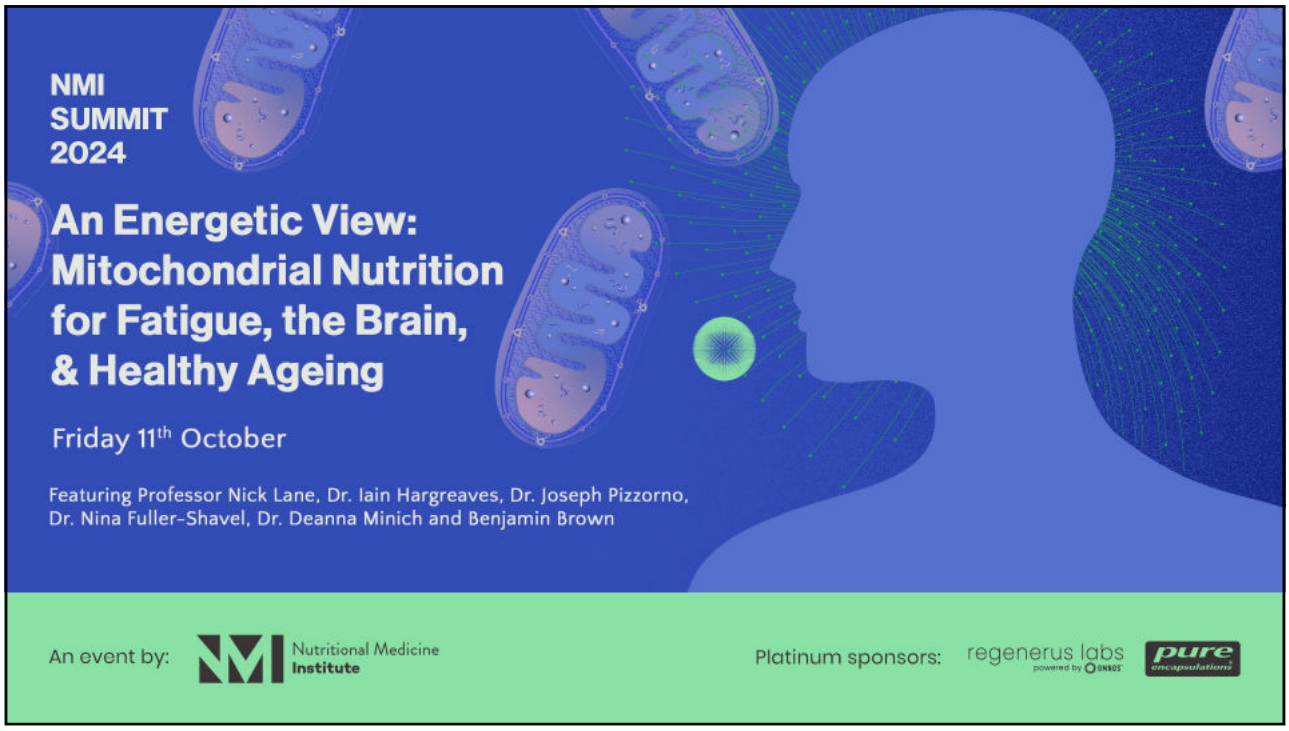
NMI
SUMMIT
2024
An Energetic View:
Mitochondrial Nutrition
for Fatigue, the Brain,
& Healthy Ageing
Friday 11th October
Featuring Professor Nick Lane, Dr. Iain Hargreaves, Dr. Joseph Pizzorno,
Dr. Nina Fuller-Shavel, Dr. Deanna Minich and Benjamin Brown
An event by:
Nutritional Medicine Institute
Platinum sponsors:
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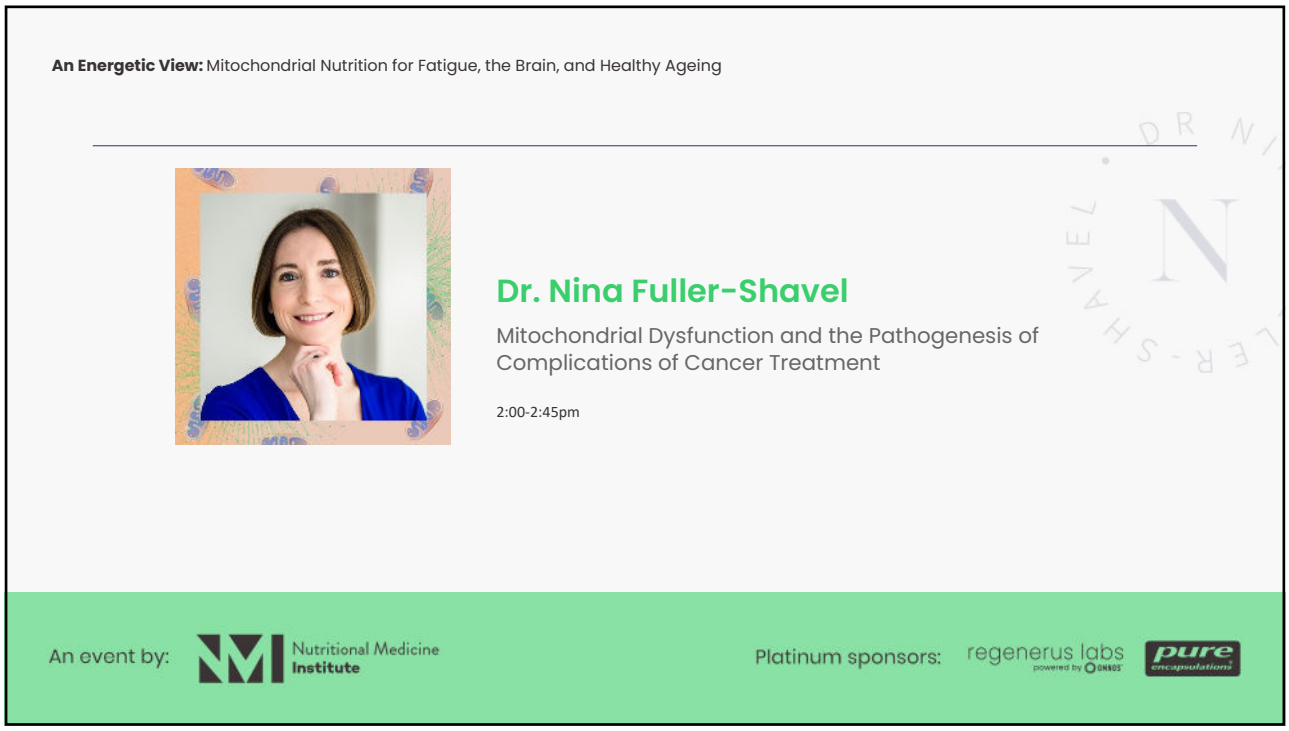
1


An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing
Dr. Nina Fuller-Shavel
Mitochondrial Dysfunction and the Pathogenesis of Complications of Cancer Treatment
2:00-2:45pm
An event by:
Nutritional Medicine Institute
Platinum sponsors:
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2

Mitochondrial Dysfunction and the Pathogenesis of Complications of Cancer Treatment

DR NINA FULLER-SHAVEL

Dr Nina Fuller-Shavel

Precision Health & Integrative Medicine Physician, Scientist & Educator

Director of Synthesis Clinic

Co-Founder and Director of Oncio CIC

CEO of the new NCIO (National Centre for Integrative Oncology) charity

Global SIO Ambassador to the UK

Immediate Past Co-Chair of BSIO (2021-2023) and current Co-Chair of BSIO Education Committee

MB BCHIR (MEDICINE) and MA HONS NAT SCI (CANTAB) MSC and PGDIP (OXON) FBANT FRSA IFMCP DIPIM DIPAC DIPCHM PG CERT DIPION RYT200

3

Affiliations and Declaration of Interest

Main roles

- Director of **Synthesis Clinic** - an innovative private multidisciplinary practice in the UK, specialising in women's health and integrative cancer care (core work in adults with a new consultant-led paediatric cancer survivorship service)
- Co-Founder and Director of **Oncio CIC** - an innovative non-profit aimed at providing high quality app-based resources for people with cancer and healthcare professionals and supporting best clinical practice and research in integrative oncology
- CEO of the new **NCIO (National Centre for Integrative Oncology)** charity – registration due to be completed Oct 2024
- Global **SIO (Society for Integrative Oncology)** Ambassador to the UK, Member of Advancement, Education, Communications and SIO conference committees
- Immediate Past Co-Chair of **BSIO** (British Society for Integrative Oncology) 2021-2023, current Executive Committee member and Co-Chair of the BSIO Education Committee (bsio.org.uk)
- CPD education provider and guest lecturer for nutrition and medical professionals, including **Systems Approach to Cancer Programme** training for nutrition professionals and physicians

Declaration of interest

- Dr Nina Fuller-Shavel has a policy of not accepting any direct honoraria from commercial organisations. Following educational events led by Dr Fuller-Shavel for industry, free/discounted products or tests have been provided to Synthesis Clinic patients by the following companies – Datar Cancer Genetics, Genova Diagnostics and Helixor Heilmittel GmbH.

Synthesis Clinic

NATIONAL CENTRE FOR INTEGRATIVE ONCOLOGY

ONCIO INTEGRATIVE ONCOLOGY IN ACTION

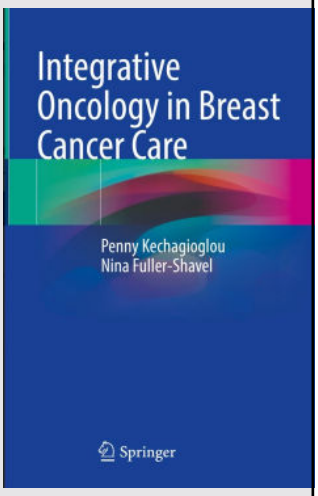
SIO Society for Integrative Oncology

BSIO BRITISH SOCIETY FOR INTEGRATIVE ONCOLOGY

4

Background

- Precision Health and Integrative Medicine physician with:
  - Degrees in **Medicine and Natural Sciences** from the University of Cambridge
  - **MSc Precision Cancer Medicin**e with distinction and **PG Dip in Health Research** from the University of Oxford
- Further qualifications in nutrition, health coaching (FMCA), Functional Medicine (IFMCP), herbal medicine, TCM (including acupuncture and CHM), integrative medicine (DipIM), yoga and mindfulness
- Fellow of the College of Medicine, BANT (British Association for Nutrition and Lifestyle Medicine) and RSA (Royal Society of Arts)
- Director of The Synthesis Clinic and winner of UK BIA Innovation Leader of the Year 2022
- Immediate Past Co-Chair of the British Society for Integrative Oncology (BSIO) 2021-2023, current BSIO Education Committee Co-Chair
- Input into international guideline development in integrative oncology – joint SIO-ASCO 2023 anxiety and depression guideline co-author (PMID: 37582238)
- Presentations at multiple national and international conferences, member of the Editorial Board for the Nutritional Medicine Journal (NMJ) and International Journal of Integrative Oncology (IJIO)
- Expert integrative and supportive oncology paper and abstract reviewer for international conferences, e.g. ECIM 2021, MASCC 2023, SIO 2024; reviewer for international trials in immuno-oncology and GI microbiome
- Co-author of the 'Integrative Oncology in Breast Cancer Care' book published by Springer in 2024



5

Affiliations and memberships

Dr Nina Fuller-Shavel

drninafullershavel.com

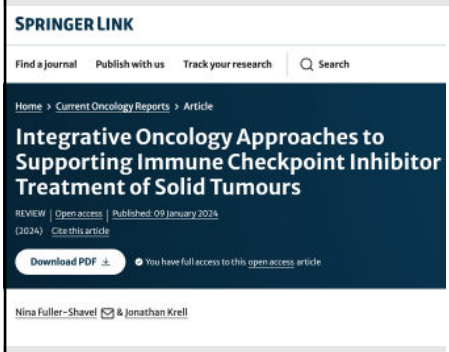
synthesisclinic.co.uk

oncio.org

bsio.org.uk

6

Recent publications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Integrative Oncology Approaches to Supporting Immune Checkpoint Inhibitor Treatment of Solid Tumours

REVIEW | Open access | Published: 09 January 2024

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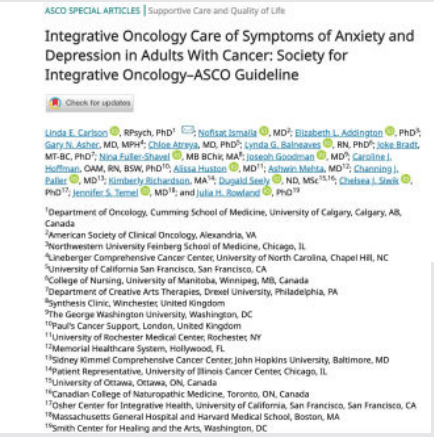
Nina Fuller-Shavel & Jonathan Krell

PMID: 38194216


ASCO SPECIAL ARTICLES | Supportive Care and Quality of Life

Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults With Cancer: Society for Integrative Oncology–ASCO Guideline

Check for updates

Linda E. Carlson, RPsych, PhD[1]; Nofisat Ismaila, MD[2]; Elizabeth L. Addington, PhD[3]; Gary N. Asher, MD, MPH[4]; Chloe Atreya, MD, PhD[5]; Lynda G. Balneaves, RN, PhD[6]; Joke Bradt, MT-BC, PhD[7]; Nina Fuller-Shavel, MB BChir, MA[8]; Joseph Goodman, MD[9]; Caroline J. Hoffman, OAM, RN, BSW, PhD[10]; Alissa Huston, MD[11]; Ashwin Mehta, MD[12]; Channing J. Paller, MD[13]; Kimberly Richardson, MA[14]; Dugald Seely, ND, MSc[15,16]; Chelsea J. Stein, PhD[17]; Jennifer S. Temel, MD[18]; and Julia H. Rowland, PhD[19]

[1]Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
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[3]Northwestern University Feinberg School of Medicine, Chicago, IL
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[10]Paul's Cancer Support, London, United Kingdom
[11]University of Rochester Medical Center, Rochester, NY
[12]Memorial Healthcare System, Hollywood, FL
[13]Sidney Kimmel Comprehensive Cancer Center, John Hopkins University, Baltimore, MD
[14]Patient Representative, University of Illinois Cancer Center, Chicago, IL
[15]University of Ottawa, Ottawa, ON, Canada
[16]Canadian College of Naturopathic Medicine, Toronto, ON, Canada
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[18]Massachusetts General Hospital and Harvard Medical School, Boston, MA
[19]Smith Center for Healing and the Arts, Washington, DC

PMID: 37582238


IJIO

SAFETY OF INTRAVENOUS AND SUBCUTANEOUS MISTLETOE ADMINISTRATION IN ADULTS WITH SOLID TUMOURS – SINGLE UK INTEGRATIVE ONCOLOGY CENTRE EXPERIENCE

ABSTRACT

Introduction

https://doi.org/10.69068/IJIO05

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Learning outcomes

By the end of this session, we will:

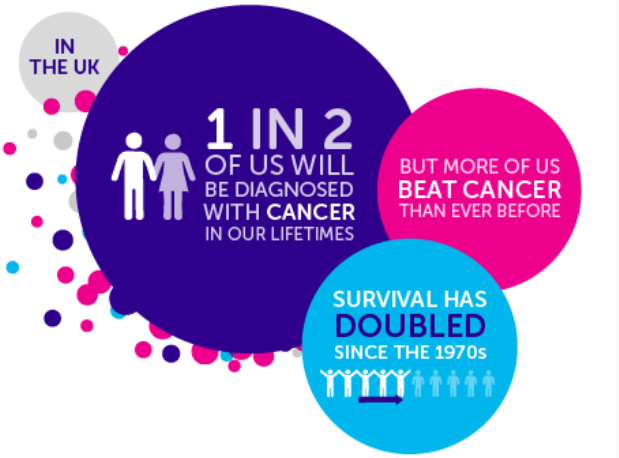
- Explore the role of mitochondrial dysfunction in the pathogenesis of several cancer treatment side effects, including CIPN (chemotherapy-induced peripheral neuropathy), CRCI (chemotherapy related cognitive impairment) and CRF (cancer-related fatigue)
- Review the role of other factors contributing to CIPN, CRCI and CRF within the Systems Approach to Cancer model
- Discuss personalised integrative and functional medicine interventions that may be supportive for people affected by these cancer treatment-related side effects

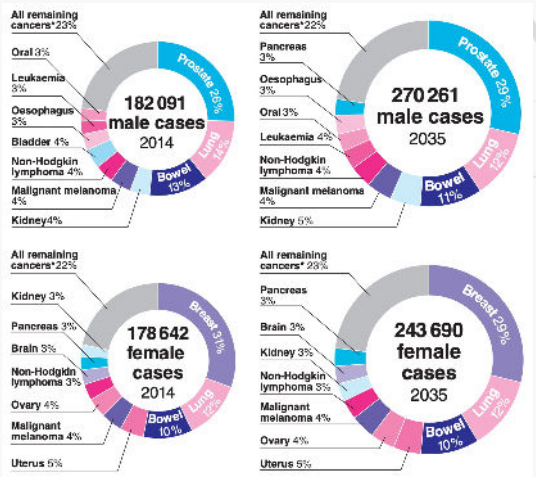
8

Context – cancer and integrative oncology

9

The scope of the problem





Smittenaar, C., Petersen, K., Stewart, K. et al. Cancer incidence and mortality projections in the UK until 2035. Br J Cancer 115, 1147–1155 (2016).

10

Examples of residual problems post-treatment

- Chemotherapy-induced peripheral neuropathy (CIPN) is the most prevalent neurological complication of chemotherapy.
  - 30-40% of patients are faced with chronicity of the symptoms
- Cancer-related fatigue (CRF):
  - Active treatment CRF rates around 62-85%
  - Survivors on maintenance therapy such as adjuvant endocrine therapy or androgen deprivation therapy (ADT) are more likely to experience CRF
    - 56% of people with BC on AIs report moderate-to-severe CRF
  - Up to 60% of BC survivors reported moderate-to-severe tiredness 12 months after diagnosis. 21-52% of survivors still experience severe CRF up to 3 years post-diagnosis.
  - 1 in 4 AYA cancer survivors is still chronically fatigued 5-30 years after diagnosis

Support Care Cancer. 2021;29(8):4223-4238; Curr Treat Options Oncol. 2020;21(2):17

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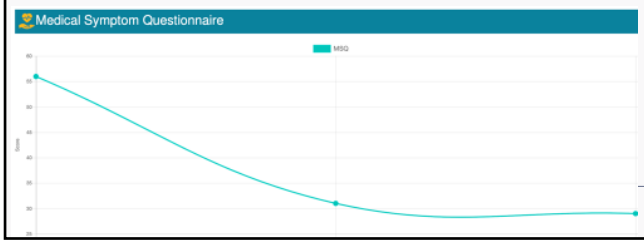
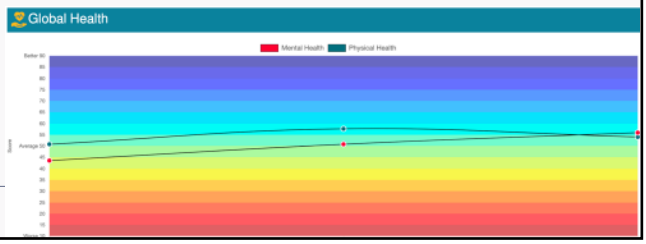
But with the right support we can thrive!

- 49 y.o. F presented following locally contained early primary G3 TNBC treatment
- Treatment – EC-T chemotherapy, WLE (lumpectomy) and radiotherapy
- High symptom burden and poor QoL as per PROMIS at presentation to clinic, struggling with return to work due to persistent fatigue
- Integrative oncology programme outcomes – now nearly 5 years in remission
  - Over 8 months – symptom burden 66% reduction from baseline with fatigue score reduced to 1; back to work and coping well
  - QoL - General health rating – improved from poor to very good; mental health rating – improved from good to excellent





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Definitions of integrative oncology

- BSIO - https://www.bsio.org.uk/
  - A rational person-centred integration of conventional cancer care with evidence-informed **nutrition, lifestyle, psycho-emotional wellbeing support and complementary medicine** to support better quality of life, improve resilience, minimise the side effects of treatment and improve outcomes
- SIO - https://integrativeonc.org/
  - "Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment."

J Natl Cancer Inst Monogr. 2017 Nov 1;2017(52).

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My personal perspective

- Integrative oncology and integrative medicine is/should be:
  - a rational integration of the best in conventional standard of care with nutrition, lifestyle, psychological support and complementary medicine
  - whole-person oriented and addresses physical, emotional, mental and spiritual needs
  - supportive of targeted, personalised medication use where necessary without over-medicalising
  - about caring for people, not mindless protocols
  - evidence-based medicine - combining the best available research evidence, clinical expertise and patient values

Remember that integrative is NOT alternative by definition.

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What does integrative oncology have to offer?

- A sense of agency and empowerment to your patients and you as a healthcare professional
  - Supporting resilience vs learned helplessness
  - Seeing the whole person, not just their cancer
- Expanded toolkit to support:
  - Cancer prevention/risk reduction
  - Prehabilitation for better treatment tolerance and recovery
  - Managing side effects of treatment and opportunities for improving outcomes
  - Faster recovery following active treatment and better management of recurrence risk
  - Care of patients with metastatic disease – both in living well with cancer and at the end of life

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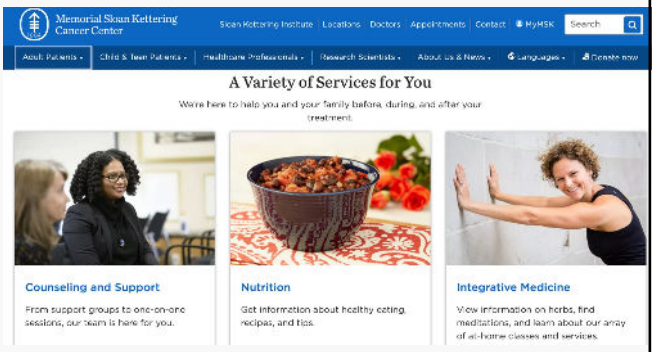
IO is not new or outside standard care - US example

- Both stand alone centres and integrated into big teaching hospitals
- Examples – Memorial Sloan Kettering Center, Dana-Farber Zakim Centre, Banner MD Anderson and many more
  - "We believe in caring for the whole person — not just the disease or symptom. Integrative medicine weaves natural treatments such as acupuncture, massage, and yoga into your overall care plan. All of our holistic health services and programs are based on the latest scientific evidence."



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Integrative oncology in Germany and Italy

Bavaria establishes department dealing with integrative medicine

Oct 27, 2020

The state of Bavaria (Bayern) in South East Germany has announced the establishment of a new department within the Ministry of Health with a focus on integrative medicine and made a commitment to establish a Chair in Integrative Health at a university in Bavaria.

ARTOI
ASSOCIAZIONE RICERCA TERAPIE ONCOLOGICHE INTEGRATE

The State Secretary spoke of the importance of research and the investment the **State department** has made in this field so far: "Modern medicine requires a patient-oriented health system in which scientific and natural medicine are on an equal footing. The future lies in the meaningful cooperation of conventional and natural medicine therapy to form integrative medicine."

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Accumulating body of evidence for IO impact

- 2021 study – a composite integrative oncology score was shown to increase **5-year breast cancer survival odds three times** for institutions in the low-mid engagement cohort compared to the low.
  - Core set of six therapies used: nutrition counselling, exercise counselling, patient support groups, spiritual services, meditation, and psycho-oncology support
- 2021 study of 189 patients with advanced gynaecological cancer were referred by their oncology healthcare professionals to an integrative physician (IP) for consultation and IO treatments. Adherence to an IO treatment program was associated with statistically significant higher survival rates among patients with advanced gynaecological cancer.
  - When compared with the integrative care group, a multivariate analysis found higher crude and adjusted hazard ratios for 3-year mortality in the non-AIC group (HR 95% CI 2.18, p = 0.010) and controls (2.23, p = 0.002). Additionally earlier research showed a significant improvement in symptom control and MYCAW scores for leading concerns and wellbeing.
- General IO service (n = 642) - statistically significant improvement in symptoms between initial consult and follow-up were observed for depression, anxiety, well-being, and subscales of GDS and PSS (all p's > 0.01). For those with moderate to severe symptoms at their initial consult (ESAS scores ≥ 4), observed **clinical response rates (improvement) were 49-75% for all ESAS symptoms at follow-up.**

PMID: 34961816; PMID: 28247032, PMID: 25752885, PMID: 33404816, PMID: 28775783

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Key organisations for professionals – join us!

https://integrativeonc.org/
Multiple SIGs available, from research, education and clinical practice to nursing, acupuncture and yoga

https://bsio.org.uk/

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SIO-ASCO guidelines in integrative oncology

- Guidelines published by SIO since 2007
- Overview:
  - https://pubmed.ncbi.nlm.nih.gov/39052420/
- The four most recent guidelines either endorsed or co-created with ASCO:
  - 2024 Management of Fatigue in Adult Survivors of Cancer: ASCO–Society for Integrative Oncology Guideline Update (PMID: 38754041)
  - 2023 Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults With Cancer: Society for Integrative Oncology–ASCO Guideline (PMID: 37582238)
  - 2022 Joint SIO-ASCO Clinical Practice Guidelines, Integrative Medicine for Pain Management in Oncology: Society for Integrative Oncology–ASCO Guideline (PMID: 36122322)
  - 2017 SIO Guidelines, Clinical Practice Guidelines on the Evidence-based Use of Integrative Therapies During and After Breast Cancer Treatment (PMID: 28436999) – needs updating


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ASCO SPECIAL ARTICLES

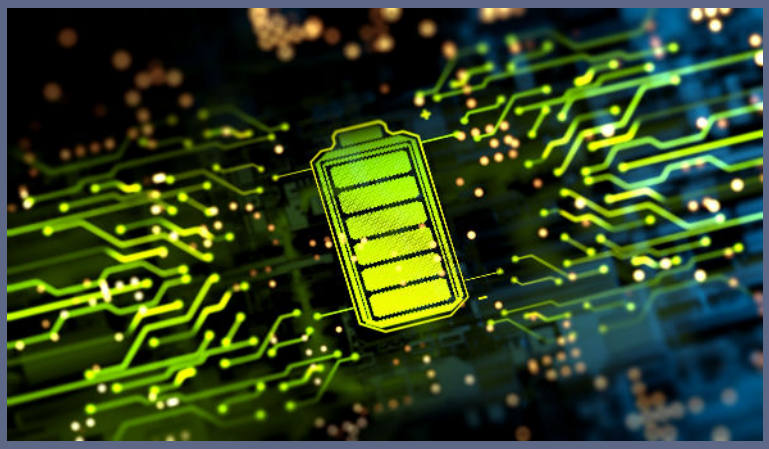
Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults With Cancer: Society for Integrative Oncology–ASCO Guideline

Check for updates

PMID: 38754041, PMID: 37582238, PMID: 36122322, PMID: 28436999

20

Mitochondrial dysfunction in CRF, CRCI and CIPN



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Definitions - CRF

- **Cancer-related fatigue (CRF)** – 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 functioning (NCCN).
  - Multidimensional and often not significantly relieved by rest
  - Multiple measurement scales, such as FACIT-F or PROMIS-F for adults

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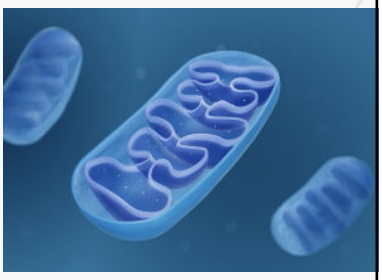
CRF and mitochondria

- In prostate cancer (PC) patients undergoing ADT+RT PBMCs of fatigued subjects exhibited decreased ATP coupling efficiency compared to non-fatigued subjects, indicative of mitochondrial dysfunction.
  - Brain tissues of ADT/RT mice exhibited decreased levels of GLUT4 and TFAM - impaired neuronal metabolic homeostasis may contribute to fatigue pathogenesis.
- Significantly downregulated BC1 ubiquinol-cytochrome c reductase synthesis-like (BCS1L) during and at 24 months post-RT in PC patients
  - An increased PROMIS-F score was trended with downregulated BCS1L in patients 24 months after completing radiation therapy.
- In a Med diet trial of stage I-III cancer patients, fatigue was associated with mitochondrial dysfunction including lower basal respiration, maximal respiration, and spare capacity ($p < 0.05$ for FACIT-F fatigue subscale and BFI, usual fatigue).
  - Mitochondrial respiration from freshly isolated T cells at baseline vs four weeks.



Int J Mol Med. 2020;45(2):485-496; Nurs Res. 2021;70(6):475-480; Cancers (Basel). 2022;14(17):4202.

23

CRF and mitochondria

Chemotherapy agents can cause mitochondrial dysfunction through:

- Disrupting mitochondrial structure
  - Chemotherapy drugs can alter the structure of mitochondria, which can lead to mitochondrial injury.
- Increasing oxidative stress
  - Chemotherapy drugs can increase oxidative stress by disrupting the antioxidant system, which can lead to mitochondrial damage.
- Altering mitochondrial transport
  - Chemotherapy drugs can alter mitochondrial transport, fission, fusion, and mitophagy.
- Forming adducts with mitochondrial DNA
  - Some chemotherapy drugs, like cisplatin and oxaliplatin, can form adducts with mitochondrial DNA, which can lead to replication inhibition, transcription disruption, and morphological abnormalities.
- Modifying mitochondrial calcium homeostasis
  - Some chemotherapy drugs, like bortezomib, can modify mitochondrial calcium homeostasis.

Cells. 2019 Jul 18;8(7):738.

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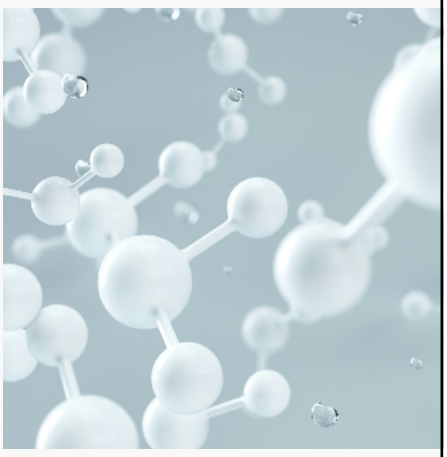
Early research on mitokines – GDF15-GFRAL axis

- Mitochondrial dysfunction may result in the release of mitokines that act locally and at distance to promote metabolic and behavioral adjustments to cellular stress.
- One of these mitokines, growth differentiation factor 15 (GDF15) and its receptor, glial cell line-derived neurotrophic factor family receptor α-like (GFRAL) may be involved in both cancer anorexia and cisplatin-induced fatigue.
  - Early research shows this as a promising avenue in cancer cachexia.



Brain Behav Immun. 2023;108:45-54.

25

CRF and examples of other key mechanisms

- Inflammation
  - CRF often co-occurs with symptoms such as pain, insomnia, lethargy, altered mood, and cognitive impairment, which are similar to "sickness behaviour"
- Hypothalamic-pituitary-adrenal (HPA) axis dysregulation
- Autonomic nervous system (ANS) dysfunction

All the other causes of fatigue as a presentation apply too, alongside cancer treatment specific causes - from steroid-induced diabetes or profound B12 deficiency following terminal ileum resection to hypothyroidism following local radiotherapy or autoimmune thyroiditis with immune checkpoint in inhibitors and many more.

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Definition - CIPN

- **Chemotherapy-induced peripheral neuropathy (CIPN)** - somatic or autonomic signs or symptoms resulting from damage to the peripheral nervous system (PNS) or autonomic nervous system (ANS) caused by chemotherapeutic agents.
- Classically presents as numbness, tingling, burning pain, and/or sensorimotor disturbances, which typically starts in the tips of the toes and fingers and may progress into a stocking-and-glove distribution.

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CIPN - personal risk factors

Risk factor	Comments
Older age	May be due to lower chance of recovery from acute CIPN
Medication: cardiovascular especially beta blockers	Opportunity to modify medication prior to starting chemotherapy.
Co-morbid health conditions	Those where there may be associated increased risk of neuropathy e.g. diabetes, HIV, excess alcohol, smoking; decreased creatinine clearance
Raised Body Mass Index (BMI)	Potential mechanism not well understood, but may be related to pro-inflammatory state associated with obesity
Low serum albumin	May reflect lower general health status
Use of opioids	Prolonged use more likely in patients with CIPN. Need further work to understand if this is due to pain severity, or to a mechanistic interaction with opioids increasing CIPN risk (OR 2.0, 1.06-3.69)

Pain. 2019;160 Suppl 1(Suppl 1):S1-S10.

28

Chemotherapy regime-related risk

Common chemotherapeutics and incidence or prevalence of reported neuropathy.

Chemotherapy	Approximate incidence/ prevalence of CIPN (%)
Oxaliplatin	Acute: 85-96; Chronic wide range: 40-93
Cisplatin	12-85
Paclitaxel	61-92
Bortezomib	47
Vincristine	20
Combined cisplatin and paclitaxel	69-76

Pain. 2019;160 Suppl 1(Suppl 1):S1-S10.

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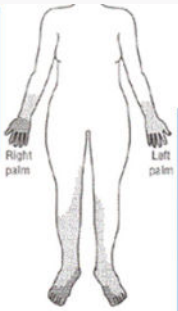
CIPN presentation

Examples of descriptors used
- Burning
- Shooting
- Stabbing
- Electric shocks
- "Like walking on glass"
- "As if wearing gloves with bees inside"

Click on image to zoom



Sensory symptoms and signs

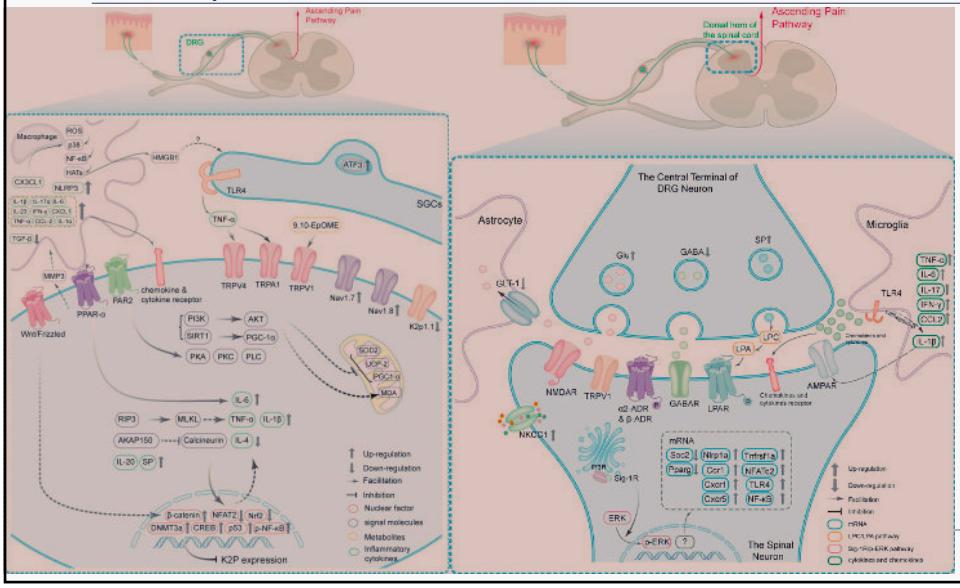
+ve
- Mechanical allodynia e.g. clothes on skin are painful
- Thermal allodynia especially cold hypersensitivity with acute oxaliplatin treatment
- Hyperalgesia
- dysaesthesia

-ve
- Numbness
- Paraesthesia
- Inability to detect temperature changes
- Loss of fine motor function (peg board)

Pain. 2019;160 Suppl 1(Suppl 1):S1-S10.

30

CIPN mechanisms are complex – paclitaxel as an example



Eur J Pharmacol. 2022;933:175288.

31

CIPN and mitochondria

- All the chemotherapy-related mechanisms listed for CRF are relevant to a certain degree with ROS/RNS being thought as particularly important (early research on flavonoid targeting_
- Cisplatin decreases mitochondrial function in sensory axons, and HDAC6 inhibition can promote axonal transport of healthy mitochondria and in animal models may reverse cisplatin-induced mechanical hypersensitivity.
- Increased malondialdehyde through paclitaxel upregulation of the PI3K/AKT pathway induces mitochondrial damage in DRG neurons (animal studies show resveratrol may target this). Mitochondrial PGC-1α, uncoupling protein 2, and SOD2 were also decreased in the DRGs.

Brain Behav Immun. 2022;100:287-296; Eur J Pharmacol. 2022;933:175288.

32

Definition - CRCI

- Lack of standardization but **CRCI (chemotherapy-induced cognitive impairment)** includes problems in the cognitive domains of memory, attention, executive function, and processing speed, although research has also found impairment in working memory, new learning, visuospatial skills, and language.
- Longitudinal neuropsychological assessment of breast cancer (BC) patients finds that **up to 75% experience CRCI during treatment**.
- Long-term prevalence of CRCI post-treatment is estimated at **35-60%** and may persist for 20 years following completion of chemotherapy.

CA Cancer J Clin. 2015;65(2):123-138; Int Rev Psychiatry. 2014;26(1):102-113.

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Cancer treatment-induced cognitive dysfunction - key mechanisms

Table 4. Suspected mechanisms involved in cognitive impairment induced by cancer treatments

Cancer treatments Main studied drugs	Brain functions (excluding complaints)	Suspected mechanisms
Chemotherapy Doxorubicin Taxol Methotrexate Fluorouracil	Clinical studies: memory, processing speed, attention, executive function Animal: working memory, attention, learning	• Diminution of neurogenesis • Disruption of myelin and of oligodendrocyte precursors • Mitochondrial dysfunction • Increased peripheral and brain cytokine production
Hormone therapies Aromatase inhibitors Antiestrogen Androgen deprivation therapy	Clinical studies: executive functions, working memory, concentration (Anastrozole), visuomotor functions	• Linked to endocrine disorders, hypothalamo-pituitary-adrenal axis
Targeted therapies Antiangiogenic therapy	Clinical studies: fatigue, one main domain of cognition in a subpopulation of patients, working memory	• Increased plasma VEGF (fatigue) • Leukoencephalopathy • Inhibition of long-term potentiation
Immunotherapy CTLA-4 Anti-PDL-1	Clinical studies: headaches, encephalopathy, fatigue, and meningitis or hypophysitis with endocrine disorders Animal: executive functions	• Brain microglial activation • Increased peripheral inflammatory cytokines crossing the BBB

VEGF, vascular endothelial growth factor; BBB, blood–brain barrier.

Ann Oncol. 2019;30(12):1925-1940.

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Risk factors

- Sociodemographic variables
  - Baseline education level
  - Cognitive reserve
  - ± Age
- Comorbidities
  - MetS, CVD, DM
- Genetics – SNPs in ApoE, COMT and BDNF (significantly more research needed due to several inconsistent findings)
  - APOE-4 may contribute to poorer cognitive performance following chemotherapy and/or hormonal therapy in breast cancer patients
  - rs165599 in the COMT gene was correlated with impaired retrospective memory in patients receiving chemotherapy
  - BDNF polymorphism (rs6265) [Val66Met] may be associated with reduced susceptibility of cognitive complaints in BC patients receiving some chemotherapy regimes

Ann Oncol. 2019;30(12):1925-1940.

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Practical aspects of IO care in CIPN, CRCI and CRF

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Our clinic's model - a physician-led MDT

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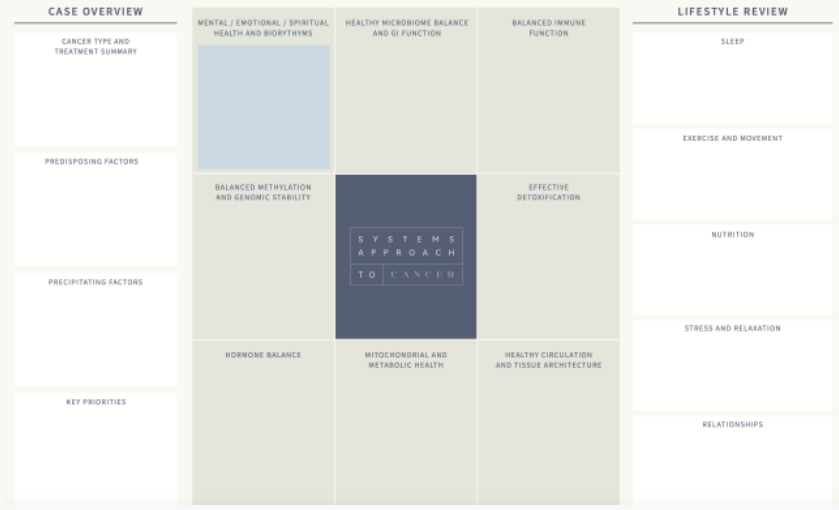
Detailed assessment framework – Systems Approach to Cancer Programme (SATCP) model



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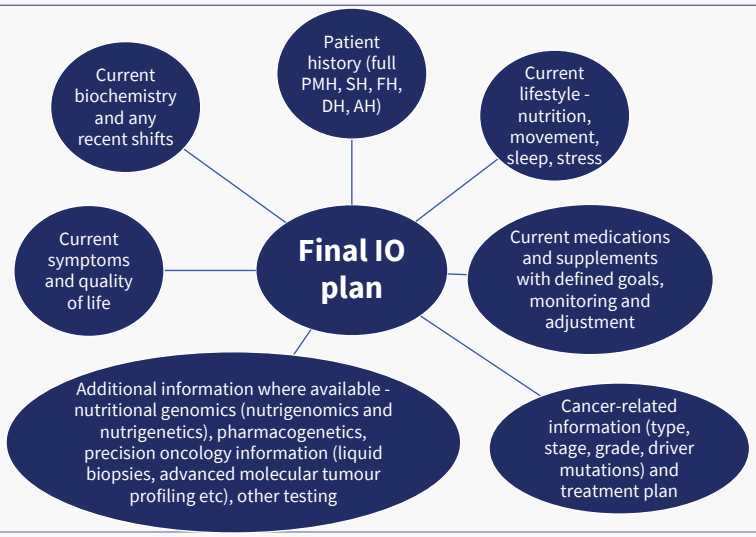
Integrating multiple inputs



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Creating a team around the person outside an IM/IO clinic

- Oncology team – available resources and referrals, e.g. psycho-oncology, physiotherapy etc.
- Consider common needs/presentations and resources you may need
  - A few examples:
    - Cancer exercise therapy (Level 4)
    - Acupuncture
    - Yoga and yoga therapy
  - And much more – according to dynamic needs assessment and personalised care plan
- Charity resource referrals
  - Oncio app (non-profit CIC)
  - Local centres, e.g. Maggie's and their offering
  - Cancer-specific charities, e.g. Future Dreams House and other charities for breast cancer, Target Ovarian etc
  - Charities targeting specific groups, e.g. Victoria's Promise and Trekstock for younger people
  - Other free resources, e.g. Vicky Fox free classes for people affected by cancer, Sleepio (CBT-I) via Macmillan Cancer Support etc
- Aiming to work in a collaborative and safety conscious environment

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CRF - assessment considerations

- Systems Approach assessment (history/symptoms/test results) to target key areas
  - Consider existing co-morbidities - anaemia, cardiac conditions, DM or psychiatric conditions that could contribute to fatigue severity at the start of cancer treatment, as well as medication side effects
- Examples – must be guided by the above:
  - Baseline bloods should usually screen for common fatigue causes, including FBC, biochemistry, inflammatory markers, thyroid and key metabolic health parameters
    - Post-treatment anaemia is not uncommon and may not have been corrected
  - Inflammation – hsCRP, ESR, ferritin (within the overall iron panel for context)
    - And then find the drivers to manage this properly!
  - Hormones – HPA, HPT, HPO, insulin (glucose homeostasis)
  - Trauma and ANS dysfunction
  - Nutrient status, particularly B complex, antioxidant status, magnesium but others may be relevant, depending on presentation
- Genetics – BDNF Val66Met may be protective, although more research is needed.

Transl Psychiatry. 2020;10(1):302.

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SIO Society for Integrative Oncology ASCO Guidelines

MANAGEMENT OF FATIGUE IN ADULT SURVIVORS OF CANCER

During Active Treatment	After Active Treatment	Post-Treatment
Recommended Interventions:		
• Exercise (aerobic, resistance, or a combination) • Cognitive behavioral therapy with or without hypnosis • Mindfulness-based programs (MBSR, MBCT) • Tai chi or qigong • Psychoeducation • American ginseng (Panax quinquefolius)	• Exercise (aerobic, resistance, or a combination) • Cognitive behavioral therapy • Mindfulness-based programs (MBSR, MBCT, MAPs) • Yoga • Acupressure • Moxibustion	• Cognitive behavioral therapy • Corticosteroids
Interventions Clinicians Should NOT Recommend:		
• Wakefulness agents • Psychostimulants • L-carnitine • Antidepressants	• Wakefulness agents • Psychostimulants	• Wakefulness agents • Psychostimulants

Bower et al *J Clin Oncol* **2024**
asco.org/survivorship-guidelines

Abbreviations. MAPs, mindful awareness practices; MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction
Note. Evidence quality and strength of recommendations are available in the guideline publication.

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CRF – personalised management considerations

- Correct the correctible (anaemia, thyroid, nutrient deficiencies etc), including appropriate management of root causes for abnormal biomarkers
  - Example – inflammation driven by dysbiosis
- Nutrition and lifestyle
  - Anti-inflammatory Mediterranean style diet may be beneficial
  - Exercise!!! (combination of resistance and aerobic conducted under the guidance of a Level 4 trained cancer exercise specialist or physiotherapist)
    - Beware self-guided where there is a risk of complications, such as lymphoedema
  - Psychological support and mind-body – CBT, MBSR/MBCT/MBCR, yoga
    - Yoga teachers must have cancer-specific training or refer to a C-IAYT yoga therapist

Cancers (Basel). 2022;14(17):4202; J Clin Oncol. 2024;42(20):2456-2487.

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CRF – personalised management considerations

- Supplementation – adaptogen trials are worth watching:
  - Siberian ginseng (*Panax quinquefolius*) 2,000 mg total daily dose recommended in the guidelines (caution re: supply/sustainability)
  - Ashwagandha (*Withania somnifera*) root extract 2g TDS shown to improve fatigue and QOL in BC patients when given throughout chemotherapy with a non-significant trend towards improved 24-month OS (72% versus 56%, p=.176)
  - Spore powder of *G. lucidum* 1000 mg three times a day for 4 weeks was found to reduce fatigue in BC patients on endocrine therapy
- Some evidence supporting specific CHM interventions but more research needed – TCM trained herbalist with interaction checks
  - Most common herbs used are Astragali Radix, Ginseng Radix (*Panax ginseng*) and Codonopsis Radix.
    - Ginseng processing affects ginsenoside content

J Clin Oncol. 2024;42(20):2456-2487; Integr Cancer Ther. 2013;12(4):312-322; Evid Based Complement Alternat Med. 2012;2012:809614; Chin Med. 2023;18(1):142.

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CIPN – assessment considerations

- Systems Approach assessment (history/symptoms/test results) to target key areas
  - Consider existing co-morbidities that increase neuropathy risk, such as T2DM
- Systemic inflammatory markers, OAT assessment of B complex and oxidative stress markers may all be useful.
- BDNF may become part of the assessment in the future (validation needed) – serum levels and genotype:
  - Patients with the Val/Val BDNF genotype demonstrated significantly higher maximum neuropathic pain scores in chemotherapy studies than those with the Val/Met and Met/Met genotypes (Val66Met carriers).

Br J Haematol. 2020;191(1):77-89; J Clin Neurol. 2019;15(4):511-516.

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CIPN – SIO-ASCO guidelines

Chemotherapy-induced peripheral neuropathy.

Recommendation 1.8.

Acupuncture may be offered to patients experiencing chemotherapy-induced peripheral neuropathy from cancer treatment (Type: Evidence based-informal consensus, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 1.9.

Reflexology or acupressure may be offered to patients experiencing chemotherapy-induced peripheral neuropathy from cancer treatment (Type: Evidence based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

J Clin Oncol. 2022;40(34):3998-4024.

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CIPN – personalised management considerations

- Prevention – consider cooling
  - Paxman Limb Cryocompression System – multi centre RCT ongoing (ICE-COMPRESS SWOG 2205)
  - Medical cannabis may play a role if initiated early
- Correct the correctible – B complex (without hyperdosing), oxidative stress, inflammation
- Ensure adequate sensory stimulation throughout treatment and consider referral for acupuncture, acupressure or reflexology
- Supplementation – clinically we find combining umPEA 600-1200mg + omega-3 1.5-3g EPA+DHA useful, although omega-3 alone at high doses ineffective in CIPN prevention
  - Mayo Clinic running phase 2 trial for PEA
  - STEFANO observational trial for OnLife- 45.9% and 37.5% of patients with paclitaxel-induced PSN and PMN, and 23.9% and 22.0% of patients with oxaliplatin-induced PSN and PMN experienced a reduction of CIPN symptoms, respectively.

Ther Adv Med Oncol. 2021;13:1758835921990203; Oncol Res Treat. 2021;44(11):613-621.

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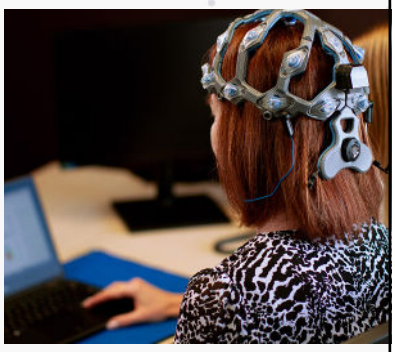
CRCI – assessment considerations

- Systems Approach assessment (history/symptoms/test results) to target key areas
  - Oxidative stress, inflammation and cardiovascular and metabolic health are particularly important to assess, as well as sleep and exercise habits
  - Don't forget menopause/andropause impact on cognitive function
- Always consider PTSD! Dissociation may be mistaken for 'chemo brain'
  - Mean cognitive score are also unsurprisingly worse with higher depression, anxiety, and insomnia scores.
  - Assess for depression (PHQ-9) and anxiety (GAD-7) as frequently co-morbid conditions and refer/manage appropriately
- Relevant genetics – SNPs in apolipoprotein E, COMT and BDNF as risk factors
- Few people will have access to psychometric testing and it is poorly standardised in this area but do document extent and areas of cognitive impairment and assess progress.
  - We are exploring WAVI EEG for both administering a Trail Making Test (TMT, psychomotor speed and executive function) and conducting serial P300 wave measures.



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CRCI – management considerations

- Address the Systems Approach targets and comorbidities within a comprehensive plan
- Lifestyle
  - Cognitive training, including recent trial on adaptive online support
  - Qigong and exercise (very fatigued patients?)
- Medication – proactive melatonin use may be helpful for prescribers (melatonin is a POM in the UK)
  - RCT with **20mg of melatonin** before and during the first cycle of adjuvant chemotherapy for breast cancer reduced the side effects associated with cognitive impairment. Melatonin improved executive function on TMT scores, enhanced episodic memory (immediate and delayed) and recognition on RAVLT, and increased verbal fluency.
- Supplementation
  - No strong evidence currently – watch this space!
- Possible consideration of electroacupuncture

Psychooncology. 2023;32(12):1848-1857; Cancer Nurs. 2023;46(5):E305-E319; Breast Cancer Res. 2022;24(1):36; PLoS One. 2020;15(4):e0231379.

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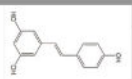
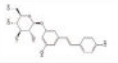
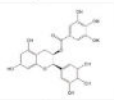
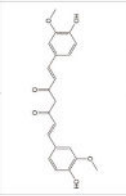
CRCI – natural product research in progress

Categories	Monomers	Chemical structures	Chemotherapeutic agents	Effects	Molecular mechanisms	Ref. (PMID)
Phenols	Resveratrol		Doxorubicin	GFAP↓, IBA-1↓	Anti-inflammation	34536813
			Docetaxel, adriamycin, and cyclophosphamide	IL-6↓,TNF-α↓,IL-4↑,IL-10↑ $GABA_AR$↑, NMDAR1↑, p-CaMKII↓, BDNF↑,TrkB↑	Anti-inflammation; Improve neuroplasticity	29534932
	Polydatin		Doxorubicin	MDA↓, GSH↑, TNF-α↓, PGE-2↓, COX-2↓, cleaved caspase-3↓, cleaved caspase-9↓	Anti-inflammation; Anti-apoptosis; Anti-oxidative stress	31992173
	Epigallocatechin-3-gallate		Cisplatin	IL-6↓, TNF-α↓, iNOS↓, MDA↓, NO↓, TAC↑, Cleaved caspase-3↓,Bax↓, Bcl-2↑, BDNF↑, AChE↑, ACh↓	Anti-inflammation; Anti-apoptosis; Anti-oxidative stress; Improve neurotransmitter release	31410684
	Curcumin		Cisplatin	Bax↓, Bcl-2↑, Bim↓, LC3-II/LC3-I↑	Improve neurogenesis and synaptogenesis Increase autophagy	31843707
			Cisplatin	MDA↓,SOD↑, AChE↑	Anti-oxidative stress	25982942
			Doxorubicin	GFAP↓, IBA-1↓	Anti-inflammation	34536813
	nanocurcumin		Doxorubicin	MDA↓,GSH↑, NO↓, AChE↑,MAO↑	Anti-oxidative stress	33882267
			Cisplatin	MDA↓,GSH↑, NO↓, caspase-3↓, TNF-α↓, AChE↓	Anti-inflammation; Anti-apoptosis; Anti-oxidative stress; Improve neurotransmitter release	30257586

Front Pharmacol. 2024;15:1292807.

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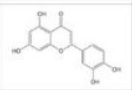
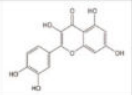
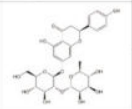
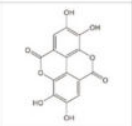
CRCI – natural product research in progress

Flavonoid	Luteolin		Doxorubicin	CAT↑, SOD↑,GST↑,GPX↑,GSH↑,TSH↑,LPO↓,RONS↓,XO↓, AChE↓,NO↓,MPO↓, TNF-α↓,IL-1β, IL-10↑, caspase-3↓	Anti-inflammation; Anti-apoptosis; Anti-oxidative stress	34766659
	Quercetin		Adriamycin	corticosterone↓, GST↑, GSH↑, MDA↓, lymphocytes↑, leukocytes↑	Anti-oxidative stress; Improve immune dysfunction	24947870
			Cyclophosphamide and doxorubicin	SOD↓, CAT↑, GSH↑, MDA↓	Anti-oxidative stress	25260542
	Naringin		Cisplatin	AChE↓, MDA↓, PCO↓, H2O2↓,ROS↓, nitrite formation↓, iNOS↓, GSH↓, Ascorbic acid↓,SOD↑,CAT↑,GPx↑	Anti-oxidative stress; Anti-inflammation; Improve neuroplasticity	25896911
			Doxorubicin	MDA↓, SOD↑, GSH↓, CAT↑, IL-1β↓,TNF-α↓	Anti-oxidative stress; Anti-inflammation	27209303
	Ellagic acid		Doxorubicin	MDA↓, GSH↓, TNF-α↓, iNOS↓, CHE activity↓, 5-HT↑, DA↑, NE↑, caspase-3↓	Anti-oxidative stress; Anti-inflammation; Improve neurotransmitter release	28815802

Fisetin?

Front Pharmacol. 2024;15:1292807.

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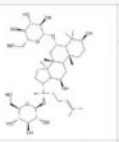
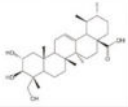
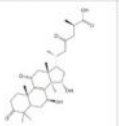
CRCI – natural product research in progress

Terpenoids	Ginsenoside		Docetaxel, adriamycin, and cyclophosphamide	TNF-α↓, IL-6↓, IL-10↑, IL-4↑, GFAP↓,IBA-1↓, BDNF↑	Anti-inflammation; Improve neuroplasticity	30659419
			Cisplatin	SOD↑, GSH↑, MDA↓,ROS↓, TNF-α↓, IL-10↑, IL-1β↓, AchE↓, Ach↑,chAt↑	Anti-inflammation; Anti-oxidative stress; Improve neuroplasticity	31695559
	Asiatic acid		5-fluorouracil	Ki-67 positive cells↑, BrdU positive cells	Improve neurogenesis	28700628
			5-Fluorouracil	p21 positive cells↑,MDA↓	Anti-oxidative stress; Improve neurogenesis	
	Ganoderic acid		5-fluorouracil	IL-6↓, IL-1β↓, iNOS↓, COX2↓, BDNF↑	Anti-inflammation; Improve neuroplasticity	34821902
	Astaxanthin		Doxorubicin	AChE↓, TNF-α↓,PGE2↓,COX-2↓,GFAP↓, Caspase-3↓,cytochrome c↓	Anti-inflammation; Anti-apoptosis	29039023

Front Pharmacol. 2024;15:1292807.

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Summary

- Integrative oncology (IO) is a rational person-centred integration of conventional cancer care with evidence-informed nutrition, lifestyle, psycho-emotional wellbeing support and complementary medicine to support better quality of life, improve resilience, minimise the side effects of treatment and improve outcomes.
- Mitochondrial dysfunction may play an important role in CRF, CIPN and CRCI, although a multisystem contribution must always be considered, and further targeted research is needed.
- Assessment may involve a full Systems Approach screen, followed by targeted appropriate investigations as needed to guide personalised management.
- Management strategies should take into account both guideline-based care and personalised assessment. Use of formal measures and building a clinical audit programme helps us evidence our care and develop rational trial programmes.

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The future of integrative oncology charity support for our patients

- Digital support – already in place through the **Oncio app** (further content development through additional fundraising 2024-2025)
- The new **NCIO (National Centre for Integrative Oncology) charity** – setting up the first CQC registered and medically-led integrative oncology service (group and telehealth care, followed by in-person support).

NATIONAL CENTRE FOR INTEGRATIVE ONCOLOGY

SCAN ME

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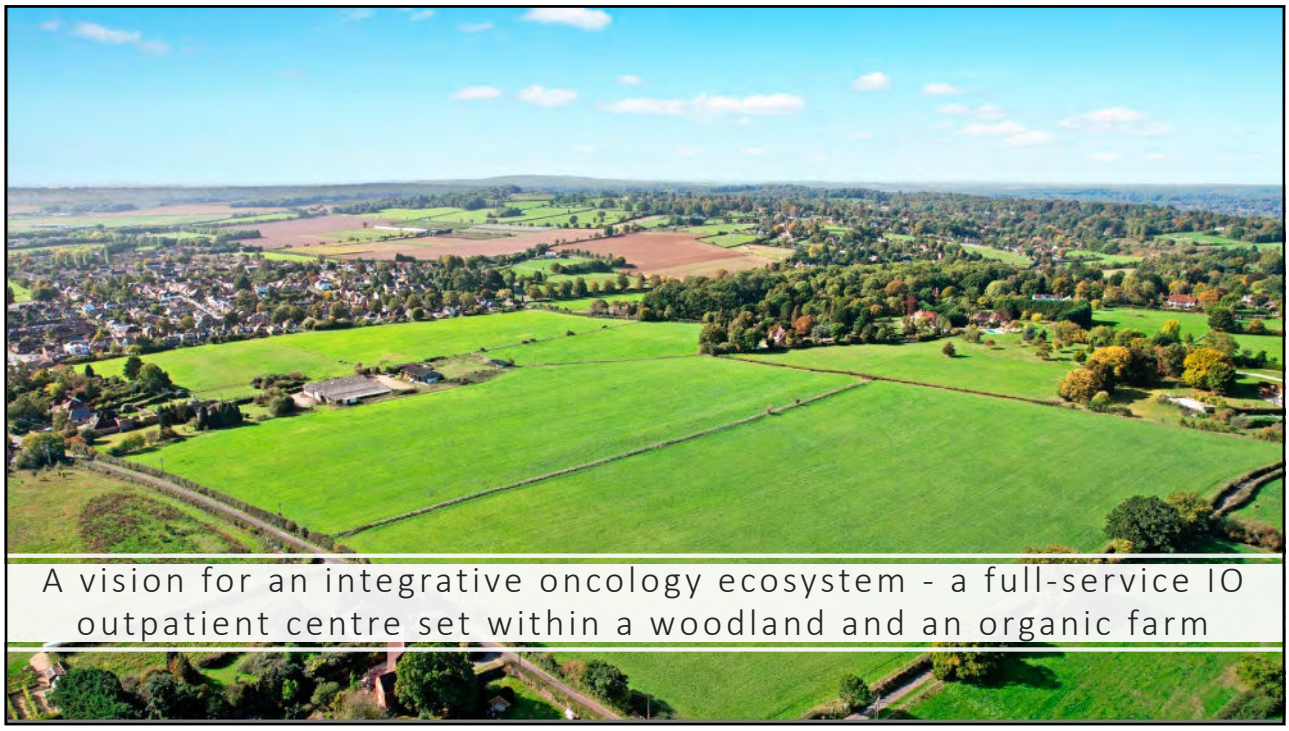

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DR NINA
FULLER-SHAVEL

Thank you for your attention

Any questions?

Dr Nina

MB BCHIR (MEDICINE) and MA HONS NAT SCI (CANTAB) MSC and PGDIP (OXON) FBANT FRSA IFMCP DIPIM DIPAC DIPCHM PG CERT DIPION RYT200

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