Current Concepts and Controversies in Palliative Medicine

Vol. XVII (Part C)

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Contents

Preface

The Tata Memorial Hospital has pioneered the cause of EBM in oncology in India and has been conducting the annual meeting on EBM in common cancers for the past sixteen years. The 18th conference on "Evidence Based Management of Cancers in India- EBM 2020" is being held from 28th February to 1st March 2020. Each year we have focused on a different aspect of cancer care; collated and published the best available evidence in the form of "EBM book" which is also easily accessible at our official website. This year we will be focusing on Contemporary Management in Neuro Oncology, Uro Oncology - Decade of Transformation and Palliative Medicine - Current Concepts and Controversies. This helps busy clinicians from all over the country and abroad to get updated on the best available evidence in oncology and palliative medicine in a span of 3-4 days, thereby translating into better overall patient care. Renowned international and national faculty members will cover the above topics in a very focused and succinct manner.

Palliative care is a rapidly evolving specialty with expertise in symptom management, psychosocial and spiritual care, caregiver care, patient-clinician communication, complex decision making, and end-of-life care. In this symposium, we will provide a state of-science review on the Current concepts and controversies in Palliative Medicine globally with a pragmatic focus on India.

Prof R A Badwe
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February 2020
Mumbai

Evidence-Based Practice of Integration of Early Palliative Care in Cancer Care

INTRODUCTION

Research has led to remarkable improvements in cancer treatment, but some cancers like metastatic lung cancer, pancreatic and biliary tract malignancies still have poor prognosis. Cancer is the second leading cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. Approximately 70% of deaths from cancer occur in low- and middle-income countries and possess significant economic hardship (GLOBOCAN-WHO 2018).

Symptoms such as pain, fatigue, drowsiness, low appetite and/or anorexia cachexia syndrome, dysphagia, nausea, diarrhea, constipation, shortness of breath, and mental confusion are often independent prognostic factors for predicting life expectancy in people with recently diagnosed incurable cancer (Trajkovic Vidakovic 2012). Incurable cancer can pose an enormous challenge for patients, their families, and medical professionals, and can affect patients' quality of life in many ways (Addington Hall 1995). It is essential that appropriate treatment plans are developed to improve survival, while aiming for a

subjectively worthwhile quality of life. Both symptom control and disease modifying therapy are needed in these situations, for which interventions tailored to improve the physical and psychological well being of people with cancer are of utmost importance. Although early access is advocated widely and is inherent in the definition of palliative care, usual practice is still limited to the terminal phase of illness.

WHAT IS EARLY PALLIATIVE CARE AND HOW IS IT BENEFICIAL?

Palliative care is provided to reduce suffering and improve quality of life among patients and their caregivers. In recent years, the term 'Early Palliative Care' was introduced to differentiate palliative care treatments applied early in the course of a life threatening disease from palliative care delivered mainly with high symptom burden or in the terminal phase of illness, as is the established clinical practice. In cases of advanced cancer, early palliative care is provided alongside active disease treatment such as chemotherapy or radiotherapy. It encompasses communication with the patient about illness and prognosis, symptom assessment and management, support for coping, and regular follow ups.

With a focus on intensified doctor patient communication, early palliative care may lead to higher levels of social support and may increase the likelihood of acceptance of the diagnosis and illness severity. These effects, along with the augmented satisfaction of the patient physician relationship, may improve the patient's openness to

symptom control and psychosocial interventions, thereby reducing distress. Reduced distress itself is associated with improved quality of life and is consistently associated with survival (Gotay 2008; Irwin 2013; Pinquart 2010).

Furthermore, patients and family members undergoing early palliative care are better informed about treatment directives and end of life decisions, which promotes higher self efficacy and a greater sense of control of decisions with respect to a person's individual values (McClain 2003). On the one hand, better symptom control and psychosocial function could promote better adherence with reasonable treatment plans. On the other hand, palliative care is linked to less aggressive cancer treatment, such as reduced use of questionable chemotherapy and less treatment time in intensive care units (Earle 2008). This tendency to de escalate treatment intensity in final, irreversible health conditions, together with extension of outpatient and community palliative care services, is important for patients' well being as well as to socioeconomics (Lowery 2013; Smith 2003). These effects stand out of regular palliative care interventions, probably because the time required to establish beneficial effects in the later may be too short (El Jawahri 2011; Gomes 2013; Higginson 2010; Zimmermann 2008).

WHAT IS THE EVIDENCE IN WORLD LITERATURE?

To date, several reviews on early palliative care interventions for patients with advanced cancer have been published (Bauman 2014; Davis 2015; El Jawahri 2011; Gomes 2013; Greer 2013; Higginson 2010; Hui 2015b;

Parikh 2013; Salins 2016; Smith 2012; Tassinari 2016; von Roenn 2011; Zambrano 2016; Zhi 2015; Zimmermann 2008). Some studies have investigated populations with heterogeneous tumour entities (Bakitas 2009; Bakitas 2015; McCorkle 2015; Tattersall 2014; Zimmermann 2014). In contrast, Temel 2010 focused on exclusive enrolment of participants with metastatic non small cell lung cancer, whereas Maltoni 2016 focussed on exclusive enrolment of participants with metastatic pancreatic cancer. Four studies investigated caregivers along with participants (Bakitas 2009; Bakitas 2015; Maltoni 2016; Zimmermann 2014). Across all these studies, investigators included slightly higher numbers of male compared with female participants, except in two studies, in which women constituted the majority of participants (McCorkle 2015, Zimmermann 2014).

Compared with usual/standard cancer care alone, early palliative care significantly improved health related quality of life at a small effect size (SMD 0.27, 95% confidence interval (CI) 0.15 to 0.38; participants analyzed at post treatment = 1028; evidence of low certainty). As re expressed in natural units (absolute change in Functional Assessment of Cancer Therapy General (FACT G) score), health related quality of life scores increased on average by 4.59 (95% CI 2.55 to 6.46) points more among participants given early palliative care than among control participants (Haun MW 2017).

Results from seven studies (Bakitas 2009; Bakitas 2015; Maltoni 2016; Tattersall 2014; Temel 2010; McCorkle 2015; Zimmermann 2014) that analyzed 1054 participants post treatment suggest a small effect for significantly lower

symptom intensity in early palliative care compared with the control condition (SMD 0.23, 95% CI 0.35 to 0.10; evidence of low certainty). The type of model used to provide early palliative care did not affect study results.

Levels of depressive symptoms among those receiving early palliative care did not differ significantly from levels among those receiving usual/standard cancer care (five studies (Bakitas 2015; Maltoni 2016; McCorkle 2015; Temel 2010; Zimmermann 2014); SMD 0.11, 95% CI 0.26 to 0.03; participants analyzed at post treatment = 762; evidence of very low certainty).

Data on survival, available from four studies (Bakitas 2009; Bakitas 2015; Tattersall 2014; Temel 2010) enrolling a total of 800 participants, did not indicate differences in efficacy (death hazard ratio 0.85, 95% CI 0.56 to 1.28; evidence of very low certainty).

One RCT (Tattersall 2014) reported potential adverse events of early palliative care, such as a higher percentage of participants with severe scores for pain and poor appetite; the remaining six studies did not report adverse events in study publications. For these six studies, principal investigators stated upon request that they had not observed any adverse events.

WHAT IS THE EVIDENCE IN INDIAN LITERATURE?

There are only a few studies on early palliative care in India as of date. In a prospective single arm feasibility study on integrating early palliative care in advanced lung cancer patients in a specialist palliative care setting, 50 patients were enrolled, assessed for symptom burden and quality

of life and followed once every 3-4 weeks for a period of 6 months (Deodhar JK 2017). The primary outcome of feasibility criteria was not achieved, as only 48% of patients (lower than the target of 60%) could complete all the questionnaires at planned assessments. The authors identified problems of mainly logistics and fatigue of patients undergoing disease modifying treatment which prevented patients from following up in the specialist palliative care clinic. Pain and anxiety symptoms improved in 1st and 2nd follow up visits and quality of life measures improved on follow up. In accordance with studies on complex interventions as is palliative care, future studies should be developed with measures to mitigate the problems recognized.

In a review on early palliative care in head and neck cancer patients, the authors report that despite the benefits of EPC, most head and neck cancer patients tended to get referred only when disease modifying treatments are not working (Satija A 2019). A randomized controlled trial on integrating EPC into standard oncology care in head and neck cancer patients has reported no significant benefit on quality of life, symptom burden and survival of patients in the intervention arm as compared to the control arm. However, this study was done on a small number of patients. Larger and multicentric studies should be undertaken in the future (Singhai and Muckaden 2018 Abstracts of the MASCC/ISOO Annual Meeting 2018).

INTERNATIONAL RECOMMENDATIONS

Recent international guidelines have incorporated early palliative care in their recommendations.

The World Health Organisation has stated that palliative care should be applied early in the disease trajectory of cancer along with disease-modifying treatment (WHO 2018).

An Expert Panel convened by the American Society of Clinical Oncology (ASCO) in 2016 after conducting a comprehensive literature review developed the 'Integration of Palliative Care into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline update 2016". The recommendation is that patients with advanced cancer should be referred to palliative care services, early in their disease trajectory whilst undergoing their disease modifying treatment and ideally within 8 weeks of diagnosis (Ferrel 2017).

ASCO has recently developed guidelines for referral of advanced cancer patients to palliative care services in the global context according to resource stratification, based on the work undertaken by a multidisciplinary international Expert Panel. This panel included expert from low- and middle-income countries (LMIC) like Kenya, India and Nepal. Their recommendation is at basic and limited resources settings (i.e. at primary and district level health care), palliative care should be considered early in the disease trajectory in cancer patients and their care provided by physicians with basic level of training in palliative care.

A recently developed framework in Canada on palliative and end-of-life care has emphasized on transmuting models of palliative care service delivery in the context of research (Bray 2018).

The “Scottish Palliative Care Guidelines” states that palliative care approach should be considered early in the course of the disease, along with disease directed treatment.

Both the Pan-Canadian and Scottish guidelines refer to chronic life-limiting and serious illnesses and not restricted to cancer.

Local guidelines can be developed based on the above documents, underling the principles of person-centered, comprehensive and timely early palliative care service provision for all patients with advanced cancer.

REFERENCES

Abstracts of the MASCC/ISOO Annual Meeting 2018. Support Care Cancer 26, 39–364 (2018) doi:10.1007/s00520-018-4193-2

Addington-Hall J, McCarthy M (1995) Dying from cancer: Results of a national population-based investigation. Palliat Med 9:295–305. doi: 10.1177/026921639500900404

Badr H, Smith CB, Goldstein NE, Gomez JE, Redd WH. Dyadic psychosocial intervention for advanced lung cancer patients and their family caregivers: results of a randomized pilot trial. *Cancer* 2015;121:150 8. [DOI: 10.1002/cncr.29009]

Bakitas M, Lyons KD, Hegel MT, Ahles T. Oncologists’ perspectives on concurrent palliative care in a National Cancer Institute designated comprehensive cancer center. Palliative & Supportive Care 2013;11:415 23. [DOI: 10.1017/S1478951512000673]

Bakitas M, Lyons KD, Hegel MT, Balan S, Barnett KN, Brokaw FC, et al. The project ENABLE II randomized controlled trial to improve palliative care for rural patients with advanced cancer: baseline findings, methodological challenges, and solutions.

Palliative & Supportive Care 2009;7:75 86. [DOI: 10.1017/S1478951509000108]

Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 2009;302(7):741 9. [DOI: 10.1001/jama.2009.1198]

Bakitas M, Stevens M, Ahles T, Kirn M, Skalla K, Kane N, et al. Project ENABLE: a palliative care demonstration project for advanced cancer patients in three settings. Journal of Palliative Medicine 2004;7:363 72. [DOI: 10.1089/109662104773709530]

Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *Journal of Clinical Oncology* 2015;33(13):1438 45. [DOI: 10.1200/JCO.2014.58.6362]

Bauman JR, Temel JS. The integration of early palliative care with oncology care: the time has come for a new tradition. *Journal of the National Comprehensive Cancer Network* 2014;12:1763 71.

Bray F, Ferlay J, Soerjomataram I, et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424. doi: 10.3322/caac.21492

Davis MP, Temel JS, Balboni T, Glare P. A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. *Annals of Palliative Medicine* 2015; 4:99 121. [DOI: 10.3978/j.issn.2224 5820.2015.04.04]

Deodhar JK, Noronha VA, Muckaden M, et al (2017) A study to assess the feasibility of introducing early palliative care in ambulatory patients with advanced lung cancer. Indian J Palliat Care 23:261–267. doi: 10.4103/IJPC.IJPC_19_17

Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality of care issue?. *Journal of Clinical Oncology* 2008;26:3860 6. [DOI: 10.1200/JCO.2007.15.8253]

El Jawahri A, Greer JA, Temel JS. Does palliative care improve outcomes for patients with incurable illness? A review of the evidence. *Journal of Supportive Oncology* 2011;9:87 94. [DOI: 10.1016/j.suponc.2011.03.003]

Ferrell B, Sun V, Hurria A, Cristea M, Raz DJ, KIm JY, et al. Interdisciplinary palliative care for patients with lung cancer. *Journal of Pain and Symptom Management* 2015;50:758 67. [DOI: 10.1016/j.jpainsymman.2015.07.005]

Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology* 2017;35:96 112. [DOI: 10.1200/JCO.2016.70.1474]

GLOBOCAN-WHO (2018) Cancer Today. Int. Agency Res.

Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost effectiveness of home palliative care services for adults with advanced illness and their caregivers. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD007760.pub2]

Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient reported outcomes in cancer clinical trials. Journal of Clinical Oncology 2008;26:1355 68. [DOI: 10.1200/JCO.2007.13.3439]

Greer JA, Jackson VA, Meier DE, Temel JS. Early integration of palliative care services with standard oncology care for patients with advanced cancer. *CA: A Cancer Journal for Clinicians* 2013;63:349 63. [DOI: 10.3322/caac.21192]

Haun MW, Estel S, Rücker G, et al (2017) Early palliative care for adults with advanced cancer. Cochrane Database Syst. Rev. 2017

Higginson IJ, Evans CJ. What is the evidence that palliative care teams improve outcomes for cancer patients and their families?. *Cancer Journal* 2010;16:423 35. [DOI: 10.1097/PPO.0b013e3181f684e5]

Hui D, Bruera E. Models of integration of oncology and palliative care. Annals of Palliative Medicine 2015;4:89 98. [DOI: 10.3978/j.issn.2224 5820.2015.04.01]

Hui D, Cruz M, Mori M, Parsons HA, Kwon JH, Torres Vigil I, et al. Concepts and definitions for "supportive care," "best supportive care," "palliative care," and "hospice care" in the published literature, dictionaries, and textbooks. Supportive Care in Cancer 2013;21:659 85. [DOI: 10.1007/s00520 012 1564 y]

Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer 2013;119:1098 105. [DOI: 10.1002/cncr.27854]

Hui D, Kim YJ, Park JC, Zhang Y, Strasser F, Cherny N, et al. Integration of oncology and palliative care: a systematic review. Oncologist 2015;1:77 83. [DOI: 10.1634/theoncologist.2014 0312]

Hui D, Shamieh O, Paiva CE, Perez Cruz PE, Kwon JH, Muckaden MA, et al. Minimal clinically important differences in the Edmonton Symptom Assessment Scale in cancer patients: a prospective multicenter study. Cancer 2015;121:3027 35. [DOI: 10.1002/cncr.29437]

Irwin KE, Greer JA, Khatib J, Temel JS, Pirl WF. Early palliative care and metastatic non small cell lung cancer: potential mechanisms of prolonged survival. Chronic Respiratory Disease 2013;10:35 47. [DOI: 10.1177/1479972312471549]

Lowery WJ, Lowery AW, Barnett JC, Lopez Acevedo M, Lee PS, Secord AA, et al. Cost effectiveness of early palliative care intervention in recurrent platinum resistant ovarian cancer. *Gynecologic Oncology* 2013;130(3):426 30. [DOI: 10.1016/j.ygyno.2013.06.011]

Maltoni M, Scarpi E, Dall'Agata M, Zagonel V, Berte R, Ferrari D, et al. Systematic versus on demand early palliative care: results from a multicentre, randomised clinical trial. *European Journal of Cancer* 2016;65:61 8. [DOI: 10.1016/j.ejca.2016.06.007]

Maltoni M, Scarpi E, Dall'agata M, Schiavon S, Biasini C, Codeca C, et al. Systematic versus on demand early palliative care: a randomised clinical trial assessing quality of care and treatment aggressiveness near the end of life. *European Journal of Cancer* 2016;69:110 8. [DOI: 10.1016/j.ejca.2016.10.004]

McClain CS, Rosenfeld B, Breitbart W. Effect of spiritual well being on end of life despair in terminally ill cancer patients. *Lancet* 2003;361:1603 7.

McCorkle R, Jeon S, Ercolano E, Lazenby M, Reid A, Davies M, et al. An advanced practice nurse coordinated multidisciplinary intervention for patients with late stage cancer: a cluster randomized trial. *Journal of Palliative Medicine* 2015;18:962 9. [DOI: 10.1089/jpm.2015.0113]

Parikh RB, Kirch RA, Smith TJ, Temel JS. Early specialty palliative care translating data in oncology into practice. *New England Journal of Medicine* 2013;369:2347 51. [DOI: 10.1056/NEJMsb1305469]

Pinquart M, Duberstein PR. Depression and cancer mortality: a meta analysis. Psychological Medicine 2010;40:1797 810. [DOI: 10.1017/S0033291709992285]

Roenn JH, Temel J. The integration of palliative care and oncology: the evidence. *Oncology (Williston Park)* 2011;25:1266.

Salins N, Ramanjulu R, Patra L, Deodhar J, Muckaden MA. Integration of early specialist palliative care in cancer care and patient related outcomes: a critical review of evidence. *Indian Journal of Palliative Care* 2016;22:253 7. [DOI: 10.4103/0973 1075.185028]

Satija A, Lorenz K, DeNatale M, Spruyt O, Deo SVS, Bhatnagar S. Role of Early Palliative Care in Advanced Head-and-Neck Cancers Patients. Indian J Palliat Care. 2019;25(1):153–155. doi:10.4103/IJPC.IJPC_142_18

Smith TJ, Coyne P, Cassel B, Penberthy L, Hopson A, Hager MA. A high volume specialist palliative care unit and team may reduce in hospital end of life care costs. *Journal of Palliative Medicine* 2003;6:600 705. [DOI: 10.1089/109662103322515202]

Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *Journal of Clinical Oncology* 2012;30:880 7. [DOI: 10.1200/JCO.2011.38.5161]

Tassinari D, Drudi F, Monterubbianesi MC, Stocchi L, Ferioli I, Marzaloni A, et al. Early palliative care in advanced oncologic and non oncologic chronic diseases. A systematic review of the literature. *Reviews on Recent Clinical Trials* 2016;11:1. [DOI: 10.2174/1574887110666151014141650]

Tattersall MHN, Martin A, Devine R, Ryan J, Jansen J, Hastings L, et al. Early contact with palliative care services: a randomized trial in patients with newly detected incurable metastatic cancer. *Palliative Care & Medicine* 2014;4(1):170. [DOI: 10.4172/2165 7386.1000170]

Temel JS, El Jawahri A, Greer JA, Pirl WF, Jackson VA, Park ER, et al. Randomized trial of early integrated palliative oncology. *Journal of Clinical Oncology* 2016;34:Suppl; abstr 10003.

Temel JS, Greer JA, El Jawahri A, Pirl WF, Park ER, Jackson VA, et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomized clinical trial. *Journal of Clinical Oncology* 2017;35:834 41. [DOI: 10.1200/JCO.2016.70.5046]

Trajkovic-Vidakovic M, de Graeff A, Voest EE, Teunissen SCCM (2012) Symptoms tell it all: A systematic review of the value of symptom assessment to predict survival in advanced cancer patients. Crit. Rev. Oncol. Hematol. 84:130–148

Zambrano SC, Fliedner MC, Eychmüller S. The impact of early palliative care on the quality of care during the last days of life: what does the evidence say?. *Current Opinion in Supportive and Palliative Care* 2016;10:310 5. [DOI: 10.1097/SPC.0000000000000240]

Zhi WI, Smith TJ. Early integration of palliative care into oncology: evidence, challenges and barriers. *Annals of Palliative Medicine* 2015;4:122 31. [DOI: 10.3978/j.issn.2224 5820.2015.07.03]

Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. *JAMA* 2008;299:1698 709. [DOI: 10.1001/jama.299.14.1698]

Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster randomised controlled trial. *Lancet* 2014; 383(9930):1721 30. [DOI: 10.1016/S0140 6736(13)62416 2]

Zimmermann C, Swami N, Krzyzanowska M, Leighl N, Rydall A, Rodin G, et al. Perceptions of palliative care among patients with advanced cancer and their caregivers. *Canadian Medical Association Journal* 2016;188:E217 27. [DOI: 10.1503/cmaj.151171]

Evidence-Based Management of Cancer Related Fatigue

INTRODUCTION

"Cancer Related Fatigue is a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning". ('NCCN Guidelines, 2019'). The prevalence of fatigue varies from 15%-99% and this can be attributed to different definitions, criteria, varied assessments, influence of disease specific sites, modalities of treatment and its occurrence with symptom clusters. (O'Higgins *et al.*, 2018) (Hsiao, Daly and Saligan, 2016) (Fox *et al.*, 2019)(Yennurajalingam *et al.*, 2013).

Literature supports the pro-inflammatory cytokine hypothesis of Cancer Related Fatigue(CRF) triggering alterations in multiple systems including the Hypothalamic Pituitary adrenal axis(HPA), endocrine function, skeletal muscle function, immune system and metabolism. (O'Higgins *et al.*, 2018)(Saligan *et al.*, 2015)A recent review shifted the focus from what causes fatigue to who are more vulnerable to fatigue by integrating across these implicated systems in CRF. Classifying risk factors into predisposing,

precipitating and perpetuating could help identify vulnerable patients and targets of intervention.(Bower, 2019)

GUIDELINES FOR CRF

Among the existing guidelines for interventions in CRF, the National Comprehensive Cancer Network(NCCN)('NCCN Guidelines, 2019') ('NCCN Guidelines 2015') remains the most widely updated and circulated for multidisciplinary clinical decision making.(Berger *et al.*, 2015)

In a Quality appraisal guideline (Pearson et al, 2016) using the AGREE -11(Brouwers *et al.*, 2010) instrument and the checklist of the Australian National Health and Medical Research Council(NHMRC) ('NHMRC, Australia', 2019) five guidelines met the inclusion criteria. These included the American Society of Clinical Oncology(ASCO), (Bower *et al.*, 2014) NCCN ('NCCN Guidelines, 2015') –(the fatigue and survivorship version), Oncology Nursing Society(ONS)(Mitchell *et al.*, 2014) and the Canadian Association of Psychosocial Oncology(CAPO).(Howell *et al.*, 2015)

This appraisal reported that the CAPO, ONS and NCCN have applications in all stages of cancer. The ASCO and NCCN survivorship guidelines are specific to those who are disease free. Four of the guidelines included screening, assessment and treatment. The ONS guideline focused on assessment and treatment. It suggested that the quality of development and reporting was most suitable in the CAPO guideline. (Pearson et al.,2016) (Pearson, Morris and McKinstry, 2017)

The study conducted by the National Cancer Institute(NCI)(Berger *et al.*, 2015) compared these guidelines and reported a significant evidence base for the recommended interventions..

Being at the tipping point between T2 and T3 on the translational continuum(Berger *et al.*, 2015) (Fort *et al.*, 2017); the implementation of the guideline recommendation, sustained adoption, integration into policies and quality standards is the way forward. The practical challenges to guideline implementation in the management of fatigue(Berger *et al.*, 2015) (Mohandas *et al.*, 2017)(Pearson *et al.*, 2018) (Berger and Mooney, 2016)(Williams *et al.*, 2016)(Smith *et al.*, 2019) include the ambiguity and subjective nature of the symptom along with patient apprehension and clinical inertia.(Table 1)

Table 1: Challenges in the Management of Fatigue

Fatigue as a symptom	Ambiguous pathogenesis and varied mechanisms Numerous unidimensional and multi-dimensional scales with a lack of consensus on valuation
Patient Factors	Perception of fatigue being inevitable Fear of reporting as it might lead to less aggressive treatment
Physician Factors	Subjective symptom Clinical Inertia about CRF Inadequate knowledge of the impact on and interaction and response to fatigue by the patient

(Contd...)

(Contd...)

	Insufficient understanding and misinterpretation of the impact on the Quality of Life Gaps in knowledge and difficulty in interpreting study results due to lack of homogeneity among interventions

MANAGEMENT OF CANCER RELATED FATIGUE

Screening and Evaluation of CRF

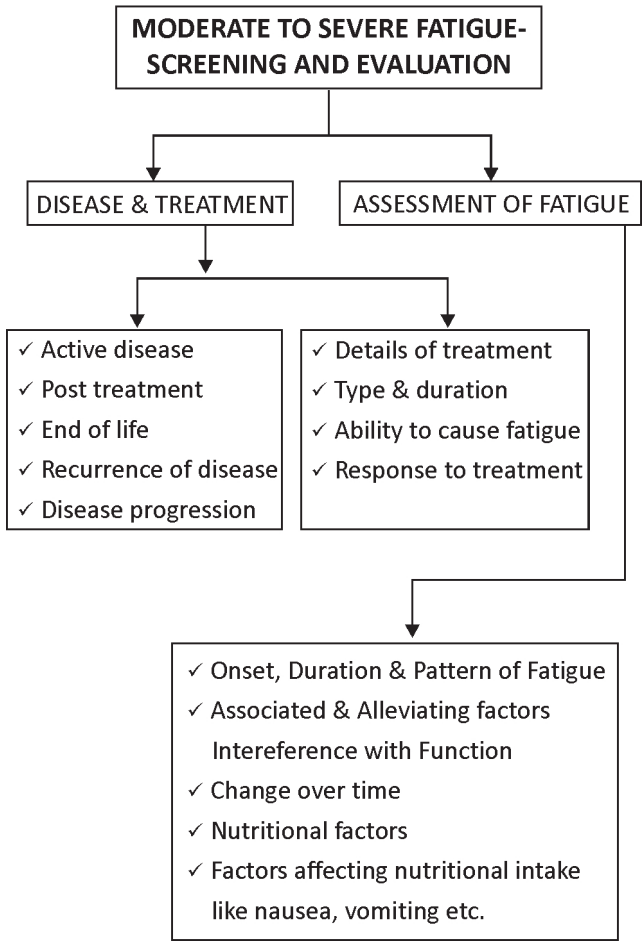
Screening every patient at regular intervals for fatigue followed by surveillance for those with mild fatigue and further evaluation for those with moderate to severe fatigue is recommended ('NCCN Guidelines, 2019')

Evaluation includes focused history, physical examination, details of the cancer along with its treatment and medication details. Recommendations also include the assessment of the reversible causes contributing to fatigue.(Mohandas *et al.*, 2017)(Campos *et al.*, 2011) {Figure 1, Table 2}

The unidimensional scales indicate the presence and severity of fatigue and the multidimensional scales measure the effect of CRF across several domains of patient function.(Pearson *et al.*, 2018)(Mohandas *et al.*, 2017)(Fisher *et al.*, 2018) A systematic review reported the 10 point Numerical Rating Scale as the best screening tool and recommended the Multidimensional Fatigue Symptom Inventory for assessment of CRF.(Fisher *et al.*, 2018)

On a 10-point scale Mild fatigue is indicated by a score of 1-3, Moderate fatigue 4-6 and Severe fatigue 7-10.

Figure 1: Screening and Evaluation of Fatigue



Reversible Factors contributing to fatigue(Mohandas *et al.*, 2017)(Campos *et al.*, 2011) (Charalambous *et al.*, 2019) (Dong *et al.*, 2014) (Rha and Lee, 2017) (Yennurajalingam *et al.*, 2013) (Olver, Eliott and Koczwara, 2014) (Kwekkeboom, 2016)(Fox *et al.*, 2019)(Ghoshal *et al.*, 2017)

Anaemia

Asthenia, Deconditioning

Sleep Disorders

Endocrinopathies

Electrolyte Disturbance

Organ dysfunction e.g. (Cardiopulmonary dysfunction, myopathy etc)

Emotional Disturbance – Anxiety , Depression and Adjustment Disorders

Pain and Medication review including opioids

Uncontrolled Symptoms

Symptom Clusters with CRF

1 CRF, Sleep disturbances and depression
2 CRF with cognitive symptoms
3 CRF with dyspnoea, drowsiness, pain
4 CRF with pain
5 CRF with Sleep disturbance
6 CRF with pain and insomnia
7 CRF with nausea
8 CRF with pain, sleep disturbances with mood disturbances of anxiety and/or depression – Psychoneurological symptom cluster

MANAGEMENT OF FATIGUE

A preliminary inclusive valuation on patient's life, education and cancer treatment and the availability of supportive caregivers to develop a management plan is recommended. Management principles are based on the severity of fatigue and the illness trajectory.('NCCN Guidelines, 2019') (Campos *et al.*, 2011)(Mohandas *et al.*, 2017)

Table 2: Principles of Management

Mild Fatigue –	Moderate/ Severe Fatigue	Fatigue at end of life
Active treatment and post treatment ➢ General Strategies of Management ➢ Education, Counselling ➢ Self Monitoring of Fatigue ➢ Initiation of Physical Activity	Active treatment and post treatment ➢ General Strategies of Management ➢ Focused Assessment and treatment of contributory factors like anaemia, infections	➢ Eliminate non essential activities ➢ Conserve energy for valued activities ➢ Consider general condition- anaemia, thrombo-cycytopenia, bone metastases, infections, safety issues

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Energy Conservation • Pace/Delegate/ Schedule activity • Structured Routine • Use of Distraction • Meaningful Interaction • Labour saving and Assisted Devices ➢ Surveillance and Reevaluation of Fatigue	➢ Non Pharmacologic Interventions ➢ Combine with Pharmacologic Interventions	➢ Effective symptom management ➢ Address emotional distress ➢ Optimise treatment for sleep dysfunction ➢ Consider Corticoster-oids

INTERVENTIONS FOR MANAGEMENT

General Strategies for Management

Education about the pattern and levels of expected fatigue during the treatment; coping with selfcare, balancing activities and rest should be offered to the patient and family at the start of treatment and along the trajectory to establish practical goals of care. ('NCCN Guidelines, 2019') (Goedendorp *et al.*, 2009) (Ream *et al.*, 2015)The Energy Conservation and Activity Management (ECAM)intervention(Barsevick *et al.*, 2004) and Beating Fatigue(Ream *et al.*, 2015), both telephonically delivered

have had beneficial effects on fatigue outcomes. A Cochrane review focusing on educational interventions on CRF concluded that though the effect on the intensity of fatigue and interference with daily life may be low, it could moderately reduce distress, anxiety and improve the global Quality of Life.(Bennett *et al.*, 2016)

A meta-analysis comparing the mean weighted effect size of the recommended interventions in the management of CRF concluded that exercise and psychological interventions are significantly better than available pharmacologic options for reducing CRF during and after cancer treatment.(Mustian *et al.*, 2017)A scoping review highlighted the diversity of self reporting, the underrepresentation of the advanced cancer subgroups, lack of adherence to guidelines ,heterogeneity among interventions and need for more robust measures to study the severity and outcome of fatigue and enable planning interventions.(Pearson *et al.*, 2018)

NON-PHARMACOLOGIC INTERVENTIONS

Physical Activity

Among the non pharmacologic interventions exercise is highly recommended by all guidelines. It is well supported by evidence and researched in patients on treatment, off treatment, advanced cancer and survivors.(Mohandas *et al.*, 2017) (Mishra *et al.*, 2012)(Tian *et al.*, 2016)(Meneses-Echávez, González-Jiménez and Ramírez-Vélez, 2015)(Sprod *et al.*, 2015)(Dittus, Gramling and Ades, 2017)(Cramp and Byron-Daniel, 2012)

A Cochrane review conducted among participants undergoing treatment and post active treatment showed that exercise resulted in a decrease in fatigue twelve weeks from baseline.(Mishra *et al.*, 2012) Another, done predominantly with patients with breast cancer found exercise to be beneficial for CRF during and post cancer therapy.(Cramp and Byron-Daniel, 2012)

Implications for practice based on the treatment status has been suggested.(Hilfiker *et al.*, 2018) During treatment relaxation training along with physical activities like yoga, exercise combinations, resistance and endurance training and psychosocial alterations is beneficial. After treatment, it is the physical rather than the relaxation interventions that are more beneficial. Benefits were found to be more in those off treatment. (Tian *et al.*, 2016)A meta-analysis showed that physical fatigue is most sensitive to physical exercise. (van Vulpen *et al.*, 2016)Another systematic review showed clear benefits of exercise for advanced cancer patients to improve aerobic fitness, strength and physical function.(Dittus, Gramling and Ades, 2017)

Exercise, in line with guidelines, individualised and supervised with a combination of aerobic, resistance and flexibility is safe and feasible. (Paramanandam and Dunn, 2015)(Minton, Jo and Jane, 2015) A longitudinal exercise intervention which recruited and retained patients showed effective benefit from fatigue and pain in the exercise group. Adherence to the supervised exercise program was much higher than the unsupervised walking that was advised.(Yee *et al.*, 2019) A structured physiotherapy program decreased fatigue significantly in a RCT of patients receiving palliative care.(Pyszora *et al.*, 2017)

Activity preferences, cost of interventions and behavioural factors contribute to self reported improvement in fatigue.(Twomey *et al.*, 2017) Distinguishing sedentary, active and average behaviour profiles could also influence interventions in physical activity in clinical practice. (Wolvers *et al.*, 2018)

Reviews on the effect of Yoga on CRF have shown variability from being not very effective to being beneficial. (Morgan et al., 2017) (O'Neill *et al.*, 2016) (Sadja and Mills, 2013) (Hilfiker *et al.*, 2018) An Indian study showed that yoga reduced fatigue severity and frequency in the study group of advanced breast cancer patients. (Vadiraja *et al.*, 2017) Tai Chi has been found beneficial in studies with patients on treatment with lung cancer (Zhang *et al.*, 2016) and nasopharyngeal carcinoma. (Zhou *et al.*, 2018)

Psychosocial Interventions

Cognitive Behavioural Therapy (CBT) is a problem focused; action oriented psycho educational beneficial supportive intervention. This focuses on individual counselling, group therapy, relaxation, stress reduction and behavioural interventions for management of CRF. ('NCCN Guidelines 2019') (Mohandas *et al.*, 2017)(Campos *et al.*, 2011) (Goedendorp *et al.*, 2009)(Mustian *et al.*, 2017) (Mustian *et al.*, 2007)

Mindfulness based stress reduction (MBSR) , a non judgmental state of self awareness on a moment to moment basis has been beneficial in decreasing fatigue. (Castanhel *et al.*, 2018)(Mehta *et al.*, 2019)Attention restorative therapy has inspired a qualitative study with the emphasis on engaging the patient's interest and

preferences in relation to daytime behaviours. Belonging, Expansive, Nurturing and Purposeful were the overarching themes. A self intervention tool to explore preferences and nurture the person could be an effective intervention. (Kirshbaum and Donbavand, 2014)

Interventions to promote self care and enhance self efficacy can improve self management outcomes. These could be facilitated by nurses but they await implementation in practice.(Myall *et al.*, 2015)(Chiba, Sasahara and Mizuno, 2019)(Chan, Yates and McCarthy, 2017)

Nurse led interventions with exercise and Cognitive Behavioural Therapy(CBT) in patients with ovarian carcinoma decreased behavioural fatigue but not affective fatigue and improved the sleep quality.(Q. Zhang *et al.*, 2018)An Untire App for behavioural and exercise modification based on the NCCN guidelines is being researched. (Kuiper *et al.*, 2018)

Complementary and Alternative Medicine (CAM)

Acupuncture(Molassiotis *et al.*, 2012) and Acupressure (Zick *et al.*, 2016) (Khanghah *et al.*, 2019)have been useful in CRF during active and post treatment with acupuncture being effective and daily acupressure being more acceptable to patients.

The beneficial effect of acupuncture depended on the number of sessions and best formulated with the patient's convenience.(Y. Zhang *et al.*, 2018)Combination of both for at least four weeks is needed to observe the effect.(Ling *et al.*, 2014)

Swedish massage therapy decreased fatigue and improved the quality of life of survivors with CRF. (Kinkead *et al.*, 2018) Aromatherapy to counter fatigue using frankincense has been reported.(Reis and Jones, 2018)

Ginseng for treating fatigue was found to be effective in a review but more research needs to be built on the evidence in terms of sample size, dose, duration of treatment and methodology in the study.(Arring *et al.*, 2018)

There is preliminary evidence that art, music, animal assisted therapy, expressive writing , distraction-virtual therapy merging, exposure to nature may help in managing fatigue.(Berger *et al.*, 2015)

Sleep and Nutrition

Managing nutritional deficiencies, maintaining hydration and electrolyte balance helps in combating CRF. ('NCCN Guidelines 2019') Protein intake less than 1gm/kg body weight is a determinant of cancer related fatigue (George *et al.*, 2014)Intake of Omega 3/Omega 6 leads to lower inflammation and fatigue. (Alfano *et al.*, 2012)

There is a correlation between CRF and various sleep parameters. Maintaining sleep hygiene, practicing sleep restriction and stimulus control can help improving sleep efficiency. ('NCCN Guidelines, 2019') (Fox *et al.*, 2019)(Charalambous *et al.*, 2019)

Bright white light therapy (BWLT)has been suggested as a measure to improve fatigue. (Ancoli-Israel *et al.*, 2012)(Johnson *et al.*, 2018)(Starreveld *et al.*, 2018) and the LITE study(Johnson *et al.*, 2016) is in process to determine the optimal use of BWLT in CRF.

Pharmacological Interventions

The mechanism of pharmacological interventions in fatigue may be its interaction with the cytokine load and the patient's host reaction to the underlying disease. It could be by supplementing physiological deficiencies eg anaemia, restoring the depleted peripheral energy or by treating metabolic disorders.

Among the various pharmacological agents studied (Appendix 1), there is limited evidence for the use of methylphenidate in treating CRF. (Gong *et al.*, 2014)(Rojí and Centeno, 2017) This Cochrane review did not find evidence for a specific drug to be beneficial in CRF and found methylphenidate most advantageous.(Mücke *et al.*, 2015)Corticosteroids are a short term option in patients with advanced cancer and predictors for a favourable response include a better performance status, lack of fluid retention and drowsiness (Matsuo *et al.*, 2016) (Yennurajalingam and Bruera, 2014) (Paulsen *et al.*, 2014)

CONCLUSION

Management of CRF includes a longitudinal assessment, addressing the underlying causes and following recommendations for interventions. The CAPO (Table 3) and NCCN (Table 4) guidelines have been summarised. Implementation of guidelines is possible with training, (Thoonsen *et al.*, 2019) a multidisciplinary team approach and shared decision making.(Table 5)

Translating evidence into practice and research is the way forward for better patient outcomes in CRF.

Table 3: Summary of CAPO (Canadian Association of Psychosocial Oncology) Guidelines (Pearson, Morris and McKinstry, 2017) (Howell *et al.*, 2015)		
CAPO Recommendations for the Management of CRF in Adults	**Level of Evidence**	**Strength of Recommendation**
Screening and Assessment		
Screen for the presence of cancer related fatigue at specified times or as clinically indicated using a valid quantitative measure	2A	Expert Panel Consensus Informed by Guideline Evidence
If screened positive for fatigue (Score > 2 on a 0–10 numeric ratingscale), complete a focused assessment of fatigue and possible medical causes	2A	Expert Panel Consensus Informed by Guideline Evidence
Treat contributing factors and/or refer for further specialist evaluation	2A	Expert Panel Consensus Informed by Guideline Evidence
Pharmacological Management		
Evidence is insufficient to recommend pharmacological agents for fatigue at any stage of disease	Insufficient evidence	Strong –Harm may outweigh benefits
Physical Activity		

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CAPO Recommendations for the Management of CRF in Adults	**Level of Evidence**	**Strength of Recommendation**
Counsel all patients as is safe to engage in moderate-intensity physical activity for at least 30 min on five or more days of the week	Sufficient	Benefit outweighs harm
All types of physical activity at lower intensity (e.g. walking, yoga) may contribute to decreasing fatigue during and after active cancer treatment	High	Strong – Benefit outweighs harm
A referral to a specialist in rehabilitation should be physically inactive patients and considered for cancer patients obese individuals eg peripheral neuropathy, pain, lymphedema	2A	Strong – Consensus based
Psychosocial/ Educational Interventions		
All patients are likely to benefit from routine patient education about fatigue self-management	Sufficient	Moderate
Cancer services should promote access to multi-component, group psycho-education programs targeted to self-management	High	Strong

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CAPO Recommendations for the Management of CRF in Adults	**Level of Evidence**	**Strength of Recommendation**
Referral to experts or fatigue clinics that are trained in cognitive behavioural therapy targeted to fatigue should be offered to patients and survivors with chronic cancer fatigue	Sufficient	Strong
There is insufficient evidence to advise seeking herbal medicines or acupuncture for treatment of fatigue. Herbal products should be used with caution and patients should discuss their use with the oncology team	Sufficient	Strong
There is preliminary evidence that mindfulness-based interventions are likely to improve fatigue	2A	Consensus based

Table 4: Summary of the NCCN Guidelines 2019 ('NCCN Guidelines, 2019')		
Treatment Trajectory	**NCCN Recommendations for the Management of Cancer Related Fatigue**	**Level of Evidence**
	Screen every patient for fatigue at regular intervals	2A
	Primary Evaluation of Moderate and severe fatigue	
	• Focused History	2A
	• Assessment of treatable contributing factors	2A
	• Management of concurrent symptoms and treatable contributing factors	2A
	General Strategies for the management of fatigue	
	• Active treatment and Post Treatment	Patient Education and Counseling
	• Physical Activity	2A
	• Self monitoring of fatigue	2A
	• Distraction	2A
	• Finding meaning in the situation	2A

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Treatment Trajectory	NCCN Recommendations for the Management of Cancer Related Fatigue	Level of Evidence
	• Referral to appropriate specialist or supportive care provider	2A
	• Energy Conservation	Insufficient evidence
	• End of Life	Patient education and Counseling
	• End of Life Symptom Care	2A
	• Eliminate non essential activity	2A
	• Conserve energy for valued activity	2A
	Interventions for patients on treatment **Non Pharmacologic**	
Active Treatment and Post Treatment	1 Physical Activity • Maintain optimal level of activity • Initiation and maintenance of an exercise program – endurance and resistance • Referral to Rehabilitation • Yoga	Category 1 2A 2A 2A 2A

(Contd...)

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Treatment Trajectory	**NCCN Recommendations for the Management of Cancer Related Fatigue**	**Level of Evidence**
Caution during active treatment – infections, bone metastases, cytopenias, safety issues –falls		2A Category 1
Caution during post treatment – cardiomyopathy , safety issues –falls		
Active Treatment	2 Physical based therapies – Massage 3 Psychosocial Interventions • Cognitive Behaviour Therapy	Category 1 Category 1
Active Treatment and Post Treatment	• Psychoeducational Therapies • Supportive Expressive Therapy	Category 1 2A
Post Treatment	• Mindfulness Based Stress Reduction	2A
Active Treatment and Post Treatment	4 Nutrition Consultation	2A
Active Treatment	5 CBT for Sleep 6 Bright White Light Therapy	Category 1 2A

(Contd...)

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Treatment Trajectory	**NCCN Recommendations for the Management of Cancer Related Fatigue**	**Level of Evidence**
Post Treatment	5 CBT for Sleep 6 Acupuncture	Category 1 2A
End of Life	Physical Activity Optimise level with consideration of bony metastases, infections, cytopenias, safety issues-falls, fever, co-morbid illness	2A
	Interventions for patients on treatment –Pharmacologic	
Active Treatment and Post Treatment	Consider psychostimulants (methylphenidate) after ruling out all causes of fatigue Treat for pain, emotional distress and anaemia	2A 2A
End of Life	Consider psychostimulants (methylphenidate) after ruling out all causes of fatigue Consider corticosteroids (prednisolone or dexamethasone) Treat for pain, emotional distress and anaemia Optimise treatment for sleep dysfunction and comorbidities	2A 2A 2A 2A

Table 5: Managing Fatigue		
For the Patient and Caregiver	**From the physician**	**Along with the TEAM**
Empowerment	Acknowledging the symptom	Multidisciplinary Team
Education about pattern and levels of expected fatigue	Training	Continuous Collaboration
Balancing activities and rest	Identifying triggers and needs	Communication
Coping with the health care system	Anticipatory Guidance Proactive Approach	Training
At the start and along the trajectory	Advance Care Planning	Palliative Care Provision services by the primary physician

REFERENCES

Alfano, C. M. *et al.* (2012) 'Fatigue, inflammation, and ω-3 and ω-6 fatty acid intake among breast cancer survivors.', *Journal of clinical oncology/ : official journal of the American Society of Clinical Oncology*. American Society of Clinical Oncology, 30(12), pp. 1280–7. doi: 10.1200/JCO.2011.36.4109.

Ancoli-Israel, S. *et al.* (2012) 'Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer', *Supportive Care in Cancer*. Springer-Verlag, 20(6), pp. 1211–1219. doi: 10.1007/s00520-011-1203-z.

Arring, N. M. *et al.* (2018) 'Ginseng as a Treatment for Fatigue: A Systematic Review', *The Journal of Alternative and Complementary Medicine*, 24(7), pp. 624–633. doi: 10.1089/acm.2017.0361.

Barsevick, A. M. *et al.* (2004) 'A randomized clinical trial of energy conservation for patients with cancer-related fatigue', *Cancer*. John Wiley & Sons, Ltd, 100(6), pp. 1302–1310. doi: 10.1002/cncr.20111.

Bennett, S. *et al.* (2016) 'Educational interventions for the management of cancer-related fatigue in adults', *Cochrane Database of Systematic Reviews*, 11, p. CD008144. doi: 10.1002/14651858.CD008144.pub2.

Berger, A. M. *et al.* (2015) 'Screening, evaluation, and management of cancer-related fatigue: Ready for implementation to practice?', *CA: A Cancer Journal for Clinicians*. American Cancer Society, 65(3), pp. 190–211. doi: 10.3322/caac.21268.

Berger, A. M. and Mooney, K. (2016) 'Dissemination and Implementation of Guidelines for Cancer-Related Fatigue', *Journal of the National Comprehensive Cancer Network*. Harborside Press, LLC, 14(11), pp. 1336–1338. doi: 10.6004/jnccn.2016.0144.

Bower, J. E. *et al.* (2014) 'Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation.', *Journal of clinical oncology/ : official journal of the American Society of Clinical Oncology*. American Society of Clinical Oncology, 32(17), pp. 1840–50. doi: 10.1200/JCO.2013.53.4495.

Bower, J. E. (2019) 'The role of neuro immune interactions in cancer related fatigue: Biobehavioral risk factors and mechanisms', *Cancer*, 125(3), pp. 353–364. doi: 10.1002/cncr.31790.

Brouwers, M. C. *et al.* (2010) 'AGREE II: advancing guideline development, reporting and evaluation in health care.', *CMAJ/ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. CMAJ, 182(18), pp. E839-42. doi: 10.1503/cmaj.090449.

Campos, M. P. O. *et al.* (2011) 'Cancer-related fatigue: a practical review', *Annals of Oncology*. Narnia, 22(6), pp. 1273–1279. doi: 10.1093/annonc/mdq458.

Castanhel, F. Del *et al.* (2018) 'Mindfulness-Based Stress Reduction on breast cancer symptoms: systematic review and meta-analysis', *Einstein (São Paulo)*. Instituto Israelita de Ensino e Pesquisa Albert Einstein, 16(4). doi: 10.31744/einstein_journal/2018RW4383.

Chan, R. J., Yates, P. and McCarthy, A. L. (2017) 'The Development and Preliminary Testing of an Instrument for Assessing Fatigue Self-management Outcomes in Patients With Advanced Cancer', *Cancer Nursing*, 40(1), pp. 48–57. doi: 10.1097/NCC.0000000000000347.

Charalambous, A. *et al.* (2019) 'Cancer-related fatigue and sleep deficiency in cancer care continuum: concepts, assessment, clusters, and management', *Supportive Care in Cancer*, 27(7), pp. 2747–2753. doi: 10.1007/s00520-019-04746-9.

Chiba, I., Sasahara, T. and Mizuno, M. (2019) 'Factors in Cancer-Related Fatigue Self-Management Behaviors of Outpatients Undergoing Chemotherapy', *Asia-Pacific Journal of Oncology Nursing*, 6(3), p. 209. doi: 10.4103/apjon.apjon_1_19.

Cramp, F. and Byron-Daniel, J. (2012) 'Exercise for the management of cancer-related fatigue in adults', *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd, (11). doi: 10.1002/14651858.CD006145.pub3.

Dittus, K. L., Gramling, R. E. and Ades, P. A. (2017) 'Exercise interventions for individuals with advanced cancer: A systematic review', *Preventive Medicine*, 104, pp. 124–132. doi: 10.1016/j.ypmed.2017.07.015.

Dong, S. T. *et al.* (2014) 'Symptom Clusters in Patients With Advanced Cancer: A Systematic Review of Observational Studies', *Journal of Pain and Symptom Management*. Elsevier, 48(3), pp. 411–450. doi: 10.1016/J.JPAINSYMMAN.2013.10.027.

Fisher, M. I. *et al.* (2018) 'Oncology Section EDGE Task Force on Cancer', *Rehabilitation Oncology*, 36(2), pp. 93–105. doi: 10.1097/01.REO.0000000000000124.

Fort, D. G. *et al.* (2017) 'Mapping the evolving definitions of translational research.', *Journal of clinical and translational science*. Cambridge University Press, 1(1), pp. 60–66. doi: 10.1017/cts.2016.10.

Fox, R. S. *et al.* (2019) 'Sleep disturbance and cancer-related fatigue symptom cluster in breast cancer patients undergoing chemotherapy', *Supportive Care in Cancer*. doi: 10.1007/s00520-019-04834-w.

George, S. M. *et al.* (2014) 'Better postdiagnosis diet quality is associated with less cancer-related fatigue in breast cancer survivors', *Journal of Cancer Survivorship*, 8(4), pp. 680–687. doi: 10.1007/s11764-014-0381-3.

Ghoshal, A. *et al.* (2017) 'Impact of symptom control on fatigue improvement in patients with advanced cancer: A prospective observational study', *Progress in Palliative Care*. Taylor & Francis, 25(2), pp. 63–74. doi: 10.1080/09699260.2016.1200818.

Goedendorp, M. M. *et al.* (2009) 'Psychosocial interventions for reducing fatigue during cancer treatment in adults', *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd, (1). doi: 10.1002/14651858.CD006953.pub2.

Gong, S. *et al.* (2014) 'Effect of Methylphenidate in Patients with Cancer-Related Fatigue: A Systematic Review and Meta-Analysis', *PLoS ONE*. Edited by L. Manchikanti, 9(1), p. e84391. doi: 10.1371/journal.pone.0084391.

Hilfiker, R. *et al.* (2018) 'Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis.', *British journal of sports medicine*. BMJ Publishing Group Ltd and British Association of Sport and Exercise Medicine, 52(10), pp. 651–658. doi: 10.1136/bjsports-2016-096422.

Howell, D. *et al.* (2015) 'A Pan Canadian Practice Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue in Adults (Version 2)'. doi: 10.7939/R33R6N.

Hsiao, C.-P., Daly, B. and Saligan, L. N. (2016) 'The Etiology and management of radiotherapy-induced fatigue', *Expert Review of Quality of Life in Cancer Care*, 1(4), pp. 323–328. doi: 10.1080/23809000.2016.1191948.

Johnson, J. A. *et al.* (2016) 'The LITE study: Rationale and protocol for a randomized controlled trial of light therapy for cancer-related fatigue in cancer survivors', *Contemporary Clinical Trials*, 49, pp. 166–173. doi: 10.1016/j.cct.2016.07.004.

Johnson, J. A. *et al.* (2018) 'Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial', *Journal of Cancer Survivorship*. Springer US, 12(2), pp. 206–215. doi: 10.1007/s11764-017-0659-3.

Khanghah, A. G. *et al.* (2019) 'Effects of Acupressure on Fatigue in Patients with Cancer Who Underwent Chemotherapy', *Journal of Acupuncture and Meridian Studies*. Elsevier, 12(4), pp. 103–110. doi: 10.1016/J.JAMS.2019.07.003.

Kinkead, B. *et al.* (2018) 'Massage therapy decreases cancer-related fatigue: Results from a randomized early phase trial', *Cancer*. John Wiley & Sons, Ltd, 124(3), pp. 546–554. doi: 10.1002/cncr.31064.

Kirshbaum, M. N. and Donbavand, J. (2014) 'Making the most out of life: Exploring the contribution of attention restorative theory in developing a non-pharmacological intervention for fatigue', *Palliative and Supportive Care*, 12(6), pp. 473–480. doi: 10.1017/S1478951513000539.

Kuiper, A. J. *et al.* (2018) 'Untire: an all-embracing self-management eHealth program to cope with cancer-related fatigue', *ecancermedicalscience*, 12, p. ed81. doi: 10.3332/ecancer.2018.ed81.

Kwekkeboom, K. L. (2016) 'Cancer Symptom Cluster Management', *Seminars in Oncology Nursing*, 32(4), pp. 373–382. doi: 10.1016/j.soncn.2016.08.004.

Ling, W. *et al.* (2014) 'Effects of Acupuncture and Acupressure on Cancer-Related Fatigue: A Systematic Review', *Oncology Nursing Forum*, 41(6), pp. 581–592. doi: 10.1188/14.ONF.581-592.

Matsuo, N. *et al.* (2016) 'Predictors of Responses to Corticosteroids for Cancer-Related Fatigue in Advanced Cancer Patients: A Multicenter, Prospective, Observational Study', *Journal of Pain and Symptom Management*, 52(1), pp. 64–72. doi: 10.1016/j.jpainsymman.2016.01.015.

Mehta, R. *et al.* (2019) 'Evidence for the Role of Mindfulness in Cancer: Benefits and Techniques.', *Cureus*. Cureus Inc., 11(5), p. e4629. doi: 10.7759/cureus.4629.

Meneses-Echávez, J. F., González-Jiménez, E. and Ramírez-Vélez, R. (2015) 'Effects of Supervised Multimodal Exercise Interventions on Cancer-Related Fatigue: Systematic Review and Meta-Analysis of Randomized Controlled Trials.', *BioMed research*

international. Hindawi, 2015, p. 328636. doi: 10.1155/2015/328636.

Minton, O., Jo, F. and Jane, M. (2015) 'The role of behavioural modification and exercise in the management of cancer-related fatigue to reduce its impact during and after cancer treatment', *Acta Oncologica*, 54(5), pp. 581–586. doi: 10.3109/0284186X.2014.996660.

Mishra, S. I. *et al.* (2012) 'Exercise interventions on health-related quality of life for people with cancer during active treatment', *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd, (8). doi: 10.1002/14651858.CD008465.pub2.

Mitchell, S. A. *et al.* (2014) 'Putting Evidence Into Practice: An Update of Evidence-Based Interventions for Cancer-Related Fatigue During and Following Treatment', *Clinical Journal of Oncology Nursing*. Oncology Nursing Society, 18(s6), pp. 38–58. doi: 10.1188/14.CJON.S3.38-58.

Mohandas, H. *et al.* (2017) 'Cancer-related fatigue treatment: An overview', *Journal of Cancer Research and Therapeutics*. Medknow Publications and Media Pvt. Ltd., 0(0), p. 0. doi: 10.4103/jcrt.JCRT_50_17.

Molassiotis, A. *et al.* (2012) 'Acupuncture for Cancer-Related Fatigue in Patients With Breast Cancer: A Pragmatic Randomized Controlled Trial', *Journal of Clinical Oncology*, 30(36), pp. 4470–4476. doi: 10.1200/JCO.2012.41.6222.

'Morgan et al., 2017. Available at: https:/ www.researchgate.net/profile/Sergio_Jimenez-Morgan/publication/315758785_Does_yoga_decrease_cancer-related_fatigue_in_women_with_breast_cancer_ Systematic_review_of_randomized_controlled_trials/links/58e28288a6fdcc5b2e9dda5a/ Does-yoga-decrease-canc (Accessed: 28 September 2019).

Mücke, M. *et al.* (2015) 'Pharmacological treatments for fatigue associated with palliative care', *Cochrane Database of Systematic Reviews*, (5), p. CD006788. doi: 10.1002/14651858.CD006788.pub3.

Mustian, K. M. *et al.* (2007) 'Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue.', *The oncologist*. AlphaMed Press, 12 Suppl 1(Supplement 1), pp. 52–67. doi: 10.1634/theoncologist.12-S1-52.

Mustian, K. M. *et al.* (2017) 'Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue', *JAMA Oncology*. American Medical Association, 3(7), p. 961. doi: 10.1001/jamaoncol.2016.6914.

Myall, M. *et al.* (2015) 'RESTORE: an exploratory trial of a web-based intervention to enhance self-management of cancer-related fatigue: findings from a qualitative process evaluation', *BMC Medical Informatics and Decision Making*, 15(1), p. 94. doi: 10.1186/s12911-015-0214-y.

'NCCN Guidelines, 2015'. Available at: https://jnccn.org/configurable/contentpage/journals$002fjnccn$002f13$002f8$002farticle-p1012.xml (Accessed: 10 September 2019).

'NCCN Guidelines, 2019'. Available at: https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf (Accessed: 2 October 2019).

'NHMRC Australia, 2019'. Available at: https://www.nhmrc.gov.au/sites/default/files/documents/reports/clinical guidelines/meeting-clinical-practice-guidelines.pdf (Accessed: 22 September 2019).

O'Higgins, C. M. *et al.* (2018) 'The pathophysiology of cancer-related fatigue: current controversies', *Supportive Care in Cancer*. Springer Berlin Heidelberg, 26(10), pp. 3353–3364. doi: 10.1007/s00520-018-4318-7.

O'Neill, M. *et al.* (2016) 'The effect of yoga interventions on cancer-related fatigue for breast cancer: A systematic review and meta-analysis of randomized controlled trials.', *Journal of Clinical Oncology*. American Society of Clinical Oncology, 34(15_suppl), pp. e21578–e21578. doi: 10.1200/JCO.2016.34.15_suppl.e21578.

Olver, I. N., Eliott, J. A. and Koczwara, B. (2014) 'A qualitative study investigating chemotherapy-induced nausea as a symptom cluster', *Supportive Care in Cancer*, 22(10), pp. 2749–2756. doi: 10.1007/s00520-014-2276-2.

Paramanandam, V. S. and Dunn, V. (2015) 'Exercise for the management of cancer-related fatigue in lung cancer: a systematic review', *European Journal of Cancer Care*. John Wiley & Sons, Ltd (10.1111), 24(1), pp. 4–14. doi: 10.1111/ecc.12198.

Paulsen, Ø. *et al.* (2014) 'Efficacy of Methylprednisolone on Pain, Fatigue, and Appetite Loss in Patients With Advanced Cancer Using Opioids: A Randomized, Placebo-Controlled, Double-Blind Trial', *Journal of Clinical Oncology*, 32(29), pp. 3221–3228. doi: 10.1200/JCO.2013.54.3926.

Pearson et al., 2016 'Appraising evidence based guidelines CRF'. Available at: https://www.researchgate.net/profile/Carol_Mckinstry/publication/301670983_Cancer-related_fatigue_appraising_evidence-based_guidelines_for_screening_assessment_and_management/links/574d4d1808ae061b3301f25f/Cancer-related-fatigue-appraising-evidence-based- (Accessed: 18 December 2019).

Pearson, E. J. M. *et al.* (2018) 'Interventions for cancer-related fatigue: a scoping review', *European Journal of Cancer Care*. John Wiley & Sons, Ltd (10.1111), 27(1), p. e12516. doi: 10.1111/ecc.12516.

Pearson, E. J. M., Morris, M. E. and McKinstry, C. E. (2017) 'Cancer related fatigue: implementing guidelines for optimal

management', *BMC Health Services Research*, 17(1), p. 496. doi: 10.1186/s12913-017-2415-9.

Pyszora, A. *et al.* (2017) 'Physiotherapy programme reduces fatigue in patients with advanced cancer receiving palliative care: randomized controlled trial', *Supportive Care in Cancer*, 25(9), pp. 2899–2908. doi: 10.1007/s00520-017-3742-4.

Ream, E. *et al.* (2015) 'Management of cancer-related fatigue during chemotherapy through telephone motivational interviewing: Modeling and randomized exploratory trial', *Patient Education and Counseling*, 98(2), pp. 199–206. doi: 10.1016/j.pec.2014.10.012.

Reis, D. and Jones, T. T. (2018) 'Frankincense Essential Oil as a Supportive Therapy for Cancer-Related Fatigue', *Holistic Nursing Practice*, 32(3), pp. 140–142. doi: 10.1097/HNP.0000000000000261.

Rha, S. Y. and Lee, J. (2017) 'Symptom clusters during palliative chemotherapy and their influence on functioning and quality of life', *Supportive Care in Cancer*, 25(5), pp. 1519–1527. doi: 10.1007/s00520-016-3545-z.

Rojí, R. and Centeno, C. (2017) 'The use of methylphenidate to relieve fatigue', *Current Opinion in Supportive and Palliative Care*, 11(4), pp. 299–305. doi: 10.1097/SPC.0000000000000296.

Sadja, J. and Mills, P. J. (2013) 'Effects of Yoga Interventions on Fatigue in Cancer Patients and Survivors: A Systematic Review of Randomized Controlled Trials', *EXPLORE*. Elsevier, 9(4), pp. 232–243. doi: 10.1016/J.EXPLORE.2013.04.005.

Saligan, L. N. *et al.* (2015) 'The biology of cancer-related fatigue: a review of the literature.', *Supportive care in cancer/ : official journal of the Multinational Association of Supportive Care in Cancer*. NIH Public Access, 23(8), pp. 2461–78. doi: 10.1007/s00520-015-2763-0.

Smith, T. G. *et al.* (2019) 'Perceptions of Patients With Breast and Colon Cancer of the Management of Cancer-Related Pain, Fatigue, and Emotional Distress in Community Oncology', *Journal of Clinical Oncology*, 37(19), pp. 1666–1676. doi: 10.1200/JCO.18.01579.

Sprod, L. K. *et al.* (2015) 'Effects of yoga on cancer-related fatigue and global side-effect burden in older cancer survivors', *Journal of Geriatric Oncology*. Elsevier, 6(1), pp. 8–14. doi: 10.1016/J.JGO.2014.09.184.

Starreveld, D. E. J. *et al.* (2018) 'Light therapy as a treatment of cancer-related fatigue in (non-)Hodgkin lymphoma survivors (SPARKLE trial): study protocol of a multicenter randomized controlled trial', *BMC Cancer*. BioMed Central, 18(1), p. 880. doi: 10.1186/s12885-018-4746-2.

Thoonsen, B. *et al.* (2019) 'Training general practitioners contributes to the identification of palliative patients and to multidimensional care provision: secondary outcomes of an RCT.', *BMJ supportive & palliative care*. British Medical Journal Publishing Group, 9(1), p. e18. doi: 10.1136/bmjspcare-2015-001031.

Tian, L. *et al.* (2016) 'Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials', *Supportive Care in Cancer*. Springer Berlin Heidelberg, 24(2), pp. 969–983. doi: 10.1007/s00520-015-2953-9.

Twomey, R. *et al.* (2017) 'Neuromuscular fatigue during exercise: Methodological considerations, etiology and potential role in chronic fatigue', *Neurophysiologie Clinique/Clinical Neurophysiology*, 47(2), pp. 95–110. doi: 10.1016/j.neucli.2017.03.002.

Vadiraja, H. S. *et al.* (2017) 'Effects of Yoga in Managing Fatigue in Breast Cancer Patients: A Randomized Controlled Trial.', *Indian journal of palliative care*. Wolters Kluwer — Medknow Publications, 23(3), pp. 247–252. doi: 10.4103/IJPC.IJPC_95_17.

van Vulpen, J. K. *et al.* (2016) 'Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: A meta-analysis', *Maturitas*, 85, pp. 104–111. doi: 10.1016/j.maturitas.2015.12.007.

Williams, L. A. *et al.* (2016) 'Patient and health care provider perceptions of cancer-related fatigue and pain', *Supportive Care in Cancer*. Springer Berlin Heidelberg, 24(10), pp. 4357–4363. doi: 10.1007/s00520-016-3275-2.

Wolvers, M. D. J. *et al.* (2018) 'Physical Behavior Profiles in Chronic Cancer-Related Fatigue', *International Journal of Behavioral Medicine*. Springer US, 25(1), pp. 30–37. doi: 10.1007/s12529-017-9670-3.

Yee, J. *et al.* (2019) 'Physical Activity for Symptom Management in Women With Metastatic Breast Cancer: A Randomized Feasibility Trial on Physical Activity and Breast Metastases', *Journal of Pain and Symptom Management*. doi: 10.1016/j.jpainsymman.2019.07.022.

Yennurajalingam, S. *et al.* (2013) 'Consistency of symptom clusters among advanced cancer patients seen at an outpatient supportive care clinic in a tertiary cancer center', *Palliative and Supportive Care*. Cambridge University Press, 11(6), pp. 473–480. doi: 10.1017/S1478951512000879.

Yennurajalingam, S. and Bruera, E. (2014) 'Role of corticosteroids for fatigue in advanced incurable cancer', *Current Opinion in Supportive and Palliative Care*, 8(4), pp. 346–351. doi: 10.1097/SPC.0000000000000093.

Zhang, L.-L. *et al.* (2016) 'Tai Chi Exercise for Cancer-Related Fatigue in Patients With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial', *Journal of Pain and Symptom Management*. Elsevier, 51(3), pp. 504–511. doi: 10.1016/J.JPAINSYMMAN.2015.11.020.

Zhang, Q. *et al.* (2018) 'Effects of nurse-led home-based exercise & cognitive behavioral therapy on reducing cancer-related fatigue in patients with ovarian cancer during and after chemotherapy: A randomized controlled trial', *International Journal of Nursing Studies*. Pergamon, 78, pp. 52–60. doi: 10.1016/J.IJNURSTU.2017.08.010.

Zhang, Y. *et al.* (2018) 'Effects of acupuncture on cancer-related fatigue: a meta-analysis', *Supportive Care in Cancer*, 26(2), pp. 415–425. doi: 10.1007/s00520-017-3955-6.

Zhou, W. *et al.* (2018) 'Effects of Tai Chi Exercise on Cancer-Related Fatigue in Patients With Nasopharyngeal Carcinoma Undergoing Chemoradiotherapy: A Randomized Controlled Trial', *Journal of Pain and Symptom Management*, 55(3), pp. 737–744. doi: 10.1016/j.jpainsymman.2017.10.021.

Zick, S. M. *et al.* (2016) 'Investigation of 2 Types of Self-administered Acupressure for Persistent Cancer-Related Fatigue in Breast Cancer Survivors', *JAMA Oncology*. American Medical Association, 2(11), p. 1470. doi: 10.1001/jamaoncol.2016.1867.

PHARMACOLOGICAL AGENTS IN CRF (APPENDIX 1)

Drug	Mechanism	RCT's	Results
Methylphenidate	Blocks Dopamine and Norepinephrine reuptake	Roth et al 2010	Effective in treating fatigue in men with prostate cancer
		Bruera et al 2006 Bruera et al 2013	Fatigue improved significantly in both groups with no difference between the methylphenidate and placebo arm
		Butler et al 2007	Slightly superior
		Moraska etal 2010	Could not show significant improvement compared to placebo
		Kerr et al 2012	In a multitype advanced cancer study group in a hospice methyl-phenidate was superior to placebo and improvement of fatigue was dose dependent
		Escalante et al 2014	Improvement in fatigue scores at stable dose of 18mg

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Drug	Mechanism	RCT's	Results
Modafanil	Wake promoting agent	Jean Pierre et al 2010	Benefit in patients with severe fatigue
		Spathis et al 2014	No difference between placebo and study groups (patients with NSCLC) though there was an improvement in FACIT-F scores in patients
		Hovey et al 2014	Double blind RGT. Potential beneficial effect on docetaxel related fatigue
Acetyl-L Carnitine	Patients on chemotherapy often develop L-Carnitine deficiency, which is a cause for generalised fatigue and its supplementation could improve fatigue.	Kraft et al 2012	Improvement in nutritional status and QOL

(Contd...)

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Drug	Mechanism	RCT's	Results
		Cruciani et al 2012	Four weeks of L Carnitine supplementation did not show a statistically significant difference between the study and the placebo arm.
Dexamethasone		Yennurajali-ngam	Dexamethasone is more effective than placebo in improving QOL and CRF in patients with advanced cancer
Methyl-prednisolone		Della Cuna 1989	Significant effect at 125mg/day for 8 weeks
		Paulsen et al 2014	Patients with advanced cancer on opioids. At a dose of 16mg bd for a week,there was improvement in fatigue,appetite and patient satisfaction

(Contd...)

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Drug	Mechanism	RCT's	Results
Bupropion	Antidepressant with a dual effect on the norepinephrine and dopamine neurotransmitter systems thus sharing its effect with psychostimulants	Ashrafi etal 2018	Four weeks of Bupropion SR 150 mg showed a significant improvement in fatigue for patients in the study
Donepezil	Acetylcholine-sterase inhibitor	Bruera et al 2007	No significant difference in the study group

Evidence-Based Management of Anorexia Cachexia Syndrome

INTRODUCTION

Anorexia is decreased caloric intake due to severe loss of appetite. Cachexia is historically defined as severe involuntary weight loss of more than 10% body weight.(Davis and Dickerson, 2000) This definition of cachexia may not correctly identify the frequency of cachexia in obese persons or those who have edema or big tumor mass.(Blum and Strasser, 2011; Fearon *et al.*, 2011)

The current consensus definition of cachexia was given in 2011 by an international group of experts. They defined Cancer Cachexia as, "a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can be partially but not entirely reversed by conventional nutritional support." They also define the three stages of cachexia as pre-cachexia, cachexia and refractory cachexia, which are assessed by five domains including food intake, catabolic derangements, functional and psychological impact and body composition (skeletal muscle mass and adipose tissue components). They also recommended using basal metabolic index (BMI) as a measure for grading of weight loss. (Fearon *et al.*, 2011)

European Palliative Care Research Collaborative (EPCRC), defines cancer cachexia as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without the loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.(*Clinical practice guidelines on Cancer Cachexia in advanced cancer patients | Literature watch | Cancer Cachexia*, 2011)

Table 1: Consensus Based Definition of Cancer Cachexia

Number	Study Group	Definition
1	EPCRC	Weight loss > 5% over past 6 months without starvation And/or Weight loss > 2% and BMI < 20 And/or Weight loss > 2% and sarcopenia
2	International group of experts (2011, Fearon et al.)	Weight loss >5% over past 6 months (in absence of simple starvation); or BMI <20 and any degree of weight loss >2%; or Appendicular skeletal muscle index consistent with sarcopenia (males <7·26 kg/m2; females <5·45 kg/m2) and any degree of weight loss >2%

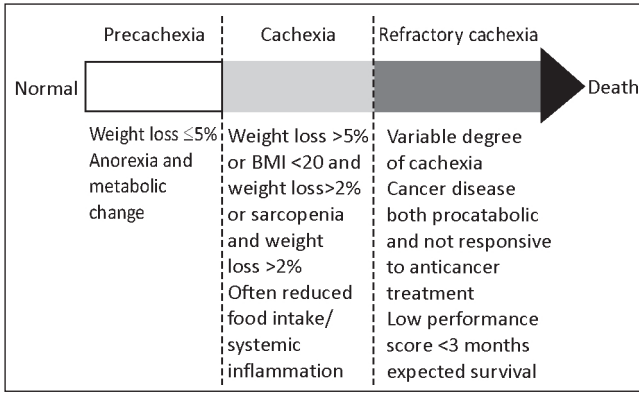

Figure 1: Stages of Cancer cachexia

Adapted from: *Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12:489*.

In a study that assessed weight loss in cancer patients at the time of diagnosis, the survival of patients correlated with the stage of cachexia; the patients with no weight loss having improved survival, precachetic having intermediate and cachectic patients having the worst survival outcomes.(Gannavarapu *et al.*, 2018) However, this difference in survival in precachetic patients was noted only after 1-year post cancer diagnosis.

A retrospective review of 3047 patients done by Eastern Cooperative Oncology Group suggested that, weight loss of more than 5 percent of premorbid weight prior to the initiation of chemotherapy was predictive of early mortality. Weight loss was independent of disease stage, tumor histology, and patient performance status in its predictive value. Also, those patients who had cachexia,

tend to show poor response to chemotherapy, although this was statistically significant only in patients with breast cancer.(Dewys *et al.*, 1980) The Spanish NUPAC study(Segura *et al.*, 2005), designed to determine the prevalence of malnutrition in advanced cancer, confirmed a 52% rate of moderate or severe malnutrition, with a distribution of 57.7% in esophageal, 50% in gastric, and 47.1% in laryngeal cancers. A sub-analysis of the PREDYCES study revealed that 36.4% of oncology patients were at nutritional risk at the time of hospital discharge. It also demonstrated its significant association with longer hospital stays and higher healthcare costs. Despite all of this, only 1/3 of patients at nutritional risk received nutritional support.(Planas *et al.*, 2016)

Various studies have demonstrated that in addition to prognosis, cancer cachexia also worsens functional status, impairs quality of life, increase risk of hospitalization and can also cause death.(O'Gorman, McMillan and McArdle, 1999; Reynolds, Donohoe and Ryan, 2011; Hopkinson, 2014)

The prevalence of anorexia is as high as 40% in settings of advanced cancers. Cancer cachexia is a frequent complication encountered in malignancies of pancreatic, esophageal, gastric, hepatic, colorectal and pulmonary origin.(Bosaeus *et al.*, 2001; Hutton *et al.*, 2006)

PATHOGENESIS

The hypercatabolic state of cachexia which leads to increased muscle loss is secondary to inflammatory response, which targets skeletal muscle gene products. There is increase in resting energy expenditure (REE), also

called as basal metabolic rate, leading to wasting.(Peacock *et al.*, 1987; Stallings *et al.*, 1989; Fredrix *et al.*, 1991; Staal-van den Brekel *et al.*, 1994) The cytokines and polypeptides released mainly by immune cells are responsible for these metabolic derangements. Tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1 beta and IL-6 are the main mediators.(Falconer *et al.*, 1994; Staal-van Den Brekel *et al.*, 1995; Kuroda *et al.*, 2007) Other pathways that have some postulated role in development of cancer cachexia are through lipolysis and lipid mobilizing factor secreted by the tumor cells(Todorov *et al.*, 1998; Khan and Tisdale, 1999), the activation of ATP-ubiquitin-proteosome pathway(Baracos *et al.*, 1995; Llovera *et al.*, 1997; Zhang *et al.*, 2013) and JAK/STAT pathway(Bonetto *et al.*, 2012; Quintás-Cardama and Verstovsek, 2013). Some cancer directed treatments like androgen deprivation for prostate cancers(Reis *et al.*, 2009), sorafenib (Sami Antoun *et al.*, 2010; S. Antoun *et al.*, 2010; Mir *et al.*, 2012; Parsons *et al.*, 2012) and bevacizumab(Poterucha, Burnette and Jatoi, 2012) may lead to sarcopenia. Further, anorexia and poor dietary intake and absorption due to various reasons may also contribute to cancer cachexia.

CLINICAL FEATURES

The characteristic feature of cancer cachexia is a disproportionate and excessive loss of lean body mass, which distinguishes it from starvation (lean body mass is preserved in starvation)(Leibel, Rosenbaum and Hirsch, 1995). Other findings include hyperglycemia, hyper-triglyceridemia, increase in very low-density lipoproteins and exaggerated insulin response to a glucose load.

Table 2: Factors contributing to development of Cancer Anorexia and Cachexia			
Symptoms that may impact oral intake	**Patient related factors**	**Disease related factors**	**Treatment related factors**
Anxiety/ depression	Body-image dissatisfaction	Site of the tumor	Mucositis
Constipation or diarrhea	Eating-related distress	Weakness or disability	Nausea/ vomiting
Difficulty chewing/ dysphagia	Fatigue	Electrolyte imbalance	Altered taste/ smell
Dysgeusia	Early satiety	Obstruction	Adrenal insufficiency Hypogonadism (in men) Hypothyroidism
Dyspnea	Appetite loss	Malabsorption	Sarcopenia from cancer treatment (androgen deprivation therapy, sorafenib, bevacizumab)
Fatigue		Impaired gut function	Prolonged high-dose steroids
Nausea/ vomiting		Inflammatory cytokines	
Pain			
Stomatitis			
Thick saliva/ secretions Xerostomia			

STANDARD OF CARE

Assessment of cancer cachexia should be multidimensional and should be done in each patient. It is important to determine the overall condition of the patient and decide over best possible treatment plan. There is no standard consensus upon the assessment of cancer cachexia.(Dev, 2019) The assessment of cachexia includes objective as well as subjective measures and the goals of management in palliative care setting is to provide maximum subjective benefit over patients presenting status.

Four major aspects of assessing cancer cachexia are (Sadeghi *et al.*, 2018):

1. Nutritional screening and assessment (Table 3)
2. Muscularity and body composition (Table 4, Table 5)
3. Quality of life (QoL) and psychosocial assessment (Table 6)
4. Biomarkers of cachexia (Table 7)

Table 3: Measures for Nutritional screening and assessment						
Tool	**Developed by**	**Main assessment criteria**	**Validated in cancer population**	**Assessment in addition to screening**	**Completed by**	**Cancer specific**
Patient-Generated Subjective Global Assessment (PG-SGA)	Ottery, 1996	Weight loss, appetite and food intake, activity and function; metabolic demand, physical assessment	Yes	Yes	Both patient and practitioner	Yes
Mini-Nutritional Assessment (MNA)	Guigoz et al., 1996	Dietary and anthropometric measurement, activity	Contradictory results	Yes	Practitioner	No
Malnutrition Screening Tool (MST)	Ferguson et al., 1999	Weight loss, appetite and food intake	Yes	No	Patient	No

Contd...

Contd... (Table 3)

Tool	Developed by	Main assessment criteria	Validated in cancer population	Assessment in addition to screening	Completed by	Cancer specific
Malnutrition Universal Screening Tool (MUST)	Malnutrition Advisory Group of the British Association of Parenteral and Enteral Nutrition	Weight loss, BMI, acute disease	Contradictory results	No	Practitioner	No
Nutritional Risk Screening-2002 (NRS-2002)	European Society for Clinical Nutrition and Metabolism	Weight loss, BMI, food intake	Contradictory results	No	Practitioner	No

Table 4: Measures for Muscularity Assessment and Body Composition			
Assessment method	**Developed by**	**Indication of muscle depletion**	
		Caucasian population	**Indian population**
Lumbar (L3) skeletal muscle index determined by CT imaging	Prado et al., 2008	Men < 55 cm^2/m^2 Women < 39 cm^2/m^2	No data specific for Indian population
Appendicular skeletal muscle index determined by DEXA	Baumgartner et al., 1998	Men < 7.26 kg/m^2 Women < 5.45 kg/m^2	
Whole body fat-free mass (FFM) index without bone determined by BIA	Janssen et al., 2002	Men < 14.6 kg/m^2 Women < 11.4 kg/m^2	
Mid upper-arm muscle area determined by anthropometry	Jetté et al., 1983	Men <32cm^2 Women < 18 cm^2	

Table 5: Weight Loss Grading System (WLGS) (Vagnildhaug *et al.*, 2017)			
Grade	**Weight loss percentage**	**BMI**	**Reported Median Survival (months)**
0	±2.4%	≥ 28 kg/m^2	Longest
1	≤2.4%	20 to 25 kg/m^2	14.6
	2.5% to 6.0%	≥ 28 kg/m^2	
2	2.5% to 6%	20 to 28 kg/m^2	10.8
	6% to 11%	≥ 28 kg/m^2	
3	<6%	≤20 kg/m^2	7.6
	6% to 11%	20 to 28 kg/m^2	
	11% to 15%	22 to >28 kg/m^2	
	>15%	≥ 28 kg/m^2	
4	6% to 11%	≤20 kg/m^2	4.3
	11% to 15%	≤22 kg/m^2	
	>15%	≤28 kg/m^2	

Table 6: Quality of Life (QoL) Assessment Tools in Cachectic Patients

Assessment Tool	Number of Items for Evaluation	Domains of Health Related QoL Covered	Condition
Cancer Rehabilitation Evaluation System (CARES)	139-long form 59-short form	Physical, Functional, Social, Psychological, Sexual, Treatment	Cancer
European Organization for the Treatment and Research of Cancer-Quality of Life Questionnaire (EORTC QLQ-CAX24	24	Food aversion, eating and weight-loss worry, eating difficulties, loss of control and physical decline	Cancer cachexia
EuroQOL	16	Physical, Functional, Social, Psychological	General (Chronic illness)
Functional Assessment of Anorexia/Cachexia Therapy (FAACT) – (Functional Assessment of Cancer Therapy [FACT] combined with anorexia and cachexia subscale [ACS])	39	Physical, Functional, Social, Emotional, Sexual	Cancer Cachexia

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Assessment Tool	Number of Items for Evaluation	Domains of Health Related QoL Covered	Condition
Functional Living Index-Cancer (FLIC)	22	Physical, Functional, Social, Psychological, Treatment	Cancer
Nottingham Health Profile (NHP)	45	Physical, Functional, Social, Psychological, Sexual	General illness (Chronic illness-cancer)
Quality of Life Index: Cancer Version – III	66	Physical, Functional, Social, Sexual	Cancer
World health Organization Quality of Life-100 item (WHOQOL-100)	100	Physical, Functional, Social, Psychological, Sexual	General illness

Table 7: Biomarkers of Cachexia		
Domain of cancer cachexia	**Associated biomarker**	**Observed change**
Systemic inflammation	CRP	Increase
	IL-1alpha	Increase
	IL-1beta	Increase/insignificant
	IL-6	Increase
	INF-gamma	Insignificant
	IL-8	Increase
	TNF-alpha	Increase/insignificant
	IL-10	Increase
	Albumin	Decrease
Hormonal dysregulation	Ghrelin	Increase/insignificant/ decrease
	Obestatin	Decrease
	Testosterone	Decrease
	IGF-1	Decrease
Adipose-derived factors	Adiponectin	Increase/insignificant/ decrease
	Resistin	Increase
	Leptin	Increase/insignificant/ decrease
Tumor-derived factors	Zinc-α2-glycoprotein (ZAG), also known as lipid- mobilizing factor (LMF)	Increase (observed in urine)
	Proteolysis Inducing Factor (PIF)	Increase (observed in urine)
	VEGF-A and VEGF-C	Increase
	Midkine	Increase

MANAGEMENT

No international standard guideline is perfectly effective for management of cancer cachexia and there is no universal gold standard. Cancer cachexia being a multidimensional problem needs a multimodality management approach. The proposed multimodality management is shown in Figure 2.(del Fabbro, 2019) Other models that can be used for management of cachexia are those based on individual preference which is targeted towards maximizing the functionality of the individual and those based on underlying mechanism of cachexia.

Patients at risk of losing weight should be offered prophylactic interventions such as nutritional counseling and physical training, as these interventions are thought to be beneficial in delaying or preventing the development of the anorexia- cachexia syndrome (level of recommendation: weak positive). Per definition, prophylaxis is not relevant for patients with refractory cachexia.

NON-PHARMACOLOGICAL

Nutrition

Cancer patients have similar nutritional requirements to the healthy population, around 25–30 kcal/kg/day, with a balance between calorie intake and expenditure, including the degree of physical activity (strength of recommendation: strong; level of evidence: low).

Protein requirements are estimated to be between 1.2 and 1.5 g/kg/day. These values should be modified according

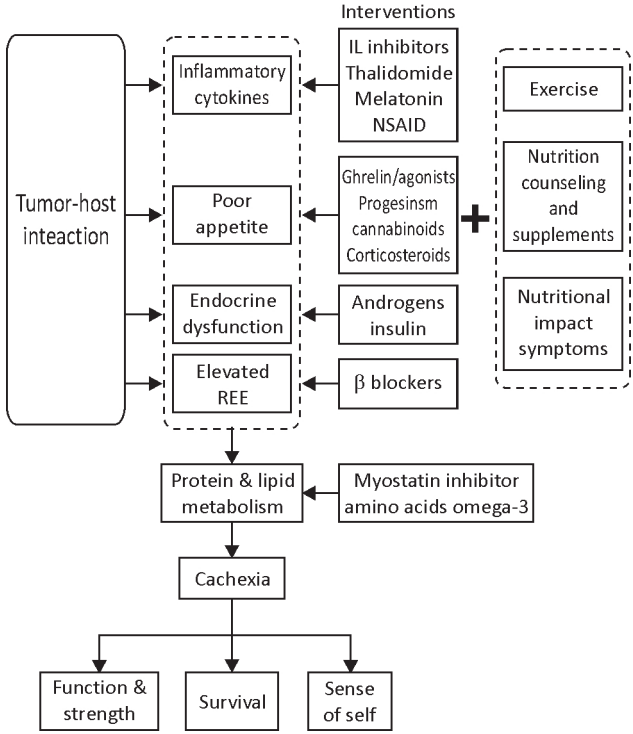

Figure 2: Multimodality Rx model.
NSAID, Nonsteroidal Anti-inflammatory Drug;
REE, Resting Energy Expenditure;
IL, interleukin. (del Fabbro, 2019)

to patients' renal function, as well as any other metabolic disturbances. The contribution of water and minerals should be evaluated, especially in certain situations in which there are associated hydroelectrolyte disturbances. The administration of high-doses of vitamins and trace

elements is not recommended, except in cases of established deficit. (strength of recommendation: strong; level of evidence: moderate).

Parenteral nutrition

Parenteral nutrition support is not routinely used as an adjunct to chemotherapy or irradiation to the head and neck, abdomen, or pelvis. In terminal patients, caution should be taken, as parenteral nutrition may harm the patient.

NCCN guidelines recommends parenteral or enteral nutrition only when survival is longer than weeks to days and the decisions about starting artificial nutrition are to be individualized on a case-by-case basis after taking into account cancer type, treatment, anticipated duration and reversibility of nutritional deficit, prognosis, and patient preferences and this should be discouraged in terminal patients.

Enteral nutrition

Vitamins and minerals be supplied in amounts approximately equal to the RDA and discourage the use of high-dose micronutrients in the absence of specific deficiencies. (strength of recommendation: strong; level of evidence: low)

Nutritional intervention to increase oral intake in cancer patients who can eat but are malnourished or at risk of malnutrition. This includes dietary advice, the treatment of symptoms and derangements impairing food intake

(nutrition impact symptoms), and offering oral nutritional supplements. (strength of recommendation: strong; level of evidence: moderate).

If a decision has been made to feed a patient, enteral nutrition is recommended if oral nutrition remains inadequate despite nutritional interventions (counselling, ONS), and parenteral nutrition if enteral nutrition is not sufficient or feasible. (strength of recommendation: strong; level of evidence: moderate).

If oral food intake has been decreased severely for a prolonged period of time, it is recommended to increase (oral, enteral or parenteral) nutrition only slowly over several days and to take additional precautions to prevent a refeeding syndrome. (strength of recommendation: strong; level of evidence: low).

In patients with chronic insufficient dietary intake and/or uncontrollable malabsorption, home artificial nutrition (either enteral or parenteral) in suitable patient is recommended. (strength of recommendation: strong; level of evidence: low).

Maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function and metabolic pattern. (strength of recommendation: strong; level of evidence: high).

Individualized resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass (strength of recommendation: weak; level of evidence: low).

Other non-drug measures

There is evidence that non-drug treatment is effective in the treatment of cancer cachexia (level of recommendation: strong positive). However, evidence for patients with refractory cachexia is insufficient.

There is some evidence that counseling has positive effects on nutritional status and quality of life in cancer patients undergoing anti-neoplastic therapy (level of recommendation: strong positive). There is no evidence to support or refute the value of counseling in advanced cancer/refractory cachexia.

There some evidence that psychotherapeutic interventions (relaxation therapy) have positive effects on quality of life (level of recommendation: strong positive). There is no evidence that psychotherapeutic interventions have an effect on nutritional status. Moreover, for refractory cachexia, reduced performance status and short prognosis may preclude this intervention.

In cancer patients, physical training and other physical treatment options are beneficial as a preventive procedure to maintain functional status. The activities and training interventions have to be individualized (overall level of recommendation: strong positive). However, most research has been done in patients treated with curative intent, and it is not clear to what extent physical training is appropriate in patients with advanced cancer/refractory cachexia.

In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care, oral/enteral immunonutrition (arginine, Ω-3 fatty acids, nucleotides) is recommended. (level of recommendation: strong, level of evidence: high)

Pharmacological (Table 8)

The major mechanisms by which drugs target cancer cachexia can be:

1 Reduction of the tumor-associated inflammation
2 Capitalization on the anabolic potential of the body to counter the wasting and hypercatabolic state
3 Appetite stimulation

These mechanisms are not exclusive and hence are difficult to interpret. The target pathways for drugs are very entangled.

Table 8: Pharmacologic Treatment Options for Cancer Cachexia in Clinical Research Phase.

Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Megestrol acetate	Medroxy-progesterone acetate (MPA)	Reduction and inhibition of pro-inflammatory cytokines (Mantovani *et al.*, 1995) and appetite stimulation through increasing the release of neuropeptide Y in the hypothalamus (David McCarthy *et al.*, 1994)	Appetite, food intake, weight gain, quality of life (López et al. 2004; W. et al. 2008; Ruiz Garcia et al. 2013)	Progestogens Increased risk of thrombo-embolic events (most important), peripheral edema, breakthrough bleeding, hyper-glycemia, hypertension and cushings syndrome (MacCiò et al. 2012)

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Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Cannabinoids (e.g., dronabinol)	Interaction with endorphin receptors, interference with IL-1 synthesis, activation of cannabinoid receptors involved in the neuronal circuit of leptin and prostaglandin synthesis inhibition.	Appetite, food intake, homeostatic mechanisms of energy storage (Gamage and Lichtman 2012)	Cannabinoids	Severe adverse effects, especially on the central nervous system, e.g., hallucinations, vertigo, psychosis. (Bagshaw and Hagen 2002; Tafelski et al. 2016) Current evidence for use is equivocal
Cyproheptadine	Serotonergic blockade	Mild stimulation of appetite (Kardinal et al. 1990)	Anti-serotonergic drugs	Sedating effects. (Mantovani et al. 2001) Further clinical trials are needed following inconsistent results. (Kardinal et al. 1990; Couluris et al. 2008)

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Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxy-genase-2 (COX-2) inhibitors such as celecoxib, ibuprofen, and indo-methacin	Reduction of tumor-associated inflammation	Lean body mass, TNF-α levels, grip strength, quality of life, Glasgow prognostic score (McMillan et al. 1999; Lai et al. 2008; Mantovani et al. 2010)	Cytokine inhibitors	Risk of renal and hepatic impairment and gastro-intestinal bleeding (NSAIDs). (MacCiò et al. 2012; Reid et al. 2013) Insufficient evidence
Thalidomide	Immuno-modulation, anti-inflammatory and TNF-α and IL-6 inhibition properties, inhibition of NF-κB (Keifer et al. 2001; JIN et al. 2002), and blockade of COX-2 (Fujita et al. 2001)	Appetite, lean body mass, weight (Gordon et al. 2005), quality of life (Davis et al. 2012)	Cytokine inhibitors	Poor tolerability in esophageal cancer. (Wilkes et al. 2011) Larger clinical trials are needed based on promising initial results (Mantovani et al. 2010; Wen et al. 2012; Yennuraja-lingam et al. 2012)

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Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Melatonin	Cytokine and TNF-α inhibition (Lissoni et al. 1996)	Contradicting results (Lissoni et al. 1996; Del Fabbro et al. 2013)	Cytokine inhibitors	More clinical trials specifically designed for the study of the effect of this hormone are needed. Phase 3 clinical trials on melatonin have been conducted without observation of any improvement
Ghrelin (and the agonists of its receptor, anamorelin and macimorelin)	Stimulation of GH secretion (Takaya et al. 2000), suppression of pro-inflammatory cytokines and inhibition of NF-κB (Li et al. 2004; Waseem et al. 2008), orexigenic effects (Kamegai et al. 2001; Cowley et al. 2003)	Body weight, appetite, lean body mass (Neary et al. 2004; Garcia et al. 2015)		Ghrelin might stimulate tumor growth. (Murphy and Lynch 2012) Confirmation requires further clinical research. Phase 3 clinical trials have been conducted.

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Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Selective Androgen Receptor Modulators (e.g., enobosarm)	Act selectively on androgen receptors of the skeletal muscle and bone, minimizing stimulation of other organs such as prostate, skin, and liver.	Physical performance and lean body mass (Dalton et al. 2011; Dobs et al. 2013)	Selective androgen receptor modulators (SARMs)	Phase 3 clinical trials have been conducted
Espindolol	Non-selective β blocker with central 5-HT1a and partial β2 receptor agonist effects	Lean body mass, weight, hand grip strength (Stewart Coats et al. 2016)	Non-selective β blocker with central 5-HT1a and partial β2 receptor agonist effects	More efficacy and safety data needed but the initial data have been promising (Stewart Coats et al. 2016)

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Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Oxy-metholone, oxandrolone, nandrolone and fluoxy-mesterone	Marked anabolic activity with minimal androgenic effects (Lesser et al. 2008)	Lean body mass, subjective anorexia score (Lesser et al. 2008)	Synthetic anabolic steroids	High hepato-toxicity. (García-Cortés et al. 2016) Confirmatory data are still lacking and have sometimes been shown to be inferior compared to other treatments. (Loprinzi et al. 1999) Most studies have been conducted in patients with cachexia of a non-oncological origin (Storer et al. 2005)

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Drug	Mechanism of Action	Effects	Class of Drug	Adverse Effects
Pentoxifylline (a methylxanthine derivative)	Anti-inflammatory and TNF-α inhibition properties (immunomodulation through inhibition of phosphodiesterase)	Not significant (Goldberg et al. 1995; Mehrzad et al. 2016)	Cytokine inhibitors	Its efficacy in cancer-associated cachexia has not been demonstrated (Goldberg et al. 1995; Mehrzad et al. 2016)
Dexamethasone Prednisone Methylprednisone	Suppression of pro-inflammatory cytokines such as TNF-α (Han et al. 1990) and IL-1 (Uehara et al. 1989)	Appetite, calorie intake, sensation of wellbeing, and nausea (Bruera et al.; Willox et al. 1984; Metz et al. 1989)	Corticosteroids	The effect is short lived (less than 4 weeks). Furthermore, long-term side effects (insulin resistance, fluid retention, steroidal myopathy, skin fragility, adrenal insufficiency, sleep and cognitive disorders) have been observed (Goldberg et al. 1995; Yennurajalingam et al. 2012; Tuca et al. 2013)

RECENT DEVELOPMENTS

The pharmacological options for cachexia in preclinical phase are as mentioned in table 9. Also, there is preclinical data supporting the role of two specific genes, CaMKIIbeta an TIE1, which also are activated with exercise, to be directly associated with weight loss in cancer cachexia. These preclinical studies open new avenues for understanding cancer cachexia and potentially identifying new therapeutic targets.

Table 9. Pharmacologic Treatment Options for Cancer Cachexia in Preclinical Research Phase.

Drug	Proposed Mechanism of Action	Effects	Class of Drug	Adverse Effects
Clenbuterol, salbutamol, salmeterol, and formoterol	Increase muscle mass through inhibition of protein degradation (Benson et al. 1991) and activation of muscle protein synthesis (Choo et al. 1992); activation of the AKT/ mTOR pathway (Kline et al. 2007)	Muscle mass and function (Busquets et al. 2004; Greig et al. 2014; Toledo et al. 2014)	Beta-2-agonists	They might have cardio-vascular side effects. (Toledo et al. 2014) Based on the initial promising results in animal models (Pinto et al. 2004), randomized trials are warranted.

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Drug	Proposed Mechanism of Action	Effects	Class of Drug	Adverse Effects
Insulin and insulin sensitizers (Thiazolid-inediones such as rosiglitazone)	Counter the peripheral insulin resistance that is frequently associated with cancer cachexia. Thiazolid-inediones decrease pro-inflammatory cytokines and increase adiponectin and also stimulate peroxisome proliferator-activated receptor (PPAR γ) (Hauner 2002)	Calorie intake (Lundholm et al. 2007), body fat and lean body mass (Yki-Järvinen 2004; Chen and Xiao 2014)	Insulin and insulin sensitizers	TZDs have proven to be promising agents against cancer-associated cachexia in animal models. (Asp et al. 2011; Chen and Xiao 2014) Clinical trials in human cancer patients present an interesting area for future research.
Metformin	Increases the activity of AMP-activated protein kinase (AMPK), and the PI3K pathway, in muscle cells, 2 mechanisms involved in muscle wasting	Body composition, protein degradation (Oliveira and Gomes-Marcondes 2016)	Insulin and insulin sensitizers	Clinical studies are yet to be conducted.

REFERENCES

Asp ML, Tian M, Kliewer KL, Belury MA (2011) Rosiglitazone delayed weight loss and anorexia while attenuating adipose depletion in mice with cancer cachexia. Cancer Biol Ther 12:957–965. doi: 10.4161/cbt.12.11.18134

Bagshaw SM, Hagen NA (2002) Medical efficacy of cannabinoids and marijuana: A comprehensive review of the literature. J. Palliat. Care 18:111–122

Benson DW, Foley-Nelson T, Chance WT, et al (1991) Decreased myofibrillar protein breakdown following treatment with clenbuterol. J Surg Res 50:1–5. doi: 10.1016/0022-4804(91)90002-4

Bruera E, Roca E, Cedaro L, et al (1985) Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 69:751–4

Busquets S, Figueras MT, Fuster G, et al (2004) Anticachectic effects of formoterol: A drug for potential treatment of muscle wasting. Cancer Res 64:6725–6731. doi: 10.1158/0008-5472.CAN-04-0425

Chen SZ, Xiao JD (2014) Rosiglitazone and imidapril alone or in combination alleviate muscle and adipose depletion in a murine cancer cachexia model. Tumor Biol 35:323–332. doi: 10.1007/s13277-013-1043-1

Choo JJ, Horan MA, Little RA, Rothwell NJ (1992) Anabolic effects of clenbuterol on skeletal muscle are mediated by beta 2-adrenoceptor activation. Am J Physiol 263:E50-6. doi: 10.1152/ajpendo.1992.263.1.E50

Couluris M, Mayer JLR, Freyer DR, et al (2008) The effect of cyproheptadine hydrochloride (Periactin) and megestrol acetate (Megace) on weight in children with cancer/treatment-related cachexia. J Pediatr Hematol Oncol 30:791–797. doi: 10.1097/MPH.0b013e3181864a5e

Cowley MA, Smith RG, Diano S, et al (2003) The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 37:649–661. doi: 10.1016/S0896-6273(03)00063-1

Dalton JT, Barnette KG, Bohl CE, et al (2011) The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: Results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2:153–161. doi: 10.1007/s13539-011-0034-6

Davis M, Lasheen W, Walsh D, et al (2012) A phase II dose titration study of thalidomide for cancer-associated anorexia. J Pain Symptom Manage 43:78–86. doi: 10.1016/j.jpainsymman. 2011.03.007

Del Fabbro E, Dev R, Hui D, et al (2013) Effects of melatonin on appetite and other symptoms in patients with advanced cancer and cachexia: A double-blind placebo-controlled trial. J Clin Oncol 31:1271–1276. doi: 10.1200/JCO.2012.43.6766

Dobs AS, Boccia R V., Croot CC, et al (2013) Effects of enobosarm on muscle wasting and physical function in patients with cancer: A double-blind, randomised controlled phase 2 trial. Lancet Oncol 14:335–345. doi: 10.1016/S1470-2045(13)70055-X

Fujita J, Mestre JR, Zeldis JB, et al (2001) Thalidomide and its analogues inhibit lipopolysaccharide-mediated Iinduction of cyclooxygenase-2. Clin Cancer Res 7:3349–55

Gamage TF, Lichtman AH (2012) The Endocannabinoid System: Role in Energy Regulation. Pediatr. Blood Cancer 58:144–148

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, et al (2016) Hepatotoxicity by Dietary Supplements: A tabular Listing and Clinical Characteristics. Int. J. Mol. Sci. 17

Garcia JM, Boccia R V., Graham CD, et al (2015) Anamorelin for patients with cancer cachexia: An integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. Lancet Oncol 16:108–116. doi: 10.1016/S1470-2045(14)71154-4

Goldberg RM, Loprinzi CL, Mailliard JA, et al (1995) Pentoxifylline for treatment of cancer anorexia and cachexia? A randomized, double-blind, placebo-controlled trial. J Clin Oncol 13:2856–2859. doi: 10.1200/JCO.1995.13.11.2856

Gordon JN, Trebble TM, Ellis RD, et al (2005) Thalidomide in the treatment of cancer cachexia: A randomised placebo controlled trial. Gut 54:540–545. doi: 10.1136/gut.2004.047563

Greig CA, Johns N, Gray C, et al (2014) Phase I/II trial of formoterol fumarate combined with megestrol acetate in cachectic patients with advanced malignancy. Support Care Cancer 22:1269–1275. doi: 10.1007/s00520-013-2081-3

Han J, Thompson P, Beutler B (1990) Dexamethasone and pentoxifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signaling pathway. J Exp Med 172:391–394. doi: 10.1084/jem.172.1.391

Hauner H (2002) The mode of action of thiazolidinediones. Diabetes Metab Res Rev 18:. doi: 10.1002/dmrr.249

JIN SH, KIM T IL, HAN DS, et al (2002) Thalidomide Suppresses the Interleukin 1â-Induced NFêB Signaling Pathway in Colon Cancer Cells. Ann N Y Acad Sci 973:414–418. doi: 10.1111/j.1749-6632.2002.tb04674.x

Kamegai J, Tamura H, Shimizu T, et al (2001) Chronic Central Infusion of Ghrelin Increases Hypothalamic Neuropeptide Y and Agouti-Related Protein mRNA Levels and Body Weight in Rats. Diabetes 50:2438–2443. doi: 10.2337/diabetes.50.11.2438

Kardinal CG, Loprinzi CL, Schaid DJ, et al (1990) A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. Cancer 65:2657–62. doi: 10.1002/1097-0142(19900615)65:12<2657::aid-cncr2820651210>3.0.co;2-s

Keifer JA, Guttridge DC, Ashburner BP, Baldwin Jr. AS (2001) Inhibition of NF-kappa B activity by thalidomide through suppression of IkappaB kinase activity. J Biol Chem 276:22382–22387

Kline WO, Panaro FJ, Yang H, Bodine SC (2007) Rapamycin inhibits the growth and muscle-sparing effects of clenbuterol. J Appl Physiol 102:740–747. doi: 10.1152/japplphysiol.00873.2006

Lai V, George J, Richey L, et al (2008) Results of a pilot study of the effects of celecoxib on cancer cachexia in patients with cancer of the head, neck, and gastrointestinal tract. Head Neck 30:67–74. doi: 10.1002/hed.20662

Lesser GJ, Case D, Ottery F, et al (2008) A phase III randomized study comparing the effects of oxandrolone (Ox) and megestrol acetate (Meg) on lean body mass (LBM), weight (wt) and quality of life (QOL) in patients with solid tumors and weight loss receiving chemotherapy. J Clin Oncol 26:9513–9513. doi: 10.1200/jco.2008.26.15_suppl.9513

Li WG, Gavrila D, Liu X, et al (2004) Ghrelin Inhibits Proinflammatory Responses and Nuclear Factor-êB Activation in Human Endothelial Cells. Circulation 109:2221–2226. doi: 10.1161/01.CIR.0000127956.43874.F2

Lissoni P, Paolorossi F, Tancini G, et al (1996) Is there a role for melatonin in the treatment of neoplastic cachexia? Eur J Cancer Part A 32:1340–1343. doi: 10.1016/0959-8049(96)00136-0

López AP, Roqué I Figuls M, Cuchi GU, et al (2004) Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. J. Pain Symptom Manage. 27:360–369

Loprinzi CL, Kugler JW, Sloan JA, et al (1999) Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J Clin Oncol 17:3299–3306. doi: 10.1200/JCO.1999.17.10.3299

Lundholm K, Körner U, Gunnebo L, et al (2007) Insulin treatment in cancer cachexia: Effects on survival, metabolism, and physical functioning. Clin Cancer Res 13:2699–2706. doi: 10.1158/1078-0432.CCR-06-2720

MacCiò A, Madeddu C, Gramignano G, et al (2012) A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: Evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecol Oncol 124:417–425. doi: 10.1016/j.ygyno.2011.12.435

Mantovani G, MacCiò A, Madeddu C, et al (2010) Phase II nonrandomized study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cancer cachexia. J Mol Med 88:85–92. doi: 10.1007/s00109-009-0547-z

Mantovani G, Macciò A, Massa E, Madeddu C (2001) Managing cancer-related anorexia/cachexia. Drugs 61:499–514

McMillan DC, Wigmore SJ, Fearon KCH, et al (1999) A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. Br J Cancer 79:495–500. doi: 10.1038/sj.bjc.6690077

Mehrzad V, Afshar R, Akbari M (2016) Pentoxifylline treatment in patients with cancer cachexia: A double-blind, randomized, placebo-controlled clinical trial. Adv Biomed Res 5:60. doi: 10.4103/2277-9175.179182

Metz CA, Robustelli Della Cuna G, Pellegrini A, Piazzi M (1989) Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: A placebo-controlled, multicenter study. Eur J Cancer Clin Oncol 25:1817–1821. doi: 10.1016/0277-5379(89)90353-2

Murphy KT, Lynch GS (2012) Editorial update on emerging drugs for cancer cachexia. Expert Opin. Emerg. Drugs 17:5–9

Neary NM, Small CJ, Wren AM, et al (2004) Ghrelin increases energy intake in cancer patients with impaired appetite: Acute, randomized, placebo-controlled trial. In: Journal of Clinical Endocrinology and Metabolism. pp 2832–2836

Oliveira AG, Gomes-Marcondes MCC (2016) Metformin treatment modulates the tumour-induced wasting effects in muscle protein metabolism minimising the cachexia in tumour-bearing rats. BMC Cancer 16:. doi: 10.1186/s12885-016-2424-9

Pinto JA, Folador A, Bonato SJ, et al (2004) Fish oil supplementation in F1 generation associated with naproxen, clenbuterol, and insulin administration reduce tumor growth and cachexia in Walker 256 tumor-bearing rats. J Nutr Biochem 15:358–365. doi: 10.1016/j.jnutbio.2004.02.002

Reid J, Hughes CM, Murray LJ, et al (2013) Non-steroidal anti-inflammatory drugs for the treatment of cancer cachexia: A systematic review. Palliat. Med. 27:295–303

Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, et al (2013) Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database Syst. Rev. 2017

Stewart Coats AJ, Ho GF, Prabhash K, et al (2016) Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). J Cachexia Sarcopenia Muscle 355–365. doi: 10.1002/jcsm.12126

Storer TW, Woodhouse LJ, Sattler F, et al (2005) A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. J Clin Endocrinol Metab 90:4474–4482. doi: 10.1210/jc.2005-0275

Tafelski S, Häuser W, Schäfer M (2016) Wirksamkeit, Verträglichkeit und Sicherheit von Cannabinoiden für die Therapie von Chemotherapie-induzierter Übelkeit und Erbrechen: eine systematische Zusammenfassung systematischer Reviews. Schmerz 30:14–24. doi: 10.1007/s00482-015-0092-3

Takaya K, Ariyasu H, Kanamoto N, et al (2000) Ghrelin strongly stimulates growth hormone (GH) release in humans. J Clin Endocrinol Metab 85:4908–4911. doi: 10.1210/jcem.85.12.7167

Toledo M, Springer J, Busquets S, et al (2014) Formoterol in the treatment of experimental cancer cachexia: effects on heart function. J Cachexia Sarcopenia Muscle 5:315–320. doi: 10.1007/s13539-014-0153-y

Tuca A, Jimenez-Fonseca P, Gascón P (2013) Clinical evaluation and optimal management of cancer cachexia. Crit. Rev. Oncol. Hematol. 88:625–636

Uehara A, Sekiya C, Takasugi Y, et al (1989) Anorexia induced by interleukin 1: Involvement of corticotropin-releasing factor. Am J Physiol - Regul Integr Comp Physiol 257:. doi: 10.1152/ajpregu.1989.257.3.r613

Lesniak W, Bala M, Jaeschke R, Krazakwski M., (2008) Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome - A systematic review and meta-analysis. Pol Arch Med Wewn 118:636–644

Waseem T, Duxbury M, Ito H, et al (2008) Exogenous ghrelin modulates release of pro-inflammatory and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. Surgery 143:334–342. doi: 10.1016/j.surg.2007.09.039

Wen H-S, Li X, Cao Y-Z, et al (2012) Clinical Studies on the Treatment of Cancer Cachexia with Megestrol Acetate plus Thalidomide. Chemotherapy 58:461–467. doi: 10.1159/000346446

Wilkes EA, Selby AL, Cole AT, et al (2011) Poor tolerability of thalidomide in end-stage oesophageal cancer. Eur J Cancer Care (Engl) 20:593–600. doi: 10.1111/j.1365-2354.2011.01255.x

Willox JC, Corr J, Shaw J, et al (1984) Prednisolone as an appetite stimulant in patients with cancer. BMJ 288:27–27. doi: 10.1136/bmj.288.6410.27

Yennurajalingam S, Willey JS, Palmer JL, et al (2012) The role of thalidomide and placebo for the treatment of cancer-related anorexia-cachexia symptoms: Results of a double-blind placebo-controlled randomized study. J Palliat Med 15:1059–1064. doi: 10.1089/jpm.2012.0146

Yki-Järvinen H (2004) Thiazolidinediones. N. Engl. J. Med. 351

Evidence-Based Management of Cancer-Related Dyspnea

INTRODUCTION

Dyspnea is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. It is one of the most common symptoms reported in patients with a terminal cancer in the last six months of life. In a series of patients with advanced cancer, approximately 30% reported dyspnea and of these 70 % reported episodic breathlessness, most often triggered by exertion (Mercadante et al. 2016). The experience derives from interactions among multiple physiological, psychological, social, and environmental factors that may induce secondary physiological and behavioral responses(White et al. 2014). Its presence and severity cannot be inferred from physical examination or laboratory investigations—we must ask about it. It can occur in the absence of physical signs (e.g., rapid, deep, or labored breathing) or abnormal findings on investigations such as blood gases or chest radiographs.

PATHOPHYSIOLOGY

The neurophysiology of dyspnea is related to but distinct from the control of ventilation. Dyspnea is the perception that the respiratory muscle response is inadequate or unsustainable. This perception arises from the sensory cortex, which integrates information from multiple sources including peripheral and central chemoreceptors, mechanoreceptors (arising from large airways, lung parenchyma and the chest wall) and respiratory motor centers (in the medulla as well as motor cortex). Dyspnea may arise from increased ventilatory demand, impairment of the mechanical process of ventilation, or both (Stendardi et al. 2008).

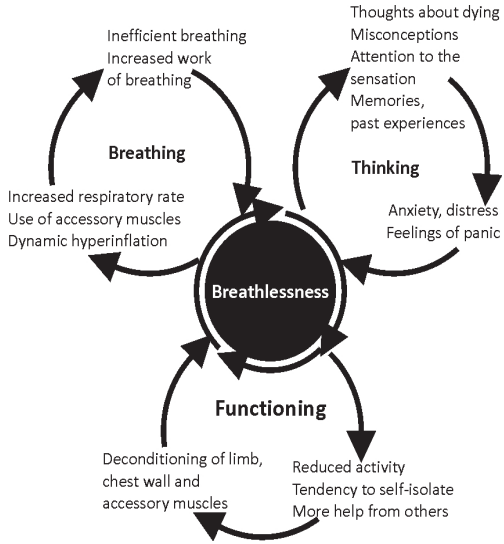

Figure : 1

The Breathing, Thinking, Functioning clinical model adapted from *Spathis A, Booth S, Moffat C, Hurst R, Ryan R, Chin C, Burkin J. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. NPJ Prim Care Respir Med. 2017 Apr 21;27(1):27. doi: 10.1038/s41533-017-0024-z. PMID: 28432286; PMCID: PMC5435098.*

ASSESSMENT

The goals of a formal assessment of dyspnea in palliative care are to understand the intensity, distress, and functional impact of dyspnea, to diagnose potentially reversible contributing factors, and to monitor the response to interventions. Patients employ a variety of terms to describe their sensation of breathlessness — air hunger, increased effort of breathing, chest tightness, rapid breathing, incomplete exhalation, or a feeling of suffocation (Yorke et al. 2010). Screening for dyspnea with a validated symptom assessment tool, such as the Memorial symptom assessment scale, short form (MSAS-SF)(Chang et al. 2000), or the revised Edmonton Symptom Assessment scale (rESAS)(Watanabe et al. 2011), is a first step in recognizing the presence of dyspnea, but not its specific characteristics. The most widely used tools for measuring the intensity of dyspnea in the clinical setting are numeric rating scales (0 to 10) and visual analogue scales (0 to 100 mm). The modified Borg scale assigns verbal descriptors to numerical values between zero and ten and is a popular tool to assess the intensity of dyspnea in the research literature(Wilson and Jones 1989). The

Oxygen Cost Diagram(Chuang et al. 2010) asks patients to identify the level of activity they are unable to perform due to dyspnea, giving clinicians valuable information regarding the functional impact of the symptom. The distress caused by dyspnea arises not only from its intensity, but also from other factors such as the functional impact and meaning of that symptom for the patient (which can be influenced by personality type, past experiences, coping mechanisms, etc.), and can be affected by psychological factors, such as anxiety and depression(De Peuter et al. 2004). Laboratory testing and imaging studies (pulse oximetry, arterial blood gases, chest radiographs, pulmonary function tests, etc.) are thus not helpful in detecting the presence or severity of dyspnea. Such investigations can, however, help determine the cause of a patient's breathlessness and guide the choice of treatment interventions.

STANDARD OF CARE

Among patients receiving palliative care for advanced terminal illness, the causes of dyspnea are often untreatable. However, if a specific treatable cause of dyspnea is found (e.g., bronchospasm, pulmonary emboli, upper airway obstruction, pleural effusion), specific treatment of that process may be appropriate depending on the invasiveness of the therapy and the patient's values and preferences.

Nonpharmacologic Management

A multidisciplinary approach to dyspnea is needed. Nurses (education), physiotherapists (exercise therapy),

respiratory therapists, occupational therapists (ergonomics and accommodation strategies), dieticians (to optimize nutrition), and psychologist/chaplains (to address symptom meaning) all have important roles to play. General supportive measures used to alleviate the sensation of breathlessness include the following(Wong et al. 2017):

Relaxation techniques and psychosocial support.

Modification in activity level and the use of bathroom aids and wheelchairs to increase the autonomy of patients and their families.

- Use of a fan with cool air blowing on the face.
- Chest wall and intrapulmonary percussive vibration and mechanical insufflation-exsufflation devices can be helpful for patients who have difficulty mobilizing secretions.
- Pulmonary rehabilitation and respiratory therapy — exercise training, psychosocial support, nutrition therapy, and self-management strategies, such as diaphragmatic and pursed lip breathing.

Oxygen — a therapeutic trial of oxygen supplementation for relief of dyspnea in hypoxemic patients can be tried. Although there is a likely a placebo effect of oxygen and the medical symbolism inherent in its administration, there may be other reasons for this perceived benefit — reversal of hypoxemia, reduced serum lactic acid, reduced pulmonary artery pressure, reduced dynamic hyperinflation, reduced ventilatory muscle and diaphragm fatigue, relief of bronchoconstriction, stimulation of facial,

nasal, or pharyngeal receptors, and increased capacity for exercise training(Abernethy et al. 2010; Higginson 2010; Davidson and Johnson 2011). In patients who are not hypoxemic, supplemental oxygen appears no more likely than room air to provide relief of dyspnea.

Noninvasive ventilation — Noninvasive ventilation (NIV) refers to positive pressure ventilation that is delivered through a noninvasive interface (nasal mask, facemask, or nasal plugs), and can be delivered using a standard ventilator or a portable ventilator (e.g., a pressure support ventilator that provides bilevel positive airway pressure [BPAP]). NIV may be considered as a palliative measure in dying patients who have severe dyspnea and have decided to forego life-prolonging therapies and focus only on comfort measures with the intent of reducing the work of breathing, easing dyspnea, and helping to maintain wakefulness by reducing the amount of opioids needed to maintain comfort (Bausewein et al. 2013).

Airway debulking and stents — For patients with dyspnea due to central airway obstruction from a tumor, debulking of the tumor with endobronchial techniques, such as endoscopic laser, electrocautery, argon plasma coagulation, and cryotherapy, followed by placement of an airway stent may provide palliation (Collins A. et al. 2010).

Helium/oxygen — The lower density of helium/oxygen combinations (relative to nitrogen/oxygen) promotes laminar flow and enables greater alveolar ventilation at a given inspiratory pressure, thus diminishing the work of breathing. Helium/oxygen (HEO2, Heliox) is therefore a potentially attractive alternative for patients with dyspnea

from partial airway obstruction, impaired ability to generate inspiratory pressure, or both(Allan et al. 2009).

Acupuncture — Acupuncture has been examined as a potential therapy to reduce dyspnea and has yielded mixed results in retrospective series(Ben-Aharon et al. 2008; Tanaka K. 2017).

Pharmacologic management

Opioids — Systemic administration of opioid agonists is the most well-established pharmacologic treatment strategy for the symptomatic management of dyspnea in patients with advanced illness. Morphine is the most widely studied drug(Currow et al. 2011), although codeine, dihydrocodeine, hydromorphone, and diamorphine have also been effective. The benefit of transmucosal or subcutaneous fentanyl is less clear. The safety of opioids is relevant, given the potential for respiratory depression, and no studies have found excess mortality associated with the use of opioids for dyspnea(Viola et al. 2008). As with use of opioids for pain relief, nausea, constipation and drowsiness are common adverse effects. Nebulized opioids have limited systemic absorption, leading to the hypothesis that they may relieve dyspnea with fewer adverse effects than systemic administration. However, at present, the data are insufficient to justify use of any opioid by the inhaled route for relief of dyspnea(Campbell 2017).

Promethazine — While small studies suggest a potential role for promethazine in the treatment of dyspnea (off-label), a class effect of phenothiazines for dyspnea has not been established(Currow 2011).

Benzodiazepines — they are an important adjunct to therapy when anxiety, a common feature in dyspnea and especially severe dyspnea, is significant(Navigante et al. 2006).

Bronchodilators — A large proportion of patients with terminal cancer and dyspnea have a history of smoking or COPD. Assessment and management of potentially reversible airway obstruction is appropriate in all dyspneic cancer patients(Rabe 2006).

Diuretics — Although there is a lack of firm evidence to support benefit, systemic administration of loop diuretics may be beneficial to reduce lung congestion in dyspneic patients with end stage heart failure or lymphangitic carcinomatosis. There is insufficient evidence to recommend nebulized diuretics for the management of dyspnea in terminally ill patients(Kloke and Cherny 2015).

Glucocorticoids — Glucocorticoids are not used for the palliation of dyspnea as a symptom. However, there are some settings in which they may effectively help to treat underlying causes of dyspnea: COPD exacerbations, tumor-related superior vena cava (SVC) syndrome in patients with glucocorticoid-responsive malignancies (e.g., lymphoma, thymoma), tumor-related upper airway obstruction, radiation pneumonitis, chemotherapy-induced pneumonitis, and pulmonary lymphangitic carcinomatosis (Kloke and Cherny 2015).

Palliative sedation — Among patients at the end of life, dyspnea sometimes causes severe distress that cannot be relieved with standard measures. In such cases, the use of

palliative sedation to relief of distress, including doses titrated to achieve unconsciousness if necessary, is an accepted strategy. Palliative sedation refers to use of a nonopioid drug to reduce a patient's awareness of refractory symptoms by decreasing their level of consciousness. Refractory symptoms are those that have been assessed and treated by an expert interdisciplinary team and have not responded to conventional symptom management (Lanken et al. 2008).

REFERENCES

Collins A., Jordan T., Ledson M., Walshaw M. (2010) Fibreoptic bronchoscopic insertion of the gianturco stent for tracheobronchial obstruction in patients with cancer at a lung cancer tertiary referral centre: 20 year experience. Thorax. doi: 10.1136/thx.2010.151043.43 LK

Abernethy AP, McDonald CF, Frith PA, et al (2010) Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: A double-blind, randomised controlled trial. Lancet. doi: 10.1016/S0140-6736(10)61115-4

Allan PF, Thomas K V., Ward MR, et al (2009) Feasibility study of noninvasive ventilation with helium-oxygen gas flow for chronic obstructive pulmonary disease during exercise. Respir Care

Bausewein C, Booth S, Gysels M, Higginson IJ (2013) Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database Syst. Rev.

Ben-Aharon I, Gafter-Gvili A, Paul M, et al (2008) Interventions for alleviating cancer-related dyspnea: A systematic review. J. Clin. Oncol.

Campbell ML (2017) Dyspnea. Crit. Care Nurs. Clin. North Am.

Chang VT, Hwang SS, Feuerman M, et al (2000) The Memorial Symptom Assessment Scale Short Form (MSAS-SF). Cancer. doi: 10.1002/1097-0142(20000901)89:5<1162::aid-cncr26>3.0.co;2-y

Chuang ML, Lee CH, Lin IF (2010) Using the oxygen-cost diagram in ramp-slope selection for dyspneic patients. Intern Med. doi: 10.2169/internalmedicine.49.3094

Currow D (2011) Scientific basis for the management of Dyspnea. J Thorac Oncol

Currow DC, McDonald C, Oaten S, et al (2011) Once-daily opioids for chronic dyspnea: A dose increment and pharmacovigilance study. J Pain Symptom Manage. doi: 10.1016/j.jpainsymman.2010.11.021

Davidson PM, Johnson MJ (2011) Update on the role of palliative oxygen. Curr. Opin. Support. Palliat. Care. doi: 10.1097/SPC.0b01/3e328346-3cd3.

De Peuter S, Van Diest I, Lemaigre V, et al (2004) Dyspnea: The role of psychological processes. Clin Psychol Rev. doi: 10.1016/j.cpr.2004.05.001

Higginson IJ (2010) Refractory breathlessness: Oxygen or room air? Lancet. doi: 10.1016/SO140-6736(10) 61346-3.

Tanaka K. (2017) Palliative management of dyspnea. J Thorac Oncol. doi: 10.1016/j.jtho.2017.09.127

Kloke M, Cherny N (2015) Treatment of dyspnoea in advanced cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 26:v169–v173. doi: 10.1093/annonc/mdv306

Lanken PN, Terry PB, DeLisser HM, et al (2008) An official American thoracic society clinical policy statement: Palliative care for patients with respiratory diseases and critical illnesses. Am. J. Respir. Crit. Care Med. doi: 10.1164/ccm.200605-587ST.

Mercadante S, Aielli F, Adile C, et al (2016) Epidemiology and characteristics of episodic breathlessness in advanced cancer

patients: An observational study. J Pain Symptom Manage. doi: 10.1016/j.jpainsymman.2015.07.020

Navigante AH, Cerchietti LCA, Castro MA, et al (2006) Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage. doi: 10.1016/j.jpainsymman.2005.06.009

Rabe KF (2006) Improving dyspnea in chronic obstructive pulmonary disease: Optimal treatment strategies. In: Proceedings of the American Thoracic Society

Spathis A, Booth S, Moffat C, Hurst R, Ryan R, Chin C, Burkin J. The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. NPJ Prim Care Respir Med. 2017 Apr 21;27(1):27. doi: 10.1038/s41533-017-0024-z. PMID: 28432286; PMCID: PMC5435098.

Stendardi L, Binazzi B, Scano G (2008) Pathophysiology of dyspnea. Rass di Patol dell'Apparato Respir

Viola R, Kiteley C, Lloyd NS, et al (2008) The management of dyspnea in cancer patients: A systematic review. Support. Care Cancer 16:329–337

Watanabe SM, Nekolaichuk C, Beaumont C, et al (2011) A multicenter study comparing two numerical versions of the Edmonton symptom assessment system in palliative care patients. J Pain Symptom Manage 41:456–468. doi: 10.1016/j.jpainsymman.2010.04.020

White DB, Jacobs SS, Fischer MD, et al (2014) An Official American Thoracic Society Workshop Report: Assessment and Palliative Management of Dyspnea Crisis. Ann Am Thorac Soc 10:S98–S106. doi: 10.1513/annalsats.201306-169st

Wilson RC, Jones PW (1989) A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. Clin Sci. doi: 10.1042/cs0760277

Wong SL, Leong SM, Chan CM, et al (2017) The Effect of Using an Electric Fan on Dyspnea in Chinese Patients With Terminal Cancer: A Randomized Controlled Trial. Am J Hosp Palliat Med. doi: 10.1177/1049909115615127

Yorke J, Moosavi SH, Shuldham C, Jones PW (2010) Quantification of dyspnoea using descriptors: Development and initial testing of the dyspnoea-12. Thorax. doi: 10.1136/thx.2009.118521