fatigue in patients with cancer has generally been reported to be from 60% to over 90% (13). However, percentages of the presence of fatigue vary among studies. For example, 25% of a sample of patients with prostate cancer (n=36)

reported fatigue during and after a course of radiotherapy when assessed using the Piper Fatigue Scale (14). However, 61% of a mixed sample of patients with cancer reported fatigue during chemotherapy or radiotherapy assessed via the Pearson Byars Fatigue Feeling Questionnaire (15).

These distinct differences are likely to be attributable to a variety of study methods and characteristics, the most likely of which to result in differences in prevalence data are (13):

- the participation of various study populations (different treatments, stages of disease and tumour sites)
- the use of several definitions of fatigue
- an array of research instruments (individual items versus lengthy multidimensional fatigue instruments)

The meaning and impact of fatigue

It has mainly been through the work of qualitative researchers that our understanding has grown as to the true meaning of fatigue and its implications for patients with cancer.

An exploratory study of fatigue demonstrated that fatigue affects every dimension of quality of life, with respondents highlighting the impact of fatigue on physical, psychological, social and spiritual well-being (16). These results were substantiated by a later telephone survey of patients who had previously received radiotherapy or chemotherapy, which established that 32% of patients had experienced fatigue daily that had disrupted their daily routines and was more troublesome than pain (2).

In comparing the fatigue experienced by patients with cancer and chronic obstructive airways disease, Ream and Richardson demonstrated that perceptions of fatigue were very similar for both groups of patients in that they shared nine common thematic structures: physical sensations, mental sensations, the impact of fatigue on everyday functioning, emotional feelings evoked by fatigue, the impact of fatigue on perceived control, the impact of emotions on the management of fatigue, the importance of recognising and understanding fatigue, the significance of setting and reaching goals and the effectiveness of self-care in alleviating fatigue (17). However, it is important to note that the patients with cancer were all in the early stages of their disease whereas the patients with chronic obstructive airways disease had been suffering from their condition for substantially longer, 14 years in one case. Consequently, it may not be appropriate to compare these two groups of individuals. Nevertheless, this study does lend substantial support to the multidimensional definitions of fatigue and contributes towards our understanding of what fatigue is and means to individuals.

Secondary analysis of data collected through qualitative interviews as part of a larger study was conducted by Messias et al to explore the experiences of fatigue from the perspectives of patients (n=127) undergoing their first cycle of chemotherapy (18). The qualitative approach used within this study provides excellent verbatim reports from patients describing the depths of their fatigue perceptions, for example:

'I was tired then, but now ... I didn't know what tired was until now'

*'I feel like someone let the plug out somewhere and all my energy drained out'
'I didn't expect the absolute fatigue... I didn't expect that exhaustion to last'*

Emotional reactions to fatigue were another thematic category and patients expressed frustration, worry, concern, displeasure, fear, depression and disappointment regarding their fatigue. Indeed, a sense of exasperating redundancy was repeatedly expressed through comments such as

'I'm tired of being tired'.

However, the study only focused on the first cycle of chemotherapy and it would have been interesting to follow patients' experiences longitudinally to explore whether patients' experiences of fatigue altered over time.

More recently, Barsevick and her colleagues aimed to describe cancer-related fatigue from the individual's perspective within a small convenience sample (n=8) of patients attending an out-patient department and reporting fatigue (19). The coping strategy that patients most commonly undertook to manage their fatigue was to rest or go to bed, with only a few statements describing energy-conservation strategies. However, this study involved a heterogeneous sample, including individuals both receiving and completed treatment for either an initial cancer diagnosis or a recurrence, questioning the generalisability of the results. Moreover, the study was a secondary analysis from two focus groups conducted on supportive interventions for cancer-related fatigue and as such the individuals may not have had the opportunity to give fuller details of their perspective of cancer-related fatigue.

Quite different from these previous findings were the results of a study conducted in Canada by Hamilton et al, exploring the impact of cancer-related fatigue in a purposive sample of patients with primary, non-small cell inoperable lung cancer without distant metastases receiving radiation to their thorax (n=22) (20). Overall results indicated that fatigue was not reported as a major concern by many of the participants and those that did report it, considered it an inconvenience and frustration that had to be dealt with for a limited period of time (20). Moreover some patients appeared to gradually adjust to the fatigue and were unaware of the changes taking place over time (20). Perhaps one of the limitations of this study lends some explanation to the results: the average age of the patients was 66 years and few had obligations outside the home. Perhaps a younger sample would have experienced a greater impact of fatigue on their roles and responsibilities. Furthermore, the authors note that patients were often unable to separate responses to fatigue from other aspects of the cancer experience. Again, the sample size was relatively small making generalisations difficult to draw. Consequently this study provides an impetus for more thorough research to explore the impact of age on experiences of fatigue.

Theories of fatigue

Our understanding of the pathophysiology of fatigue is incomplete and numerous competing hypotheses exist, with explanations often being speculative and preliminary. Although causes of fatigue have been explored in numerous studies, no clear support for any of the major hypotheses has emerged (21) and specific hypotheses regarding fatigue in patients with cancer remain untested. Indeed, it is

unlikely that fatigue is solely a simple physiological condition as a result of sustained activity, nor can it be related only to biochemical changes in muscle or nerves. Psychological variables should also be considered as causes of fatigue (22). Moreover, the extent to which findings from research on fatigue are applicable to patients with cancer is unknown as one can question whether subtle nuances exist between normal acceptable tiredness and tiredness associated with disease. Various theories and models have been developed that explain how fatigue occurs and speculate on the influence and interaction of various factors. These will now be discussed.

Accumulation hypothesis

This was the result of early research on fatigue, which led to the proposal that a build up of waste products in the body results in fatigue. While this theory was supported when rapid accumulation of lactic acid and other metabolic products was found during strenuous exercise, subsequent research was unable to relate the accumulation of waste products to the occurrence of fatigue (23). However, it has been proposed that the by-products of cell death released during/after chemotherapy or radiotherapy may be contributing factors to the fatigue experienced by patients (24).

Depletion hypothesis

The depletion hypothesis was based on the supposition that muscular activity is impaired when certain substances such as carbohydrates, fats, proteins, adenosine triphosphate and adrenal hormones are not readily available (23). The relationship between nutrition and fatigue is complex involving both the supply and use of nutrients. When carbohydrates or fats are available for conversion into glycogen, protein is spared however, with sustained muscle activity, glycogen is depleted leading to fatigue (25). This hypothesis could be seen as relevant to patients with cancer as they may have problems that can lead to the inadequate intake of nutrients and the way their body uses nutrients may change in the presence of cancer (26). Additionally, the tumour may successfully compete with normal tissues for available nutrients (26).

Fatigue experienced as a result of anaemia can also be thought of as an example of the depletion mechanism. Anaemia decreases the blood's oxygen carrying capacity, inhibiting the delivery of essential nutrients to cells consequently decreasing the delivery of essential nutrients to the cells and decreasing the energy available to the organism. One can argue that this theory is upheld because individuals suffering from anaemia subsequently experience less fatigue following a blood transfusion.

Biochemical and physiochemical phenomena

Changes in the production, distribution, use, balance and movement of substances such as muscle proteins, glucose, electrolytes and hormones have been suggested as important factors that influence the experience of fatigue (27). In relation to cancer, many of the drugs used for treatment, management of side effects of treatment and symptom control can also produce biochemical and physiochemical changes related to those believed to cause fatigue (28).

Adaptation and energy reserves

Every individual has a certain amount of energy available for adaptation to fatigue and, that when that energy supply is depleted, resting for a time allows energy to be replenished so that adaptation can continue (29). However, one can question this theory in relation to cancer-related fatigue as it suggests that if patients with cancer rested, their fatigue would be resolved: a case known not to be true (30). Indeed, patients receiving chemotherapy rate rest as moderately, rather than completely, effective as a method for relieving fatigue (29).

The psychobiologic-entropy hypothesis

This model defines fatigue in relation to energy and function and seeks to associate activity, fatigue, symptoms and functional status (31). It is based on the observation that an individual who becomes less active as a result of disease or treatment loses energising metabolic resources. Decreased physical activity leads to decreased energetic capacity for activity. Four propositions emphasise the optimal balance between restorative rest and restorative activity:

1. Too much as well as too little rest contributes to feelings of fatigue
2. Too much as well as too little activity contributes to feelings of fatigue
3. A balance between activity and rest promotes restoration; an imbalance promotes fatigue and deterioration
4. Any symptom that contributes to decreased activity will lead to increased fatigue and decreased functional status

Pipers Integrated Fatigue Model

Piper's Integrated Fatigue Model (IFM) is a commonly cited theoretical framework on fatigue in cancer (32) and provides a thorough and complex framework for explaining the fatigue of cancer. The model addresses the many potential causes of fatigue so highlighting the importance of considering the multiple aspects of manifestations of fatigue. The pathophysiological mechanisms contributing to fatigue can be grouped into four categories:

- Accumulation of metabolites
- Depletion of energy-yielding substances
- Changes in regulation or transmission
- Humoral factors

Although the model is chiefly based upon mechanisms in healthy people, it has been particularly useful in guiding assessment of potential etiological factors relating to fatigue (24). Indeed, the significant theoretical and scientific outcome of Piper's model is the Piper Fatigue Scale – an assessment instrument based on the model, which will be discussed later. Barton-Burke (5) notes that the strengths of Piper's theory include:

1. Offering a comprehensive approach to looking at fatigue
2. Blending of knowledge about fatigue from a number of disciplines
3. Grounding in the clinical phenomena
4. May be used for assessing the fatigued individual

Thus, while a wide variety of hypotheses exist, it is unfortunate that they have not been tested in populations of patients with cancer. Nevertheless, all are potentially relevant for explaining at least some of the fatigue experienced by individuals with

cancer and one could argue that at present the most reasonable approach would be to consider multiple factors responsible for fatigue for individuals with cancer. While such theories regarding the pathophysiology of fatigue can appear vague at times, research based evidence citing cancer treatments as the causes of fatigue is available.

Causes of fatigue

It is now widely agreed that the causes of fatigue are multifactorial, arising from both physiological abnormalities and psychological factors (8).

Physiological factors

Cytokines

It has been suggested that cytokines (interleukins, interferons and tumour necrosis factors) have a significant role in cancer-related fatigue (11, 13). Cella and his colleagues report that patients describing chronic fatigue syndrome may have higher levels of circulating cytokines (13). Furthermore, clinically important and, at times, dose-limiting fatigue has been observed in patients who are receiving biological response modifier therapy (13).

Anaemia

Anaemia may be caused by myelosuppressive effects of chemotherapy and radiotherapy, blood loss, iron deficiency, stem cell failure or haemolysis (5, 8, 13). Fatigue and anaemia have long been associated with one another (1, 11, 12). In a paper describing the development and validation of the Function Assessment of Cancer Therapy – Anaemia Scale (FACT-An) and in a clinical follow-up paper, a high correlation between anaemia, fatigue and quality of life in patients with cancer was demonstrated (33, 34). For example, 25% of patients whose haemoglobin was <12g/dL rated themselves 'unable to work' as a result of fatigue whereas only 8% of patients with a haemoglobin of >12g/dL said the same thing (33).

Endocrine disorder and electrolyte imbalance

Thyroid abnormality or adrenal insufficiency commonly result in fatigue (8, 11, 12). Hypercalcaemia (as a consequence of bone metastases) and hypomagnesaemia (due to cisplatin chemotherapy) also result in fatigue (8, 13).

Infection

Myelosuppression, either as a consequence of cancer treatments or bone marrow involvement, makes patients more susceptible to infection which may increase the sensation of fatigue (8, 12, 13).

Nutritional deficiency

Nutritional support is essential for patients to combat the catabolic state that cancer can cause (5, 8, 11-13). Dehydration also causes fatigue and patients should be

advised of not only ensuring adequate hydration but also avoiding caffeine and alcohol (8).

Altered sleep/activity patterns

Sleep disorders can also contribute to cancer-related fatigue (12). The ‘common sense’ intervention of increasing rest and sleep to help alleviate fatigue have been shown to be not only ineffective but also to increase fatigue experiences (5, 8). Indeed, fatigue has been found to be associated with less daytime activity (35). Higher fatigue has been shown to be associated with more sleep problems (36, 37) and a change in sleep patterns is among the most frequently mentioned symptom to which patients attribute their fatigue (38).

Other factors

The presence of other symptoms and side effects can also contribute to patients’ perceptions of fatigue (12). Uncontrolled pain or nausea may alter sleeping patterns resulting in increased daytime sleepiness (8, 13). In patients with breast cancer, more severe fatigue before treatment has been associated with pain (37) while the severity of fatigue experiences has also been associated with pain in patients with advanced cancer (36). It is interesting to note that a weak-moderate association has been made between levels of fatigue reported by patients with ovarian cancer receiving chemotherapy and their CA125 levels (a tumour marker associated with ovarian cancer used to follow response to treatment) (39). Further exploration is needed to evaluate whether this relationship is indicative of fatigue associated with advanced disease states.

Medication

Certain medications can contribute to experiences of fatigue (5). Opioids as well as some antiemetics, antidepressants and anticonvulsants commonly causes fatigue and lethargy (12).

Psychological factors

Feeling sad, depressed, anxious, confused or angry are normal reactions to a diagnosis of cancer and subsequent treatment and the associated emotional distress can undoubtedly contribute to experiences of fatigue (4, 5). Psychological distress is a potentially important variable to consider in studies of fatigue experiences (11, 40). Psychological difficulties such as depression and anxiety have also been linked with fatigue over the years and although fatigue may be thought of as a symptom of anxiety or depression, it can also be argued that anxiety and depression can be caused by fatigue’s disruption of life. Indeed, the necessary alterations to life as a result of fatigue are adjusted to better by some individuals than others (21). While it has been shown that patients not suffering from depression were able to remain confident and optimistic despite reports of fatigue (41), others have argued that fatigue influenced psychological well-being, resulting in feelings of uselessness, depression or anxiety (16). Thus, it is evident that the impact of the severity of the fatigue and associated changes in activity depends on the individual’s perception of what limitations are acceptable to both self and family as well as the expected duration of the limitations

and will undoubtedly differ substantially between individuals. More recently, a comprehensive review of correlates of fatigue found that while some studies demonstrate a strong correlation between fatigue intensity and psychological distress such as depression and anxiety, other studies provided contradictory results (4).

Cancer Treatments

It is unquestionable that patients' experiences of fatigue are related to their anti-cancer treatments. As more people are treated with a combination of anticancer therapies, the number of people affected by fatigue is increasing (42). Indeed, it has been suggested that fatigue experiences increase as therapies are combined (43). A recent review found that conclusions were difficult to draw regarding the relationship between fatigue and treatment characteristics as these relationships were seldom properly investigated (4). Nevertheless, patterns of fatigue are now being explored according to the type of therapy that the patient receives.

Chemotherapy

A number of studies have attempted to establish patterns associated with fatigue in relation to chemotherapy (39, 44, 45). Indeed although in general the nature and severity of the side effects of chemotherapy vary according to the drugs prescribed, fatigue is one of the most reported side effects of chemotherapy (25). On average, patients receiving chemotherapy tend to feel tired for several days following treatment and then gradually feel better until the next cycle (8) however, this pattern should never be presumed (42). Peaks in fatigue have been reported to be associated with the nadir (when blood counts reach their lowest points) (42). A more detailed examination of 2 key studies can be found below.

Richardson and her colleagues conducted a descriptive, longitudinal study to prospectively evaluate onset, pattern, intensity and distress associated with fatigue in patients receiving chemotherapy for a variety of cancer diagnoses (n=109) (44). From information collected by means of a daily diary, patterns of fatigue in relation to chemotherapy administration became clear. Patients receiving conventional 3-4 week cycles of chemotherapy typically experienced high levels of fatigue for 4-5 days following chemotherapy which gradually lessened until the nadir period, when they experienced a transient rise in fatigue levels (44). Patients receiving weekly injections of chemotherapy displayed moderate levels of fatigue that fluctuated cyclically (44). Patients experiencing the most severe fatigue were those who received a combination of bolus and continuous chemotherapy: these patients experienced a sharp rise in fatigue during the first week of treatment with a gradual decline before their next cycle. In general patients were more likely to experience fatigue in the afternoon and evening (44). This study did have a number of limitations, importantly the fact that patients were not all at the same stage of their treatment course, which could potentially influence fatigue experiences. The heterogeneity of the sample must be considered as well as the fact that there were only small numbers in each of the chemotherapy regime groups. Thus, replication of this research is important for the future. Furthermore, the increased use of oral chemotherapy makes it important to include this patient population in future studies.

More recently, Schwartz investigated patterns of fatigue in women with breast cancer receiving chemotherapy in relation to their exercise patterns (45). Several distinct patterns of fatigue emerged from this study, the most common being a sharp rise in fatigue following chemotherapy. However, several women demonstrated chaotic patterns of fatigue, with their fatigue swinging wildly throughout their entire treatment. This study did not support the work of Richardson and colleagues highlighted above in that fatigue was not seen to worsen in relation to the haematological nadir. However, marked increases in fatigue were demonstrated in relation to adverse events such as infections and invasive procedures and it is certainly intriguing that women experienced increasing fatigue before the onset of neutropaenic fever (45). This warrants further investigation in a larger sample as it may support the use of instructing patients to maintain daily fatigue logs and give some indication of when is most appropriate to contact healthcare providers. Also of interest is the finding that the level of most severe daily fatigue decreased with each cycle of chemotherapy (in those women who exercised) (45), a finding that Richardson and Ream were unable to demonstrate as they only collected data over a single cycle of chemotherapy. Not only does this support the theory that undertaking exercise has a positive impact on fatigue levels, it also begs the question of whether symptom reorganisation or a response shift whereby women adjust and reset their interpretation of fatigue over time is taking place. Further investigation is undoubtedly necessary.

Radiotherapy

Although radiotherapy is a localised treatment, fatigue associated with radiotherapy has been shown to increase gradually throughout the course of therapy (8, 42). Typically, it takes a number of weeks or months for patients to return to their baseline energy levels following radiotherapy (8). Fatigue has been shown to be the only common systemic side effect of local radiation treatment (25).

Patterns of fatigue as a consequence of radiotherapy have been shown to be many and varied. Women receiving radiotherapy for node-negative breast cancer experience an initial decrease in fatigue from the first to the second week of radiotherapy, followed by a rise in week three and a plateau in week four, with no decrease in fatigue on weekend days, the traditional 'days off' from treatment (41). In contrast, using a longitudinal design, Irvine and her colleagues discovered that patients with breast cancer experienced fatigue that increased significantly over the course of the treatment, was highest at the last week of treatment and returned to pre-treatment levels by 3 months after treatment (46). However, more recently this pattern was not supported by Molassiotis who found that patients receiving radiotherapy had increased fatigue at the end of their first and second weeks of treatment, with higher levels observed in the afternoon and evening (47).

Significant increase in fatigue has been correlated with increases in symptom distress, mood disturbance and alteration in usual activity for patients receiving a five or six week course of radiotherapy (15). A study that focused on radiotherapy for prostate cancer found that initial increase in fatigue could be correlated with an increase in serum interleukin-1 levels, indicating that it may be a marker for systemic reaction and subjective fatigue related to radiotherapy (41).

Biotherapy

Biotherapies, used either in combination or alone, have frequently been implicated in patients' experience of fatigue. These therapies have been shown to result in fatigue that is both cumulative and dose-related resulting in dose-limiting toxicity (42, 48). Biotherapy-related fatigue is most commonly associated with flu-like symptoms such as malaise, headache, fever, chills and myalgia and is the primary reason given by patients for refusing or stopping treatment (8). It has been suggested that administering the treatment 2 hours before bedtime would allow patients to sleep through the resultant fever, chills and fatigue (49). However, patients can often have problems sleeping through chills and fevers, and it has been suggested that continuing with normal activities may be more helpful in fighting fatigue (50).

Surgery

Surgery is one of the most common treatments for cancer and is usually combined with other anti-cancer treatments. The theory that one would expect the effects of repeated anaesthetics and analgesics to result in fatigue experiences is upheld as it would seem that patients often feel extremely tired following surgery and that this is seldom completely resolved before they go on to have subsequent treatment (8). However although most patients with cancer undergo surgery for diagnosis or treatment, surgery is the least explored treatment modality in relation to fatigue (7). This can be seen as a missed opportunity as patients with cancer often endure repeated operative procedures over a short period of time and could provide health professionals with rich information regarding their perception of fatigue during this time.

Rhoten investigated postoperative fatigue in five patients undergoing abdominal surgery using both an observational checklist of fatigue behaviours and the 10 point Rhoten Fatigue Scale (51). Preoperative condition, surgery, anaesthesia, pain and use of opiate analgesia and psychoactive drugs were identified as potential etiological factors for fatigue in this study (51). However, almost all studies relating to fatigue following surgery tend not to include patients with cancer, are often limited by small samples sizes, are hampered by incomplete information regarding research methods and clinical care and lack replication (24).

Assessing fatigue

While the measurement of fatigue is especially desirable in oncology nursing, the study of fatigue has interested many groups such as those in industry as well as those involved in the aviation industry. However, the seventies saw the nursing profession becoming interested in fatigue initially comparing the fatigue patterns of healthy individuals and patients with multiple sclerosis (52). This interest has increased steadily over the years and there are now a number of key publications addressing the importance of fatigue in cancer nursing and the resulting assessment issues.

In the absence of a common definition of fatigue, it is not surprising that there is a lack of consensus about the most appropriate way to assess fatigue (53). While fatigue has often been incorporated into tools that measure a broader concept such as the Profile of Mood States and the Symptom Distress Scale, it has also been advocated

that fatigue as a concept should not be buried in tools which measure a wide range of responses to human conditions (54).

The plethora of fatigue assessment tools available is staggering. As fatigue is consistently conceptualised as a subjective experience, it should surely be measured through self-report techniques. Indeed, there is evidence to suggest that proxy ratings of patients' symptoms by both nursing staff and relatives often vary (55, 56). However, although several self-report instruments have been developed, further psychometric testing of them has been recommended (9). Using such scales to evaluate fatigue is undoubtedly valuable as patients often feel that fatigue is an inevitable consequence of cancer and treatment (13). Although it is outwith the scope of this review to consider all the tools available to assess fatigue, an evaluation of key assessment tools is considered below.

Rhoten Fatigue Scale

Developed in 1982, this graphic rating scale was developed to assess current levels of fatigue post-surgery rather than in relation to cancer. Although simple to complete and short, the scale's reliability has not been assessed and it also fails to provide a holistic picture of fatigue (9, 11).

Profile of Mood States

The Profile of Mood States (POMS) is a 65 item five-point, adjective rating scale that measures 6 identifiable mood states, with the fatigue and vigour subscales used most frequently to measure fatigue in patients with cancer (9). The monopolar version of the Profile of Moods States (POMS) is the most frequently used measure of fatigue in cancer research (24). However, the crucial aspect to be highlighted with the use of this scale is that, despite established reliability and validity, it was developed for use as a mood scale to give a total mood disturbance score. Indeed the pattern of relationships among the fatigue and vigour subscales and other measures of mood, symptoms and functioning are not consistent. This is illustrated by Nail who found that fatigue as a side-effect of treatment exhibited a different pattern than the pattern of fatigue scores from the POMS among women undergoing intracavity radiation treatment for gynaecological cancer (25). Consequently, this leads one to question whether an emotional component of fatigue exists that differs from the physical sensation component.

Piper Fatigue Self-Report Scale

Recognising that nursing practice was compromised by a lack of knowledge about fatigue in patients with cancer, Piper and her colleagues developed the first validated instrument that assessed fatigue in patients with cancer - the Piper Fatigue Scale (PFS) (28). Items and dimensions incorporated in the scale were guided by the authors' clinical expertise and the literature regarding the conceptualisation and management of fatigue and the scale includes a range of diagnostic dimensions and is designed to measure changes in fatigue patterns in ill populations. The total fatigue score is calculated on the basis of the scores from the four subscales representing the temporal, intensity, affective and sensory dimensions of fatigue. The PFS contains 76 items, each of which is rated on a visual analogue scale from 0 (least) to 10 (most).

Assessment of these four dimensions leads to a more global view of fatigue and its impact on quality of life. The length of this questionnaire meant that it was more useful for research rather than clinical practice and as a result, although it was probably the most sophisticated attempt to capture the fatigue experience of patients, it was revised for simplicity in 1998 (57). This revised version of the Piper Fatigue Scale consists of 22 items and 4 subscales: behavioural/severity (6 items), affective meaning (5 items), sensory (5 items) and cognitive/mood (6 items) (58).

Brief Fatigue Inventory

This 9 item scale uses a 0-10 numeric rating scale to assess the severity and impact of cancer-related fatigue (59). This tool defined fatigue as a one-dimensional experience and this is somewhat limiting when one considers the multi-dimensional impact that fatigue has on patients' quality of life (59). Also, although the tool identifies cut off points to discriminate between levels of fatigue severity, the cut off between mild and moderate severity are unclear and one can question the appropriateness of arbitrary cut off points (9). Furthermore, it is important to note that the tool was not developed from the patients' perspective (9).

The Cancer-related Fatigue Distress Scale

This numerical rating scale was developed from 23 in-depth interviews with patients experiencing cancer-related fatigue. Five people with a history of cancer were used to evaluate the content validity, with factor analysis used to assess construct validity (60). This has been reported to be a clinically useful (short, requires no training and easy to read) and psychometrically sound tool for the measurement of distress associated with cancer-related fatigue (60). However, further use of the tool in clinical practice is required.

Multidimensional Assessment of Fatigue

More recently developed tools include that developed by Tack (1990) who developed the Multidimensional Assessment of Fatigue (MAF) which contains 16 items, measuring 4 dimensions of fatigue: severity, distress, timing and degree of interference in daily living (61). Fourteen of these items are responded to using a VAS, while two have multiple choice responses. Scoring the MAF results in the Global Fatigue Index which ranges from 0 (no fatigue) to 500 (extreme fatigue). The MAF has been shown to be short, easy to complete and appropriate for use in a variety of clinical settings for a multitude of purposes such as baseline assessment and assessing the effects of therapeutic interventions for fatigue.

Managing fatigue

Fatigue represents a challenge to nursing management because of its numerous causes and the multiple effects that it has on patient's lives. Physical symptoms such as unrelieved pain, dyspnoea as well as nausea and vomiting have reportedly contributed to fatigue as such problems can interfere with an individual's ability to rest and sleep (32). Additionally, while some medications such as opiates, sedatives, hypnotics or antihistamines can cause drowsiness resulting in fatigue, the withdrawal of other medications such as adjuvant steroid therapy may also cause fatigue (62).

Consequently, the initial approach to cancer-related fatigue should be to correct potential aetiologies such as elimination of non-essential drugs, treatment of any sleep disorders, reversal of anaemia or metabolic disorders or the management of major depression (12).

There are also barriers, both patient- and professional-related, that result in the under-utilisation of effective interventions (13). Indeed, patients may under-report fatigue as they do not want to distract the physician from curing their disease, their misconception that fatigue is inevitable or indeed their belief that there is no effective intervention for the management of the problem (13). Not only this, physicians may also be to blame as they may under-estimate the impact of fatigue on a patient's quality of life and may fail to address the issue of fatigue if it is not introduced by the patient themselves (13). A Fatigue Management Barriers Questionnaire (FMBQ) has been developed to evaluate the extent to which patients have concerns that could act as barriers to fatigue management (13). The following issues are addressed within the 28 item scale to which patients reply 'yes' or 'no':

1. Treatment futility
2. Fear of disease progression
3. Desire to be a 'good' patient
4. Fear of distracting the doctor
5. Lack of concern
6. Fear of stigma
7. General medication concerns
8. Preference for non-medication interventions
9. Fear of jeopardising cancer/AIDS treatment
10. Lack of communication

When a patient is diagnosed with cancer, they have to develop a wide repertoire of skills and knowledge that will allow them to adapt to living with the disease as well as the demands made by treatment (63). Many side-effects will require the patient to undertake self-care activities to relieve them (63). Much of the fatigue-related literature recommends that efforts should be directed towards developing effective interventions for the management of cancer-related fatigue. As treatment and survival rates improve, developing interventions to control and manage fatigue become increasingly important. However, common sense methods of managing fatigue such as increased rest and sleep that are often undertaken by patients with cancer have been proved to be insufficient (30, 47)] and some of the most common interventions are based on little or no empirical evidence from people with cancer (40). This indicates a need for further intervention studies to ensure structured, systematic evaluation to better manage patients' experiences of fatigue. Some evidence to support specific interventions is presented below.

Pharmacological management

Stimulants

Psychostimulants have been used for patients with cancer (64). One such study explored the use of methylphenidate to treat fatigue in 9 of 11 consecutive patients with advanced cancer (64). Categorical scales were used to assess fatigue, pain and sedation on days 0, 3, 5 and 7 after starting methylphenidate and a quality of life

questionnaire was also administered at this time, although no details were given regarding the choice of scale. Sarhill and colleagues report that a rapid onset of benefit was noted, even in the presence of mild anaemia, with improvements in sedation and pain also in some individuals (64). However, it should be noted that patients were classified as complete responders if they rated their fatigue as none or mild at any assessment and the appropriateness of this classification should be questioned.

Corticosteroids

Although corticosteroids are often prescribed for their beneficial effects on appetite and mood, there is little direct evidence to support their use in the management of cancer-related fatigue (11). Studies that have evaluated steroids in relation to 'strength', 'activity level' and 'weakness' have produced inconclusive results however, in none of these studies was fatigue the primary endpoint, which leaves the role of corticosteroids in the management of cancer-related fatigue still open for debate (11).

Patient education

Education greatly benefits some patients (12) as many appear to be unprepared for the fatigue associated with cancer and treatment (11). Education can be used to structure an individual's expectations about the impact of treatment. Indeed, patients should be informed about the patterns of fatigue exhibited by other patients receiving similar treatments. This type of preparatory information combined with suggestions about planning for rest periods has had positive effects on patients' maintenance of normal activities when combined with similar information about various aspects of the experience of receiving radiation treatment for prostate cancer (65). Indeed, patients who are prepared for fatigue report less fatigue than those who receive no preparatory information (65). One could argue that realistic expectations from the patient's point of view may reduce the distress they experience and enable them to use self-care and coping strategies more effectively. Indeed, patients' perceived ability to manage symptoms correlates with fatigue distress (39). This is concerning when one considers that Love and colleagues reported that of 238 patients with breast cancer or lymphoma who were undergoing chemotherapy, 86% reported experiencing fatigue although only 8% had expected to feel tired (66).

Education also encourages patients and families to choose the most appropriate intervention for the fatigue that may be experienced. Both Graydon and Richardson and their colleagues found that patients often use rest and sleep as a method of relieving fatigue as opposed to a balance of activity and rest which may be more beneficial for the management of fatigue (44, 67). Consequently, education regarding the appropriateness of fatigue interventions could produce more positive patient outcomes, ultimately leading to improvements in quality of life.

Fatigue as a symptom of a treatment has been shown not to disappear instantly the treatment ends but rather to gradually lessen over time (25). Patients must be made aware of this to alleviate unnecessary anxiety and associated distress. Consequently, the interventions implemented during treatment should be continued and activities resumed gradually. However, for individuals with advanced cancer, the end of

treatment may result in a worsening of their fatigue and in this situation it is crucial for individual education and systematic planning of activities to include those most valued by the individual and careful conservation of energy to maintain the best possible quality of life (68).

The following are some suggestions that can be made to patients to help them manage their own fatigue:

- Talk to your doctor or nurse
- Take steps to promote a good night's sleep
- Allow for frequent rest periods
- Eat a nutritious diet
- Ensure adequate hydration
- Balance activity and rest
- Delegate tasks to family and friends
- Keep a journal or diary
- Plan activities

Psychological support

The effects of individual counselling by professionals (69-72) and from former patients themselves (73) have also been explored on patients' experiences of fatigue. Contents of these individual sessions included preparatory information, improving coping skills, psychological support, health education, stress management, cognitive restructuring and relaxation. Three of these five studies used the Profile of Mood States – Fatigue assessment scale (69, 71, 73) while Forester and colleague chose the Schedule of Affective Disorders and Schizophrenia (70) and Gaston-Johansson et al preferred a visual analogue scale (72). Although some studies demonstrated the positive and immediate impact of this support (70, 72) as well as the lasting effects (69, 71), this was not consistent across all studies, indeed the positive effects of such counselling were seen to wear over time: at 4 and 8 weeks follow-up (70) and at 6 and 12 weeks after starting treatment (73).

Two intervention studies, in which the effects of an supportive group meetings (74) and psychiatric group meetings (75) have been undertaken. Both used the Profile of Mood States – Fatigue questionnaire to evaluate fatigue in patients with metastatic breast cancer (74) and patients with malignant melanoma (75). Both these studies demonstrated that those individuals participating in the group meetings experienced significantly less fatigue than those of the control groups and that this effect lasted for as long as measurement continued: up to 12 months (74) and up to 6 months (75).

Considered together, it certainly appears that psychotherapeutic approaches can reduce fatigue in patients with cancer. This is certainly a therapeutic area that deserves increasing amount of research attention (11), especially in relation to how best to achieve lasting benefits.

Activity management strategies

Rest and sleep

Rest is not merely inactivity but a feeling of physical calm and control, freedom from worry, relaxation without emotional stress and comfort (76). For patients with cancer, rest is a frequent and 'common sense' intervention for fatigue and can take the form of a nap, a period of inactivity, a lower level of activity than usual or a momentary respite from contact with others. Additionally, increasing the duration of night-time sleep may be considered a form of rest. Sleep has been defined as a period of diminished responsiveness to external stimuli and a definite amount of sleep has been shown to be required for maintaining physiological and psychological functioning (76). Sleep hygiene principles should be tailored to the individual and might include the establishment of a specific bed time and wake time as well as routines prior to sleep (12). It follows that control of other symptoms or side effects such as pain or nausea should be achieved as far as possible to allow for adequate rest. In a review of the relationship between fatigue and sleep in patients with cancer, Ancoli-Israel posits that some degree of cancer-related fatigue experienced during the day may relate to disrupted sleep and desynchronised sleep/wake rhythms (77). This supports the work of Berger and Farr in 1998 who established that women who were less active and had increased night awakenings consistently reported higher levels of fatigue (35). Consequently, the use of medications that induce sleep or relieve anxiety that interferes with sleep may be appropriate for some individuals.

However, rest may not improve the fatigue experience for all individuals (30, 44, 67). One can question the advice given to patients to rest when considered alongside the psychobiologic-entropy hypothesis described earlier which suggests that too much rest can result in feelings of fatigue and advocates a balance between rest and activity. The benefits of exercise will be discussed shortly.

Rearranging activities

Rearranging activities to allow for rest periods or to shorten the length of time that high-energy output is required is another approach to dealing with the limitations imposed on daily living by fatigue. Examples of this include spreading errands throughout the week or scheduling activities to the time of day when they have the most energy. Rhodes and colleagues provided a valuable description of these changes in patients' lives as part of their research regarding self-care for the side effects of chemotherapy (78). They found that tiredness and weakness were the side effects that most interfered with self-care and consequently the subjects limited energy expenditure through careful planning and scheduling, decreasing activities and depending on others to complete some activities (78).

Manipulating the environment

Both in the hospital and at home, manipulating the environment to allow undisturbed time for sleep and rest as well as providing adequate stimulation to prevent boredom-related fatigue are important nursing interventions. Suggestions include the scheduling of provision of care and opportunities to allow for appropriate periods of rest and to make full use of times of high energy levels. One recent study utilised a virtual reality system that made patients feel they were somewhere else in a virtual

world (79). In this randomised study, patients were asked to choose a content (lake, forest or country town) and an aromatic essential oil for the time during which their chemotherapy was administered. Using the Cancer Fatigue Scale and a visual analogue scale, the study demonstrated that patients in the intervention group (n=15) were statistically less fatigued 3-5 days after chemotherapy compared to patients in the control group (n=15) (79). This small study has produced results that warrant further investigation.

Patient diaries

Patients can be encouraged to keep notes or a diary in which they keep a record of their levels of fatigue. Such diaries, that record periods of peak energy and peak fatigue, may help patients in planning their lives through identifying times when their fatigue is lowest and so when they would be able to continue their usual activities to the greatest extent possible (7, 12).

Exercise

Activity has also been identified as playing a role in relieving fatigue (11). However, as this is counterintuitive to patients, considerable education may be required to foster their co-operation with an exercise programme (12). Winningham and her colleagues were the first to identify the benefits of exercise for patients with cancer through their finding that cycling increased exercise tolerance and enhanced functional capacity in patients receiving treatment for breast cancer (80). Exercise is beneficial to both healthy individuals and those who have chronic physical or psychological problems (76). Continued inactivity decreases orthostatic tolerance, muscle strength, endurance, skeletal strength and physiological well-being (81). MacVicar and Winningham found that patients with breast cancer who were participating in a supervised, aerobic, interval training exercise programme exhibited an improvement in mood that included the perception of fatigue (82).

Within recent years the impact of exercise on fatigue experiences has been explored in more depth (45, 83-88). Although these studies measured fatigue using different methods (metabolic equivalents: allows the estimation of physical fitness (83, 84, 86), the Piper Fatigue Scale (85, 88), the Profile of Moods Scale (87) and a visual analogue fatigue scale (45)), they consistently demonstrated that participating in exercise such as walking or using a cycling machine results in reduced experiences of fatigue (45, 83-88). Furthermore, an additional benefit of exercise may be improved appetite and increased nutritional intake (12). However, these studies have predominantly involved patients with breast cancer or patients undergoing stem cell transplant and it is important that future research explores the benefits of exercise in patients with a full range of cancer diagnoses.

Despite these positive findings, the risks of exercise should be considered at all times. For individuals for whom exercise is not contraindicated, short walks or their usual exercise should be encouraged to try to relieve the fatigue (89). Consequently, one can argue that a goal for individuals suffering from fatigue could be to conserve, maintain or regain activity levels. Again, the benefits of exercise lead one to question the common advice given to patients with cancer to 'take it easy' and 'get plenty of rest'. Such advice is unhelpful when one acknowledges the fact that decreased activity

secondary to a cancer diagnosis and treatment may cause rapid decline and potentially irreversible losses in energy and functioning that affect every organ system (89).

Attention-restoring activities

Attentional fatigue has been defined as a decreased capacity to concentrate or direct attention (90). Further education does not help patients who are having difficulty understanding new information and thinking clearly instead, activities related to the natural environment such as walking or gardening can help restore the ability to think clearly and enable patients to participate in their care and life activities (90). Further study of this concept concerning the attentional deficits of women in the three month period following mastectomy illustrated that women who used attentional restoring activities three times weekly showed an increased rate of recovery and higher rates of returning to work and engaging in new activities than a control group when assessed using the Total Attention Score and Attentional Function Index (91). Such findings provide a basis for further testing of the efficacy of attention-restoring interventions in people with cancer.

Physiological strategies

As cancer-related anaemia is often reported in patients undergoing treatment, oxygenation of the blood is now recognised as a cause of fatigue. Patients receiving epoetin alpha have been shown to experience significantly improved quality of life and less fatigue, findings that correlate directly with an increase in haemoglobin levels (92). Additionally patients receiving epoetin alpha needed significantly fewer blood transfusions, and for those who needed transfusion, fewer units were required (92).

Proper metabolism and energy production are dependent on the ingestion of adequate calories in the form of protein, carbohydrates and fats with adequate levels of vitamins, minerals and trace elements (76). However, patients with cancer may have problems that lead to the inadequate intake of nutrients while the way that their body uses nutrients may change in the presence of cancer (26). Thus, patients should be educated in the benefits of a healthy diet. Furthermore, substances thought to combat fatigue such as coffee and alcohol may be responsible for undue fatigue, even when their use has not been excessive (93).

Alternative methods

Acupressure

This is a method by which the energy of the body is replenished, revitalised and brought into balance through the application of topical pressure on certain points of the body (76). When acupressure is applied to a total body system, the state of relaxation is often initiated (94).

Massage

Therapeutic total body massage combines the effect of muscle massage with those of acupressure and manually releases muscle tension, thereby facilitating the state of relaxation (76).

Reflexology

This relates to the stimulation of the thymus gland and its immune function and is purported to result in the strengthening and balancing weakened muscles and systems of the body (76).

However, despite the growing amount of evidence regarding intervention strategies for managing fatigue, no consensus has been reached regarding a gold standard and it would seem that individual variations exist concerning the effectiveness of such interventions. Perhaps then we should continue to follow the advice of Richardson who recommended a multi-method fatigue therapy programme incorporating energy conservation activities, planned exercise, stress reduction strategies and nutritional counselling – all tailored to the individual patient (40).

Researching fatigue

Recommendations for future research and critique of previous work have been presented throughout this review. Fatigue research has been and continues to be plagued by logistical and methodological flaws and complications. Some issues that should be considered when evaluating or undertaking cancer-related fatigue research are presented below.

Choice of measure

Exploring the fatigue experienced by patients with cancer has been characterised by a range of methodological challenges. Firstly, as fatigue commonly lacks an accepted and general definition it is not surprising that there is a lack of consensus about the most appropriate means through which to assess fatigue. In research to-date, definitions of fatigue vary from terms used to depict a physical sensation or experience to those meaning a mental concept such as lack of concentration or deficits in cognitive functioning (5). Furthermore, as well as researcher-defined definitions, the patient is also likely to construct definitions for their fatigue (5). Consequently, a variety of self-report measures have been used, ranging from a single item embedded within a range of symptoms such as the Symptom Distress Scale (95) to multi-item measures such as Functional Assessment of Cancer Therapy – Fatigue (FACT-F)(96).

Research design

In addition to these issues, is the limitation of the frequent use of cross-sectional research designs that clearly restricts the conclusions that can be drawn about changes in fatigue over time (53). Although more methodically sound, longitudinal designs tend to be costly in terms of both time and resources. However, the data they produce would be more accurate about the natural history of fatigue in patients with cancer.

Use of comparison groups

A further complication of fatigue research is frequently the lack of a comparison group. While this would undoubtedly provide a valuable frame of reference, a comparison group would also be helpful in evaluating the sensitivity of different fatigue measures and for identifying differences in fatigue across patient and non-patient populations (53).

Timing of fatigue assessment

The timing of fatigue assessment is also a crucial factor in research. Richardson and her colleagues demonstrated that patients felt fatigued more commonly in the afternoon and evening (44) so it is important to consider this fact when comparing research findings as well as when planning a research project.

Response shift

If patients experience extreme fatigue during treatment, they may later judge their level of fatigue differently than they would have judged it before (97). This change in internal standard has been termed 'response shift'. The presence of such a phenomenon in fatigue experiences has been demonstrated by Visser and colleagues with patients who had undergone radiotherapy, demonstrating that patients retrospectively minimised their pre-treatment level of fatigue (97). Consequently, not only should we be aware of such a phenomenon when reviewing research, but also the phenomenon itself warrants further research.

Areas for future research

Areas for future research should include testing a range of interventions with different groups of patients to determine their value across a variety of cancer diagnoses as well as treatments (63). Ream and Richardson make worthy recommendations for future fatigue research in their comprehensive review of both fatigue theory and practice such as:

- Base research on current fatigue theory
 - Describe clearly the theoretical framework that the research is based on
 - Employ consistent methods and instruments to measure fatigue to allow comparison of results
 - Test a range of interventions with different groups of patients to determine their comparative value across the spectrum of diagnoses and treatments
 - Design and evaluate global interventions that can be tailored to meet individual needs and preferences
 - Focus on the relationship between fatigue and psychological status
 - Determine the impact of other symptoms on fatigue and vice versa
- (63)

Conclusion

From this review of the literature it would seem that cancer-related fatigue remains a difficult subject to manage, while also an elusive one to study. However, it is clearly a symptom that causes immense distress to patients with cancer and as such is of great importance to oncology healthcare workers. Although further research is undoubtedly needed, many patients could benefit from more comprehensive evaluation and greater use of available interventions (12). Future research should continue to build on previous work, generating evidence regarding explanations and predictors of fatigue as well as exploring remedies and interventions.

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APPENDIX L – NAUSEA SUMMARY REVIEW



Chemotherapy-Related Nausea & Vomiting

Summary Review of the Literature

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Introduction

It is unquestionable that chemotherapy-induced nausea and vomiting represent a significant problem for patients with cancer. Although the introduction of 5-HT₃ receptor antagonists reduced the incidence of vomiting, incidence of nausea has actually risen (Roscoe, Morrow et al. 2000). Inadequate control of nausea and vomiting reduces patients' quality of life and functional status, can affect compliance and precipitate physiological complications including fluid and electrolyte imbalance, malnutrition and oesophageal injury and jeopardises the delivery of optimal treatment, making it an important focus for cancer nursing care.

Assessing nausea and vomiting

Adequate diagnosis of a symptom is a prerequisite for its management. Nursing staff should consider:

- the emetogenic potential of the chemotherapy regime
- patient expectations
- patient age (the young are more severely affected than older individuals)
- gender: women are more affected than men
- history of alcohol intake: patients with a history of chronic alcohol ingestion appear to experience less nausea and vomiting
- history of motion sickness: susceptibility to motion sickness is associated with increased nausea and vomiting following chemotherapy
- emetic response to previous chemotherapy: previous uncontrolled emesis following chemotherapy is likely to lead to severe nausea and vomiting despite aggressive antiemetic coverage

A number and range of assessment tools exist, each of which have advantages and disadvantages. A multidimensional assessment that considers incidence, severity and symptom distress are especially useful in gaining a complete understanding of the patient's symptom experience. Whilst patients are receiving a course of chemotherapy, assessment of nausea and vomiting should include:

- The nature and character of the nausea and vomiting (onset, frequency, severity)
- Interference with daily activities
- The impact of nausea and vomiting on nutritional status, fluid balance and metabolic homeostasis
- The presence of risk factors such as infection, change in mental status
- The presence of side effects from antiemetic medications

(Fitch 1993)

Managing nausea and vomiting

As there are multiple pathways for the stimulation of the vomiting centre in the brain, it follows that drug combinations are more effective than single agents in controlling nausea and vomiting that occurs as a result of chemotherapy. In addition to multiple drug combinations, behavioural strategies, such as progressive muscle relaxation and guided imagery, have also been tried and tested for their effectiveness in the prevention and control of chemotherapy-induced nausea and vomiting. Prevention of nausea and vomiting before they occur is the key to successful management (Goodman 1997) and the best management is based on treating the patient as an individual, in conjunction with careful consideration of the drug regimen prescribed, convenience, cost-effectiveness and combination pharmacotherapy.

Pharmacological management

Treatment with two or more antiemetics may improve their efficacy and/or reduce unwanted side effects. The main classes of anti-emetic drugs are:

- Serotonin Receptor Agonists (for example *Ondansetron*)
- Phenothiazines (for example *Prochlorperazine*)
- Butyrophenones (for example *Haloperidol*)
- Substituted benzamides (for example *Metoclopramide*)
- Cannabinoids (for example *Dronabinol*)
- Corticosteroids (for example *Dexamethasone*)
- Benzodiazepines (for example *Lorazepam*)

The side-effect profile of these drugs should also be considered. Further information about each of these classes and their clinical effectiveness can be found in the full literature review or on the wisecare website at www.wisecare.org/.

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Complementary therapies

Complementary strategies should be within the regular repertoire of nurses' interventions. These should not replace standard antiemetic therapies, rather they can be used as adjuncts to maximise quality of life (Bauer 1996). Talking with the patient before incorporating these interventions into their plan of care is important as some patients may be sceptical and uninterested (Bauer 1996).

Complementary interventions are helpful as they:

- can decrease affective and psychological arousal and reduce general feelings of distress
- can serve as cognitive distracters, redirecting patients' attention from conditioned stimulus and refocusing it on neutral or relaxing images
- can promote feelings of control and reduce feelings of helplessness by demonstrating to patients that they can successfully help themselves reduce treatment side effects
- can easily be administered and learned within the chemotherapy environment and would have few if any side effects

(Burish and Tope 1992; Bauer 1996; King 1997)

Examples of complementary therapies include:

- progressive muscle relaxation training
- guided imagery
- self-hypnosis
- acupressure and acupuncture
- biofeedback
- cognitive distraction
- music therapy

More information about each of these techniques is available in the full review of the literature and also at www.wisecare.org/.

Conclusion

Although the pharmacological management of chemotherapy-induced nausea and vomiting has been well explored and the most efficacious antiemetic regimes available to date have been identified, a significant proportion of patients continue to report symptoms of nausea and vomiting. This may be due to poor dissemination of study results in tandem with their lack of adoption into clinical practice.

Non-pharmacological methods of managing nausea and vomiting are also of great interest to cancer nurses and preliminary evidence points to the positive benefits that can be achieved through their use. However, the evidence-base to support many of these techniques is, at best, weak due to small sample sizes as well as being complicated by confounding variables such as stage of disease, the various chemotherapy regimes administered, culture and patients' continued compliance with performing these non-pharmacological techniques. Indeed, the lasting effects (or not) of many non-pharmacological interventions can only be speculated at. Further research, building programme of research is clearly required.

Reducing the unpleasant side effects of chemotherapy-induced nausea and vomiting will clearly enhance patients' quality of life. Well planned, prophylactic strategies that are tailored to each individual patient's characteristics, personality and chemotherapy treatment are essential to maximise the response to therapies initiated. Where possible, these therapies should be both pharmacological and non-pharmacological.

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APPENDIX M – FATIGUE SUMMARY REVIEW



Cancer-Related Fatigue

Summary Literature Review

Background

Fatigue is a highly prevalent condition among patients with cancer and is now described by patients as more common than nausea, depression and pain (1). With the improvements in cancer treatment and the resultant increase in survival, managing symptoms and optimising quality of life are key concerns for those caring for people with cancer. The prevalence of fatigue in this population means that it is a natural priority for symptom management initiatives.

What is fatigue?

Definitions of fatigue are many and varied and may cause confusion during discussions between health professionals and also between health professionals and patients. Cancer-related fatigue is reported to be different to 'normal' fatigue experienced as a result of exertion as it is unrelieved by sleep or rest. Cancer-related fatigue has been defined as 'a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with an individual's ability to function to their normal capacity' (2).

The meaning of fatigue

Qualitative research methods have been used to explore just how individuals experience cancer-related fatigue. Fatigue has been shown to affect the physical, psychological, spiritual and social aspects of an individual's life (3). The emotional reaction to fatigue experiences has also been identified, with individuals expressing frustration, worry, concern, displeasure, fear, depression and disappointment regarding their fatigue (4).

Causes of fatigue

A number of theories and models about the causes of fatigue have been developed such as the accumulation hypothesis (5), depletion hypothesis (6), the psychobiologic-entropy hypothesis (7) and Piper's integrated fatigue model (8).

Causes of fatigue may be physiological, such as anaemia, electrolyte imbalances, nutritional deficiency, altered sleeping patterns, certain medications and other symptoms, for example pain. Psychological factors also play a role in the development of fatigue and feelings such as sadness and distress can undoubtedly contribute to experiences of fatigue. However, fatigue and depression should not be confused as they are distinctly different symptoms.

Patients' experiences of fatigue are also related to their anti-cancer treatments. Exploring fatigue within specific patient populations receiving chemotherapy and radiotherapy has demonstrated patterns of fatigue. For example, patients receiving conventional 3-4 weekly cycles of chemotherapy typically experience high levels of fatigue for 4-5 days following chemotherapy which gradually lessen until the nadir period when they experience a transient rise in fatigue levels (9). Fatigue patterns in relation to radiotherapy are many and varied: ranging from decreased fatigue during the first and second weeks of treatment, followed by a rise then plateau in week four (10) to increased fatigue during the first and second week with higher levels observed in the afternoon and evening (11). Furthermore, as more people are treated with a combination of anti-cancer therapies, the prevalence of fatigue is likely to increase dramatically.

Assessing fatigue

Assessing fatigue is complicated by the lack of agreed definitions of the concept. Despite the confusion, it is essential that nurses undertake some measure of patients' fatigue levels. Fatigue assessment is often incorporated into tools that measure broader concepts such as the Profile of Mood States of the Symptom Distress Scale. However, it has also been argued that fatigue should not be buried in tools that measure a wide range of concepts and as a consequence a plethora of fatigue-specific tools are available for use. Many of these tools are self-report in nature, complying with the belief that a subjective sensation such as fatigue is most appropriately measured by the individual. While a recent review of a variety of self-report fatigue assessment tools recommended further psychometric testing (12), using such scales clinically is invaluable as patients often believe their fatigue to be an inevitable consequence of their disease or treatment and merely acknowledging their fatigue experiences helps.

Managing fatigue

Fatigue provides a challenge to nurses not only because of its numerous causes but also because of the multitude of effects that it has on the lives of those affected. Following a thorough assessment, the initial approach to managing fatigue should be to correct any potential aetiologies such as elimination of non-essential drugs, treatment of sleep disorders, reversal of anaemia or metabolic disorders and the management of major depression (13). Additional interventions are detailed below.

Patient education greatly benefits some patients and can be used to structure individuals' expectations about cancer-related fatigue. Patients should be informed about patterns of fatigue experienced by other patients receiving similar treatments as well as about the benefits of planning for and prioritising activity. Indeed patients who are prepared for fatigue report less fatigue than those who receive no preparatory information (14). This education should also include the fact that fatigue does not resolve instantly on treatment completion but rather that it gradually lessens over time (15).

The effects of psychological support on fatigue experiences has been explored in the form of counselling by professionals (16-19) and by former patients (20). These sessions included preparatory information, coping skills, psychological support, health education, stress management, cognitive restructuring and relaxation. While initial improvement in fatigue scores were demonstrated in the majority of the studies, lasting effects were more difficult to obtain. Based on these findings, psychotherapeutic approaches deserve increasing research attention, especially in relation to how best to maintain lasting effects.

Activity management strategies such as rest and sleep, rearranging activities, manipulating the environment and exercise also offer benefits to the individual experiencing cancer-related fatigue. Sleep hygiene principles should include the establishment of a specific bedtime and wake time as well as routines prior to sleep (13). Rearranging and prioritising activities may also help deal with the limitations that fatigue imposes on daily living. Examples of this would be spreading tasks throughout the week or scheduling activities to the time of day that the individual has most energy. Manipulating the environment to allow for undisturbed sleep or relieve boredom-related fatigue is also an important nursing intervention. However, the greatest amount of evidence surrounds the role of exercise in relieving fatigue, with the majority of studies focusing on women with breast cancer receiving chemotherapy or patients undergoing bone marrow transplantation. Whether walking or cycling, participating in exercise has consistently been associated with reduced fatigue experiences (21-27). There are two important issues to consider here. Firstly as this concept is often counterintuitive to patients, a considerable amount of education may be required. Secondly, the risks associated with exercise should be considered at all times and the prior fitness level of individuals should be considered when recommending exercise.

Attention restoring exercises were developed through the study of attentional deficits in women with breast cancer (28, 29). Such attention restoring exercises include activities such as gardening or other hobbies in which individuals can become involved.

The final fatigue management strategy is that of physiological management. Anaemia is now commonly acknowledged as a cause of cancer-related fatigue. Patients receiving epoetin alpha have been shown to have an increase in haemoglobin which directly relates to improved quality of life and decreased levels of fatigue (30).

Conclusion

The multi-dimensional symptom of cancer-related fatigue causes a great degree of distress to patients with cancer and as such is of concern for healthcare professionals. Although further research is required regarding the explanations and predictors of fatigue as well as remedies, patients could undoubtedly benefit from more comprehensive assessment and greater use of interventions.

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APPENDIX N – NCCN ANTIEMESIS



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- [Breakthrough Treatment for Chemotherapy Induced Nausea and Vomiting \(AE-5\)](#)
- [Emetogenic Potential of Antineoplastic Agents \(AE-6\)](#)
- [Principles of Managing Multi-Day Emetogenic Chemotherapy Regimens \(AE-A\)](#)
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NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#)

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SUMMARY OF GUIDELINES UPDATES

Change in the 3.2008 version of the NCCN Antiemesis Guidelines from the 2.2008 version is the addition of fosaprepitant dimeglumine to pages **AE-2** and **AE-3** for prevention of emesis in chemotherapy with high and moderate emetic risk. Also added was the following footnote: Fosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

Change in the 2.2008 version of the NCCN Antiemesis Guidelines from the 1.2008 version is the addition of the 2008 manuscript.

Summary of changes in the 1.2008 version of the NCCN Antiemesis Guidelines from the 1.2007 version include:

General

- Deleted recommendation prochlorperazine for 15 mg Spansule PO every 8 or every 12 h throughout the guidelines.

AE-4

- Added footnote g: "Monitor for dystonic reactions; use diphenhydramine for dystonic reactions."

AE-7

- Added Vorinostat to the list of agents with low emetic risk.
- Added Cetuximab, Lapatinib, Panitumumab, and Temeirolimus to the list of agents with minimal emetic risk.

AE-B Principles for Managing Breakthrough Emesis

- The general principle of breakthrough treatment is to give an additional agent from a different drug class. Added the following statement: No one treatment is better than the other for managing breakthrough emesis.
- Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Added the following statement: Dopamine antagonists (eg, metoclopramide), haloperidol, corticosteroids and agents such as lorazepam may be required.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

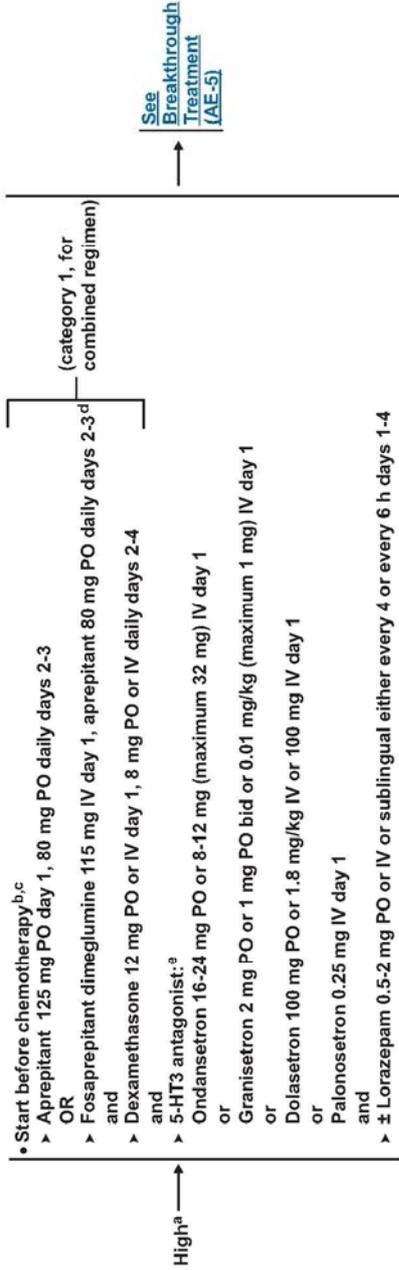
PRINCIPLES OF EMESIS CONTROL IN THE CANCER PATIENT

- Prevention of nausea/vomiting is the goal.
- The risk of emesis and nausea for persons receiving chemotherapy of high and moderate emetic risk lasts for at least 4 days. Patients need to be protected throughout the full period of risk.
- Oral and IV antiemetic formulations have equivalent efficacy.
- Consider the toxicity of the specific antiemetic(s).
- Choice of antiemetic(s) used should be based on the emetic risk of the therapy, prior experience with antiemetics, as well as patient factors.
- There are other potential causes of emesis in cancer patients. These may include:
 - > Partial or complete bowel obstruction
 - > Vestibular dysfunction
 - > Brain metastases
 - > Electrolyte imbalance: hypercalcemia, hyperglycemia, hyponatremia
 - > Uremia
 - > Concomitant drug treatments including opiates
 - > Gastroparesis, tumor or chemotherapy (vincristine etc) induced.
 - > Psychophysiological:
 - * Anxiety
 - * Anticipatory nausea and vomiting
- For use of antiemetics for nausea and vomiting that is not related to radiation and/or chemotherapy, [See NCCN Palliative Care Guidelines](#)

Note: All recommendations are category 2A unless otherwise indicated.
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HIGH EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION^{b,c}

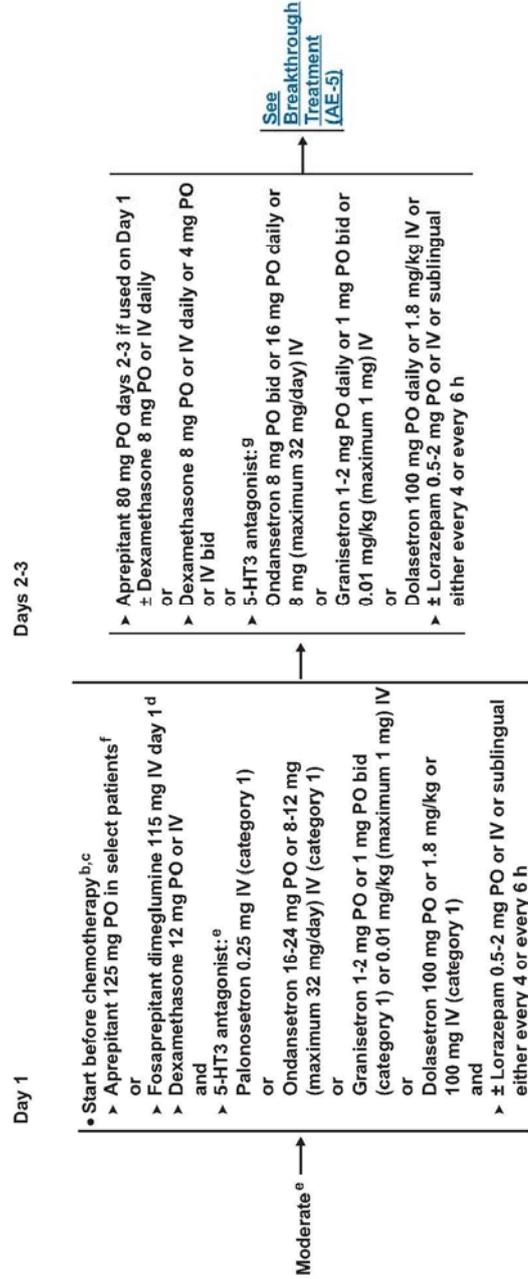


[See Principles of Emesis Control \(AE-1\)](#)

^aData for post-cisplatin (≥ 50 mg/m²) emesis prevention are category 1, others are category 2A.
^bAntiemetic regimens should be chosen based on emetogenic potential of the chemotherapy regimen as well as patient specific risk factors.
^cSee Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).
^dFosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.
^eOrder of listed antiemetics does not reflect preference.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MODERATE EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION^{b,c}



^bAntiemetic regimens should be chosen based on emetogenic potential of the chemotherapy regimen as well as patient specific risk factors.

^cSee Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).

^dFosaprepitant dimeglumine (115 mg) may be substituted for aprepitant (125 mg) 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

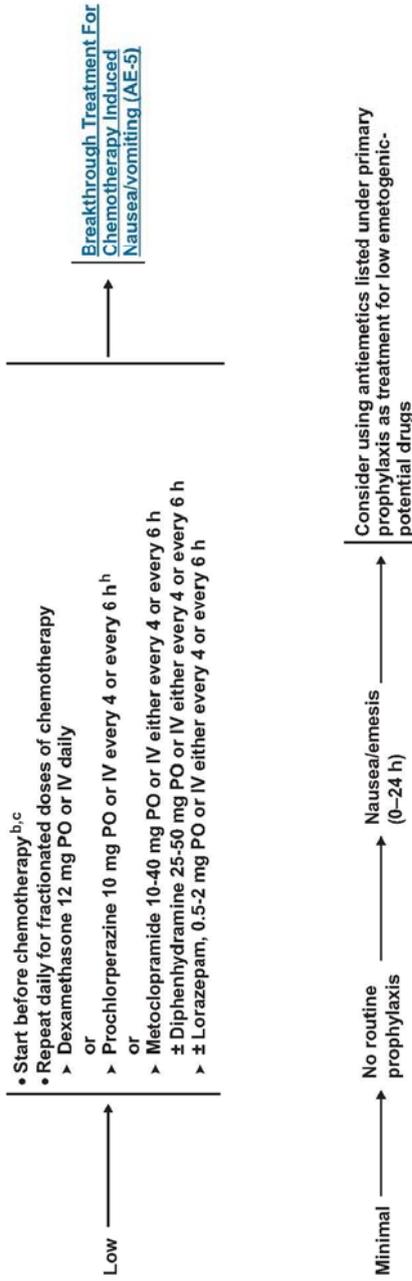
^eOrder of listed antiemetics does not reflect preference.

^fAprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for patients receiving the combination of an anthracycline and cyclophosphamide and select patients receiving other chemotherapies of moderate emetic risk (for example, carboplatin, cisplatin, doxorubicin, epirubicin, floxamide, irinotecan or methotrexate).

^gData for post-carboplatin ≥ 300 mg/m², cyclophosphamide ≥ 600-1000 mg/m², doxorubicin ≥ 50 mg/m² emesis prevention are category 1.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

LOW AND MINIMAL EMETIC RISK CHEMOTHERAPY - EMESIS PREVENTION^{b,c}

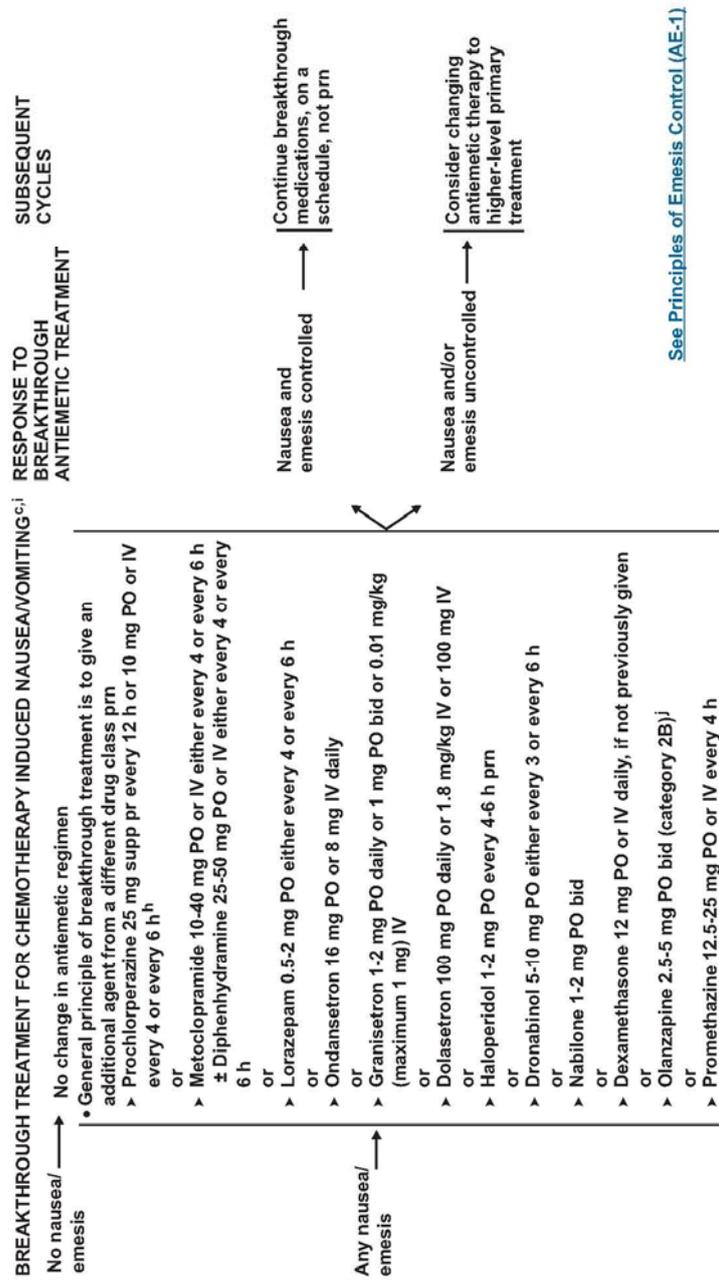


See Principles of Emesis Control (AE-1)

^bAntiemetic regimens should be chosen based on emetogenic potential of the chemotherapy regimen as well as patient specific risk factors.
^cSee Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).
^hMonitor for dystonic reactions; use diphenhydramine for dystonic reactions.

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See Principles of Emesis Control (AE-1)

^cSee Principles for Managing Multi-day Emetogenic Chemotherapy Regimens (AE-A).
^hMonitor for dystonic reactions; use diphenhydramine for dystonic reactions.
ⁱSee Principles of Managing Breakthrough Treatment (AE-B).
^jSee blackbox warning/label indication regarding type II diabetes and hyperglycemia.

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EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS

LEVEL	AGENT
High emetic risk (> 90 % frequency of emesis) ^k	<ul style="list-style-type: none"> • AC combination defined as either doxorubicin or epirubicin with cyclophosphamide • Altretamine • Carmustine > 250 mg/m² • Cisplatin ≥ 50 mg/m² • Cyclophosphamide > 1,500 mg/m²
Moderate emetic risk (30- 90 % frequency of emesis) ^k	<ul style="list-style-type: none"> • Aldesleukin > 12-15 million units/m² • Amifostine > 300 mg/m² • Arsenic trioxide • Azacitidine • Busulfan > 4 mg/d • Carboplatin • Carmustine ≤ 250 mg/m² • Cisplatin < 50 mg/m² • Cyclophosphamide ≤ 1,500 mg/m² • Cyclophosphamide (oral) • Cytarabine > 1 g/m² • Dactinomycin • Daunorubicin • Doxorubicin

Low emetic risk,
 level 2 (See AE-7)
 Minimal emetic risk,
 level 1 (See AE-7)

^kProportion of patients who experience emesis in the absence of effective antiemetic prophylaxis
^lDaily use of antiemetics is not recommended based on clinical experience.

Adapted with permission from:
 Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J. Clin Onc 15: 103-9, 1997.
 Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity---an update. Support Care Cancer 2005; 13:80-84.
 Epub 2004 Dec 14.

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EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS

LEVEL	AGENT
Low emetic risk (10-30 % frequency of emesis) ^k	<ul style="list-style-type: none"> • Amifostine ≤ 300 mg • Bexarotene • Capecitabine • Cytarabine (low dose) 100-200 mg/m² • Docetaxel • Doxorubicin (liposomal) • Etoposide • Fludarabine (oral) • 5-Fluorouracil • Alemtuzumab • Alpha Interferon • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Busulfan • Cetuximab • Chlorambucil (oral) • Cladribine (2-chlorodeoxyadenosine) • Decitabine • Denileukin diftitox • Dasatinib • Dexrazoxane • Erlotinib • Fludarabine • Gefitinib • Gemtuzumab ozogamicin • Hydroxyurea (oral)
Minimal emetic risk (< 10 % frequency of emesis) ^k	<ul style="list-style-type: none"> • Gemcitabine • Methotrexate > 50 mg/m² < 250 mg/m² • Mitomycin • Mitoxantrone • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Topotecan • Vorinostat • Lapatinib • Lenalidomide • Melphalan (oral low-dose) • Methotrexate ≤ 50 mg/m² • Nelarabine • Panitumumab • Pentostatin • Rituximab • Sorafenib • Sunitinib • Temsirolimus • Thalidomide • Thioguanine (oral) • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vinorelbine

^kProportion of patients who experience emesis in the absence of effective antiemetic prophylaxis

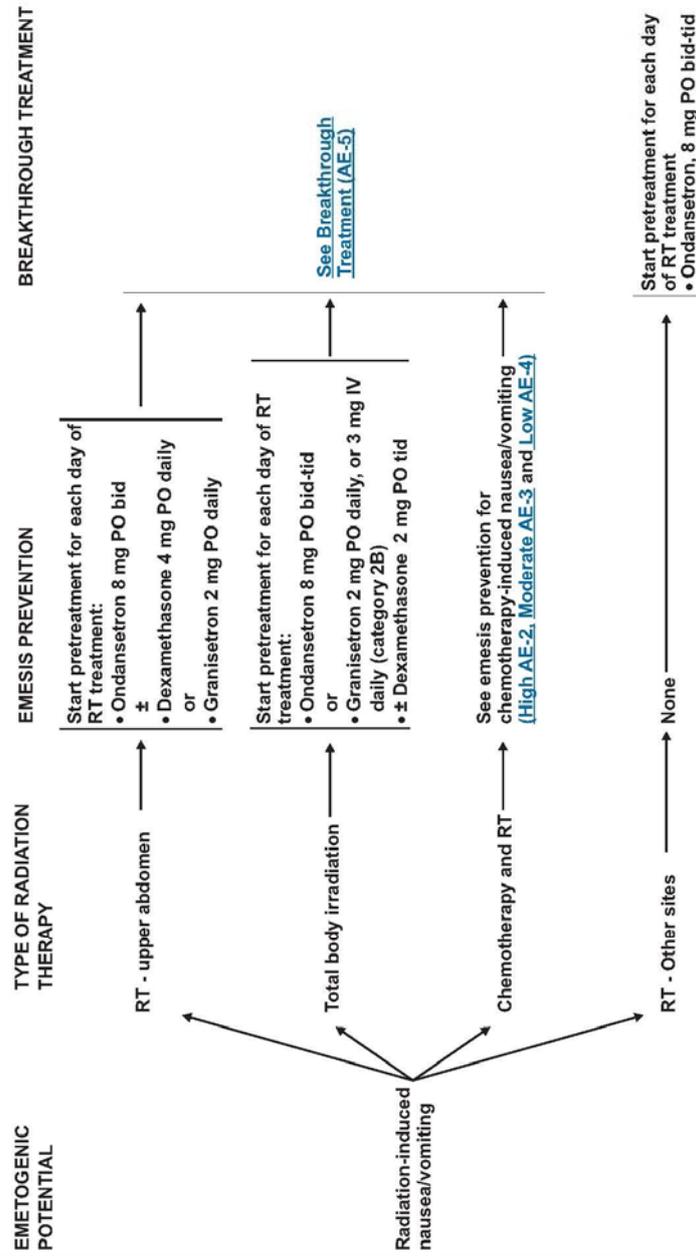
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Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity---an update. Support Care Cancer 2005; 13:80-84.
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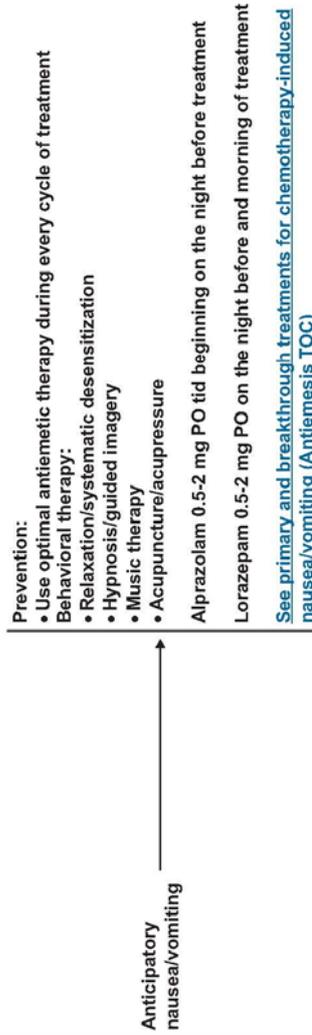
Antiemesis



See Principles of Emesis Control (AE-1)

Note: All recommendations are category 2A unless otherwise indicated.
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ANTICIPATORY EMESIS PREVENTION/TREATMENT



[See Principles of Emesis Control \(AE-1\)](#)

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AE-9

PRINCIPLES OF MANAGING MULTI-DAY EMETOGENIC CHEMOTHERAPY REGIMENS

- Patients receiving multi-day chemotherapy are at risk for both acute and delayed nausea and emesis based upon the emetogenic potential of the individual chemotherapy agents and their sequence. It is therefore difficult to recommend a specific antiemetic regimen for each day especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy. The period of risk for delayed emesis after chemotherapy administration has concluded also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen.
- Examples illustrating the above include BEP (bleomycin 30 units IV weekly, etoposide 100 mg/m² IV days 1-5 and cisplatin 20 mg/m² IV days 1-5) versus ASHAP (doxorubicin 25 mg/m² IV day 1, methylprednisolone 500 mg/day IV days 1-5, cisplatin 25 mg/m² IV continuous infusion days 1-4 followed by cytarabine 2000 mg/m² on day 5). BEP is moderately emetogenic with risk for emesis on days 1-8) whereas ASHAP is moderately emetogenic on days 1-4 but becomes highly emetogenic on day 5 due to the administration of high-dose cytarabine). Risk for acute and delayed emesis for ASHAP may last up to 10 days.

Accordingly, the panel recommends the following as general principles (category 2B).

- A 5-HT3 receptor antagonist should be administered prior to each days 1st dose of moderately or highly-emetogenic chemotherapy.
- Dexamethasone should be administered once daily either orally or intravenously for every day of moderately or highly emetogenic chemotherapy and for 2-3 days after chemotherapy for regimens that are likely to cause significant delayed-emesis. Dexamethasone should not be added when the chemotherapy regimen already includes a corticosteroid (as in ASHAP illustrated above).
- Palonosetron may be used prior to the start of a three day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 receptor antagonists. Repeat dosing of palonosetron 0.25 mg is likely to be safe, based upon the dose ranging Phase II trial where up to 30 times the FDA approved dose (90 mcg/kg) was administered and the 3 Phase III trials that evaluated palonosetron 0.75 mg as a single fixed dose. Compared to the approved dose of palonosetron 0.25 mg, these higher doses were not associated with significantly different grades or durations of adverse events. In terms of efficacy, need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multi-day chemotherapy is not yet known.
- Aprepitant may be used for multi-day chemotherapy regimens likely to be highly-emetogenic and associated with significant risk for delayed nausea and emesis. As per the labeled indication aprepitant should be administered 125 mg orally 1 hour prior to chemotherapy on day one, along with a 5-HT3 receptor antagonist and dexamethasone. Aprepitant 80 mg should be administered daily on days 2 and 3 after the start of chemotherapy along with dexamethasone. Based upon Phase II data, aprepitant 80 mg may be safely administered on days 4 and 5 after chemotherapy. It is not yet known if dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting.

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PRINCIPLES FOR MANAGING BREAKTHROUGH EMESIS

- Breakthrough emesis presents a difficult situation as correction of refractory ongoing nausea and vomiting is often challenging to reverse. It is generally far easier to prevent nausea and vomiting than to treat it.
- The general principle of breakthrough treatment is to give an additional agent from a different drug class. No one treatment is better than the other for managing breakthrough emesis.
- One should strongly consider routine, around the clock, administration rather than PRN dosing.
- The PO route is not likely to be feasible due to ongoing vomiting, therefore, rectal or IV therapy is often required.
- Multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Dopamine antagonists (eg, metoclopramide), haloperidol, corticosteroids and agents such as lorazepam may be required.
- Ensure adequate hydration or fluid repletion, simultaneously checking and correcting any possible electrolyte abnormalities.
- Prior to administering the next cycle of chemotherapy the patient should be reassessed, with attention to various possible non chemotherapy related reasons for breakthrough emesis with the current cycle:
 - Brain metastases
 - Electrolyte abnormalities
 - Tumor infiltration of the bowel or other gastrointestinal abnormality
 - Other comorbidities
- Prior to the next cycle of chemotherapy, reassess both the Day 1 and post chemo antiemetic regimen which did not protect the patient during the present cycle and consider alternatives: (Suggestions are not in order of preference)
 - Addition of aprepitant
 - Additional other concomitant antiemetics, eg, dopamine antagonists (metoclopramide) or haloperidol
 - Possibly adjusting dose(s), either intensity or frequency, of the 5-HT3 antagonist. Based on the patient's experiences, the chemotherapy regimen in question may actually be more emetogenic than generally classified (eg, Hesketh method)
 - Possibly switching to a different 5-HT3 although not necessarily likely to be effective, anecdotal and limited investigational trial data suggest it may sometimes be efficacious.
 - If the goal of chemotherapy is palliative or adjuvant, consider other appropriate regimens, if any, which might be less emetogenic.
 - Addition of an anxiolytic agent in combination with the antiemetic agents.
- If patient has dyspepsia consider antacid therapy (H2 blocker or proton pump inhibitor).

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NCCN Categories of Evidence and Consensus

Category 1: Based on high-level evidence and uniform consensus.

Category 2A: Based on lower-level evidence including clinical experience and uniform consensus.

Category 2B: Based on lower-level evidence including clinical experience and nonuniform consensus (but no major disagreement).

Category 3: Based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Chemotherapy-induced nausea and vomiting (emesis) can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. In addition, nausea and vomiting can result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient's performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.¹⁻⁴

The incidence and severity of nausea and/or vomiting in patients receiving chemotherapy are affected by numerous factors, including: (1) the specific chemotherapeutic agents used; (2) dosage of the agents; (3) schedule and route of administration of the agents; and (4) individual patient variability (eg, age, sex, prior chemotherapy, history of alcohol use). Approximately 70% to 80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting,^{5,6} whereas 10% to 44% experience anticipatory nausea and/or vomiting.⁷⁻¹⁰ Patients often experience more nausea than vomiting.¹¹

Pathophysiology of Emesis

Vomiting results from stimulation of a multistep reflex pathway controlled by the brain. Vomiting is triggered by afferent impulses to the vomiting center (located in the medulla) from the chemoreceptor trigger zone, pharynx and gastrointestinal (GI) tract (via vagal afferent fibers), and cerebral cortex. Vomiting occurs when efferent impulses are sent from the vomiting center to the salivation center, abdominal muscles, respiratory center, and cranial nerves.¹²

The chemoreceptor trigger zone, vomiting center, and GI tract have many neurotransmitter receptors. Activation of these receptors by chemotherapeutic agents or their metabolites may be responsible for chemotherapy-induced emesis. The principal neurotransmitters involved in the emetic response are the serotonin (5-hydroxytryptamine [5-HT₃]) and dopamine receptors.^{13,14} Other neurotransmitters involved in emesis include acetylcholine, corticosteroid, histamine, cannabinoid, opiate, and neurokinin-1 (NK-1) receptors, which are located in the vomiting and vestibular centers of the brain.¹⁵

Antiemetic agents can block different neuronal pathways, exert their effects at different points during the course of emesis, or behave synergistically with other antiemetic agents to potentiate an antiemetic effect. When used at a certain concentration, each antiemetic agent predominantly blocks one receptor type. A final common pathway for emesis has yet to be identified. Therefore, no single agent can be expected to provide complete protection from the various emetic phases of chemotherapy.

Types of Nausea and/or Vomiting

Chemotherapy-Induced Nausea and/or Vomiting

Nausea and/or vomiting induced by chemotherapy is commonly classified as acute, delayed, anticipatory, breakthrough, or refractory.

Acute-onset nausea and/or vomiting usually occurs within a few

minutes to several hours after drug administration and commonly resolves within the first 24 hours. The intensity of acute-onset emesis generally peaks after 5 to 6 hours. The occurrence of acute emesis is influenced by the patient's age and gender, environment in which chemotherapy is administered, whether the patient has a history of chronic alcoholism (which decreases the incidence of emesis) or motion sickness, previous episodes of nausea and vomiting, dosage of the emetogenic agent, and efficacy of the antiemetic regimen.^{16,17} *Delayed-onset* emesis develops in patients more than 24 hours after chemotherapy administration.^{16,17} It occurs commonly with the administration of cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin. For cisplatin, emesis reaches its maximal intensity 48 to 72 hours after chemotherapy and can last 6 to 7 days.

Anticipatory nausea and/or vomiting is the occurrence of nausea and/or vomiting before patients receive their next chemotherapy treatment. Because it is a conditioned response, anticipatory emesis can occur only after a negative past experience with chemotherapy. The incidence of anticipatory nausea and/or vomiting ranges from 18% to 57%, and nausea is more common than vomiting.^{18,19} Younger patients may be more susceptible to anticipatory nausea and vomiting, because they generally receive more aggressive chemotherapy and, overall, have poorer emesis control than older patients.²⁰ *Breakthrough* emesis refers to vomiting that occurs despite prophylactic treatment and/or requires "rescue." *Refractory* emesis refers to emesis that occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles.

Radiation-Induced Nausea and/or Vomiting

Patients receiving whole body or upper abdominal radiation therapy have the greatest likelihood of developing nausea and/or vomiting.²¹ The GI tract (specifically, the small intestine) contains rapidly dividing cells that are particularly sensitive to radiation. In addition, the potential

for nausea and vomiting increases with larger daily fractional doses of radiotherapy, larger total doses, and larger amounts of irradiated tissue. Total body irradiation, when given before bone marrow transplantation, also commonly induces nausea and/or vomiting.^{22,23}

Emetogenicity of Chemotherapy

The frequency of chemotherapy-induced emesis depends primarily on the emetogenic potential of the specific chemotherapeutic agents used. Several classifications have been developed to define the emetogenicity of chemotherapy; however, none has been universally accepted.^{1,2,4-27}

Hesketh and colleagues developed a classification of the acute emetogenicity of anticancer chemotherapeutic agents and developed an algorithm to define the emetogenicity of combination chemotherapeutic regimens.²⁸ The classification was updated by Grunberg and colleagues and divides chemotherapeutic agents into 4 levels according to the percentage of patients not receiving antiemetic prophylaxis who experience acute emesis.²⁹ This classification, which has been updated with recently introduced drugs, is used in these NCCN practice guidelines. Panel members from all of the published antiemetic treatment guidelines met to prepare a single consensus document. Although this process is ongoing, the consensus guidelines have been published.³⁰ NCCN guidelines currently outline treatment using 4 categories of emetogenic potential (see [AE-6](#) and [AE-7](#)), which correspond to the Grunberg classification as follows:

- High emetic risk—90% or more of patients experience acute emesis
- Moderate emetic risk—30% to 90% of patients experience acute emesis
- Low emetic risk—10% to 30% of patients experience acute emesis
- Minimal emetic risk—fewer than 10% of patients experience acute emesis.

In addition, the NCCN guidelines attempt to define antiemetic regimens for particular chemotherapy drugs that cover the entire duration of time a patient is at risk for nausea and vomiting. Panel members were concerned that some patients may not receive adequate prophylaxis for delayed emesis; therefore, the algorithms were revised for high and moderate emetogenic potential agents to incorporate a dosing schedule that covers both acute and delayed emesis into a single algorithm.

Types of Antiemetic Therapies

In general, to provide maximal protection against chemotherapy-induced emesis, antiemetic therapy should be initiated before chemotherapy. The antiemetic therapy should also be continued for the same length of time as the duration of the emetic activity of the chemotherapeutic agent being used. However, daily use of antiemetics is not recommended for some therapeutic agents that are taken long term (eg, imatinib, bortezomib, trastuzumab) (see [AE-6](#)). Antiemetic agents can be administered by the oral, rectal, intravenous (IV), or intramuscular route. When compared with other routes of administration, oral formulations of antiemetic agents are equally effective, safe, more convenient, and less costly. For patients unable to swallow or digest tablets because of emesis, IV antiemetics are required. Although studies may show drugs to be equally effective on a population basis, individual patients may respond differently. Therefore, some drug options may be based on a patient's individual experience.

Serotonin (5-HT₃) Receptor Antagonists

The development of the 5-HT₃-receptor antagonists (such as ondansetron, granisetron, dolasetron mesylate, palonosetron) represents a significant advance in antiemetic therapy.^{3,1-33} All of these agents have been shown to be effective in controlling the acute nausea and/or vomiting associated with cancer chemotherapy.^{3,3-47}

Palonosetron is a 5-HT₃ antagonist with an approximately 100-fold higher binding affinity for the 5-HT₃ receptor compared to the other serotonin antagonists (ie, ondansetron, granisetron, and dolasetron). It has a half-life of approximately 40 hours, which is significantly longer than other commercially available 5-HT₃ antagonists.³³ Initial studies in patients receiving moderately emetogenic chemotherapy showed that a single IV dose of palonosetron was comparable to a single IV dose of dolasetron for the prevention of acute chemotherapy-induced nausea and emesis; however, palonosetron was superior to dolasetron in preventing delayed emesis.⁴⁸ The safety and side-effect profiles of palonosetron were indistinguishable from the control 5-HT₃ antagonists (ondansetron and dolasetron) using data submitted to the FDA. Palonosetron is administered intravenously and is FDA approved as a single dose of 0.25 mg IV over 30 seconds on day 1; it is recommended (category 1) for acute and delayed emesis prevention when using moderate emetic risk chemotherapy.⁴⁸ Palonosetron is superior to other 5-HT₃ antagonists for preventing delayed nausea. However, repeat dosing of palonosetron in the days after chemotherapy (ie, days 2 or 3) is not supported by the scientific literature. Repeat dosing of palonosetron in the setting of multiday chemotherapy regimens has not been studied.

Many clinical trials directly comparing ondansetron, granisetron, dolasetron mesylate, and palonosetron have been conducted. These trials have used various doses, routes, and schedules of administration.⁴⁸⁻⁶⁸ Studies have demonstrated that the 5-HT₃ antagonists are equally effective and have mild, infrequent side effects. A recent meta-analysis found no difference in efficacy, except that granisetron may be more efficacious than tropisetron during the first 24 hours.⁶⁹ The addition of dexamethasone improves the efficacy of the antiemetic regimen containing 5-HT₃ antagonists. Ondansetron, granisetron, and dolasetron are effective in preventing acute emesis but appear to be less effective for delayed emesis. However, palonosetron

is effective for preventing both delayed and acute emesis. A meta-analysis of randomized controlled trials found that adding a 5-HT3 antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis.⁷⁰ Another recent study found that 5-HT3 antagonists (except palonosetron, which was not studied) were not more effective than prochlorperazine for preventing delayed emesis.¹¹

NK-1–Receptor Antagonist

In March 2003, the Food and Drug Administration (FDA) approved aprepitant (oral), which selectively blocks the binding of substance P at the NK-1 receptor in the central nervous system. Thus, aprepitant provides a different and complementary mechanism of action to all other commercially available antiemetics. Aprepitant has been shown to augment the antiemetic activity of the 5-HT3–receptor antagonists and the corticosteroid dexamethasone to inhibit both acute and delayed cisplatin-induced emesis.

When combined with 5-HT3 antagonists and dexamethasone on day 1 before cisplatin-based highly emetogenic chemotherapy and continued orally along with dexamethasone on days 2 and 3 after chemotherapy, aprepitant significantly improved control of acute and delayed chemotherapy-induced nausea and emesis.^{71,72} The oral doses of aprepitant are 125 mg on day 1 (before chemotherapy) and then 80 mg on days 2 and 3 (after chemotherapy).⁷³ There are no studies showing efficacy or safety of chronic dosing with aprepitant. It is possible that the drug-drug interaction profile may change with chronic dosing. An IV version of aprepitant (fosaprepitant dimeglumine), which can be given on day 1 only, has been approved by the FDA (<http://www.fda.gov/cder/foi/label/2008/022023lbl.pdf>).

A phase III study (866 patients) showed that an aprepitant regimen is better than a standard regimen for preventing vomiting in patients

receiving moderately emetogenic chemotherapy (non-cisplatin based) during 120 hours after initiation of chemotherapy (complete response, 50.8% versus 42.5%, $P=0.015$); however, 40% of patients (receiving either regimen) still had significant nausea.^{74,75} The aprepitant regimen included aprepitant, ondansetron, and dexamethasone; the standard regimen included ondansetron and dexamethasone. An analysis of 2 phase III randomized trials found that an aprepitant regimen is useful for patients receiving moderately emetogenic chemotherapy plus high-dose cisplatin.⁷⁶ The FDA has approved the use of aprepitant for preventing emesis in patients receiving moderately emetogenic chemotherapy. A meta-analysis (7 randomized controlled trials) in patients receiving highly emetogenic chemotherapy found that NK-1 receptor antagonists used alone or with standard therapy for acute emesis were not better than the control; however, for delayed emesis, NK-1 receptor antagonists were better than the control.⁷⁷ A recent phase II study (58 patients) found that combining palonosetron, aprepitant, and dexamethasone was useful for various chemotherapeutic regimens (moderate to moderate-highly emetogenic); 78% of patients had a complete response (no emetic episodes and no rescue medication).⁷⁸

Drug Interactions

Aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4); aprepitant also induces CYP2C9.⁷⁹ Thus, aprepitant can alter the metabolism of certain drugs and change their plasma concentrations (ie, AUCs [area under the curve]). These interactions are more significant with orally administered forms of these drugs than with IV forms because of first-pass metabolism. Patients should not take aprepitant with pimozide, terfenadine, astemizole, or cisapride; these combinations are contraindicated, because they may cause "serious or life-threatening reactions" (see the aprepitant package insert <http://www.fda.gov/cder/foi/label/2007/021549s012lbl.pdf>).

Chemotherapeutic agents known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical trials, aprepitant was used concurrently with etoposide, vinorelbine, or paclitaxel; although chemotherapy doses were not adjusted for potential drug interactions in phase III trials, caution is urged when using any chemotherapeutic agent that is metabolized by CYP3A4.

Aprepitant has been shown to interact with several nonchemotherapeutic drugs (including warfarin, dexamethasone, methylprednisolone, oral contraceptives). These interactions are more significant with orally administered forms of these drugs than with IV forms because of first-pass metabolism.

Induction of warfarin metabolism by aprepitant may lead to clinically significant reductions in INR (international normalized ratio) values, particularly for patients on therapeutic (as compared to prophylactic) warfarin regimens. These changes, although brief in duration, may require increased patient monitoring (<http://www.fda.gov/cder/foi/label/2007/021549s012bl.pdf>).

When given with aprepitant, the AUC of dexamethasone is increased; thus, the NCCN guidelines include reduced dose recommendations for dexamethasone in this setting. The AUC of methylprednisolone is also increased when given with aprepitant; thus, the methylprednisolone dose should also be decreased in this setting. However, if dexamethasone (or prednisone or any corticosteroid) is being administered as part of anticancer therapy (eg, CHOP regimen), the corticosteroid dose should not be reduced.²³

Aprepitant decreases the AUC for patients taking oral contraceptives; the package insert should be consulted in this setting.

Certain drugs can affect the AUCs of aprepitant. Concomitant administration with CYP3A4 inhibitors (eg, ketoconazole, itraconazole, erythromycin) may lead to increased aprepitant AUCs, whereas concomitant administration with CYP3A4 inducers (eg, carbamazepine, rifampin, phenytoin) may lead to decreased levels of aprepitant.

Other Non-5-HT₃-Receptor Antagonist Antiemetics

Before the advent of the 5-HT₃-receptor antagonists, the available antiemetic agents included phenothiazines,⁸⁰ substituted benzamides,^{81,82} antihistamines,⁸³ butyrophenones,⁸⁴ corticosteroids,⁸⁵⁻⁸⁷ benzodiazepines,^{88,89} and cannabinoids.^{90,91} Most drugs used to prevent chemotherapy-induced emesis are classified as dopamine antagonists, serotonin antagonists, and other antagonists. Combination antiemetic therapy is more effective than single-agent therapy. Olanzapine (thiobenzodiazepine) was found to be effective for acute and delayed emesis in a phase II trial in patients (n = 30) who received cyclophosphamide, doxorubicin, and/or cisplatin,^{92,93} other studies have also showed the value of olanzapine for delayed and refractory emesis as well as nausea.⁹⁴⁻⁹⁷ However, olanzapine should be used with caution in elderly patients (see boxed warning/label indication regarding type II diabetes and hyperglycemia (http://www.fda.gov/cder/foi/label/2007/020592s042s043_021086s022s023_021253s026bl.pdf)).⁹⁸

Treatment Issues

Selected issues that arose in the panel's deliberations on the guidelines are discussed in the following sections. As new data about the use of antiemetics in patients receiving chemotherapy become available, clinicians should consider these data when caring for such patients, even if the information has not been included in the guidelines. In contrast to other NCCN guidelines in which most of the recommendations are category 2A, many of the recommendations for antiemetic management are classified as category 1, reflecting the

large number of randomized controlled trials that have focused on antiemetic management.

Principles of Emesis Control

These principles are discussed in the algorithm (see [AE-1](#)).

- The goal is to prevent nausea and/or vomiting.
- The risk of emesis and nausea lasts for at least 4 days for persons receiving chemotherapy of high and moderate emetogenic potential. Patients need to be protected throughout the full period of risk.
- Oral and IV antiemetic formulations have equivalent efficacy.
- The toxicity of the specific antiemetic(s) should be considered.
- Antiemetic regimens should be chosen based on the emetogenic potential of the chemotherapy regimen, previous experience with antiemetics, and patient-specific risk factors.

In addition to emesis induced by chemotherapy, emesis in cancer patients can also potentially be caused by:

- Partial or complete bowel obstruction
- Vestibular dysfunction
- Brain metastases
- Electrolyte imbalance: hypercalcemia, hyperglycemia, hyponatremia
- Uremia
- Concomitant drug treatments, including opiates
- Gastroparesis induced by a tumor or chemotherapy (such as vincristine).
- Psychophysiological factors, including anxiety as well as anticipatory nausea and vomiting.

- For use of antiemetics for nausea and vomiting that is not related to radiation and/or chemotherapy, see the [NCCN Palliative Care Guidelines](#).

Prevention of Acute Emesis

To prevent acute emesis, antiemetic therapy should start before the administration of chemotherapy and then should cover the first 24 hours. For highly emetogenic drugs, the regimens are described on [AE-2](#). For moderately emetogenic drugs, the regimens are described on [AE-3](#). For low and minimally emetogenic drugs, the regimens are described on [AE-4](#). This section discusses prechemotherapy and postchemotherapy emesis prevention rather than primary treatment.

Prechemotherapy Emesis Prevention

The guidelines specify different primary antiemetic regimens for cancer patients receiving chemotherapy of different emetogenic potential (ie, high, moderate, low, minimal). Prophylactic antiemetics should be administered before chemotherapy. The recommendations for primary antiemetic treatment include drug dosages. The guidelines reflect accumulating experience with the 5-HT₃-serotonin antagonists, demonstrating their effectiveness in a range of doses. Unless indicated, the order of listed antiemetics in the algorithm does not reflect preference.

Highly emetogenic drugs include altretamine, carmustine > 250 mg/m², cisplatin at 50 mg/m² or more, cyclophosphamide > 1500 mg/m², dacarbazine, mechlorethamine, procarbazine (oral), streptozocin, or anthracycline and cyclophosphamide (AC) combinations (doxorubicin or epirubicin with cyclophosphamide). The antiemetic regimen for these highly emetogenic drugs on day 1 includes aprepitant, dexamethasone, and a 5-HT₃ antagonist with or without lorazepam (category 1 for the combined regimen [see [AE-2](#)]).^{7,123,99} note that the regimen and doses are often modified on days 2 to 4 after chemotherapy.

A Canadian meta-analysis suggests that it is not cost-effective to use 5-HT₃ antagonists (ie, ondansetron) on days 2 to 4 to prevent delayed emesis; however, ondansetron (when used alone) did protect against

delayed emesis in this meta-analysis.¹⁰⁰ Palonosetron was not assessed in these studies. The NCCN panel recommends the use of 5-HT3 antagonists as one of several options to prevent delayed emesis for moderately emetogenic agents (see [AE-3](#)).

The antiemetic regimen for moderately emetogenic drugs (see [AE-6](#)) on day 1 includes dexamethasone and a 5-HT3 antagonist with or without lorazepam; aprepitant should be added for patients receiving the combination of an anthracycline and cyclophosphamide and for select patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate) (see [AE-3](#)).^{23,75} Any one of the 5-HT3 antagonists can be used, because they are all category 1. Note that the regimens differ on days 2 to 3. There are 3 possible regimens on days 2-3 (lorazepam can be added to each of these regimens) including: 1) aprepitant with or without dexamethasone; 2) dexamethasone; or 3) 5-HT3 antagonist, such as ondansetron, granisetron, or dolasetron.

The antiemetic regimen for low emetogenic drugs (see [AE-7](#)) includes non-5-HT3 antagonists, such as dexamethasone, prochlorperazine, or metoclopramide, with or without lorazepam (see [AE-4](#)). When using prochlorperazine, patients should be monitored for dystonic reactions; diphenhydramine can be used for dystonic reaction.

For regimens with high emetogenic potential, aprepitant is used at a oral dosage of 125 mg on day 1 and then 80 mg on days 2 and 3 (see [AE-2](#)). When given with aprepitant, dexamethasone is used at a dosage of 12 mg on day 1 and then 8 mg on days 2 to 4; the dose can be oral or IV. Because aprepitant increases dexamethasone levels, it is necessary to reduce the dose of dexamethasone when using it as an antiemetic with aprepitant.^{71,101} However, if dexamethasone (or any corticosteroid) is being administered as part of anticancer therapy, the corticosteroid dose should not be reduced.²³ All four 5-HT3-receptor antagonists (ie, ondansetron, granisetron, dolasetron, palonosetron)

are considered to have similar effectiveness for control of acute emesis. If appropriate, lorazepam (0.5-2 mg either every 4 or every 6 hours on days 1-4; either oral, IV, or sublingual) may be used with each of these regimens (ie, high, moderate, or low).

Postchemotherapy/Delayed Emesis Prevention

The best management for delayed emesis is prevention. For chemotherapy involving agents with high emetogenic potential, the primary treatment is continued through the period when delayed emesis may occur. Using this strategy, prophylaxis continues for 2 to 3 days after completion of a chemotherapy cycle.

For drugs with moderate emetogenic potential, postchemotherapy prevention depends on what antiemetics were used before chemotherapy. For example, palonosetron (category 1) is only administered on day 1 (see [AE-3](#)).⁴⁹ If aprepitant was used on day 1, then it is continued on days 2 and 3 and is given with or without dexamethasone or lorazepam. Alternatively, either dexamethasone, or a 5-HT3 antagonist can be used; lorazepam may be used with either agent.

Breakthrough Treatment

Breakthrough emesis presents a difficult situation, because refractory ongoing nausea and/or vomiting is often challenging to reverse (see [AE-8](#)). Generally, it is much easier to prevent nausea and/or vomiting than to treat it. Thus, routine around-the-clock administration of antiemetics should be strongly considered to prevent emesis, rather than PRN (as required) dosing. The general principle of breakthrough treatment is to give an additional agent as needed from a different drug class. However, no one treatment is better than another for managing breakthrough emesis. The oral route is not likely to be feasible because of ongoing vomiting; therefore, rectal or IV therapy is often required. Multiple concurrent agents, perhaps in alternating schedules or by

alternating routes, may be necessary. Dopamine antagonists (for example, metoclopramide), haloperidol, corticosteroids, and agents such as lorazepam may be required. Nabilone (cannabinoid) is approved by the FDA for nausea and vomiting in patients who have not responded to conventional antiemetic agents. Adequate hydration or fluid repletion should be ensured, and any possible electrolyte abnormalities should be assessed and corrected. Before administering the next cycle of chemotherapy, the patient should be reassessed with attention to various possible nonchemotherapy-related reasons for breakthrough emesis with the current cycle, such as brain metastases, electrolyte abnormalities, tumor infiltration of the bowel or other GI abnormality, and other comorbidities (see [AE-1](#)). In addition, before the next cycle of chemotherapy, the antiemetic regimen (both the day 1 and postchemotherapeutic) that did not protect the patient during the present cycle should be assessed and alternatives should be considered (see [AE-B](#)). Consider using antacid therapy (eg, proton pump inhibitors, H2 blockers) if patients have dyspepsia, because patients sometimes have difficulty discriminating heartburn from nausea.

Radiation-Induced Nausea and/or Vomiting

Primary prophylaxis for radiation-induced nausea and/or vomiting is based on the site of radiation and whether it is combined with chemotherapy (see [AE-3](#)). When radiation is combined with chemotherapy, prophylaxis is dictated by the emetogenic potential of the chemotherapy regimen.

Radiation to the upper abdomen may be treated with oral ondansetron (8 mg 2 to 3 times daily), with or without oral dexamethasone, based on the results of a randomized study comparing oral ondansetron with placebo in patients receiving daily fractionated radiotherapy including the abdomen. In this study, 67% of patients given ondansetron had complete control of emesis compared with 45% of patients who

received placebo.¹⁰² A recent study showed that the addition of oral dexamethasone (4 mg daily) to the ondansetron regimen decreases emesis and nausea, although the effect is modest.¹⁰³ Other options are oral dexamethasone (2 mg 3 times daily) or oral granisetron (2 mg every day).

Total body irradiation may be treated with either ondansetron (8 mg 2 to 3 times daily) or granisetron; either agent can be given with or without oral dexamethasone (2 mg 3 times daily).¹⁰³ The dose of granisetron is either 2 mg oral every day or 3 mg IV every day.^{104,105} (category 2B recommendation, because this dose of granisetron is higher than the dose typically used). No primary treatment is recommended for patients receiving irradiation to other sites.

Treatment of breakthrough radiation-induced emesis is similar to chemotherapy-induced emesis. Patients who do not receive primary prophylaxis and experience breakthrough nausea and/or vomiting may be treated with ondansetron, similar to primary prophylaxis.

Anticipatory Nausea and/or Vomiting

The most effective way to treat anticipatory nausea and/or vomiting is to prevent it by using optimal antiemetic therapy during every cycle of treatment (see [AE-9](#)). Behavioral therapy has been used in patients with anticipatory nausea and/or vomiting.¹⁰⁶⁻¹⁰⁸ Systematic desensitization may also be helpful.¹⁰⁷ Hypnosis with guided imagery is another behavioral technique that has shown some success in treating this condition.¹⁰⁸ The anti-anxiety agents lorazepam and alprazolam have both been combined with antiemetics for anticipatory nausea and/or vomiting with mixed results.¹⁰⁹ The usual starting dose of alprazolam is 0.25 to 0.5 mg orally 3 times daily, beginning on the night before treatment. In elderly patients, patients with debilitating disease, and patients with advanced liver disease, the usual starting dose of alprazolam is 0.25 mg orally 2 or 3 times daily for treatment of anxiety

(<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5816#hl34068-7>). This dose may be gradually increased if needed. Note that the elderly are especially sensitive to the effects of benzodiazepines. The dose should be gradually reduced when decreasing or discontinuing alprazolam therapy.

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Managing Multiday Emetogenic Chemotherapy Regimens

Patients receiving multiday chemotherapy are at risk for both acute and delayed nausea as well as emesis based on the emetogenic potential of the individual chemotherapy agents and their sequence. It is difficult to recommend a specific antiemetic regimen for each day, especially because acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy. The period of risk for delayed emesis after chemotherapy administration has concluded also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen. General principles for managing multiday emetogenic chemotherapy regimens recommended (category 2B) by the panel are described in the algorithm (see [AE-A](#)).

Disclosures for the NCCN Antiemesis Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support, for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Academy for Healthcare Education; Amgen Inc.; Bristol-Myers Squibb; CytoGen; Educational Concepts Group; Eli Lilly and Company; Genentech; GlaxoSmithKline; Hoffman La Roche; INCE-Interactive Network for Continuing Education; Ligand; Merck & Co.; MGI PHARMA, INC.; MK Medical Communications; Novartis; Ortho Biotech Products; Pfizer;

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APPENDIX O – NCCN FATIGUE



NCCN Clinical Practice Guidelines in Oncology™

Cancer-Related Fatigue

V.4.2007

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- | | | |
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 ◌ Urology
 £ Supportive care including palliative, pain management,
 pastoral care and oncology social work
 ‡ Hematology/Hematology oncology
 § Bone marrow transplantation
 P Internal medicine
 * Writing Committee Member

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nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Consensus](#)

[Summary of Guidelines Updates](#)

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

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Summary of the Guidelines Updates

The change in the 4.2007 version of the Cancer-Related Fatigue Guidelines from the 3.2007 version is the addition of several new references in the manuscript. The panel also deleted the anemia portion of the manuscript (Guidelines and supporting text regarding anemia can be found in the [NCCN Cancer and Treatment-Related Anemia Guidelines](#)).

The change in the 3.2007 version of the Cancer-Related Fatigue Guidelines from the 2.2007 version is the addition of new references throughout the manuscript.

The change in the 2.2007 version of the Cancer-Related Fatigue Guidelines from the 1.2007 version is the addition of the updated manuscript representing the changes to the algorithm.

Summary of major changes in the 2007 version of the Cancer-Related Fatigue guidelines from the 1.2006 version include:

- Replaced “Pediatric” with “Children/Adolescents” in title of page [\(T-2\)](#).
- Screening, Far Left: To clarify the severity scale, “None” was included before “mild, moderate, severe” [\(T-3\)](#).
- Footnote “b”: Replaced the phrase “Pediatric” with “Children” [\(T-3\)](#).
- Assessment of treatable contributing factors: “hypogonadism” and “adrenal insufficiency” were added as examples of endocrine dysfunction [\(T-4\)](#).
- Specific Interventions [\(T-5\)](#), [\(T-6\)](#), [\(T-7\)](#):
 - ▶ Non-pharmacologic
 - ◊ Under sleep therapy, “Consider sleep hygiene and/or sleep medication” was changed to “Optimize sleep quality.”
 - ▶ Pharmacologic
 - ◊ Consider sleep medication was added as an option.

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UPDATES

DEFINITION OF CANCER-RELATED FATIGUE

Cancer-related fatigue is a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.

Note: All recommendations are category 2A unless otherwise indicated.
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FT-1

Cancer-Related Fatigue

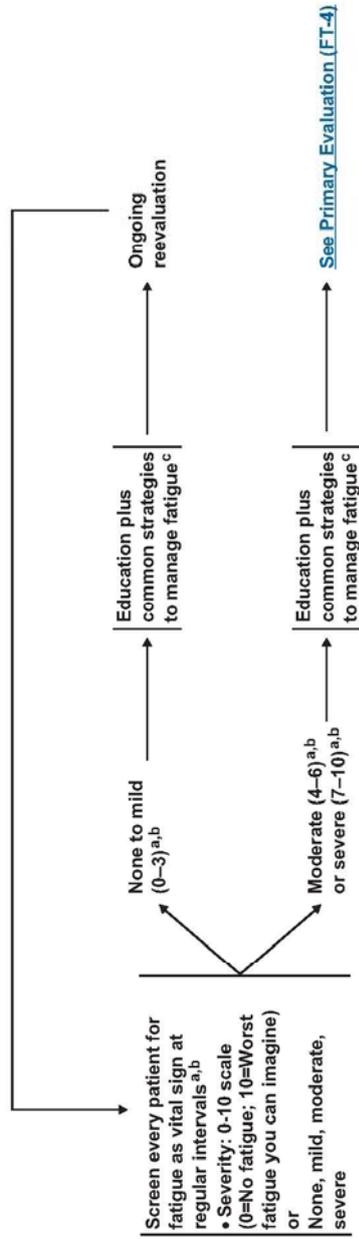
STANDARDS OF CARE IN CHILDREN/ADOLESCENTS AND ADULT CANCER-RELATED FATIGUE MANAGEMENT

- Fatigue is a subjective experience that should be systematically assessed using patient self-reports and other sources of data.
- Fatigue should be screened, assessed, and managed according to clinical practice guidelines.
- All patients should be screened for fatigue at their initial visit, at regular intervals during and following cancer treatment, and as clinically indicated.
- Fatigue should be recognized, evaluated, monitored, documented, and treated promptly for all age groups, at all stages of disease, during and following treatment.
- Patients and families should be informed that management of fatigue is an integral part of total health care.
- Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner.
- Implementation of guidelines for fatigue management is best accomplished by interdisciplinary committees.
- Educational and training programs should be implemented to ensure that health care professionals have knowledge and skills in the assessment and management of fatigue.
- Cancer-related fatigue should be included in clinical health outcome studies.
- Quality of fatigue management should be included in institutional continuous quality improvement (CQI) projects.
- Medical care contracts should include reimbursement for the management of fatigue.
- Disability insurance should include coverage for the continuing effects of fatigue.
- Rehabilitation should begin with the cancer diagnosis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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SCREENING



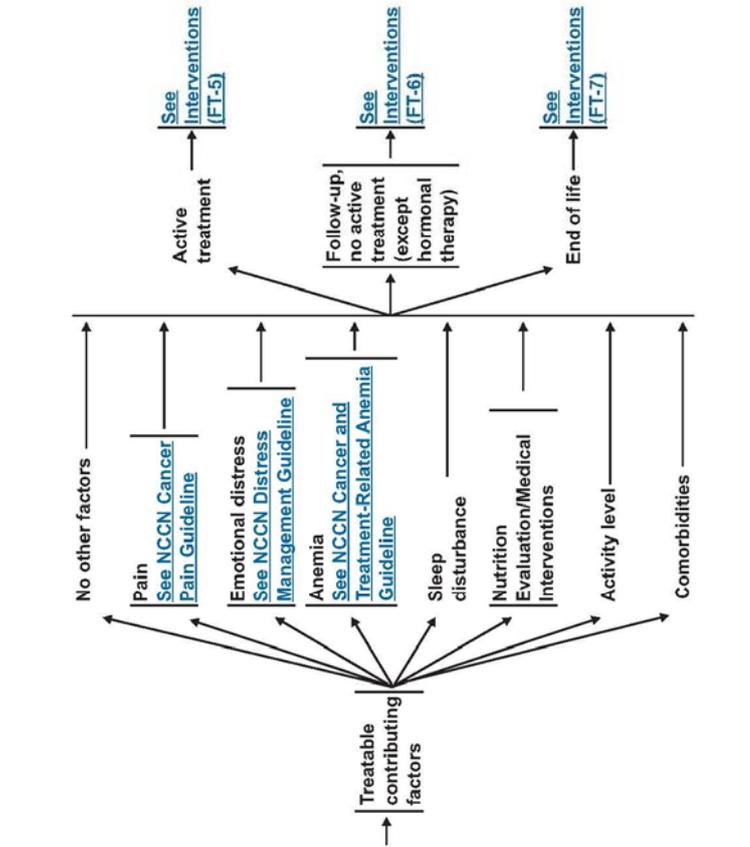
^a Recommended screen: "How would you rate your fatigue on a scale of 0-10 over the past 7 days?"
^b Fatigue scale for children is simplified: Use "tired" or "not tired" as screen for young children (age < 6 or 7 y).
^c See "Patient/Family Education and Counseling" and "General Strategies for Management of Fatigue" based on clinical status: [Active Treatment \(FT-5\)](#), [Long Term Follow-up \(FT-6\)](#), [End of Life \(FT-7\)](#).
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Cancer-Related Fatigue

PRIMARY EVALUATION FATIGUE SCORE: 4-10 (MODERATE OR SEVERE)

- Focused history**
- Disease status and treatment
 - Rule out recurrence or progression
 - Current medications/medication changes
 - Review of systems
 - In-depth fatigue assessment
 - Onset, pattern, duration
 - Change over time
 - Associated or alleviating factors
 - Interference with function
 - Assessment of treatable contributing factors:
 - Pain
 - Emotional distress
 - Depression
 - Anxiety
 - Sleep disturbance
 - Anemia
 - Nutrition Assessment
 - Weight/caloric intake changes
 - Fluid electrolyte imbalance: sodium, potassium, calcium, magnesium
 - Activity level
 - Decreased activity
 - Decreased physical fitness
 - Comorbidities
 - Infection
 - Cardiac dysfunction
 - Pulmonary dysfunction
 - Renal dysfunction
 - Hepatic dysfunction
 - Neurologic dysfunction
 - Endocrine dysfunction (hypothyroidism, hypogonadism, adrenal insufficiency)

PATIENT CLINICAL STATUS



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

INTERVENTIONS FOR PATIENTS ON ACTIVE TREATMENT

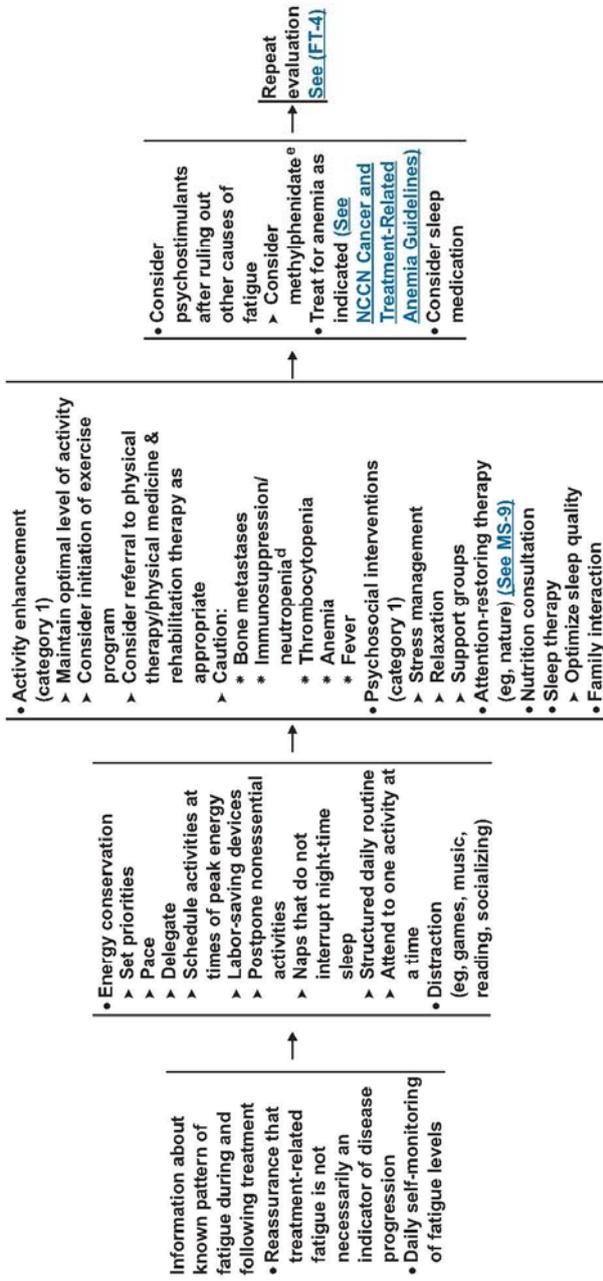
SPECIFIC INTERVENTIONS

Nonpharmacologic

Pharmacologic

General Strategies for Management of Fatigue

Pharmacologic



^dConcern is with environment. Limit activity to environments where risk of infection is low.
^eOptimal dosing and schedule have not been established for cancer patients. Use caution and consider possible drug interactions for patients on active therapy.
 Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

INTERVENTIONS FOR PATIENTS ON LONG-TERM FOLLOW-UP

SPECIFIC INTERVENTIONS

General Strategies for Management of Fatigue

Nonpharmacologic

Pharmacologic

- Energy conservation
 - ▶ Set priorities
 - ▶ Pace
 - ▶ Delegate
 - ▶ Schedule activities at times of peak energy
 - ▶ Labor-saving devices
 - ▶ Postpone nonessential activities
 - ▶ Naps that do not interrupt night-time sleep
 - ▶ Structured daily routine
 - ▶ Attend to one activity at a time
- Distraction (eg, games, music, reading, socializing)

Information about known pattern of fatigue during and following treatment

- Regular self-monitoring of fatigue levels

- Activity enhancement (category 1)
 - ▶ Maintain optimal level of activity
 - ▶ Consider initiation of exercise program
 - ▶ Consider referral to physical therapy/physical medicine & rehabilitation therapy as appropriate
 - ▶ Caution:
 - * Late effects of treatment (eg, cardiomyopathy)
- Psychosocial interventions (category 1)
 - ▶ Stress management
 - ▶ Relaxation
 - ▶ Support groups
 - ▶ Attention-restoring therapy (eg, nature) (See MS-9)
 - ▶ Nutrition consultation
 - ▶ Sleep therapy
 - ▶ Optimize sleep quality
 - ▶ Family interaction

- Consider psychostimulants after ruling out other causes of fatigue
 - ▶ Consider methylphenidate^e
 - ▶ Treat for anemia as indicated (See NCCN Cancer and Treatment-Related Anemia Guidelines)
 - ▶ Consider sleep medication

Repeat evaluation
See (FT-4)

^eOptimal dosing and schedule have not been established for cancer patients. Use caution and consider possible drug interactions for patients on active therapy.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

INTERVENTIONS FOR PATIENTS AT THE END OF LIFE^f

SPECIFIC INTERVENTIONS

Patient/Family Education and Counseling

General Strategies for Management of Fatigue

Nonpharmacologic^f

Pharmacologic

- Energy conservation
- ▶ Set priorities
- ▶ Pace
- ▶ Delegate
- ▶ Schedule activities at times of peak energy
- ▶ Labor-saving and assistive devices
- ▶ Eliminate nonessential activities
- ▶ Naps that do not interrupt night-time sleep
- ▶ Structured daily routine
- ▶ Attend to one activity at a time
- ▶ Conserve energy for valued activities
- Distraction (eg, games, music, reading, socializing)

Information about known pattern of fatigue during and following treatment

- Expected end-of-life symptom
- May vary in intensity

- Activity enhancement
- ▶ Optimize level of activity
- ▶ Consider referral to physical therapy/physical medicine & rehabilitation therapy as appropriate
- ▶ Caution:
 - * Bone metastases
 - * Immunosuppression/neutropenia^d
 - * Thrombocytopenia
 - * Anemia
 - * Fever
- Psychosocial interventions (category 1)
 - ▶ Stress management
 - ▶ Relaxation
 - ▶ Support groups
 - ▶ Attention restoring therapy (eg, nature) [\(See MS-9\)](#)
 - ▶ Nutrition consultation
 - ▶ Sleep therapy
 - ▶ Optimize sleep quality
 - ▶ Family interaction

- Consider psychostimulants after ruling out other causes of fatigue
 - ▶ Consider methylphenidate^e
 - Treat for anemia as indicated [\(See NCCN Cancer and Treatment-Related Anemia Guidelines\)](#)
 - Consider sleep medication
- Repeat evaluation [\(See FT-4\)](#)

^dConcern is with environment. Limit activity to environments where risk of infection is low.
^eOptimal dosing and schedule have not been established for cancer patients. Use caution and consider possible drug interactions for patients on active therapy.
^fAlso see [NCCN Palliative Care Guidelines](#).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

pain or nausea and vomiting, which, for most patients, can generally be managed by medications.^{24,25}

Fatigue in cancer patients has been under-reported, under-diagnosed, and under-treated. Persistent cancer-related fatigue affects quality of life (QOL), as cancer patients become too tired to participate fully in the roles and activities that make life meaningful.^{15,26-28} Health care professionals have been challenged in their efforts to help patients manage this distressful symptom and to remain as fully engaged in life as possible. Because of the successes in cancer treatment, health care professionals are now likely to see patients with prolonged states of fatigue related to the late effects of treatment. Disability-related issues are relevant and often challenging, especially for cancer patients who are cured of their malignancy but have continued fatigue. Despite biomedical literature documenting this entity, it is often difficult for patients with cancer-related fatigue to obtain or retain disability benefits from insurers. Health care professionals should advocate for patients who require disability benefits and educate insurers about this issue.

Overview

Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.¹⁻¹⁰ The problem, which affects 70% to 100% of cancer patients, has been exacerbated by the increased use of fatigue-inducing multimodal treatments and dose-dense, dose-intense protocols.¹¹ In patients with metastatic disease, the prevalence of cancer-related fatigue exceeds 75%, and cancer survivors report that fatigue is a disruptive symptom months or even years after treatment ends.¹²⁻²¹ The distinction between tiredness, fatigue, and exhaustion has not been made consistently, despite conceptual differences.^{22,23} Patients perceive fatigue to be the most distressing symptom associated with cancer and its treatment, more distressing even than

Despite the prevalence of cancer-related fatigue, the exact mechanisms involved in its pathophysiology are unknown. Proposed mechanisms include abnormal accumulation of muscle metabolites, production of cytokines, changes in neuromuscular function, abnormalities in adenosine triphosphate (ATP) synthesis, serotonin dysregulation, and vagal afferent activation.³² Limited evidence supports these proposed mechanisms, and much of the research to date has focused on correlates of fatigue.

To address the important problem of cancer-related fatigue, the NCCN convened a panel of experts. The NCCN Cancer-Related Fatigue Guideline, first published in 2000³³ and updated annually (see www.nccn.org),³⁴ synthesizes the available research and clinical experience in this field as well as provides recommendations for patient care.

Defining Cancer-Related Fatigue

The panel defines cancer-related fatigue as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Compared with the fatigue experienced by healthy individuals, cancer-related fatigue is more severe, more distressing,^{1,2,35} and less likely to be relieved by rest.³⁶ In terms of the defining characteristics, it is important to note the subjective sense of tiredness reported by the patient. As with pain, the clinician must rely on patients' descriptions of their fatigue and accompanying distress. Fatigue that interferes with usual functioning is another substantial component of the definition for cancer-related fatigue and the source of much distress for patients.^{8,37,38} Investigations have documented a significant effect of fatigue on physical functioning during cancer treatment, and it is uncertain whether patients regain full functioning when treatment is over.^{39,40}

Standards of Care for Assessment and Management

The panel developed Standards of Care for Cancer-Related Fatigue Management (see [FI-2](#)), using the [NCCN Cancer Pain Guideline](#) and the [NCCN Distress Management Guideline](#) as exemplar models. These fatigue standards represent the best level of care for the assessment and management of fatigue in cancer patients, including children, adolescents and adults, and should provide guidance for health care professionals as they implement the guideline in their respective institutions and clinical settings. The overall goal of the standards and guideline is to ensure that all cancer patients with fatigue are identified as well as treated promptly and effectively.

The first standard recognizes fatigue as a subjective experience that should be systematically assessed using patient self-reports and other sources of data. Because it is a symptom that is perceived by the patient, fatigue can be described most accurately by self-report. The

history and physical examination, laboratory data, and descriptions of patient behavior by family members, especially in children, are important sources of additional information.

Fatigue should be screened, assessed, and managed for most patients according to clinical practice guideline. This guideline provides "best care" information based on current evidence to support treatment.⁴¹ Patients should be screened for fatigue at their initial clinical visit, at appropriate intervals during and/or following cancer treatment, and as clinically indicated. Screening should identify the presence and severity of fatigue. Patients may be hesitant to initiate a discussion of their fatigue, so the responsibility for initiating screening must reside with the members of the primary oncology team.

Fatigue should be recognized, evaluated, monitored, documented, and treated promptly for all age groups at all stages of the disease, both during and after treatment. Implementation of this standard will ensure that fatigue is not overlooked or untreated in any patients.

Patients and families should be informed that managing fatigue is an integral part of total health care. All patients should receive symptom management. Furthermore, if patients cannot tolerate their cancer treatment or if they must choose between treatment and QOL, control of their disease may be diminished.⁴²

Health care professionals experienced in fatigue evaluation and management should be available for consultation in a timely manner. Implementation of the guideline for fatigue is best managed by an interdisciplinary institutional committee, including medicine, nursing, social work, physical therapy, and nutrition.⁴³ The panel recognizes that education and training programs are needed to prepare experts in fatigue management, so that oncology health care professionals are knowledgeable and skilled in assessing and managing fatigue. These educational programs are now being offered, but much more attention

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to these programs within institutional settings is necessary if professionals are to become skilled in managing fatigue.

Cancer-related fatigue should be included in clinical health outcome studies, and the NCCN Panel recommends that assessment of fatigue levels be included in outcomes research. Quality of fatigue management should be included in institutional continuous quality improvement (CQI) projects. Institutions can make faster progress in implementing the guidelines if they monitor adherence and progress with the guidelines. Medical care contracts should include reimbursement for the management of fatigue whether the patient needs referral to a physical therapist, dietitian, or the institution's symptom management service. In addition, disability insurance should include coverage for the continuing effects of fatigue that lead to persistent disability. Rehabilitation should begin with a cancer diagnosis and should continue even after cancer treatment ends.

Guidelines for Evaluation and Treatment

The general schema of the fatigue algorithm incorporates the following phases: screening, primary evaluation, intervention, and re-evaluation. During the first phase, the health care professional must screen for fatigue, determine its presence or absence, and assess its intensity level. If the intensity level is moderate to severe, the health care professional is directed to conduct a more focused history and physical examination during the primary evaluation phase of the algorithm. This phase includes an in-depth fatigue assessment and an evaluation of contributing factors (eg, pain, emotional distress, anemia, altered nutritional status, sleep disturbance, decreased activity, comorbidities) that are frequently associated with fatigue and can be treated as an initial step in managing fatigue (see [ET-4](#)). If, however, a patient either does not have one of these treatable contributing factors or continues to have moderate-to-severe fatigue after treatment of the factors, the

health care professional should recommend additional treatment based on the NCCN fatigue guidelines.

After the evaluation phase, the guideline delineates a set of interventions for the amelioration of fatigue based on the patient's clinical status (ie, active cancer treatment, long-term follow-up, or end of life). Education and counseling are believed to be central to the effective management of fatigue. Additional interventions are nonpharmacologic and pharmacologic; however, in many instances a combination of approaches must be used. Finally, the algorithm calls for re-evaluation, leading to an iterative loop in fatigue screening and management.

Screening

The first phase of the algorithm emphasizes screening of every patient for the presence or absence of fatigue. If fatigue is present, a quantitative or semiquantitative assessment should be performed and documented. For example, on a 0 to 10 numeric rating scale (zero = no fatigue and 10 = worst fatigue imaginable), mild fatigue is indicated as a score of 1 to 3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10.^{4,45} The fatigue scale for children is simplified; thus, young children (age < 6 or 7 years) may be asked if they are "tired" or "not tired." Valid and reliable instruments are available to measure fatigue in children and adolescents.^{9,46-48} If the screening process determines that fatigue is absent or at a mild level, the patient and family should receive education about fatigue and common strategies for managing it. Periodic re-screening and re-evaluation are recommended; for inpatients this should be carried out daily and for outpatients at subsequent routine and follow-up visits. It should be emphasized that survivors or patients who have been taken off treatment must still be monitored for fatigue, because fatigue may exist beyond the period of active treatment.^{12,13,49}

Currently, screening is not systematic or effective in many practice settings for various reasons, which often include patient or family barriers and clinician barriers.⁴⁰ For example, patients may not want to bother their health care professional in the clinic or office or when they are hospitalized. Patients are also concerned that if they report high levels of fatigue, they might have their treatment altered. Also, patients do not want to be perceived as complaining and, therefore, may not mention fatigue. Or, they may assume that they just have to live with fatigue, because they believe there is no treatment for it. Health care professionals may not initiate a discussion about fatigue for many of the same reasons. First, clinicians may not recognize that fatigue is a problem for the patient. Fatigue, as a symptom, has been unrecognized and untreated. Conversely, medical advances have led to better control over the more noticeable or less-subtle acute symptoms of nausea, vomiting, and pain. Researchers have begun to document not only the prevalence and incidence of fatigue but also how it significantly disrupts a patient's QOL.⁵¹⁻⁵³ Second, health care professionals probably do not mention fatigue, because they may not be aware that there are effective treatments for fatigue. In addition, health care professionals strive to understand and explain the underlying pathophysiology and mechanisms of medical conditions; however, these processes have not been elucidated for fatigue.

Given these barriers, screening for cancer-related fatigue must be emphasized. Clinical experience with fatigue assessment has shown that some patients cannot put a numeric value on their fatigue. Consequently, some patients may need to rate fatigue as mild, moderate, or severe. In addition, in some circumstances, other sources of data must be used. For example, the patient may not be aware that fatigue has negatively affected his or her life; however, the spouse, parents, or other family members may be more cognizant of these changes and the effect of fatigue. An appendix to this manuscript

provides additional information and resources to assist in the selection of instruments to measure cancer-related fatigue.

Using the numeric rating scale (ie, 0 to 10 scale), fatigue studies in cancer patients have revealed a marked decrease in physical functioning at the level of 7 or higher.^{44,54} The authors of an international study on fatigue in breast and prostate cancer patients evaluated and compared fatigue-intensity levels with scores from the MOS-SF-36 Physical Functioning Subscale.⁴⁵ The study documented a dramatic decrease in physical functioning when fatigue intensity levels were at level 7 (on a 0 to 10 scale). Based on these validated levels of intensity, the panel believes that this rating scale can be used as a guide in practice settings and decision-making.

Primary Evaluation Phase [Fatigue Score: moderate-to-severe (4-10)]

Focused History and Physical Examination

When fatigue is rated as moderate to severe, with a score 4-10, a more focused history and physical examination should be conducted as part of the primary evaluation phase. A component of this evaluation is an assessment of the patient's current disease status, the type and length of treatment as well as its capacity to induce fatigue, and the patient's response to treatment. If possible, it should be determined whether the fatigue is related to a recurrence of malignancy for those patients assumed to be disease-free or related to a progression of malignancy for those patients with underlying disease. This is often an important factor causing patients with fatigue to seek further evaluation. If the fatigue is determined not to be related to disease recurrence, informing patients and family members will substantially reduce their anxiety levels.

Review of current medications (including over-the-counter, herbal, vitamins, and other supplements) is essential. In addition, recent medication changes should be noted. Medications and medication

interactions may contribute to worsening of fatigue. For example, certain cardiac medications (such as beta-blockers) may elicit bradycardia and subsequent fatigue. Combinations of different classes of medications (such as narcotics, antidepressants, antiemetics, and antihistamines) may contribute to excessive drowsiness and increasing fatigue. It may be appropriate to delete or adjust the dose of medications to treat fatigue. In some cases, altering either the dosage or dosing interval of a medication may subsequently improve fatigue.

A review of systems should be completed. This review may be helpful in determining the various organ systems affected and in directing the physical evaluation and diagnostic workup. Another component of the focused history is an in-depth fatigue assessment⁶⁵ that includes evaluation of aspects of fatigue onset, pattern, duration, change over time, associated or alleviating factors, and interference with function. Physical, emotional, and cognitive symptoms may be associated with fatigue. The health care professional must evaluate fatigue's effect on normal functioning and its effect on the patient's daily living or enjoyable activities. Because fatigue is a subjective condition involving a combination of symptoms and is experienced and reported differently by each person, it is important that the in-depth assessment should also include the patient's self assessment of the causes of fatigue.

Assessment of Treatable Contributing Factors

As part of this focused evaluation, the panel identified seven factors that are often causative elements in the fatigue experience and, therefore, should be specifically assessed. These factors include pain, emotional distress, sleep disturbance, anemia, nutrition, activity level, and other comorbidities.

Appropriate assessment of pain along with emotional distress and institution of effective treatment are essential. Descriptive studies have shown that, in adults as well as in children, fatigue seldom occurs by

itself and that it more commonly clusters with sleep disturbance, emotional distress (eg, depression, anxiety), or pain.^{8,56-59}

Fatigue and depression have been documented as concurrent symptoms in cancer patients. In 987 lung cancer patients, Hopwood and Stephens⁶⁰ documented depression in 33% and that fatigue was an independent predictor of depression in this group. Newell and colleagues⁶¹ found fatigue was the most commonly experienced and debilitating physical symptom for 201 oncology patients; about 25% of these patients also experienced depression. In 457 patients with Hodgkin's disease, Loge and colleagues⁶² found that 26% had fatigue for 6 months or longer (defined as fatigue "cases") and that fatigue correlated moderately with depression ($r = .41$). Fatigue cases had higher levels of depression than non-cases. Visser and Smets⁶³ studied the relationship between fatigue and depression in 308 adults in Amsterdam who were treated as outpatients with radiation therapy for cure or control of cancer. They concluded that fatigue and depression were independent conditions with different patterns over time: fatigue increased over the course of treatment but depression decreased. Fatigue was not predictive of depression, and depression did not predict fatigue in this sample.

Sleep disturbances are a neglected problem in oncology⁶⁴ and may range from hypersomnia to insomnia.^{65, 66} Sleep disturbances are prevalent in 30% to 75% of patients with cancer.⁶⁷ Several studies have shown that fatigued cancer patients in active treatment spend increased time resting and sleeping but that their pattern of sleep is often severely disrupted.^{68,69} When sleep disturbances are present, the patient should be assessed for depression, because this is a common manifestation.⁷⁰ Patients may benefit from evaluation and education to improve sleep quality. In addition, sleep apnea can develop as a consequence of cancer treatment in the settings of surgery affecting the upper airway, changes in body composition, and alterations in hormone

status (ie, thyroid, estrogen, testosterone), therefore, obstructive sleep apnea should also be evaluated.

Studies have shown fatigue's association with anemia in cancer patients and its amelioration with erythropoietin (see section on "Treatment of Anemia-Related Fatigue with Erythropoietin"). Patients should undergo a nutritional assessment to evaluate weight gain and loss, caloric intake changes, impediments to nutritional intake, and fluid and electrolyte imbalances. Weight and weight changes should be carefully noted. The health care provider should also review and discuss changes in caloric intake with the patient. If there are substantial abnormalities, a consultation with a nutrition expert may be appropriate. Often fatigue symptoms can be improved by improving dietary intake, with appropriate caloric exchanges. Careful assessment of fluid and electrolytes should be performed. Imbalances in sodium, potassium, calcium, and magnesium serum levels are often reversible and, with appropriate supplementation, may improve fatigue. Nutritional intake may be affected by nausea, vomiting, loss of appetite, food disinterest, mucositis, odynophagia, bowel obstruction, diarrhea, and constipation.

Patients with moderate-to-severe fatigue should be queried about their activity level, including changes in exercise or activity patterns and the influence of deconditioning. This assessment is important when formulating a treatment plan that may include exercise. Can patients accomplish normal daily activities? Can they participate in formal or informal exercise programs? What is the amount and frequency of exercise? Has the patient modified exercise or other activity patterns since the development of fatigue? Exercise has been beneficial in lowering fatigue levels in certain populations of cancer patients.⁷¹⁻⁷³ However, before recommending an exercise program, the health care provider or exercise expert (eg, physiatrist, physical therapist) should assess the conditioning level of the patient. It is often difficult to

convince fatigued patients that exercise will improve their symptoms. It may be best to begin with discussions and low levels of activities, which gradually increase over a period of time. This is especially important if the patient is significantly deconditioned.

Non-cancer comorbidities may contribute substantially to symptoms of fatigue in the cancer patient. The status of each comorbidity must be reviewed in conjunction with the present treatment management of that comorbidity. If the comorbidity is not optimally managed, it may be necessary to further evaluate and improve that management. For example, if a patient has underlying congestive heart failure secondary to anthracycline cardiomyopathy and is experiencing symptoms of dyspnea and angina, fatigue may often be improved by stabilizing the condition and decreasing the frequency of episodes of congestive heart failure. This may entail introduction of new medications, titration of current medications, or both. It may also involve an invasive interventional assessment of the patient's cardiac status. Comorbidities that need review and assessment include infection as well as cardiac, pulmonary, renal, hepatic, neurologic, and endocrine dysfunction (including hypothyroidism, hypogonadism or adrenal insufficiency). Canaris and colleagues⁷⁴ noted the high incidence of thyroid dysfunction in normal individuals and in patients receiving thyroid medications; they suggested that more attention must be given to thyroid problems in both the general and cancer-patient populations. Development of hypothyroidism occurs after radiation therapy for Hodgkin's disease and other non-Hodgkin's lymphomas, head and neck cancers, and breast cancer, as well as after total body irradiation in bone marrow transplantation. Also, hypothyroidism has been noted in patients who have received interferon alfa-2b, aldesleukin (interleukin-2), L-asparaginase, and a multitude of combination chemotherapies. Hypogonadism is often seen in patients with advanced cancer. A recent cross-sectional pilot study by Strasser and colleagues⁷⁵ explored whether hypogonadism contributes to fatigue in

men with advanced cancer. The results of the study indicate that abnormally low levels of testosterone are associated with fatigue. However, additional research with larger samples is needed to clarify the incidence of hypogonadism and its association with specific malignancies and neurotoxic chemotherapy. The prevalence of hypogonadism may change with treatment and/or disease progression and, therefore, deserves further study.

Patient Clinical Status

After the primary fatigue evaluation is completed, the patient's clinical status (active cancer treatment, long-term follow-up with no active treatment except hormonal therapy, or end of life) should be determined, because it will influence cancer-related fatigue management and treatment strategies (see [ET-5](#), [ET-6](#), and [ET-7](#)). However, some general treatment guidelines apply across all clinical categories.⁷⁶

If any of the seven contributing factors (including pain, emotional distress, sleep disturbance, anemia, nutritional alterations, decrease in activity level, and comorbidities) known to be associated with cancer-related fatigue is identified during the primary evaluation phase, it should be treated as an initial approach to fatigue management. NCCN clinical practice guidelines are also available to guide the treatment of pain (see [NCCN Cancer Pain Guideline](#)), distress (see [NCCN Distress Management Guideline](#)), and anemia (see [NCCN Cancer and Treatment-Related Anemia Guideline](#)). Updated guidelines are available at www.nccn.org. Treatment of sleep disturbances, nutritional alterations, and physical deconditioning are discussed under "Nonpharmacologic Interventions" (see [ET-5](#)) for the three levels of clinical status.

Interventions for Patients on Active Treatment

Education and Counseling of Patient and Family

Education about fatigue and its natural history should be offered to all cancer patients⁶⁹ but is particularly essential for patients beginning fatigue-inducing treatments. Optimally, information about the usual pattern and duration of fatigue should be given to patients and their families before the onset of fatigue. All patients should be informed that they might develop moderate-to-severe fatigue when they are undergoing therapy (such as radiation, chemotherapy, or biotherapy). Patients should also be informed that if fatigue does occur, it may be a consequence of the treatment and not necessarily an indication that the treatment is not working or that the disease is progressing. Daily self-monitoring of fatigue levels in a treatment log or diary can be helpful.

In addition to education, the panel recommends counseling for patients about general strategies useful in coping with fatigue. These include strategies such as energy conservation and distraction. Energy conservation encompasses a common sense approach that helps patients to prioritize and pace activities, and to delegate less essential activities.⁷⁷ Patients should be counseled that it is permissible to postpone all nonessential activities if they are experiencing moderate-to-severe fatigue. One useful plan is to maintain a daily and weekly diary that allows the patient to ascertain peak energy periods.⁷⁸ The fatigued patient can then plan activities accordingly. A multisite clinical trial of energy conservation in 296 patients receiving cancer treatment by Barsevick and colleagues⁷⁹ reported significantly lower fatigue in those receiving the experimental intervention. Some participants in descriptive studies have suggested that activities designed to distract (eg, games, music, reading, socializing) are helpful in decreasing fatigue, although the mechanism is unknown.^{80,81}

Nonpharmacologic Management

Of the specific nonpharmacologic interventions during active cancer treatment, activity enhancement (category 1) and psychosocial interventions (category 1) have the strongest evidence base for treating fatigue; however, attention-restoring therapy, dietary management, and sleep therapy all have some evidence to support them.⁸²

Activity Enhancement.

In cancer patients, toxic treatments and a decreased level of activity during treatment are presumed to reduce physical performance. Therefore, patients must use greater effort and expend more energy to perform their usual activities, which leads to fatigue. Activity enhancement using physical exercise training programs, however, can decrease the loss in physical performance and increase functional capacity leading to a reduced effort and decreased fatigue.⁸³ Courneya and colleagues reported that aerobic exercise improved cardiopulmonary function and QOL in cancer survivors.^{84,85} It is reasonable to encourage all patients to maintain as normal a level of activity as possible during cancer treatment. However, some patients, especially those with comorbidities or substantial deconditioning, should be referred to physical therapy or to physical medicine and rehabilitation as indicated for assessment and exercise prescription. Specific exercise programs should be preceded by a careful evaluation of comorbidities and exercise contraindications. The exercise program itself should be individualized using the patient's age and gender, the type of cancer present, the treatment the patient is receiving for cancer, and the patient's physical fitness level. The program should begin at a low level of intensity and duration, progress slowly, and be modified as the patient's condition changes. Any exercise program must be cautiously prescribed if patients have comorbidities, such as bone metastases, immunosuppression or neutropenia, low platelet counts or thrombocytopenia, anemia, fever, or other treatment complications. A safe and beneficial exercise program provides guidance related to the

type of exercise and its intensity, duration, and frequency.⁸⁶ If the patient is neutropenic, activity should be limited to such environments in which the risk of infection is low (eg, public swimming pools are contraindicated).

Research about the effects of exercise on cancer-related fatigue includes studies of patients during treatment and studies of patients who have completed treatment. These studies are rapidly increasing in number, because exercise for cancer patients is no longer a novel idea, and because the benefits of exercise as well as the safety have been demonstrated. A number of meta-analyses⁸⁷⁻⁹⁰ and systematic reviews^{76,91-95} have addressed exercise as an intervention for cancer patients in active treatment as well as those in long-term follow-up. The reviewed studies included supervised laboratory programs^{72,85,86} and home-based programs.^{71,84,97} The type of aerobic exercise has varied: there were some walking programs,^{71,84} some exercise bicycling,^{72,88} and studies in which patients were able to choose the kind of exercise they preferred.^{73,99} In a recent clinical trial of men with prostate cancer receiving androgen deprivation therapy, resistive strength training was found to decrease fatigue and to increase muscle strength.¹⁰⁰ Some regimens were applied in laboratories and some were home-based regimens. The programs varied in length from 6 weeks for patients who were going through radiation therapy to 6 months for those in chemotherapy and the entire duration of bone marrow transplantation. The exercise interventions have varied somewhat but most include progressive programs of 20 to 30 minute sessions, three to five days a week, at an intensity equal to 60% to 80% of maximum heart rate (Rate of Perceived Exertion of 11 to 14). In one study, a dose-response pattern was observed with fatigue levels inversely related to three increasing levels of exercise.⁹⁹ However, patients who exercised more than 60 minutes per day were more likely to report higher levels of fatigue, suggesting a maximum effective dose for patients receiving adjuvant chemotherapy for breast cancer.

No serious adverse events were reported in any of the studies, although high-risk patients with serious comorbidities were excluded, and most exercise programs were flexible and symptom limited. All of these studies showed lower levels of fatigue and emotional distress as well as decreased sleep disturbance (if this was studied as an outcome) in patients who exercised during treatment compared to controls or to baseline scores in single-group designs. Exercise has a powerful effect on cancer-related fatigue, and fatigue levels were 40% to 50% lower in exercising participants, even in studies with relatively small sample sizes. The evidence supporting exercise as an intervention for fatigue is category 1 based on the number of studies conducted, the good quality of the designs, the large effect size of exercise on cancer-related fatigue, and the consistent outcomes across studies. Some additional studies on the effects of exercise in patients receiving cancer treatment that have not looked specifically at fatigue as an outcome have, nevertheless, shown increases in functional capacity, lending support to the theory regarding the positive effects of exercise on decreasing fatigue.^{101,102} Studies have also shown decreases in emotional distress and increased QOL in patients who engaged in exercise during cancer treatment.^{100,103}

Psychosocial Interventions.

Patients should be counseled about stress management and methods for dealing with depression and anxiety, which are commonly associated with fatigue during cancer treatment.¹⁰⁴ Although a strong correlation exists between emotional distress and fatigue, the precise relationship is not clearly understood. Both depression and anxiety may be characterized by fatigue, but it is also evident that high levels of fatigue may cause emotional distress when valued roles and activities are affected. Preliminary evidence in a recent study suggests that the relationship between fatigue and depression in cancer patients is mediated by functional status.¹⁰⁵

Studies testing interventions to reduce stress and to increase psychosocial support in cancer patients have shown reductions in fatigue levels, usually measured as a component of mood state.¹⁰⁶⁻¹¹¹ The interventions have included education,¹⁰⁹⁻¹¹¹ support groups,^{107,108} individual counseling,^{106,112} a comprehensive coping strategy,¹¹³ stress management training,¹¹⁴ and a tailored behavioral intervention.³⁹ The studies were randomized controlled trials, with good experimental designs and adequate sample sizes, and included various cancer populations; thus, the level of evidence for using psychosocial interventions to treat fatigue is category 1. However, in many of these studies, fatigue was a secondary endpoint measured by a single item or a subscale of an instrument to measure emotional distress.

Attention-restoring Therapy.

Attention-restoring therapy is another type of nonpharmacologic intervention. Attentional fatigue, which is an aspect of the sensory dimension of fatigue, has been defined as a decreased capacity to concentrate or to direct attention during stressful or demanding situations.¹¹⁵ Cimprich developed and tested attention-restoring interventions in women with breast cancer.¹¹⁶⁻¹¹⁸ Patients who received these interventions displayed improved concentration and problem solving on neurocognitive tests and returned earlier to work after surgery compared with control individuals.¹¹⁷ When the intervention was begun before surgery, the experimental group showed greater preoperative to postoperative recovery of capacity to direct attention.¹¹⁶ Birci watching and sitting in the park are examples of experiences in natural environments that have a restorative influence on cancer patients.

Nutrition Consultation.

Many cancer patients have changes in nutritional status. Because cancer and treatment can interfere with dietary intake, nutrition consultation may be helpful in managing the nutritional deficiencies that

result from anorexia, diarrhea, nausea, and vomiting.¹¹⁹ Adequate hydration and electrolyte balance are also essential in preventing and treating fatigue.

Sleep Therapy.

Cancer patients report significant disturbances in sleep patterns. Both insomnia and hypersomnia are common, with disrupted sleep as a common denominator.^{64,67,120} Nonpharmacological interventions identified for sleep therapy include cognitive-behavioral therapy (CBT) and complementary therapies. These interventions are designed to optimize sleep quality and may also decrease fatigue.¹²¹

The cognitive-behavioral interventions include relaxation training along with stimulus control, sleep restriction, and sleep hygiene. Stimulus control includes going to bed when sleepy, going to bed at approximately same time each night, and maintaining a regular rising time each day. Sleep restriction includes avoiding long or late afternoon naps and limiting time in bed. Sleep hygiene includes techniques to promote a good night's sleep and optimal functioning the next day, such as avoiding caffeine after noon and establishing an environment that is conducive to sleep (eg, dark, quiet, and comfortable). These strategies were employed in a pilot study with women during adjuvant breast cancer chemotherapy. Sleep/wake patterns remained consistent with normal values except for increased number and length of nighttime awakenings.¹²² For children with cancer, a consistent bedtime and routine, a conducive environment, and presence of security objects (such as blankets and toys) are effective measures. A number of published studies¹²³⁻¹²⁶ support the conclusion that cognitive-behavioral therapy interventions designed to optimize sleep quality may also improve fatigue.

Complementary therapies such as massage therapy,^{127,128,129} yoga,¹³⁰⁻¹³² muscle relaxation,^{133,134} and mindfulness-based stress reduction¹³⁵⁻¹³⁸ have been evaluated in pilot studies; the preliminary

data suggest that they may be effective in reduction of fatigue in cancer patients.

Pharmacologic Interventions

The last type of cancer-related fatigue treatment is pharmacologic therapy. Aside from the well-established treatment of anemia with erythropoietin (see the [NCCN Cancer and Treatment-Related Anemia Guideline](#)), there have been few reports of systematic investigation of drugs to treat cancer-related fatigue, although there have been some clinical reports.¹³⁹ Studies on a selective serotonin reuptake inhibitor paroxetine showed no influence by this antidepressant on fatigue in patients receiving chemotherapy.^{140,141} Antidepressant is no longer a recommended option.

Psychostimulants, such as methylphenidate, can be considered after ruling out other causes of fatigue. Psychostimulants have been found to reduce fatigue in other chronic conditions^{142,143} and are now being evaluated in some studies on cancer patients to ameliorate opioid-induced somnolence. Most recently, a randomized, double-blind, placebo-controlled study with methylphenidate in cancer related fatigue showed that both placebo and methylphenidate improved fatigue, with no significant difference from placebo at one week.¹⁴⁴ Another phase III, randomized, placebo-controlled trial for dexmethylphenidate was conducted in adult cancer patients and significantly more effective improvement of fatigue than placebo was achieved for dexmethylphenidate.¹⁴⁵ The psychostimulant, modafinil, has been approved by the Food and Drug Administration for use in narcolepsy. A case report using modafinil showed improvements in daytime wakefulness and normalization of sleep-wake cycle¹⁴⁶ in 2 adult patients with advanced cancer; modafinil has been reported to be helpful in cancer-related fatigue,¹⁴⁷ but no studies have been published as yet. Therefore, the panel does not believe there is sufficient evidence at this time to recommend pharmacologic therapy for cancer

patients who have moderate or severe fatigue and recommends that more research be done in this area.

Interventions for Patients on Long-Term Follow-Up

More than 9 million U.S. people now living have a history of cancer. Of the approximately 1,399,790 persons in the United States who will be diagnosed with cancer in 2006, 65% are expected to survive at least 5 years.¹⁴⁸ These improvements in survival have led to efforts to enhance symptom management, QOL, and overall functioning of individuals entering long-term follow-up after cancer treatment. As previously mentioned, fatigue is an acute effect of cancer (or medical treatment), but fatigue can also be a long-term or late effect of disease or treatment.^{149,150} Those disease-free individuals who are no longer receiving treatment may continue to report unusual fatigue for months or years after treatment cessation.^{12,14,16-21} Researchers have suggested that such fatigue may be due to persistent activation of the immune system^{16,151} or to other factors, such as late effects of treatment on major organ systems.¹⁵¹ However, there are few longitudinal studies examining fatigue in long-term disease-free patients for its prevalence, correlates, duration, and underlying mechanisms. We have limited knowledge of fatigue in survivors.

Incidence and prevalence rates for fatigue in this population range from 17% to 21% when strict ICD-10 diagnostic criteria are applied¹⁵² and range from 33% to 53% when other criteria (such as a score of 4 or more on the 0 to 10 fatigue scale) are used.¹⁵³ In contrast to these findings, Canadian and U.S. ovarian cancer survivors (n = 100), who were diagnosed a mean of 7.2 years before the survey, reported equivalent energy levels when compared with the general population.¹⁵⁴ As a consequence, what constitutes valid incidence and prevalence rates in disease-free patients requires more study.

In general, most research reports to date are limited by their cross-sectional designs,^{24,51,150,152,155-157} lack of comparison groups,^{24,51,157} heterogeneous samples,^{152,158} use of differing fatigue scales, small sample sizes,¹⁵¹ varying baseline survivorship definitions (ie, time since diagnosis versus time since treatment cessation), and different mean survivorship durations (ie, from 12-18 months to 7 plus years). These design issues make it difficult to reach conclusions about the effect of fatigue's prevalence, incidence, duration, associated risk factors, and QOL. Additionally, most fatigue studies of post-treatment disease-free patients have been conducted in Caucasian, English-speaking breast cancer,^{16,151,155} and peripheral stem cell or bone marrow transplant patients^{86,158} with few exceptions.^{17,19,21}

The cause of fatigue in post-treatment disease-free patients is unclear and probably multifactorial.¹⁰⁹ One cross-sectional comparative study investigated fatigue and physiologic biomarkers of immune system activation in 20 breast cancer survivors who were fatigued (a mean of 5 years since diagnosis) and in 20 non-fatigued survivors.¹⁵¹ Fatigued survivors had significantly higher serum markers (interleukin-1 receptor antagonist [IL-1ra], soluble tumor necrosis factor type II [sTNF-RII], and neopterin) and lower cortisol levels when compared with non-fatigued survivors. Significantly higher numbers of circulating T lymphocytes that also correlated with elevated serum IL-1ra levels suggesting that persistent fatigue in survivors may be caused by a chronic inflammatory process involving the T-cell compartment.¹⁶

Other risk factors associated with fatigue in post-treatment disease-free patients include pretreatment fatigue, anxiety and depression levels,¹⁶⁰ physical level activities,^{161,162} coping methods and cancer-related stressors, comorbidities,¹⁶² type of malignancy, prior treatment patterns,¹⁵⁷ and treatment late effects.¹⁵⁰ For example, in one Norwegian study, a small proportion of long-term disease-free cancer patients who had pre-existing coronary artery disease had 30% higher

fatigue levels compared with controls.¹⁶³ In another Norwegian study that investigated fatigue in Hodgkin's disease survivors in remission for more than 5 years, higher fatigue levels were documented in those who had pulmonary dysfunction.¹⁶³ In these survivors, the prevalence of chronic fatigue was 2 to 3 times higher than in survivors who did not have such impairment. No significant correlations in this study were found between fatigue and cardiac sequelae as measured by echocardiography, exercise testing, and chest radiography.¹⁶³ Prior treatment patterns may affect the survivor's fatigue. For example, in a study of 322 post-treatment disease-free breast cancer patients, the highest fatigue scores occurred in women who had received previous combination therapy versus other forms of treatment.¹⁶⁷ Women who had received radiation therapy had the lowest fatigue scores. Two studies testing the effects of physical activity interventions on fatigue in breast cancer survivors found that individualized, prescriptive exercise reduced fatigue. However, researchers emphasize it is critical that exercise be individualized to the survivors' abilities to prevent exacerbation of cancer treatment toxicities.^{161,162}

Education and Counseling of Patient and Family

Patients who are completing treatment and entering the phase of long-term follow-up and their families should be educated about the pattern and level of fatigue that can be expected during this period. Although a significant subset of patients continue to experience distressing levels of fatigue that interfere with function,^{12,13} most patients experience a gradual decrease in fatigue and return of energy to normal levels.^{14,154} Regular self-monitoring of fatigue levels is helpful to document the decrease of fatigue that normally occurs after treatment. Oncology care providers should continue to screen regularly for fatigue during follow-up visits.

Nonpharmacologic Management

The specific interventions recommended to manage fatigue during active cancer treatment are also recommended for disease-free

patients on long-term follow-up.⁷⁶ Activity enhancement is a category 1 recommendation. In fact, improving strength, energy, and fitness through regular exercise, even a moderate walking exercise program, has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression,¹⁶⁴ improve body image, and increase tolerance for physical activity.⁸⁸ However, if the patient is significantly deconditioned, weak, or may have relevant late effects of treatment (such as cardiopulmonary limitations), referral to a physiatrist or a supervised rehabilitation program may be indicated. Exercise should be recommended with caution in patients who have fever or remain anemic, neutropenic, or thrombocytopenic after treatment. Although exercise has the best evidence to support its effectiveness,^{76,89-95,165} psychosocial interventions (category 1), energy conservation, distraction, attention-restoring therapy, sleep therapy,^{121,166} family interaction, and nutritional therapy are all helpful in this population as well.

Pharmacologic Interventions

Cause-specific pharmacologic therapy may include hypnotics as a possible short-term treatment for insomnia; if indicated, anemia should also be treated (see [NCCN Cancer and Treatment-Related Anemia Guideline](#)). Whether psychostimulants are useful for treating fatigue in disease-free patients on long-term follow-up has not been reported, although psychostimulants, such as methylphenidate, can be considered after ruling out other causes of fatigue.

Interventions for Patients at the End of Life

Although the assessment and management of fatigue at the end of life parallels the general principles of this guideline, there are a few issues that are specific to this population. Factors that have a greater likelihood of association with fatigue at the end of life include anemia, medication adverse effects and polypharmacy, cognitive impairment,

adverse effects of recent treatment, and malnutrition.¹⁶⁷ Evaluating and correcting these contributing factors could reduce fatigue severity.

At the end of life, most research has demonstrated that cancer patients experience fatigue in the context of multiple symptoms. In a study of 278 Swedish adults admitted to a palliative care unit, 100% reported fatigue; other symptoms included pain (83%), dyspnea (77%), and appetite loss (75%).¹⁶⁸ Among 58 Australian cancer patients receiving inpatient or home-based care, the most prevalent symptoms were weakness (87%), fatigue (84%), sleep during the day (75%), and pain (72%).¹⁶⁹ Walsh and Rybicki¹⁷⁰ cluster analyzed 25 symptoms in 1000 consecutive admissions to a palliative care program and found seven symptom clusters. The fatigue cluster included easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste changes. The report of multiple symptoms is not without consequences. Mysiakidou and colleagues¹⁷¹ reported that patient desire for a hastened death was predicted by feeling sad, lack of appetite, pain, and fatigue.

Education and Counseling of Patient and Family

Individuals with advanced cancer and their caregivers need information about the management of symptoms, including fatigue,¹⁷² with specific information related to the disease trajectory.^{173,174} This includes information about the causes, patterns, and consequences of fatigue during treatment for advanced cancer and at the end of life. As noted in these NCCN guidelines, there are many causes of fatigue in this group, including disease progression, medications, sleep disturbances, pain, poor nutrition, depression, and anemia.

It is likely that fatigue will increase substantially as the disease progresses; however, patterns of fatigue are variable. For some adults, fatigue may be characterized as constant and unrelenting; for others, it is unpredictable and may come on suddenly.^{52,175} In both adults and children, fatigue is likely to occur in the context of multiple symptoms. In

a large sample of adults (N = 1000) receiving palliative care, Walsh and colleagues¹⁷⁶ noted that individuals with advanced cancer had multiple symptoms. Pain was the most prevalent (84% of patients), followed by easy fatigue (69%), weakness (66%), and lack of energy (61%). Children with advanced cancer also experienced multiple symptoms at the end of life, most commonly fatigue, pain, and dyspnea.¹⁷⁷ There is also the possibility, suggested by Given and colleagues,^{37,178} that pain and fatigue together could have a synergistic effect that worsens the overall symptom experience in elderly cancer patients.

Several major consequences of fatigue have been described, including its effect on functional status, emotional distress, and suffering. As fatigue escalates, it is likely to interfere increasingly with usual activities.¹⁷⁵ Families need to be apprised of this problem so they can begin planning for it. In addition, fatigue is likely to have increasing effect on emotional well-being.^{175,177} According to parents who cared for a child at the end of life, more than 90% of the children experienced fatigue and almost 60% experienced a great deal of suffering from it.¹⁷⁷ In a case study of 15 adults with advanced disease, Krishnasamy found that fatigue resulted in substantial regret, sadness, and sense of loss due to the deterioration of one's health.¹⁷⁶

Given the high prevalence of fatigue and other symptoms at the end of life, symptom management needs to be a major focus of care. Active commitment by the health care team to palliative care is critical when aggressive cancer therapy is given to those with a low likelihood of long-term survival.¹⁷⁷ Although there is no effective therapy for some causes of fatigue and other symptoms, treatment of those more amenable to therapy could help to relieve suffering.⁷⁶

General Strategies for Management of Fatigue

Energy conservation is a self-care strategy for individuals with advanced cancer and their caregivers.⁷⁹ Energy conservation is defined as the deliberately planned management of one's personal energy

resources to prevent their depletion. The goal of energy conservation is to maintain as balance between rest and activity during times of high fatigue so that valued activities can be maintained. Energy conservation strategies include priority setting, delegating activities of lesser importance, pacing oneself, taking extra rest periods, and planning high-energy activities at times of peak energy. It may also include the use of labor-saving devices (such as a bedside commode, walker, raised toilet seat, energy-saving appliances, and grabbing tools). In a situation of escalating fatigue at the end of life, family members may wish to designate individuals to assume activities relinquished by the individual with cancer.

Nonpharmacologic Interventions

Although fatigue may increase at end of life, individuals may choose to be active despite failing health. As noted earlier, exercise is effective in reducing fatigue during active treatment. There is also some evidence that exercise is beneficial to individuals with incurable cancer and short life expectancy. A group exercise program was pilot-tested in 63 Norwegian palliative care outpatients.¹⁷⁹ The program consisted of two 50-minute sessions twice a week for six weeks. A combination of strength building, standing balance, and aerobic exercise was used. The exercise participants had less physical fatigue and increased walking distance. There were no adverse effects of exercise although 46% of the 63 participants did not complete the program.

A small pilot study was conducted to evaluate an exercise program for nine individuals with advanced cancer enrolled in a home hospice program.¹⁸⁰ A physical therapist guided participants in the selection of several activities (such as walking, performing arm exercises with resistance, marching in place, and dancing). These were performed at different times throughout the day on a schedule devised jointly by the therapist and participant. All participants were able to increase their activity level over a 2-week period without increased fatigue. There was

also a trend toward increased QOL and decreased anxiety. Although more research is needed, enhanced activity shows promise as a fatigue management strategy at the end of life. Psychosocial interventions (category 1), attention-restoring therapy, sleep therapy, family interaction, and nutritional therapy are also helpful to this population.

A 12-week exercise program tested on 82 men with locally advanced or metastatic prostate cancer was compared to a wait-list control group (N = 73).¹⁰⁰ The men in the exercise group reported less interference of fatigue with daily activities and better quality of life. They also demonstrated better upper and lower body muscle fitness. Body composition was not affected.

Based on a systematic review of 20 exercise studies relevant to fatigue and muscle wasting in multiple myeloma, Strong⁸¹ summarized weight-bearing precautions for bone metastases as well as exercise guidelines for adults with solid tumors and hematological cancers; older cancer survivors; and individuals with cancer-related fatigue. They also recommended an exercise protocol for multiple myeloma that incorporated aerobic, resistance, and flexibility exercises.

Pharmacologic Interventions

There continues to be interest in psycho-stimulant drugs although studies have had mixed results. Bruera et al¹⁸² compared 52 palliative care outpatients who received methylphenidate (titrated up to 20 mg per day for 7 days) with a placebo control group (N = 53). Fatigue intensity decreased in both groups; methylphenidate was not superior to placebo. Other studies of fatigued breast cancer survivors,¹⁸³ advanced cancer patients,¹⁸⁴ and HIV patients¹⁸⁵ support the use of this drug. Additional studies are needed.

In Sweden, the corticosteroid, betamethosone (a dexamethosone equivalent), has been widely used to treat fatigue in palliative care patients. In a survey, 40% of palliative care physicians reported using it

to treat fatigue and 80% reported very good or some effect of the drug on fatigue.¹⁸⁶ Modafinil also shows some promise for cancer-related fatigue. Morrow et al.¹⁸⁷ conducted an open label study of modafinil for 82 breast cancer survivors with persistent fatigue. The dose was 200 mg per day for one month. Eighty-three percent reported reduction of fatigue, 10% had no improvement, and 7% dropped out of the study. In a randomized pilot study of 16 adults with brain tumors, Kaleita and colleagues¹⁸⁸ titrated modafinil dose from 100 mg to 600 mg (optimal dose) for 13–17 days and concluded that modafinil was a safe and effective treatment for fatigue.

In addition to psycho-stimulants, the progestational agent, megestrol acetate (MA) has demonstrated dose-dependent improvement in fatigue as well as appetite and well being.^{182,189} In fact, a study comparing MA with dexamethasone showed that MA had fewer side effects than dexamethasone.¹⁹⁰ The authors suggested that for planned long term use (weeks or months) MA might be preferable. A systematic review paper demonstrated the safety and efficacy of MA for cancer patients.¹⁹¹

Micronutrient deficiency could also be responsible for increased fatigue in advanced cancer patients. Carnitine is a micronutrient involved in the production of energy at the cellular level,¹⁹² that has been shown to be deficient in people who are chronically ill. Advanced cancer patients are at risk for carnitine deficiency because of decreased intake and increased renal loss. L-carnitine supplementation has been examined in an open label Phase I/II study.¹⁹³ L-carnitine was given to 27 advanced cancer patients in escalating doses (250–3000 mg per day). Twenty-one individuals completed the study with 17 showing increases in carnitine levels. In a responder analysis, a dose-response relationship was observed for fatigue. Although this work is very preliminary, carnitine supplementation shows some promise for fatigue management.

Re-Evaluation Phase

Because fatigue may arise at many points in the course of a patient's disease and treatment, ongoing re-evaluation of the patient's status (with appropriate modifications and institution of new treatments) is an integral part of effective, overall fatigue management (see [ET-4](#)).

Summary

The NCCN Cancer-Related Fatigue Guidelines propose a treatment algorithm in which patients are evaluated regularly for fatigue using a brief screening instrument and are treated as indicated by their fatigue level. The algorithm's goal is to identify and treat all patients with fatigue that causes distress or interferes with their daily activities or functioning.

Management of fatigue begins with primary oncology team members who perform the initial screening and either provide basic education and counseling or expand the initial screening to a more focused evaluation for moderate or higher levels of fatigue. At this point, the patient is assessed for current disease and treatment status, a review of body systems, and an in-depth fatigue evaluation. In addition, the patient is assessed for the presence of seven treatable factors known to contribute to fatigue: pain, emotional distress, sleep disturbance, anemia, alteration in nutrition, deconditioning, and comorbidities. If any of these conditions are present, they should be treated according to practice guidelines, with referral to other care professionals as appropriate, and the patient's fatigue should be re-evaluated regularly. If none of the seven factors are present or if the fatigue is unresolved, selection of appropriate fatigue management and treatment strategies is done within the context of the patient's clinical status: (ie, receiving active cancer treatment, disease-free long-term follow-up, or care at the end of life). Management of fatigue is cause-specific when conditions known to cause fatigue (such as infection, fluid and electrolyte imbalances, or cardiac dysfunction) can be identified and treated. When

specific causes of fatigue cannot be identified and corrected, nonpharmacologic and pharmacologic treatment of the fatigue should still be done.

Nonpharmacologic interventions may include a moderate exercise program to improve functional capacity and activity tolerance, psychosocial programs to manage stress and increase support, attention-restoring therapies to decrease cognitive alterations and improve mood state, energy conservation to maintain energy, and nutritional and sleep interventions for patients with disturbances in eating or sleeping. Pharmacologic therapy may include drugs, such as antidepressants for depression or erythropoietin for anemia. A few clinical reports of the use of psychostimulants suggest the need for further research on these agents as potential treatment modalities in managing fatigue.

Effective management of cancer-related fatigue involves an informed and supportive oncology care team that assesses patients' fatigue levels regularly, counsels and educates patients regarding strategies for coping with fatigue,¹⁹⁴ and uses institutional experts for referral of patients with unresolved fatigue.⁴³

Disclosures for the NCCN Cancer-Related Fatigue Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Some Members of the panel indicated that they have received support from the following: Amgen, Cephalon, Forest Laboratories, Inc., and Ortho Biotech. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

Appendix**Fatigue Measurement*****A resource to facilitate selection of instruments to measure fatigue***

Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *The Lancet* 2003;262:640-650.
(*This resource provides a detailed description of six scales frequently used in cancer patients to measure fatigue.*)

Jacobsen PB. Assessment of fatigue in cancer patients. *J Natl Cancer Inst Monogr* 2004; 32: 93-97.
(*Includes factors to consider in selecting a fatigue measure.*)

Meek PM, Nail LM, Barsevick A, et al. Psychometric testing of fatigue instruments for use with cancer patients. *Nurs Res* 2000;49:181-190.
(*Study evaluates psychometric properties of several commonly used fatigue measures.*)

National Cancer Institute. Fatigue (PDQ) Health Professional Version (11/18/05). Retrieved from <http://www.ncl.nih.gov/cancertopics/bdq/supportivecare/fatigue/healthprofessional/>
(*Gives citation links to nine commonly used scales to measure fatigue.*)

Oncology Nursing Society. Measuring oncology nursing-sensitive patient outcomes: Fatigue evidence-based summary (June 22, 2004). Retrieved from <http://onsopcontent.ons.org/toolkits/evidence/Clinical/Summaries.shtml>
(*Provides two detailed tables summarizing scale descriptions and psychometric properties for 13 scales.*)

Piper BF. Measuring fatigue. In: Frank-Stromborg M, Olsen SJ, eds. Instruments for clinical health-care research. 3rd ed. Boston, MA: Jones & Bartlett. 2004:538-553.
(*Provides four detailed tables that summarize scale descriptions and psychometric properties for all fatigue scales that have been developed to date including single item and multiple item, single dimension scales and multidimensional scales.*)

Wu HS, McSweeney M. Measurement of fatigue in people with cancer. *Oncol Nurs Forum* 2001;28:1371-1384.
(*Qualitative review of commonly used fatigue measures.*)

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APPENDIX P – SUMMARY OF QUANTITATIVE DATA

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	8	14	8	4	4	0	14	10	3	5	2
	9	14	6	2	3	1	14	11	4	4	3
	10	14	6	2	4	0	14	9	3	4	2
	11	14	6	3	3	0	14	10	5	3	2
	12	14	4	4	0	0	14	10	6	2	2
	13	14	3	3	0	0	14	10	5	3	2
	14	14	3	3	0	0	14	10	5	5	0
8	1	13	6	1	5	0	13	6	1	3	2
	2	13	7	2	5	0	13	7	2	4	1
	3	13	6	1	5	0	13	7	0	6	1
	4	13	6	3	3	0	13	8	5	2	1
	5	13	5	4	1	0	13	6	2	3	1
	6	13	4	3	1	0	13	6	2	3	1
	7	13	2	2	0	0	13	6	4	1	1
	8	13	5	2	3	0	13	8	4	2	2
	9	13	5	1	3	1	13	7	1	4	2
	10	13	6	3	3	0	13	7	4	2	1
	11	13	4	2	2	0	13	7	5	1	1
	12	13	4	3	1	0	13	7	4	3	0
	13	13	3	2	1	0	13	7	4	3	0
	14	13	2	2	0	0	13	6	3	2	1

Table X: Summary of quantitative data												
Cycle	Day	Nausea						Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	
Group 1: Experimental site, Time 1												
1	1	30	19	12	5	2	30	13	8	5	0	
	2	30	18	10	7	1	30	20	11	8	1	
	3	30	16	6	9	1	30	18	11	6	1	
	4	30	14	10	4	0	30	18	9	3	6	
	5	30	11	6	2	3	30	15	8	3	4	
	6	30	10	2	7	1	30	18	8	7	3	
	7	30	7	3	3	1	30	15	10	3	2	
	8	30	5	3	1	1	30	14	7	6	1	
	9	30	4	3	0	1	30	11	6	4	1	
	10	30	2	1	1	0	30	14	6	8	0	
	11	30	2	2	0	0	30	12	7	3	2	
	12	30	0	0	0	0	30	13	10	3	0	
	13	30	1	1	0	0	30	12	9	3	0	
	14	30	1	1	0	0	30	9	6	3	0	
2	1	26	12	8	3	1	26	13	8	4	1	
	2	26	13	4	7	2	26	16	8	7	1	
	3	26	15	8	5	2	26	15	7	6	2	
	4	26	14	9	4	1	26	16	10	4	2	
	5	26	11	5	5	1	26	17	8	5	4	
	6	26	10	5	4	1	26	18	8	7	3	
	7	26	8	2	6	0	26	16	6	7	3	
	8	26	6	3	2	1	26	15	7	6	2	
	9	26	4	1	2	1	26	14	7	6	1	
	10	26	6	3	3	0	26	14	8	6	0	
	11	26	2	1	1	0	26	15	11	4	0	

Cycle	Day	Nausea						Fatigue					
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)		
	12	26	2	2	0	0	26	9	6	2	1		
	13	26	2	1	1	0	26	13	10	2	1		
	14	26	3	1	2	0	26	11	5	6	0		
3	1	26	7	2	2	3	26	11	5	3	2		
	2	26	12	6	3	3	26	13	6	3	4		
	3	26	9	5	2	2	26	15	9	4	2		
	4	26	9	6	1	2	26	17	10	5	2		
	5	26	10	6	2	2	26	15	7	7	1		
	6	26	9	6	0	3	26	17	7	8	2		
	7	26	7	2	3	2	26	16	7	6	3		
	8	26	5	2	2	1	26	14	5	6	3		
	9	26	5	3	1	1	26	14	7	5	2		
	10	26	3	2	0	1	26	12	8	3	1		
	11	26	1	0	0	1	26	11	6	4	1		
	12	26	2	0	2	0	26	12	8	3	1		
	13	26	1	1	0	0	26	12	9	2	1		
	14	26	1	1	0	0	26	12	8	4	0		
4	1	24	6	3	4	1	24	12	5	5	2		
	2	24	6	3	4	1	24	13	5	5	3		
	3	24	6	3	3	2	24	14	6	5	3		
	4	24	6	3	3	2	24	15	4	7	2		
	5	24	6	2	5	1	24	14	2	8	4		
	6	24	5	3	3	1	24	15	5	6	4		
	7	24	6	6	2	0	24	15	7	5	3		
	8	24	5	4	1	0	24	14	5	8	1		
	9	24	3	2	1	0	24	15	7	7	1		
	10	24	3	3	0	0	24	10	6	3	1		

Cycle	Day	Nausea						Fatigue					
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)		
	11	24	2	2	0	0	24	12	10	2	0		
	12	24	1	1	0	0	24	12	10	2	0		
	13	24	1	1	0	0	24	12	10	2	0		
	14	24	1	1	0	0	24	12	10	2	0		
5	1	16	4	1	0	3	16	8	5	1	2		
	2	16	6	2	0	4	16	9	3	3	3		
	3	16	7	4	03	3	16	10	4	4	2		
	4	16	5	1	2	1	16	8	1	5	2		
	5	16	5	2	3	1	16	8	0	5	3		
	6	16	5	2	2	0	16	11	4	5	2		
	7	16	4	1	4	1	16	11	5	4	2		
	8	16	4	0	0	0	16	9	3	4	2		
	9	16	6	5	1	1	16	9	3	4	2		
	10	16	3	2	0	0	16	10	4	3	3		
	11	16	1	1	1	0	16	9	1	5	3		
	12	16	2	1	0	0	16	8	1	7	0		
	13	16	2	2	0	0	16	8	4	3	1		
	14	16	3	3	2	0	16	9	4	3	2		
6	1	13	4	2	2	0	13	7	5	1	1		
	2	13	3	1	2	0	13	7	3	3	1		
	3	13	5	3	1	1	13	7	0	5	2		
	4	13	4	2	1	1	13	10	3	5	2		
	5	13	3	1	1	1	13	9	2	4	3		
	6	13	3	1	1	1	13	10	2	4	4		
	7	13	3	1	1	1	13	8	2	3	3		
	8	13	3	2	0	1	13	7	1	4	2		
	9	13	2	1	0	1	13	8	2	3	3		

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	10	13	3	2	0	1	13	9	2	4	3
	11	13	2	1	0	1	13	8	3	3	2
	12	13	1	0	0	1	13	8	3	2	3
	13	13	0	0	0	0	13	6	3	2	1
	14	13	0	0	0	0	13	7	3	3	1
7	1	10	4	2	2	0	10	6	2	3	1
	2	10	4	2	1	1	10	7	3	1	3
	3	10	3	0	3	0	10	7	2	3	2
	4	10	3	0	2	1	10	7	2	3	2
	5	10	3	1	1	1	10	8	2	3	3
	6	10	4	2	1	1	10	8	2	2	4
	7	10	3	3	0	0	10	7	2	2	3
	8	10	2	2	0	0	10	7	2	3	2
	9	10	1	1	0	0	10	7	2	4	1
	10	10	2	2	0	0	10	7	4	2	1
	11	10	2	1	1	0	10	7	4	1	2
	12	10	1	1	0	0	10	6	3	1	2
	13	10	2	2	0	0	10	6	3	1	2
	14	10	2	2	0	0	10	7	4	2	1
8	1	7	1	1	0	0	7	2	1	0	1
	2	7	2	0	2	0	7	2	1	0	1
	3	7	2	1	1	0	7	3	2	0	1
	4	7	2	1	0	1	7	3	0	2	1
	5	7	1	1	0	0	7	3	0	2	1
	6	7	1	1	0	0	7	3	1	1	1
	7	7	0	0	0	0	7	3	1	1	1
	8	7	0	0	0	0	7	3	1	1	1

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
Group 2: Experimental site, Time 2											
1	1	20	4	1	2	1	20	7	3	3	1
	2	20	8	4	4	0	20	12	9	1	2
	3	20	8	7	0	1	20	14	9	4	1
	4	20	6	5	1	0	20	14	1	1	1
	5	20	3	1	1	1	20	11	6	4	1
	6	20	4	3	1	0	20	12	5	7	0
	7	20	4	2	2	0	20	15	8	7	0
	8	20	4	4	0	0	20	12	8	4	0
	9	20	4	2	2	0	20	10	6	4	0
	10	20	4	3	1	0	20	8	6	2	0
	11	20	1	1	0	0	20	8	7	1	0
	12	20	0	0	0	0	20	8	4	3	1
	13	20	0	0	0	0	20	7	4	1	2
	14	20	0	0	0	0	20	7	5	1	1
2	1	17	2	1	0	1	17	9	5	3	1
	2	17	5	3	2	0	17	10	4	5	1
	3	17	4	1	3	0	17	8	3	3	2
	4	17	4	2	2	0	17	11	4	5	2
	5	17	4	1	1	2	17	9	5	3	2
	6	17	4	1	1	2	17	10	3	5	2

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	7	17	4	0	2	2	17	11	4	5	2
	8	17	3	0	3	0	17	10	4	5	1
	9	17	2	1	1	0	17	11	6	4	1
	10	17	3	3	0	0	17	10	4	5	1
	11	17	3	1	2	0	17	11	5	4	2
	12	17	1	0	1	0	17	10	5	4	1
	13	17	0	0	0	0	17	11	7	3	1
	14	17	0	0	0	0	17	11	7	4	0
3	1	14	1	0	1	0	14	6	2	3	1
	2	14	4	3	0	1	14	7	4	2	1
	3	14	3	2	0	1	14	8	3	4	1
	4	14	4	2	2	0	14	9	2	4	3
	5	14	4	3	1	0	14	8	2	5	1
	6	14	4	1	3	0	14	10	2	3	5
	7	14	4	2	2	0	14	10	2	6	2
	8	14	4	2	2	0	14	10	2	4	4
	9	14	4	2	2	0	14	10	3	4	4
	10	14	2	2	0	0	14	9	4	4	1
	11	14	1	1	0	0	14	10	3	4	2
	12	14	1	1	0	0	14	8	6	1	3
	13	14	3	3	0	0	14	6	4	2	2
	14	14	3	3	0	0	14	7	3	2	1
4	1	13	3	2	1	0	13	7	3	2	2
	2	13	4	1	2	1	13	7	3	3	1
	3	13	4	0	3	1	13	7	2	3	2
	4	13	3	1	2	0	13	7	4	2	1
	5	13	4	2	2	0	13	7	2	1	4

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	6	13	3	0	3	0	13	8	4	3	1
	7	13	3	2	1	0	13	7	3	2	2
	8	13	3	1	2	0	13	7	3	3	1
	9	13	3	0	3	0	13	7	3	3	1
	10	13	3	1	2	0	13	6	2	3	1
	11	13	3	2	1	0	13	6	3	2	1
	12	13	3	2	1	0	13	6	3	1	2
	13	13	2	1	1	0	13	5	3	1	1
	14	13	2	2	0	0	13	7	4	2	1
5	1	11	1	0	0	1	11	7	5	1	1
	2	11	1	0	0	1	11	5	2	1	2
58	3	11	1	0	0	1	11	6	4	2	0
59	4	11	1	1	0	0	11	9	7	1	1
60	5	11	1	0	1	0	11	8	4	2	2
61	6	11	1	0	1	0	11	8	3	5	0
62	7	11	1	1	0	0	11	7	3	2	2
63	8	11	1	0	1	0	11	7	2	4	1
64	9	11	1	1	0	0	11	6	4	2	0
65	10	11	1	0	0	1	11	6	3	2	1
66	11	11	1	0	1	0	11	6	2	3	1
67	12	11	1	1	0	0	11	6	2	3	0
68	13	11	1	1	0	0	11	7	3	4	0
69	14	11	1	1	0	0	11	7	4	2	1
70	1	9	1	1	0	0	9	3	3	0	0
6	2	9	2	2	0	0	9	4	3	1	0
	3	9	1	1	0	0	9	4	2	1	1
	4	9	1	1	0	0	9	2	0	0	2

Cycle	Day	Nausea					Fatigue								
		N(Tot)	N(Exp)	N0(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)				
	5	9	1	1	0	0	0	0	0	0	9	6	3	2	1
	6	9	0	0	0	0	0	0	0	0	9	5	1	2	2
	7	9	0	0	0	0	0	0	0	0	9	5	2	2	1
	8	9	0	0	0	0	0	0	0	0	9	4	3	0	1
	9	9	2	2	2	0	0	0	0	0	9	4	2	1	1
	10	9	0	0	0	0	0	0	0	0	9	4	2	1	1
	11	9	0	0	0	0	0	0	0	0	9	4	2	0	2
	12	9	0	0	0	0	0	0	0	0	9	4	3	0	1
	13	9	0	0	0	0	0	0	0	0	9	5	4	1	0
	14	9	0	0	0	0	0	0	0	0	9	4	1	3	0
7	1	8	0	0	0	0	0	0	0	0	8	4	2	1	1
	2	8	1	1	1	0	0	0	0	0	8	3	1	2	0
	3	8	2	2	2	0	0	0	0	0	8	4	2	2	0
	4	8	2	2	1	1	0	0	0	0	8	3	2	1	0
	5	8	2	2	2	0	0	0	0	0	8	4	2	2	0
	6	8	0	0	0	0	0	0	0	0	8	4	3	0	1
	7	8	1	1	1	0	0	0	0	0	8	3	1	2	0
	8	8	1	1	1	0	0	0	0	0	8	3	1	1	1
	9	8	1	1	1	0	0	0	0	0	8	2	1	1	0
	10	8	1	1	1	0	0	0	0	0	8	3	1	1	1
	11	8	1	1	1	0	0	0	0	0	8	4	2	2	0
	12	8	2	2	2	0	0	0	0	0	8	3	3	0	0
	13	8	1	1	0	1	0	0	0	0	8	3	2	1	0
	14	8	1	1	1	0	0	0	0	0	8	2	1	1	0
8	1	8	0	0	0	0	0	0	0	0	8	1	1	0	0
	2	8	0	0	0	0	0	0	0	0	8	1	1	0	0
	3	8	0	0	0	0	0	0	0	0	8	1	1	0	0

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	4	8	0	0	0	0	8	2	1	1	0
	5	8	0	0	0	0	8	2	2	0	0
	6	8	0	0	0	0	8	1	1	0	0
	7	8	0	0	0	0	8	1	1	0	0
	8	8	0	0	0	0	8	1	1	0	0
	9	8	0	0	0	0	8	1	1	0	0
	10	8	0	0	0	0	8	1	1	0	0
	11	8	0	0	0	0	8	2	2	0	0
	12	8	0	0	0	0	8	2	2	0	0
	13	8	0	0	0	0	8	2	2	0	0
	14	8	0	0	0	0	8	1	1	0	0
Group 3: Control site, Time 1											
1	1	30	16	11	5	0	30	13	8	5	0
	2	30	16	11	3	2	30	13	8	4	1
	3	30	13	7	4	2	30	12	7	5	0
	4	30	13	7	4	2	30	13	9	3	1
	5	30	13	10	2	1	30	21	14	5	2
	6	30	11	7	2	2	30	20	12	6	2
	7	30	8	5	2	1	30	18	14	3	1
	8	30	9	5	2	2	30	19	13	3	3
	9	30	7	5	1	1	30	13	8	2	3
	10	30	6	4	1	1	30	11	7	3	1
	11	30	4	0	2	2	30	15	12	2	1
	12	30	6	3	3	0	30	13	10	2	1
	13	30	3	1	1	1	30	10	7	3	0
	14	30	4	3	0	1	30	11	7	4	0
2	1	28	11	7	4	0	28	15	11	4	0

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	2	28	12	8	4	0	28	18	10	8	0
	3	28	13	8	4	1	28	19	9	9	1
	4	28	11	7	3	1	28	16	9	6	1
	5	28	9	7	2	0	28	17	10	5	2
	6	28	8	3	4	1	28	16	6	8	2
	7	28	8	5	2	1	28	15	8	4	3
	8	28	7	6	1	0	28	13	5	8	0
	9	28	5	4	1	0	28	11	5	6	0
	10	28	3	2	1	0	28	10	6	4	0
	11	28	3	2	1	0	28	13	9	3	1
	12	28	3	2	1	0	28	10	6	3	1
	13	28	3	1	2	0	28	11	5	4	2
	14	28	4	2	1	1	28	9	5	3	1
3	1	25	8	6	1	1	25	13	7	6	0
30	2	25	10	6	3	1	25	14	8	6	0
31	3	25	9	4	3	2	25	13	7	5	1
32	4	25	8	5	3	0	25	13	10	2	1
33	5	25	7	6	1	0	25	14	10	3	1
34	6	25	5	4	1	0	25	15	7	8	0
35	7	25	7	4	3	0	25	16	5	11	0
36	8	25	6	3	3	0	25	14	5	9	0
37	9	25	5	4	1	0	25	13	10	3	0
38	10	25	3	3	0	0	25	10	6	4	0
39	11	25	4	4	0	0	25	12	8	3	1
40	12	25	3	2	1	0	25	11	9	2	0
41	13	25	2	1	1	0	25	9	8	0	1
42	14	25	2	2	0	0	25	8	7	0	1

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
4	1	20	7	7	0	0	20	9	6	2	1
	2	20	8	6	2	0	20	10	5	4	1
	3	20	9	5	3	1	20	10	5	4	1
	4	20	7	4	3	0	20	11	6	5	0
	5	20	6	2	3	1	20	11	6	4	1
	6	20	5	2	3	0	20	10	5	5	0
	7	20	3	1	1	1	20	12	7	4	1
	8	20	4	2	2	0	20	12	7	5	0
	9	20	4	3	1	0	20	12	8	4	0
	10	20	4	3	1	0	20	9	5	4	0
	11	20	4	4	0	0	20	9	7	1	1
	12	20	3	3	0	0	20	9	7	2	0
	13	20	3	3	0	0	20	10	8	2	0
	14	20	2	2	0	0	20	7	5	2	0
5	1	14	2	2	0	0	14	5	5	0	0
	2	14	4	4	0	0	14	5	4	1	0
	3	14	4	2	2	0	14	7	4	3	0
	4	14	2	1	1	0	14	7	4	2	1
	5	14	3	2	1	0	14	5	1	2	2
	6	14	3	2	1	0	14	7	2	2	3
	7	14	2	1	1	0	14	6	2	3	1
	8	14	2	1	1	0	14	5	1	3	1
	9	14	3	1	2	0	14	4	2	1	1
	10	14	2	2	0	0	14	5	2	3	0
	11	14	2	2	0	0	14	4	2	2	0
	12	14	2	2	0	0	14	4	2	2	0
	13	14	2	2	0	0	14	4	2	2	0
	14	14	2	2	0	0	14	5	4	1	0

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
6	14	14	1	0	1	0	14	4	2	2	0
	1	9	2	0	2	0	9	5	5	0	0
	2	9	2	2	0	0	9	4	3	1	0
	3	9	2	1	1	0	9	5	2	3	0
	4	9	2	2	0	0	9	5	5	0	0
	5	9	1	1	0	0	9	6	6	0	0
	6	9	1	1	0	0	9	4	4	0	0
	7	9	1	0	1	0	9	5	5	0	0
	8	9	1	1	0	1	9	5	3	2	0
	9	9	1	1	0	0	9	4	2	2	0
	10	9	1	0	1	0	9	5	3	2	0
	11	9	1	1	0	0	9	6	5	1	0
	12	9	1	1	0	0	9	4	2	2	0
	13	9	1	1	0	0	9	5	3	2	0
7	14	9	0	0	0	0	9	6	5	1	0
	1	7	1	1	0	0	7	2	1	1	0
	2	7	1	1	0	0	7	3	2	1	0
	3	7	1	0	1	0	7	3	2	1	0
	4	7	1	1	0	0	7	3	1	2	0
	5	7	1	1	0	0	7	4	3	1	0
	6	7	1	1	0	0	7	2	1	1	0
	7	7	1	1	0	0	7	2	2	0	0
	8	7	1	1	0	0	7	4	3	1	0
	9	7	1	0	1	0	7	4	3	1	0
	10	7	1	1	0	0	7	2	0	2	0
	11	7	1	1	0	0	7	3	2	1	0
12	7	1	1	0	0	7	3	2	1	0	

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	13	7	2	2	0	0	7	3	2	0	1
	14	7	1	0	0	1	7	3	2	0	1
8	1	5	1	0	1	0	5	3	2	1	0
	2	5	1	0	1	0	5	3	1	2	0
	3	5	1	0	1	0	5	3	1	2	0
	4	5	1	1	0	0	5	2	0	2	0
	5	5	1	0	1	0	5	2	0	2	0
	6	5	1	1	0	0	5	2	1	1	0
	7	5	2	2	0	0	5	2	1	1	0
	8	5	2	2	0	0	5	2	1	1	0
	9	5	2	2	0	0	5	3	2	1	0
	10	5	1	1	0	0	5	3	1	2	0
	11	5	1	1	0	0	5	3	2	0	1
	12	5	0	0	0	0	5	3	2	1	0
	13	5	0	0	0	0	5	3	2	1	0
	14	5	0	0	0	0	5	2	1	1	0
Group 4: Control site, Time 2											
1	1	25	5	3	1	1	25	9	4	5	0
	2	25	7	5	1	1	25	7	5	1	1
	3	25	5	2	2	1	25	9	7	1	1
	4	25	5	2	3	0	25	9	4	4	1
	5	25	3	1	2	0	25	10	7	2	1
	6	25	4	2	1	1	25	10	4	4	2
	7	25	3	2	1	0	25	9	5	2	2
	8	25	3	3	0	0	25	9	7	2	0
	9	25	1	1	0	0	25	8	5	3	0
	10	25	1	1	0	0	25	10	6	4	0

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	11	25	0	0	0	0	25	9	7	2	0
	12	25	0	0	0	0	25	7	6	1	0
	13	25	0	0	0	0	25	5	2	3	0
	14	25	1	1	0	0	25	8	6	3	0
2	1	19	8	4	3	1	19	9	6	3	0
	2	19	10	6	4	0	19	11	8	2	1
	3	19	7	4	2	1	19	13	9	4	0
	4	19	8	6	2	0	19	13	9	3	1
	5	19	7	5	1	1	19	12	6	4	2
	6	19	6	5	0	1	19	10	3	4	3
	7	19	6	4	1	1	19	10	4	5	1
	8	19	3	3	0	0	19	13	9	2	2
	9	19	3	3	0	0	19	10	6	3	1
	10	19	1	1	0	0	19	11	6	4	1
	11	19	2	2	0	0	19	9	4	5	0
	12	19	1	1	0	0	19	11	6	5	0
	13	19	1	1	0	0	19	10	6	4	0
	14	19	0	0	0	0	19	10	7	3	0
3	1	18	8	2	3	3	18	11	5	5	1
	2	18	8	5	3	0	18	6	2	4	0
	3	18	8	5	3	0	18	10	6	3	1
	4	18	5	2	3	0	18	11	8	2	1
	5	18	5	2	3	0	18	10	7	2	1
	6	18	7	6	1	0	18	10	6	3	1
	7	18	4	1	3	0	18	12	3	6	3
	8	18	4	3	1	0	18	12	4	5	3
	9	18	2	1	1	0	18	10	6	4	0

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	10	18	2	2	0	0	18	11	8	3	0
	11	18	1	1	0	0	18	12	6	6	0
	12	18	1	1	0	0	18	10	8	2	0
	13	18	1	1	0	0	18	10	7	3	0
	14	18	1	1	0	0	18	10	7	3	0
4	1	18	8	5	2	1	18	11	7	4	0
	2	18	6	3	3	0	18	10	3	6	1
	3	18	6	3	3	0	18	11	6	5	0
	4	18	6	3	2	1	18	10	5	4	1
	5	18	3	1	2	0	18	9	3	5	1
	6	18	4	2	2	0	18	12	5	5	2
	7	18	3	2	1	0	18	11	5	3	3
	8	18	3	1	2	0	18	10	4	3	3
	9	18	2	2	0	0	18	10	5	3	2
	10	18	2	2	0	0	18	10	5	4	1
	11	18	2	2	0	0	18	11	7	3	1
	12	18	1	1	0	0	18	10	5	4	1
	13	18	2	2	0	0	18	9	4	4	1
	14	18	1	1	0	0	18	8	4	4	0
5	1	18	9	3	6	0	18	11	7	3	1
	2	18	11	4	6	1	18	12	5	7	0
	3	18	10	5	4	1	18	13	6	5	2
	4	18	11	6	5	0	18	16	7	7	2
	5	18	10	5	5	0	18	14	7	4	3
	6	18	7	4	3	0	18	13	6	7	0
	7	18	6	4	2	0	18	14	8	6	0
	8	18	8	4	4	0	18	13	5	8	0

Cycle	Day	Nausea					Fatigue				
		N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)	N(Tot)	N(Exp)	N(Mild)	N(Mod)	N(Sev)
	9	18	6	3	3	0	18	12	4	7	1
	10	18	5	4	1	0	18	13	4	8	1
	11	18	5	4	1	0	18	14	8	5	1
	12	18	5	4	1	0	18	12	6	5	1
	13	18	3	3	0	0	18	13	6	6	1
	14	18	2	1	1	0	18	11	5	5	1
6	1	18	10	7	3	0	18	8	6	1	1
	2	18	10	5	4	1	18	13	5	6	2
	3	18	9	6	3	0	18	12	5	6	1
	4	18	8	3	5	0	18	12	4	6	2
	5	18	7	4	3	0	18	15	7	6	2
	6	18	6	4	2	0	18	16	8	6	2
	7	18	4	3	1	0	18	13	4	7	2
	8	18	8	5	3	0	18	14	5	6	3
	9	18	10	4	6	0	18	13	6	4	3
	10	18	9	5	4	0	18	12	6	3	3
	11	18	6	4	2	0	18	11	4	5	2
	12	18	4	2	2	0	18	12	8	2	2
	13	18	4	2	2	0	18	12	6	6	0
	14	18	5	4	1	0	18	8	5	3	1
7	1	14	9	7	2	0	14	10	6	3	1
	2	14	8	3	5	0	14	10	4	4	2
	3	14	8	4	3	1	14	9	5	3	1
	4	14	6	3	3	0	14	10	4	5	1
	5	14	5	3	2	0	14	11	5	3	3
	6	14	4	2	2	0	14	9	3	5	1
	7	14	3	3	0	0	14	8	4	4	0