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**Treatment-related problems experienced by cancer patients undergoing chemotherapy: a scoping review**

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**Treatment-related problems experienced by cancer patients undergoing chemotherapy: a scoping review**

**ABSTRACT**

Cancer patients undergoing chemotherapy experience a range of treatment-related problems, and variations in prevalence exist between treatment centres. A scoping review was undertaken to map reported rates of problem prevalence in the literature. This will inform development of a patient-reported outcome measure (PROM) to monitor prevalence and severity of problems over time and assist service providers optimise supportive care provision. Two databases (Embase and Medline) were searched from 2002 to 2013. Fifty one published papers and conference abstracts reporting problem prevalence rates were identified. The papers reported 98 different problems, from which a typology of 27 problem domains was developed, including both physical symptoms and psychosocial issues. The problem domains most often studied were nausea, vomiting and fatigue. This review reflects the chemotherapy-associated problems to which researchers attach the most importance. The range in reported prevalence across studies was very broad (e.g. nausea: 9-74%), with even less frequently studied problems showing high prevalence in some studies (e.g. gynaecological problems: up to 94%). The wide variation in prevalence and range of problems experienced raises challenges for PROM development. Patients should therefore be involved in consensus exercises to assist selection of items to ensure any instrument is complete and robust.

Key words: Cancer; Chemotherapy; Symptoms; Quality of Life; Supportive Care

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**INTRODUCTION**

People being treated for cancer frequently experience a range of physical, psychological and social problems associated with chemotherapy that can reduce quality of life (QoL). The extent of such problems can vary substantially between cancer treatment centres even after controlling for case mix (Armes et al. 2011) as can the corresponding support services designed to address those problems (Hjorleifsdottir et al. 2010; Mort et al. 2008; Malin et al. 2006; Weingart et al. 2007; Ekwall et al. 2011). Chemotherapy drugs are constantly evolving and while for some cancer types the regimens used will have become increasingly aggressive over time, with greater potential toxicities and related problems, for other cancers they will have become less so. Some between centre variations in prevalence of treatment-associated problems may be explained by differences in treatment regimens used and drugs such as anti-emetics used for management of their side-effects. Different socio-demographic characteristics and patient expectations may also play a part in variations.

Increasing recognition that patient-reported outcome measures (PROMs) can convey important information for assessing the condition of patients has led to much work to develop psychometrically sound and clinically meaningful PROMs (Lipscomb et al. 2007). Internationally recognised systems measuring toxicity of cancer treatment exist, such as the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in the United States (NIHR 2013). Taxonomies of cancer patient-reported outcome domains are being developed in the form of the Patient Reported Outcomes Measurement Information System (PROMIS) in the United States (Cella et al. 2006; Garcia et al. 2007), and the PROMS-Cancer Core in Canada (Howell et al. 2013). At the same time Cancer Patient Experience Surveys (CPES) in the UK are conducted to explore the experiences of all cancer patients, which have indicated significant variation in reported experiences of patients undergoing chemotherapy between providers (DH 2013). Work is also on-going to develop the routine use of computer-based questionnaires and remote monitoring systems that measure and feed-back individual patients’ real-time health-related QoL (HRQoL) and symptom profiles to clinicians (Velikova et al. 2004; 2002). This approach can improve patient-physician communication regarding symptoms and psychosocial problems and so improve the delivery of care (Velikova et al. 2002).

However, despite these developments there is still a need for a PROM to assess the prevalence and severity of treatment-related problems experienced by patients in chemotherapy units and the extent to which supportive care addresses these problems. Toxicity scales do not include all the problems chemotherapy patients potentially find most bothersome, and core PROM domains do not allow patients to record perceived adequacy of supportive care they receive. Moreover, while real-time patient-to-health professional feedback of HRQoL enhances care on an individual level it does not readily allow assessment of a whole unit.

The treatment-related problems to be measured by such a PROM should be those experienced by patients treated for the most common tumour types that affect 90% of cancer patients: breast; haematological; gastrointestinal; urological; lung and gynaecological (DH 2013). The PROM could then be used to monitor the prevalence of problems experienced by patients within chemotherapy departments, how they change over time depending upon case-mix, treatment regimens used and other patient characteristics, and to allow service providers optimise supportive care interventions to address them.

The aim of this scoping review was to explore the existing research on the most frequently researched problems experienced by patients and their reported prevalence. The problem list generated will be ranked from most to least reported prevalence as the first step in identifying those that should be considered in any PROM development. The next step will be to gain consensus by an expert reference panel comprising clinicians and former patients to reach agreement on the importance of each problem identified, the severity of problems when experienced, and whether any further problems should be included within the PROM that are rarely reported in the literature. A key strength of a scoping study is that it can provide a rigorous and transparent method for mapping the extent, range and nature of research activity, especially in broader topic areas where many different study designs may be used, or where it is difficult to visualise the range of relevant material (Arksey & O’Malley 2005; Davis et al. 2009; Levac et al. 2010).

**METHODS**

**Data sources and inclusion criteria**

Two electronic databases (Embase and Medline) were searched from 2002 to 2013. Advances in chemotherapy in the previous decade means the types and prevalence of treatment-associated problems experienced prior to this date range may be quite different. A combination of search terms included Medical Subject Headings and text words available in Medline: (oncology OR cancer OR neoplasm OR tumour) AND (symptom\* prevalence/ burden OR experience OR quality of life /(QoL) OR (social function) AND (chemotherapy). Studies were eligible if they reported in English as full manuscript peer reviewed journals or as published scientific conference abstracts, and reported on the prevalence of one or more problems experienced by patients receiving cytotoxic chemotherapy. We also scrutinised reference lists of relevant papers to identify additional material, reaching a saturation point where no new papers were found.

We included longitudinal or cross sectional studies on samples of patients who were being treated for one or more of the most common tumour types: breast, haematological, gastrointestinal, urological, lung and gynaecological (DH 2013). We also included reviews of evidence which met our inclusion criteria and where findings related to the population of interest. Studies were excluded if they: compared treatments impacting on disease or treatment related problems; included children (<18) or patients undergoing concurrent radiotherapy, or populations from lower frequency tumour groups; investigated problem persistence amongst survivors; reported only mean scores or only assessed impact of problems on global QoL.

**Data abstraction and management**

Endnote was used to manage the references retrieved and an abstraction tool was utilised to ensure consistent findings were extracted across studies. From a total 935 references, 315 duplicates were removed. The abstracts of the remaining 620 papers were read and the relevance of each study assessed against the inclusion/ exclusion criteria. Although meta-prevalence scores for some problems were provided by some systematic reviews, these were not included within the scoping review as they included studies that would otherwise have been excluded (i.e. published before 2002 or involving excluded cancer types). Rather, papers cited within reviews were separately assessed for eligibility for the scoping review. Where two papers reported the same problem prevalence amongst largely the same population of individuals (i.e. multiple reports from the same study) the study that reported most problems or highest prevalence rates was included and the others excluded, irrespective of year of publication. Similarly, for longitudinal studies reporting problem prevalence changes over time within a population sample the time point included within the review was that with the highest prevalence rate.

**ANALYSIS**

The process of conducting a scoping review is an iterative rather than linear process, requiring researchers to engage with each stage in a reflexive way (Arksey & O’Malley 2005; Levac et al. 2010). Two researchers (RW and PG) reviewed abstracts for inclusion, and any disagreement was discussed with a third reviewer (AR). Papers were then read and the prevalence rates of particular problems extracted. The final list of studies proposed for inclusion was circulated and discussed at a full team meeting.

The analysis of included studies involved three steps. Firstly, the disparate definitions of problems reported within included studies were categorised thematically into domains within a workable problem typology. Secondly, we identified the frequency with which problems that fell into each of the typology’s problem domains were studied. Thirdly, the reported rates of prevalence within each of the categorised problem domains were explored.

**RESULTS**

The search strategy identified 625 papers once duplicates were removed, of which fifty one papers were finally included within the scoping review following application of the exclusion criteria (see Table 1). The studies incorporated 10,092 participants, mean number per study 198 (median: 120).

**Categorisation of problem definitions**

Amongst the included studies there were 40 different outcome measurement instruments used to determine the prevalence of problems amongst participant samples, with some studies incorporating several tools (see Table 1). Some studies used instruments designed for assessment of single problems (i.e. Beck Anxiety Index; Multi-dimensional Fatigue Inventory) (Steer et al. 1997), or two problems (Hospital Anxiety and Depression Scale (HADS) (Zigmond et al. 1983), while other studies used instruments that covered several (i.e. Symptom Distress Scale (SDS), Rotterdam Symptom Checklist) (McCorkle et al. 1999; Haes et al. 1996).

This diverse group of instruments provided a total of 98 different problem definitions, with associated prevalence rates. These ranged from symptoms and syndromes that could be clinically defined (e.g. anxiety, depression, malnourishment and cognitive impairment) through physical problems that were clearly observable (i.e. vomiting, alopecia), subjectively experienced physical and psychological problems (e.g. fatigue) to self-reported social and financial problems. While the terms used to describe some problems were similar across instruments (e.g. diarrhoea, constipation, hair loss) other problems could be described in several ways in different tools (e.g. ‘appetite loss’, ‘poor appetite’, ‘lack of appetite’ and ‘change in appetite’).

To make the disparate terminology manageable, and render the findings useable, it was necessary to combine differently defined problems into a smaller number of problem domains, and to exclude problems very rarely reported. Terms that were similar were easily categorised, others required discussion within the team. For some problem domains, such as ‘pain’, different studies using different instruments described different types of pain, including ‘joint pain’, ‘muscle pain’, ‘generalised pain’, ‘stomach pain’ and ‘lower abdominal pain’. For the purposes of this study, however, they were coded together in one problem domain. Similarly, the two symptoms reported by Kohli et al. (2007), ‘memory problems’ and ‘concentration problems’, were both incorporated into the ‘cognitive problems’ domain. The greatest number of problem definitions collapsed in this way were the seven different types of pain identified by the Rotterdam Symptom Checklist (Haes et al. 1996) reported by Skerman et al. (2012).

Eventually 27 separate problem domains were developed from the total number of problem definitions reported in the studies (see Table 2). There were, however, several problem definitions that were identified by only one instrument and only reported in one included study. Consequently, these were not included within the typology of problem domains we developed. Amongst these were ‘relationships with others’ and ‘bloating’. Only one included study reported prevalence of the negative impact chemotherapy had upon patients’ social relationships (Farrell 2005).

**Frequency of reported problem domains across included studies**

Once agreement was reached within the team on the typology of problem domains, the next step was to rank the frequency with which these problem domains were identified in studies, and the prevalence rates reported for them. The resulting ranking of the domains illustrates the problems that authors of studies had determined as the most important to report. As indicated by Table 3, the problem domain in which the most number of studies reported prevalence rates was nausea (n=22), followed in descending order by vomiting (n=19), fatigue (n=18), depression (n=14), cognitive problems (n=13) and pain (n=13). Problem domains such as dietary problems, alopecia, drowsiness and weight changes were reported on by less than a quarter the number of studies reporting nausea. The domain reported by the least number of studies (n=2) was urinary problems.

**Prevalence of problem domains**

The problem domains include a range of rates of prevalence recorded across the studies. As can be seen in Table 3, these prevalence ranges were often very broad, with reported incidence of the most commonly studied problems ranging from 9-74% for nausea, 5-70% for vomiting, and between 11-100% for fatigue. The reasons for prevalence variations remain unclear and may be the consequence of different measurement scales, different participant characteristics, or of the way in which problems were categorised.

**DISCUSSION**

This scoping review illustrates that patients being treated for common cancers experience a wide range of problems. In addition to the commonly studied problems such as nausea, vomiting and fatigue other problems which are not so commonly studied such as drowsiness, weight changes and dizziness are also reportedly highly prevalent for patients with common cancers. Nevertheless, there is great uncertainty in determining overall prevalence rates for these problems given the heterogeneity of measurement tools used in the studies reporting them. This uncertainty presents challenges for services seeking to ensure they are equipped to provide support to patients experiencing problems associated with their treatment.

The experience of problems is subjective, as indicated by two studies that sought to compare the degree of impairment reported by patients with that objectively measured by clinicians (Schagen et al. 2008; Schilling et al. 2005). In both studies the proportion of patients reporting cognitive problems with memory and concentration exceeded the numbers showing measurable objective decline, and it was suggested that perceived cognitive impairment was more closely associated with emotional distress, fatigue and poor QoL (Schagen et al. 2008; Schilling et al. 2005). Three studies also showed how problems experienced by patients were frequently undetected by health care professionals (HCPs) (Farrell 2005; Grunberg et al. 2004; Liau et al. 2005). If HCPs are to adequately address the information and support needs of patients undergoing chemotherapy, then patients need a method of communicating the nature of the problems they experience, their severity and extent.

Different chemotherapy regimens cause different problems (Cooley et al. 2003; Sun et al. 2005), and evidence also suggests that problems cancer patients undergoing chemotherapy perceive most bothersome change from one decade to the next (Carelle et al. 2002). This may in part be due to advances in chemotherapy and associated supportive treatments such as anti-emetics. Coates et al. (1983) were one of the first research teams to identify the most troubling treatment-related problems for patients, and found vomiting, nausea and alopecia to be the three worst. Griffin et al. (1996) conducted a similar study ten years later and found vomiting was less prevalent, ranking it fifth, with nausea, fatigue and alopecia reported as most prevalent. Griffin et al. (1996) also noted an emerging shift from concerns about physical side-effects to psychosocial issues. Seventeen years on Carelle et al. (2002) found the most troubling problem faced by patients was now psychological. Indeed, evidence confirms that patients’ chemotherapy-associated problems impact on others, especially carers who find them stressful (Ream et al. 2013), and often miss days at work when providing care (Curt et al. 2000). However, this shift to emotional concerns was not reflected in research included in this scoping review, with only one included study reporting prevalence of such concerns amongst participants (Farrell 2005). Indeed, most previous research focussed on identification of the most common physical and life-threatening side-effects and toxicities informing treatment dose reductions, rather than exploring the full range of potentially bothersome problems.

As noted, Carelle et al. (2002) found alopecia to be one of the most severe physical problems reported by chemotherapy patients after nausea. A systematic review of 38 studies examining evidence of the effects of alopecia on QoL also found it to be consistently ranked amongst the most distressing treatment-related problems, with evidence that some women refuse or consider refusing chemotherapy because of the risk of hair loss (Lemieux et al. 2008). However, while this scoping review reflects the importance of nausea to patients, ranked as the problem for which the most number of studies (n=22) reported prevalence, this is not the case for alopecia, where it is ranked seventeenth with only five studies reporting prevalence. None of the 16 studies reviewed by Lemieux et al. (2008) and published after 2002 reported prevalence rates. Moreover, while eight of the studies included in this scoping review that reported prevalence of nausea were specifically designed to examine the impact of that problem (with vomiting), the five studies reporting alopecia prevalence only did so as part of reporting multiple symptoms.

The relatively small number of symptom scales that include alopecia and paucity of recent studies reporting its prevalence amongst chemotherapy patients may be an example of the previous focus of research upon life-threatening toxic side-effects outlined above. Nevertheless, the literature has shown alopecia to be an important concern for patients and just as the incidence and prevalence of particular problems change over time, so too may the types of problems investigated by researchers. Such changes confirm the importance of obtaining on-going feedback from patients as both cancer treatments and supportive therapies continue to evolve.

The findings from this scoping review will now inform the development of a PROM that attends to a broad range of physical, emotional and social patient concerns. Variations in type, prevalence and range of such problems reported in the literature nevertheless raise challenges for developing a PROM that both accurately reflects the subjective problems most commonly experienced by the majority of cancer patients undergoing chemotherapy, and the outcomes of supportive care designed to address them. The next step in PROM development, therefore, is to conduct a consensus exercise with a reference panel comprising clinicians and former patients to garner their views on the frequency that each of the identified problems occur in individuals receiving chemotherapy and, for those who experience the problem, how often it is severe. The consensus exercise would also determine whether there were still important items missing from the list, as the problems most often researched are not necessarily those most frequently experienced. Integrating data from different sources in this way will ensure the final PROM is complete and robust.

**Study limitations**

A strength of scoping reviews of this kind is that a wide range of study designs and methods are included, while an associated weakness is that it does not undertake quality assessment of included studies or synthesize findings (Arksey & O’Malley 2005; Levac et al. 2010). Included studies had wide variations in participant numbers and associated prevalence rates. Moreover, smaller studies involving fewer participants usually reported higher prevalence rates than studies with larger participant numbers. A methodological issue emerged with the categorisation of problems reported in studies into typology domains, when very specific problems (e.g. heavy menstrual flow) and vaguer and possibly overlapping problems (e.g. menopausal problems) were sometimes categorised together into one domain (e.g. gynaecological problems). The consequence might be to give a misleading rate of prevalence within those domains. Another limitation is that chemotherapy treatments are constantly evolving and while treatment-related problems will vary for patients depending upon the chemotherapy drugs administered, no analyses were conducted to adjust problem prevalence rates according to different treatment regimens. Such analysis would be difficult as many of the included papers incorporated patients on various regimens. Moreover, our aim was to develop a generic PROM for use without adjustment in any cancer chemotherapy setting. Finally, because of the broad scope of the search and range of potential papers this review may not be a fully comprehensive list. Nevertheless, we reached a saturation point where hand searching references of papers identified no new papers. Thus we consider it is representative of the body of literature as a whole and forms an appropriate basis for a scoping study.

**Conclusion**

This scoping review identified problems experienced by patients undergoing cancer chemotherapy treatment that included both symptoms and psychosocial issues. Great uncertainty exists regarding problem prevalence but even problems that appear to be under-researched (e.g. psychosocial problems) may have high prevalence for patients with common cancers. These findings will help inform PROM development to measure incidence of a broad range of problems amongst cancer patients receiving treatment in chemotherapy units and facilitate targeted supportive care.

**Conflicts of interest**

There are no conflicts of interest for any of the authors.

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**Table 1: Studies included within the scoping review**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **No. of patients**  | **Study design** | **Objective** | **Prevalence of problem domains reported**  | **Tools used** |
| Harder et al (2003) | 19 | Case control | To evaluate cognitive status and QoL amongst cancer patients | Cognitive problems | Battery of cognitive tests, including items from: * Wechsler Memory Scale Revised (WMS-R)
* Wechsler Adult Intelligence Scale-Revised (WAIS-R)
* D2 Test
 |
| Cooley et al (2003) | 117 | Longitudinal | To describe which symptoms are most distressing, prevalence of symptoms, and how they change over time | Fatigue; pain; constipation; sleep problems; chest problems | * Symptom Distress Scale (SDS)
 |
| De Jong et al (2004) | 157 | Cohort study  | To determine prevalence and course of fatigue as a function of chemotherapy  | Fatigue  | * Rotterdam Symptom Checklist
* Multi-dimensional Fatigue Inventory
 |
| Hipkins et al (2004) | 63 | Longitudinal  | To describe the levels of anxiety and depression in patients in 3 months following chemotherapy | Depression; anxiety | * Hospital Anxiety and Depression Scale (HADS)
 |
| Glaus et al (2004) | 243 | Cross-sectional | To evaluate the occurrence of CINV and effects on daily life activities | Nausea  | * Patient diaries
* Visual Analogue Scale (VAS)
* Functional Living Index for Emesis (FLIE)
 |
| Grunberg et al (2004) | 298 | Observational  | To determine the incidence of acute and delayed CINV | Nausea and vomiting  | * Staff questionnaire on observed incidence of CINV
* Patient diaries (6 days)
 |
| Williams et al (2004) | 38 | RCT(Prevalence reported for the control group only) | To determine the effectiveness of informational audiotapes on self-care behaviours; to describe the occurrence and intensity of common side-effects  | Nausea; vomiting; fatigue; taste & smell | * Patient diaries
 |
| Wefel et al (2004) | 18 | Longitudinal  | To evaluate the incidence, nature, severity and chronicity of cognitive dysfunction among patients with BC receiving CT | Cognitive problems | Battery of cognitive tests including items from: * Verbal Selective Reminding Test (VSRT)
* Wechsler Adult Intelligence Scale-Revised (WAIS-R)
* Nonverbal Selective Reminding Test (NVSRT)
* Multilingual Aphasia Examination (MAE)
* Minnesota Multiphasic Personality Inventory (MMPI)
 |
| Liau et al (2005) | 107 | Observational  | To determine incidence and prevalence of acute and delayed CINV among pts receiving CT and assess accuracy with which medical providers perceive the incidence of CINV  | Nausea; vomiting  | * Visual Analogue Scale (VAS)
 |
| Farrell et al (2005) | 104 | Cross-sectional | To identify key concerns of cancer patients receiving in-patient chemotherapy | Nausea; vomiting; cognitive problems; depression; anxiety; job/ financial | Concerns Checklist (bespoke tool used in a previous study)* Hospital Anxiety and Depression Scale
 |
| Nieboer et al (2005) | 430 | Longitudinal  | To determine whether standard or high dose CT leads to fatigue and other factors | Fatigue; pain | * Fatigue – vitality scale
* Muscle and joint pain – Rotterdam Symptom Scale
 |
| Cheung et al (2005) (CA) | 85 | Cross sectional  | To compare severity of perceived cognitive disturbance in patients receiving CT and those not receiving CT. | Cognitive problems; anxiety | * Functional Assessment of Cancer Therapy – Cognitive Function (FACT\_Cog)
* Beck Anxiety Inventory
 |
| Chate (2006) | 40 | Pilot audit  | To identify how many patients attending an upper GI oncology OPD had weight loss or nutritional problems | Nausea; fatigue; pain; mouth, throat & Swallowing; constipation; appetite; taste & smell; diarrhoea; dietary problems; weight changes; indigestion | * Short questionnaire specifically designed for the study
 |
| Downie et al (2006) | 21 | Observational  | To examine the relationship between experience with fatigue, menopausal symptoms and cognitive performance in patients treated with chemotherapy | Fatigue, cognitive problems; gynaecological  | * High Sensitivity Cognitive Screen (HSCS)
* Functional Assessment of Cancer Therapy – Fatigue (FACT-F)
* FACT – Endocrine Symptoms (FACT-ES)
* Interview
 |
| Jenkins et al (2006) | 85 | Longitudinal  | To identify impact of cancer treatment on cognitive functioning | Cognitive problems | * Cognitive test battery assessing several broad areas of cognitive function
 |
| Pandey et al (2006) | 117 | Observational  | To evaluate the effect of CT on anxiety and depression  | Depression; anxiety | * Hospital Anxiety and Depression Scale (HADS)
 |
| Hurria et al (2006) | 28 | Longitudinal | To report longitudinal cognitive functioning of older adults receiving adjuvant chemotherapy | Cognitive problems | * Neuropsychological battery of tests across seven domains: attention; verbal memory; visual memory; and verbal. Spatial and psychomotor.
 |
| Booth et al (2007) | 143 | Observational  | To evaluate CINV in patients with breast cancer | Nausea and vomiting | * Patient daily diaries
 |
| Ballatori et al (2007) | 152 | Observational | To estimate frequency of patients reporting CINV on daily life and evaluate determinants of impact | Nausea; vomiting | * Functional Living Index-Emesis (FLIE)
 |
| Hoffman et al (2007) | 80 | Secondary analysis of a RCT  | To examine relationships between pain, fatigue and insomnia | Nausea; vomiting; fatigue; cognitive problems; pain; mouth, throat & swallowing; constipation; appetite; diarrhoea; sleep problems; chest problems; fever/chills;  | * Cancer Symptom Experience Inventory
 |
| Hermelink et al (2007) | 101 | Longitudinal  | To determine whether cognitive impairment is attributable to chemotherapy | Cognitive problems | * Battery of cognitive tests, including items from:
* Wechsler Memory Scale Revised (WMS-R)
* Wechsler Adult Intelligence Scale-Revised (WAIS-R)
* D2 Test
* Trail Making Test Part B (TMT-B)
* Regensburg Word Fluency Test (RWT)
 |
| Kohli et al (2007) | 595 |  | To investigate the frequency and severity of self-reported problems with memory and concentration | Cognitive problems | * Adapted University of Texas M.D. Anderson Symptom Inventory (MDSAI)
 |
| Chou et al (2007) | 25 | Cohort Study | To explore the cancer experience among patients during chemotherapy | Nausea; fatigue; depression; pain; mouth, throat & Swallowing; constipation; appetite; sleep problems; alopecia; drowsiness;  | * Memorial Symptom Assessment Scale (MSAS)
 |
| Chen et al (2008) | 115 | Longitudinal  | To describe the sleep disturbances of patients undergoing their fourth cycle of chemotherapy | Sleep problems | * Pittsburg Sleep Quality Index (PSQI)
 |
| Bernhardson et al (2008) | 518 | Observational  | To explore prevalence of self-reported taste and smell changes during chemotherapy | Nausea; vomiting; fatigue; cognitive problems; depression; pain; mouth, throat and swallowing; constipation; appetite; taste and smell; diarrhoea; sleep problems; mood change/emotional distress; alopecia  | * Questionnaire specifically designed for study, informed by findings of previous qualitative study
 |
| Jensen et al (2008) | 45 | Longitudinal case control | To examine oral mucosal lesions, microbial changes and taste disturbances induced by CT  | Mouth, throat & swallowing | * Oral mucosa changes assessed by clinical examination
* Candida smear test
 |
| Molassiotis et al (2008) | 102 | Longitudinal  | To assess levels of CT induced nausea and vomiting in routine practice | Nausea; vomiting | * MASCC Antiemesis Tool
 |
| Gwede et al (2008) | 133 | Longitudinal  | To explore differential experience of chemotherapy related symptoms | Nausea; vomiting; fatigue; cognitive problems; pain; mouth, throat & swallowing; constipation; appetite; taste & smell; diarrhoea; sleep problems; mood change/ emotional distress; alopecia; drowsiness; weight changes; skin problems; fever/chills; indigestion; numbness/ tingling; dizziness; gynaecological | * Memorial Symptom Assessment Scale (MSAS)
 |
| Schagen et al (2008) | 70 | Cross sectional | To examine both cognitive complaints and neuropsychological performance of cancer patients following CT | Cognitive problems | * Objective - Cognitive neuropsychological tests
* Subjective – interviews with likert scale questionnaire asking to indicate experience of cognitive problems in domains of memory, attention, thinking and language.
 |
| Yamagishi et al (2009) | 462 | Observational  | To identify symptom prevalence and intensity in cancer patients receiving CT  | Nausea; fatigue; depression; pain; mouth, throat & swallowing; constipation; appetite; sleep problems; chest problems; mood change/ emotional distress; drowsiness; numbness/ tingling | * MD Anderson Symptom Inventory (MDSAI)
 |
| Haiderali et al (2009) | 192 | Observational  | To examine the clinical burden and economic impact of CINV  | Nausea; Vomiting | * Patient diaries
* Functional Living Index-Emesis (FLIE)
* Work Productivity and Assessment Inventory-N/V (WPAI-NV)
* Case report forms
 |
| So et al (2010) | 130 | Cross-sectional | To examine anxiety and depression and their effects on the quality of life of BC patients undergoing CT | Depression; anxiety | * Hospital Anxiety and Depression Scale (HADS)
 |
| Saevarsdottir et al (2010) | 144 | Longitudinal | To describe QoL and symptoms of anxiety and depression | Anxiety; Depression | * HADS
 |
| Barton et al (2010) | 152 | Longitudinal  | To describe the degree of bother produced by symptoms before, during and up to two years after adjuvant treatment | Fatigue  | * Greene Climacteric Scale (GCS)
 |
| Fernandez-Ortega et al (2010) | 160 | Observational  | To analyse the impact of CINV on quality of life | Nausea and vomiting | * Patient diaries
* Functional Living Index-emesis (FLIE)
 |
| Debess et al (2010) | 120 | Longitudinal  | To examine cognitive function in patients before and after chemotherapy | Fatigue; cognitive problems; depression; anxiety; mood changes/ emotional distress | * Neuropsychological test battery from the International Study of Postoperative Cognitive Dysfunction (ISPOCD)
* Profile of Mood States (POMS)
 |
| Isenring et al (2010) | 191 | Cross-sectional | To identify prevalence of malnutrition, utilisation of nutrition resources, patient nutrition needs, external sources of nutritional information | Nausea; vomiting; pain; mouth, throat & swallowing; constipation; appetite; taste & smell; diarrhoea; dietary problems | * Patient Generated-Subjective Global Assessment (PG-SGA)
 |
| Zabernigg et al (2010) | 197 | Longitudinal  | To assess prevalence of taste alterations | Taste & smell | * Two items concerning taste alterations taken from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 EORTC QLQ-C30)
 |
| Loeliger et al (2011) | 88 | Longitudinal | To investigate changes in nutritional status among CT patients | Dietary problems | * Patient Generated-Subjective Global Assessment (PG-SGA)
 |
| Perwitasari et al (2011) | 178 | Cohort study | To examine the impact of delayed CINV on QoL | Vomiting | * Patient diaries
 |
| Pirri et al (2011) | 200 | Longitudinal  | To examine CINV incidence and its risk factors | Nausea; vomiting | * Symptom scales from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 EORTC QLQ-C30)
 |
| Spichiger et al (2011) | 77 | Longitudinal  | To explore prevalence of symptoms, with focus on fatigue and changes of symptoms over 3 months in OPD receiving CT | Nausea; vomiting; fatigue; cognitive problems; depression; pain; mouth, throat & swallowing; anxiety; constipation; appetite; taste & smell; diarrhoea; sleep problems; chest problems; alopecia; drowsiness; weight changes; skin problems; fever/chills; numbness/ tingling; dizziness; urinary | * Memorial Symptom Assessment Scale (MSAS)
* Fatigue measured by Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale
 |
| Daudt et al (2012) | 252 | Observational  | To evaluate screening for nutritional and psychosocial status of patients at an OPD oncology clinic | Depression; anxiety; dietary problems | Retrospective chart review of health assessment forms, which included:* Nutritional (Patient-Generated Subjective Global Assessment), and
* Psychological (Psychological Screen for Cancer)
 |
| Kaufman et al (2012)(CA) | 188 | Cohort  | To explore correlations between HRQoL, symptoms and ADLs and work productivity of a subsample of participants of a larger study  | Job/ financial | * Work Productivity and Activity Impairment Questionnaire (WP)
 |
| Gamper et al (2012) | 103 | Longitudinal  | To examine prevalence and severity of taste alterations and their impact on QoL  | Taste and smell | * EORTC-QLQ-C30 with two validated items taken from the EORTC item bank concerning taste alterations
 |
| Rey et al (2012) | 222 | Longitudinal Cohort study | To describe the prevalence and evolution of self-reported cognitive impairment | Depression | * Centre for Epidemiological Studies Depression Scale (CES-D)
 |
| Halawi et al (2012) | 100 | Cross-sectional  | To assess symptom profiles of chemotherapy patients in Lebanon | Nausea; vomiting; fatigue; pain; mouth, throat & swallowing; constipation; appetite; taste & smell; diarrhoea; chest problems; dietary problems; weight changes; skin problems; fever/chills; indigestion; urinary  | * National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
 |
| Skerman et al (2012) | 202 | Longitudinal  | To investigate symptom clusters over time for symptom management of patients after commencement of CT | Nausea; vomiting; fatigue; pain; mouth, throat & swallowing; constipation; appetite; taste & smell; diarrhoea; sleep problems; chest problems; alopecia; drowsiness; weight changes; skin problems; fever/chills; indigestion; numbness/ tingling; dizziness | * (clinician modified) Rotterdam Symptom Checklist (42 physical symptoms)
 |
| Pertle et al (2012)(CA) | 186 | Longitudinal  | To explore the trajectory of fatigue from before chemotherapy and to examine the predictors of fatigue over time | Fatigue  | * Not stipulated (questionnaires)
 |
| Farrell et al (2013) | 33 | Observational | To assess impact of nausea on nutritional status | Depression; anxiety; mood change/ emotional distress | * Multinational Association of Supportive Care in Cancer Antiemesis Tool MASCC-AT
* Nutritional status: Patient-Generated Subjective Global Assessment (PGSGA)
* Hospital Anxiety and Depression Scale (HADS)

  |
| Armes et al (2013) | 2466 | Cross sectional | To validate and test a PROM | Nausea; vomiting; fatigue; depression; pain; Mouth, throat and swallowing; mood change/emotional distress | * PRECISE
 |

**Table 2: Typology of problems domains**

|  |  |
| --- | --- |
| **Problem domain (n=27)** | **Problem definitions reported in included studies (n=98)** |
| Nausea | Nausea; nausea and vomiting; delayed nausea; acute nausea |
| Vomiting  | Vomiting; nausea and vomiting; delayed vomiting; acute vomiting |
| Anxiety  | Anxiety; feeling nervous; tension; worrying |
| Depression | Depression; feeling sad; feeling down |
| Fatigue | Fatigue; mental fatigue; lack of energy; weakness in body; muscle weakness; muscle soreness  |
| Mood change/ emotional stress | Psychological distress; emotional upset; mood swings; feeling irritable; anger |
| Diarrhoea  | Diarrhoea  |
| Constipation  | Constipation  |
| Indigestion  | Indigestion; heartburn belching |
| Alopecia  | Alopecia; hair loss |
| Taste and smell changes | Bad taste in mouth; loss of taste; smell changes |
| Mouth, throat & swallowing problems | Mouth sores; throat sores; mouth/throat infections; sore throat; sore mouth or pain when swallowing; dysphagia; swallowing difficulties |
| Numbness/ tingling | Numbness/ tingling |
| Appetite changes | Appetite loss; poor appetite; lack of appetite; change in appetite |
| Sleep problems | Sleep problems; sleep disturbance; drowsiness |
| Weight changes  | Weight loss; weight gain |
| Cognitive problems | Cognitive impairment; language problems; memory problems; concentration; confusion; mental fatigue; mental vigour  |
| Gynaecological problems | Menstrual problems; vaginal dryness; menopausal problems; hot flashes  |
| Fever/chills | Chills; shivering; hot/cold spells; fever; night sweats; sweats |
| Dizziness  | Dizziness  |
| Skin problems  | Skin irritation; itchiness; skin symptoms |
| Chest problems  | Cough; chest pain; dyspnoea |
| Pain | Pain; generalised pain; stomach pain/ ache; lower back pain; lower abdominal pain; joint pain; muscle pain; headache |
| Dietary symptoms | Malnourishment; nutritional risk; feel full quickly; early satiety |
| Urinary  | Problems with urination; urinary symptoms |
| Drowsiness  | Drowsiness; feeling drowsy; sleepy during the day; somnolence  |
| Job/financial  | Job; finances; work productivity |

**Table 3: Ranked problem domains**

|  |  |  |  |
| --- | --- | --- | --- |
| **Rank** | **Problem domain** | **Number of studies (n=) reporting prevalence** | **Reported range of prevalence (%)** |
| **1** | Nausea  | 22 | 9 - 74 |
| **2** | Vomiting  | 19 | 5 – 70 |
| **3** | Fatigue  | 18 | 11 -100 |
| **5** | Depression  | 14 | 4 – 56 |
| **4** | Cognitive problems | 13 | 3 – 95 |
| **6** | Pain  | 13 | 7 – 69 |
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