

CANCER-RELATED FATIGUE: AN UPDATE

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OUTLINE

- Cancer Fatigue Burden
- Aetiology
- Assessment
- Management
 - Non-pharmacological
 - Pharmacological



CANCER RELATED FATIGUE

NOT JUST TIRED

“The Deadening Fatigue Which Invades The Very Bones Of Cancer Patients Is Totally Unlike Even The Most Profound Fatigue Of An Otherwise Well Person”

POULSON, JCO, 2001

CANCER RELATED FATIGUE

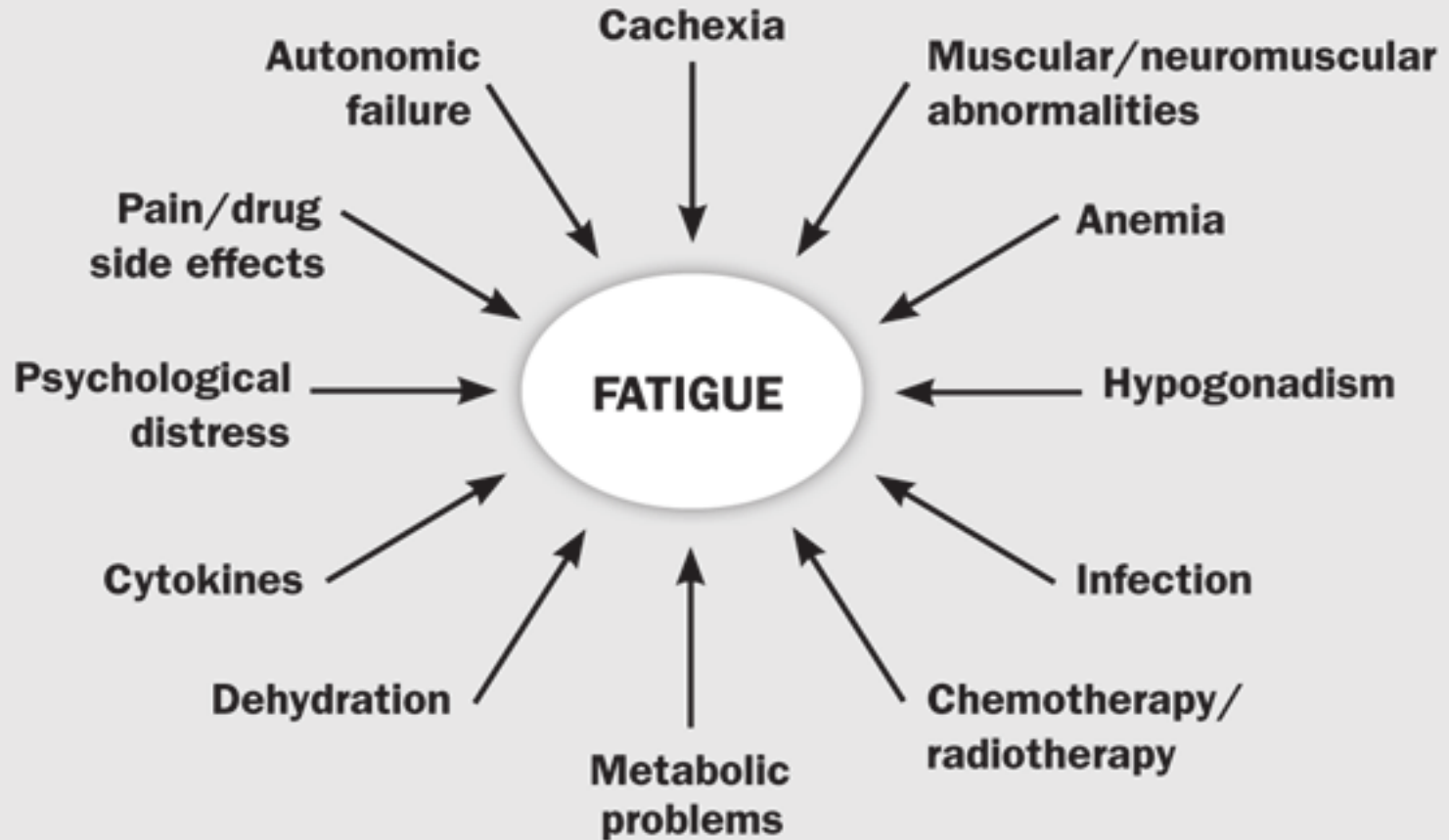
- Distressing, Persistent, Subjective Exhaustion
- Related To Cancer/Treatment
- Not Proportional To Recent Activity
- Interferes With Usual Function

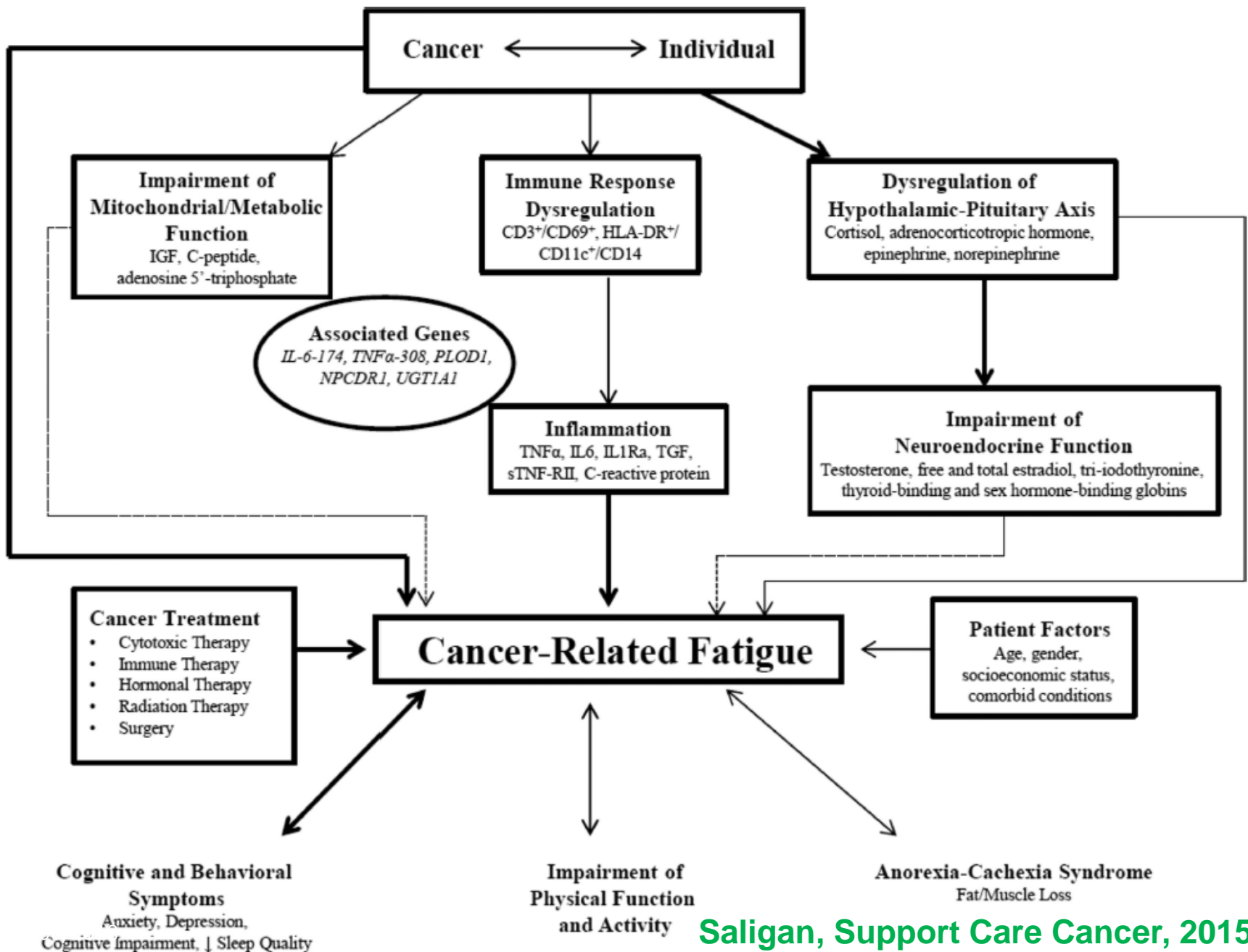
- More Severe, More Distressing
- Not Relieved By Rest

CANCER RELATED FATIGUE

- 70-100% On Multimodal Treatment
- >75% Metastatic Disease
- Months → Years
- Most Distressing Symptom
- Remains Under-evaluated & Under-treated

MULTIFACTORIAL AETIOLOGY





ASSESSMENT & MANAGEMENT: BEST PRACTICE SYSTEMATIC REVIEW

AIMS

- Evidence Base: Assessment & Management

CONCLUSIONS

1. Routine Screening: Establish Problem & Impact Early
2. Focused Assessment: Subjective
 - a. Fatigue History; Duration; QoL
 - b. Underlying Cause/Co-morbidities

CRF ASSESSMENT DIFFICULTIES

- Lack of Standardised Definition
- No One Assessment Tool
- Mainly Subjective Evaluation
- What Qualifies as a Clinically Meaningful Response?

MANAGEMENT: NON-PHARMACOLOGICAL

EDUCATIONAL INTERVENTIONS FOR CRF

COCHRANE REVIEW

METHOD

- Literature Review to 01/11/16: 14 RCT; N=2213
- GRADE: Low-Moderate Quality Evidence

CONCLUSIONS

1. Small: ↓ General Fatigue, Intensity, Daily Life Interference
2. Moderate: ↓ Fatigue Distress
3. May ↓ Anxiety, ↑ Global QoL
4. Unsure: ADL Impact, Depression
5. Further Research: Delivery, Timing, Content

EXERCISE & CRF

COCHRANE REVIEW

- Exercise Efficacy During & After Treatment

CONCLUSIONS

1. Solid Tumours: Aerobic Exercise ↓ Fatigue
2. Resistance & Other Training: Not significant
3. Breast & Prostate
4. Further Research: Type; Intensity; Timing

AEROBIC EXERCISE & CRF

RCT META-ANALYSIS

AIM

- Compare Aerobic Exercise with Standard of Care

CONCLUSIONS

1. Aerobic: Moderate CRF effect
2. Significant Effect: 50 min Sessions
3. Small Effect: Supervised Aerobic Exercise; 20-30 min sessions; 3 sessions/week

PSYCHOSOCIAL INTERVENTIONS DURING TREATMENT WITH PALLIATIVE INTENT

COCHRANE REVIEW

- Psychosocial Interventions in Incurable Cancer

METHOD

- Definition: Interventions to Influence Cognitions, Emotions, Behaviours, Social Interactions
- Literature Search to 29.11.16: 12 Studies; N= 535
- GRADE: Low Quality

CONCLUSIONS

1. Little Evidence of Benefit for CRF
2. Limited by Heterogeneity, Subset Analysis & Sample Size

NUTRACEUTICALS: GINSENG

- Ginseng Root: Chinese Medicine
- Fatigue, Debility, Concentration, ↓ Work Capacity
- Evidence of effect:
 - Cognition/memory
 - Sleep Disturbance
 - Anxiety/Depression
 - Pain
 - Inflammatory Cytokines

HIGH DOSE ASIAN GINSENG (PANAX GINSENG) FOR CRF

PROSPECTIVE OPEN-LABEL STUDY

AIM

- Assess Safety of High Dose Panax Ginseng (PG)

METHOD

- N=30, 24 evaluable
- PG 800mg/day X 29 days

CONCLUSIONS

1. PG Safe & Tolerable
2. CRF Improvement Reported
3. Also ↑ QoL, Appetite, Sleep

RCT PANAX GINSENG FOR CRF

RCT (DOUBLE BLIND, PLACEBO CONTROLLED)

AIM

- Assess PG vs Placebo

METHOD

- N= 112
- PG 800mg/day X 28 days

CONCLUSIONS

1. No Significant Benefit over Placebo
2. No Justification for CRF Use

MANAGEMENT: PHARMACOLOGICAL

PSYCHOSTIMULANTS

- Methylphenidate
- Modafinil
- Dextroamphetamine

METHYLPHENIDATE

- CNS Stimulant
- Inhibits Catecholamine Re-uptake
- Increases Central Dopamine & Noradrenaline
- Short-acting; Half-life 1-4 hours
- Previously ADHD
- Cancer: Fatigue & Depression

PSYCHOSTIMULANTS FOR CRF

SYSTEMATIC REVIEW & META-ANALYSIS

Summarise Methylphenidate Evidence

METHOD

- Medline, Embase, Cinahl to October 2009

CONCLUSIONS

1. 4 Studies (n=426); Heterogenous; Small
2. Meta-analysis: Significant effect over placebo
3. Similar side-effect rate

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

- Focus on Advanced Malignant & Non-malignant Illness

METHODS

- RCT's to 28th April 2014- Pharmacological Fatigue Agents
- Patient Reported Fatigue

CONCLUSIONS

1. Methylphenidate: 5 Studies; N=318
2. 4/5: Clinically Significant Benefit Over Placebo
3. Doses Ranged From 5-54mg

MODAFINIL

- Novel CNS Stimulant Licenced for Narcolepsy
- Used by Healthy (e.g. pilots) for Cognitive and Mood Enhancing Effects After Sleep Deprivation
- More Selective Site of Brain Action
- Half-life: 12-15 hours
- Proposed Less Side-Effects and Abuse Potential

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

METHODS

- 2 studies; N=704
- Modafinil 100- 200mg/day

CONCLUSIONS

1. Benefit in severe fatigue only
2. No benefit over placebo

MODAFINIL FOR FATIGUE IN LUNG CANCER

RCT (DOUBLE BLIND PLACEBO CONTROLLED)

AIM

- Efficacy & Tolerability in NSCLC

METHOD

- N= 208
- Day 1-15: 100mg; Day 15-28: 200mg vs Placebo

CONCLUSIONS

- No CRF effect
- Significant placebo effect: Both ↑ 5 Points FACIT Score
- Similar rate of side-effects

PSYCHOTROPIC DRUGS FOR CRF

SYSTEMATIC REVIEW & META-ANALYSIS

METHOD

- PRISMA: Pubmed, Cochrane, Web of Science to July 2014

CONCLUSIONS

1. Methylphenidate: 7 studies; N=661
 - a. Significant ↓ CRF vs placebo
 - b. No impact on sleep quality, depression, QoL
2. Modafinil: 3 studies; N= 921
 - a. No ↓ CRF vs placebo
 - b. No impact on sleep quality, depression, QoL
3. Adverse events higher in Modafinil

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

- Dextroamphetamine (N=39)
- No significant effect vs placebo

CORTICOSTEROIDS

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

- Methylprednisolone (N=403)
- 125mg/day for 8 weeks
- Significant effect

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

- Dexamethasone
- 84 pts with advanced cancer
- Dex 4mg significantly superior to placebo

REDUCTION OF CRF WITH DEXAMETHASONE

RCT (DOUBLE BLIND, PLACEBO)

AIM

- Compare Dexamethasone vs Placebo

METHOD

- N=84 (Dex=43, Placebo=41)
- Dexamethasone 4mg bd or Placebo X 14/7
- Change in FACIT-F from Baseline

CONCLUSIONS

1. Dexamethasone: Significant Improvement in FACIT-F & QoL
2. Adverse Effects: No Significant Difference

DEXAMETHASONE & PLACEBO ON SYMPTOM CLUSTERS: PRELIMINARY SECONDARY ANALYSIS RCT

AIM

- Examine Dexamethasone effect on Symptom Cluster

METHOD

- Data review of previous RCT (N=114)
- Dexamethasone 4mg bd or Placebo X 14/7
- Symptom Clusters: Fatigue/Anorexia/Depression (FAD); Sleep/Anxiety/Drowsiness (SAD); Pain/Dyspnoea (PD)

CONCLUSIONS

1. FAD symptoms significantly improved
2. Possible Common Aetiology

PREDICTORS OF CORTICOSTEROID RESPONSE

MULTI-CENTRE OBSERVATIONAL STUDY

AIM

- Identify Potential Factors Predicting Response

METHOD

- 182 Inpatients; 22 Japanese Sites; 26 Months
- Fatigue ≥ 4 on NRS
- Assessment: Baseline & Day 3

CONCLUSIONS

1. 53%: >2 Point NRS reduction
2. Predictors: ECOG >3 ; PPS $>40\%$; Baseline NRS >5 ; Alb $>3\text{mg/dL}$; Na $>135\text{ mEq/dL}$; Absent ascites, drowsiness or depression

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

- a. Donepezil (N=142): No superiority to placebo
- b. Acetyl-L-Carnitine (N= 29; 209) : No significant effect over placebo
- c. Medroxyprogesterone (N=134): No significant effect over placebo
- d. Megestrol Acetate (N= 255): No improvement in QoL. 320mg/day for 12 weeks
- e. Mistletoe Extract PS76A2 (N= 337 Breast Ca): Significant Positive Effect

PHARMACOLOGICAL TREATMENTS FOR FATIGUE IN PALLIATIVE CARE

COCHRANE

CONCLUSIONS

- Implications for practice
- No evidence to support a specific drug
- Overall lack of evidence
- Methylphenidate advantageous
- Further Research: Dexamethasone, Methylprednisolone, Modafinil, Carnitine

SUMMARY

- Complex Multidimensional Symptom; No Common Pathway
- Assessment & Treatment Remain Difficult
- Evolving Role for Modern Technology
- Non-pharmacological: Exercise
- Pharmacological: Methylphenidate & Dexamethasone
- Multi-modal Intervention