癌因性疲憊症

張正雄
內科部血液腫瘤科
彰化基督教醫院

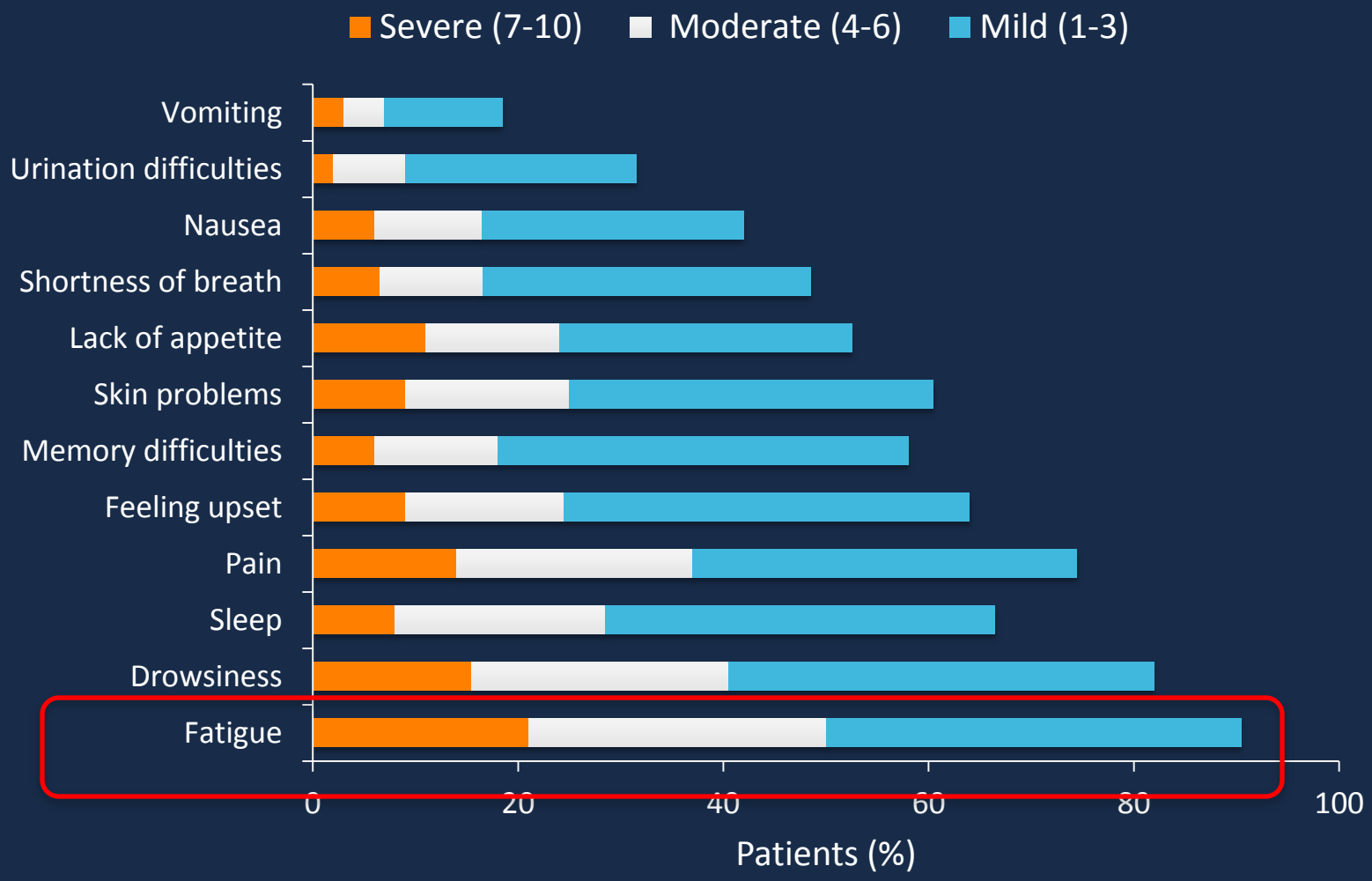
Epidemiology -1

- 43% of cancer patients had little awareness that there were interventions to assess and treat their fatigue

- That rate of fatigue as high as 90% have been reported for those undergoing treatment for various types of cancer

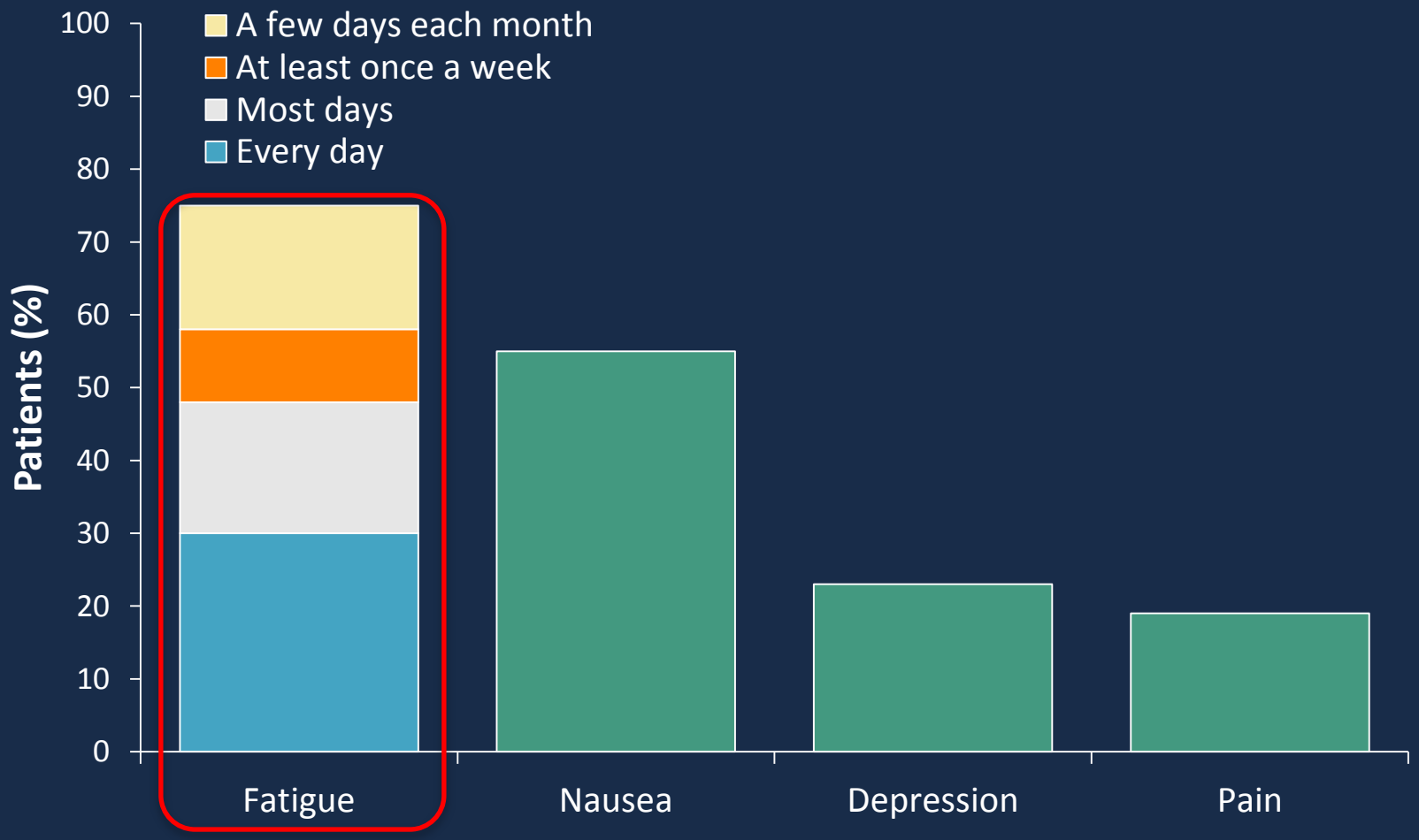
Psychosomatics 2008; 49:283–291

Prevalence and Intensity of Side Effects



J Pain Symptom Manage 2005:30:433–442

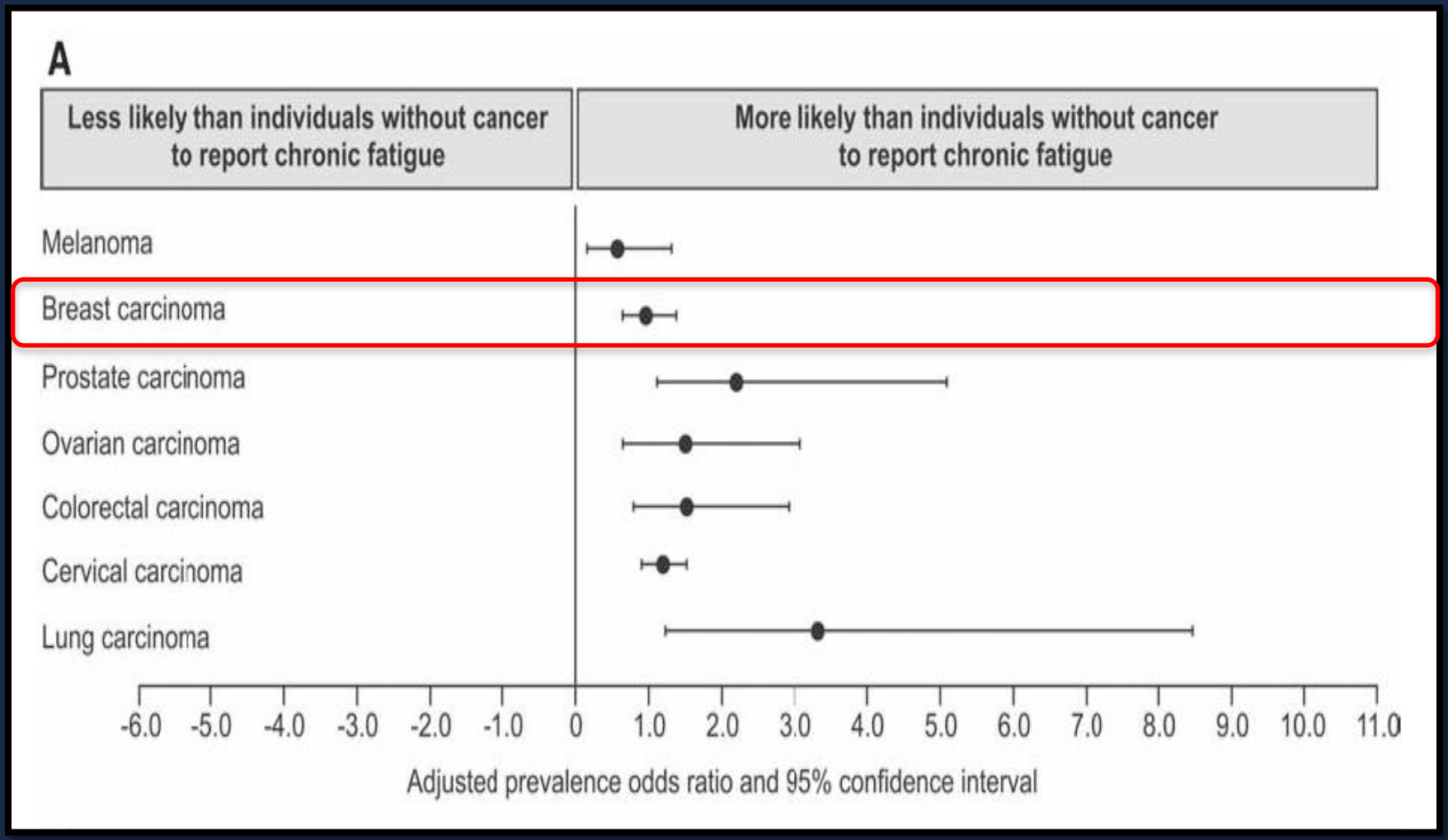
Frequency of Side Effects – C/T



Symptom reported at least a few days each month

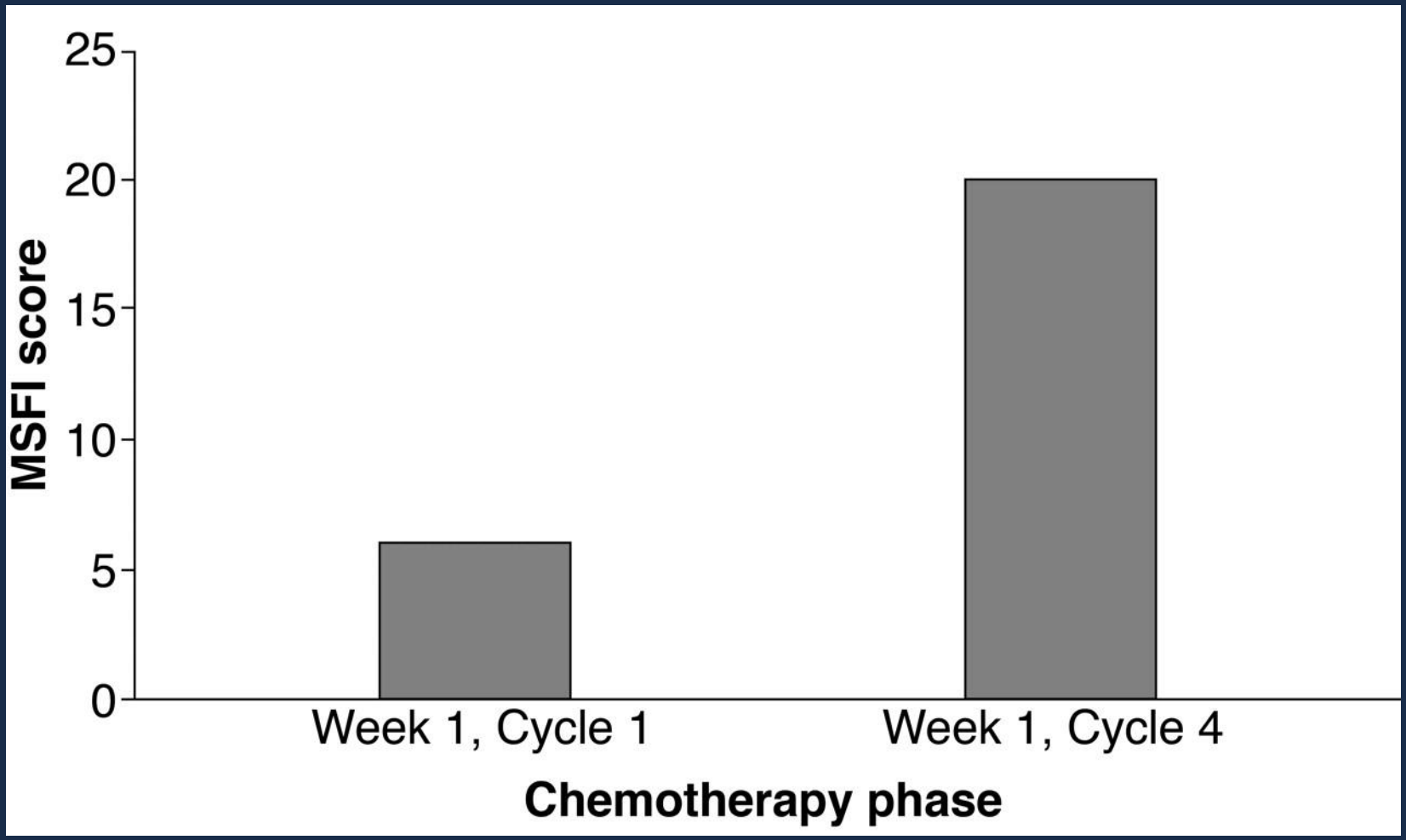
The Oncologist 2000;5:353–360

Likelihood of Reporting Chronic Fatigue by Cancer Type



Cancer 2005;104:2022–2031.

Temporal profile of fatigue evaluated using the Multidimensional Fatigue Symptom Inventory (MFSI) during anthracycline-based therapy for breast cancer



Jean-Pierre P et al. The Oncologist 2007;12:11-21

The Oncologist

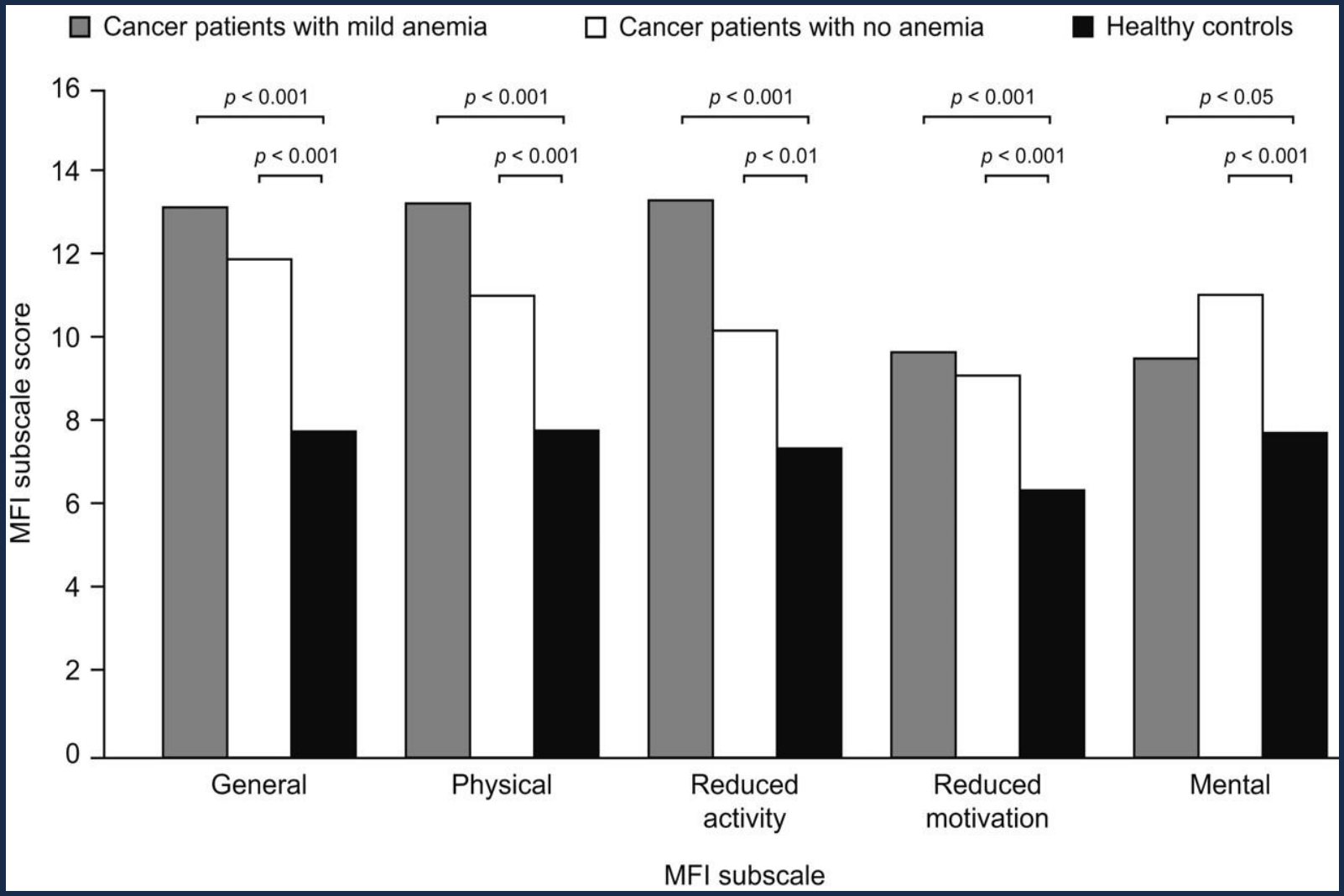
Epidemiology - 2

- More clearly correlated with complaints of fatigue during breast cancer treatment are symptoms of both depression and anxiety

- Further exacerbating factors for cancer related fatigue (CRF) include pain, sleep disruption, and anemia

Psychosomatics 2008; 49:283–291

Multidimensional Fatigue Inventory (MFI) subscale scores among patients with cancer with/without anemia and healthy controls



Jean-Pierre P et al. The Oncologist 2007;12:11-21

The Oncologist

Fatigue *after* Treatment

- Evidence of fatigue rates in the range of 17%–38%
- May be sustained several years after treatment
- Longer-term fatigue may lead to adverse impacts on patients' quality of life and a delayed return to work

Algorithm for Assessment and Management of CRF(NCCN)

Screening
(Initial and periodic)
0-10 scale

Fatigue level 0-3
Education and periodic reassessment

Fatigue level 4-10
Primary assessment:
ascertain medical history
and do physical examination
- Disease status and treatment
- In-depth fatigue assessment
- Assessment of primary factors—ie. anaemia, emotional distress, sleep disturbance, pain, hypothyroidism

Treat identified problems

Reassess degree of fatigue

Fatigue level 4-10
Comprehensive assessment
- Review of body systems
- Review of medications
- Assessment of comorbidities
- Nutritional or metabolic assessment, or both
- Assessment of activity level

Management of fatigue
- Refer as indicated
- Reassess regularly

Correction of possible causes
- Treatment of the primary factors
- Management of comorbidities, malnutrition, deconditioning

Symptomatic therapy

Non-pharmacological

Pharmacological

Reassess fatigue

Mangements

Education and counseling of patient and family

Nonpharmacologic management

Pharmacologic interventions

CRF Treatment Interventions

TABLE 2. Cancer-Related Fatigue Treatment Interventions

Nonpharmacologic interventions	Pharmacologic interventions
Psychosocial (Category 1) • Education • Support groups • Individual counseling • Coping strategies • Stress management training • Individualized behavioral intervention Exercise (Category 1) Sleep Therapy • Behavioral Therapy Stimultus Control Sleep Restriction Sleep Hygiene Acupuncture	Stimulants • Methylphenidate • Modafanil Antidepressants • Selective serotonin re-uptake inhibitors Paroxetine Sertraline • Other antidepressant Bupropion Steroids 植物新藥

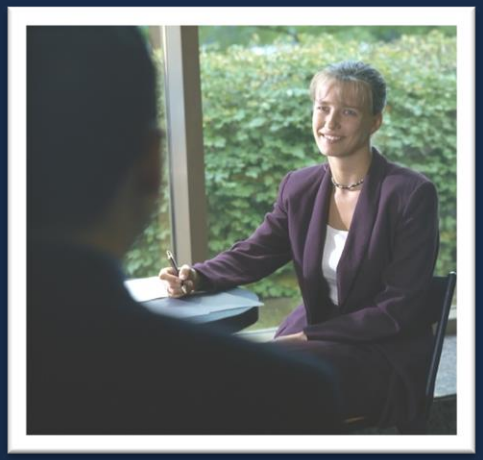
J Gen Intern Med 24(Suppl 2):412–6

CRF Management

Non-pharmacological interventions

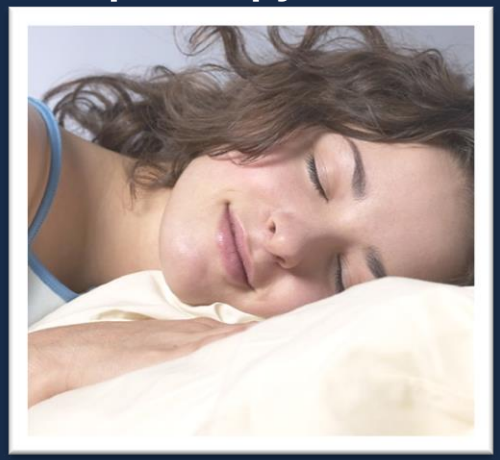
Activity enhancement

Psychosocial interventions



Attention-restoring therapy

Sleep therapy

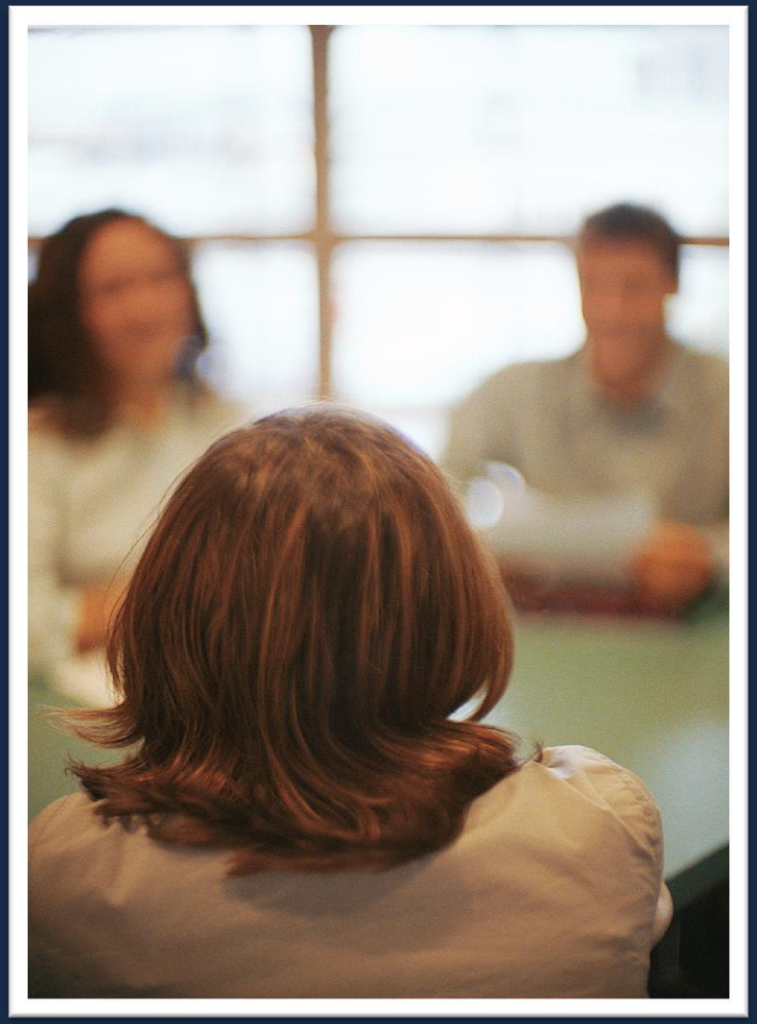


Nutrition consultation

Family interaction

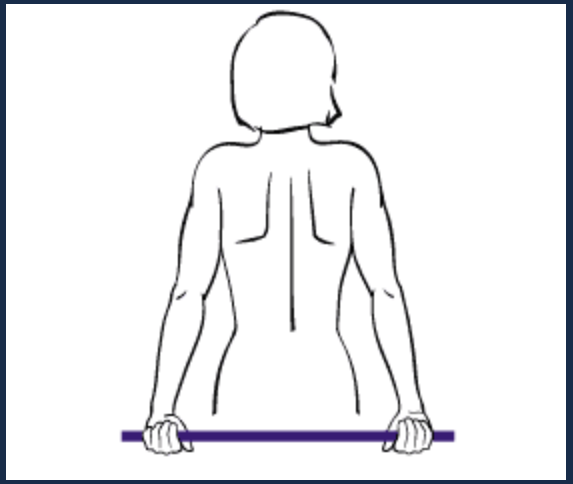
Karin Ahlberg, The Lancet 2003

Exercise and Psychosocial Intervention

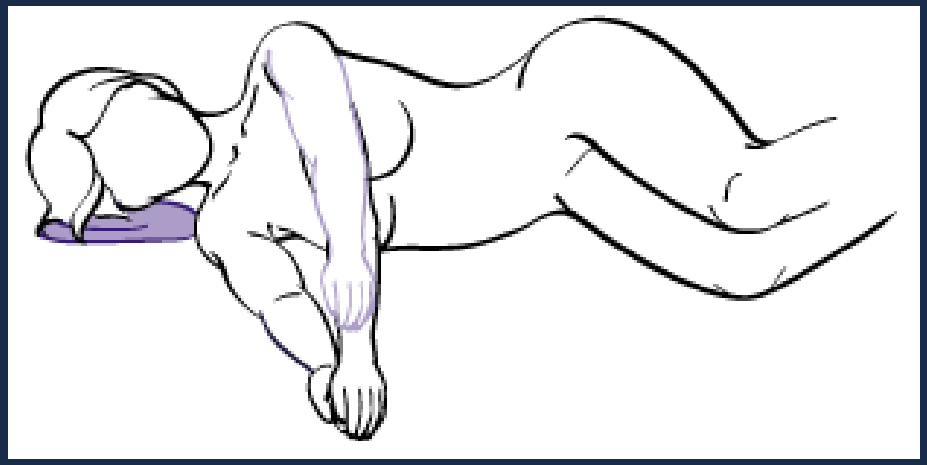


Breast Cancer Rehab: MRM

- Phases I Exercises post-op [10]
  - Shoulder shrugs
  - Shoulder rolls
  - Front bar lifts
  - Side bar lifts
  - Back bar lifts
  - Active shoulder flexion
  - Wall walking



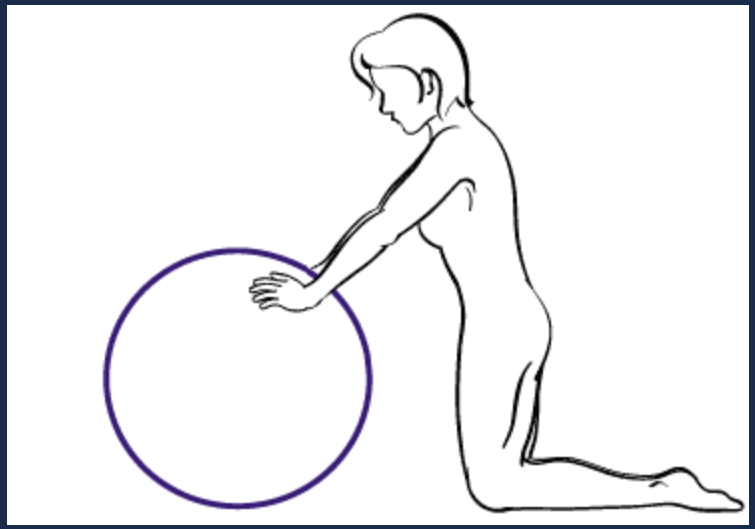
Breast Cancer Rehab: MRM



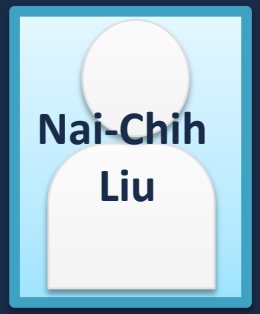
- Phase II (3-6 weeks)
  - Rotator cuff elevation
  - Side triceps extensions
  - Shoulder extensions
  - Shoulder abduction
  - Sidelying horizontal arm lifts
  - Sidelying shoulder ER
  - Bilateral shoulder flexion

Breast Cancer Rehab: MRM

- Phase III (6-10 weeks post-surgery)
  - Continued bar lifts, ER, arm lifts
  - Internal rotation towel stretching
  - Forward ball stretch
  - Shoulder rotation with ball
  - Bridging
  - Shoulder pullovers



Evaluation of a Counseling Service in Psychosocial Cancer Care: A Pioneer Program and Study in Taiwan



Department of Psychology, National Chengchi University, Taipei

Department of Psychology, National Chengchi University, Taipei

Central Hill Medical Group

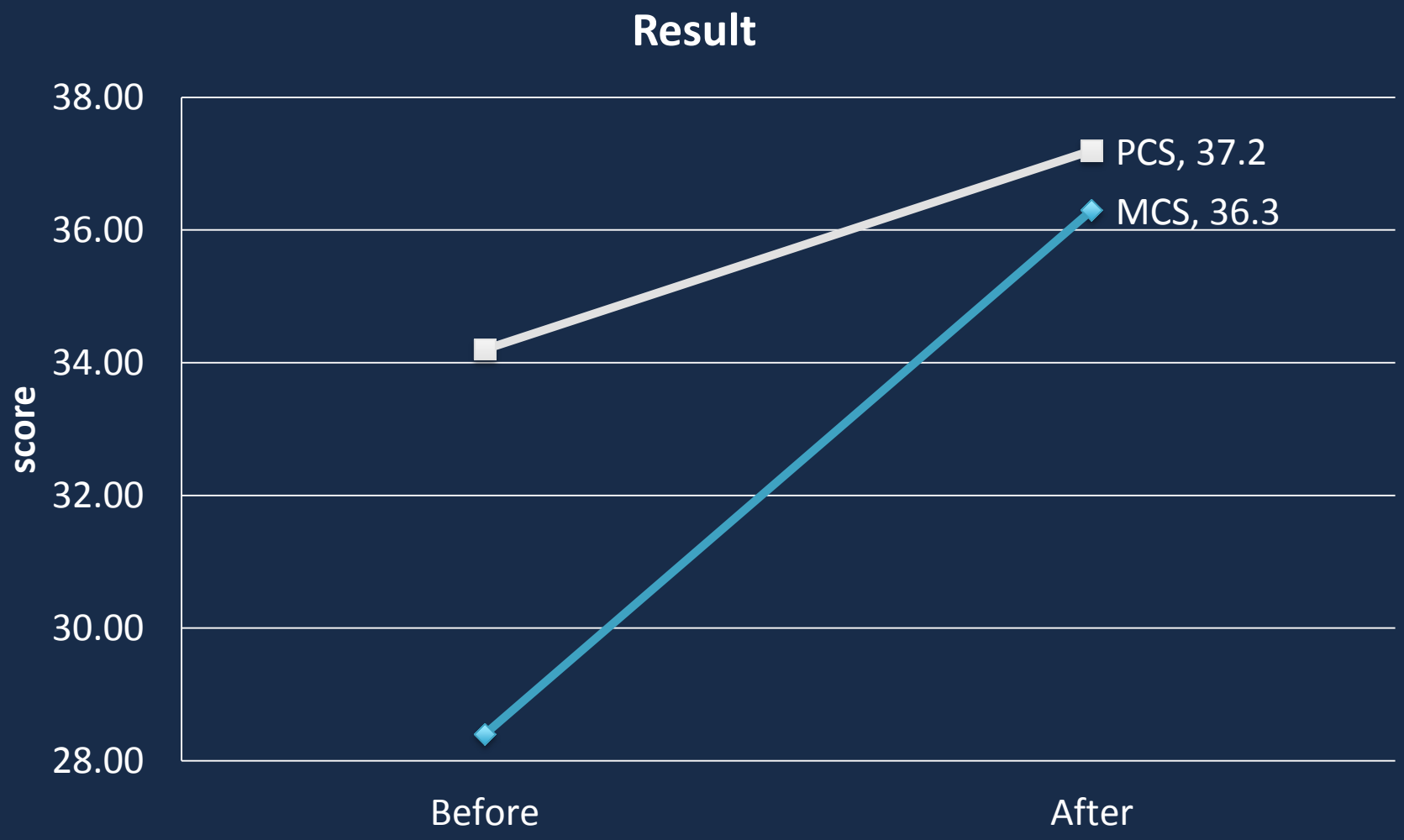
Division of Hemato-Oncology, Department of Internal Medicine, Changhua Christian Hospital

Department of Psychology, National Chengchi University, Taipei

Department of Psychology, Chung Yuan Christian University

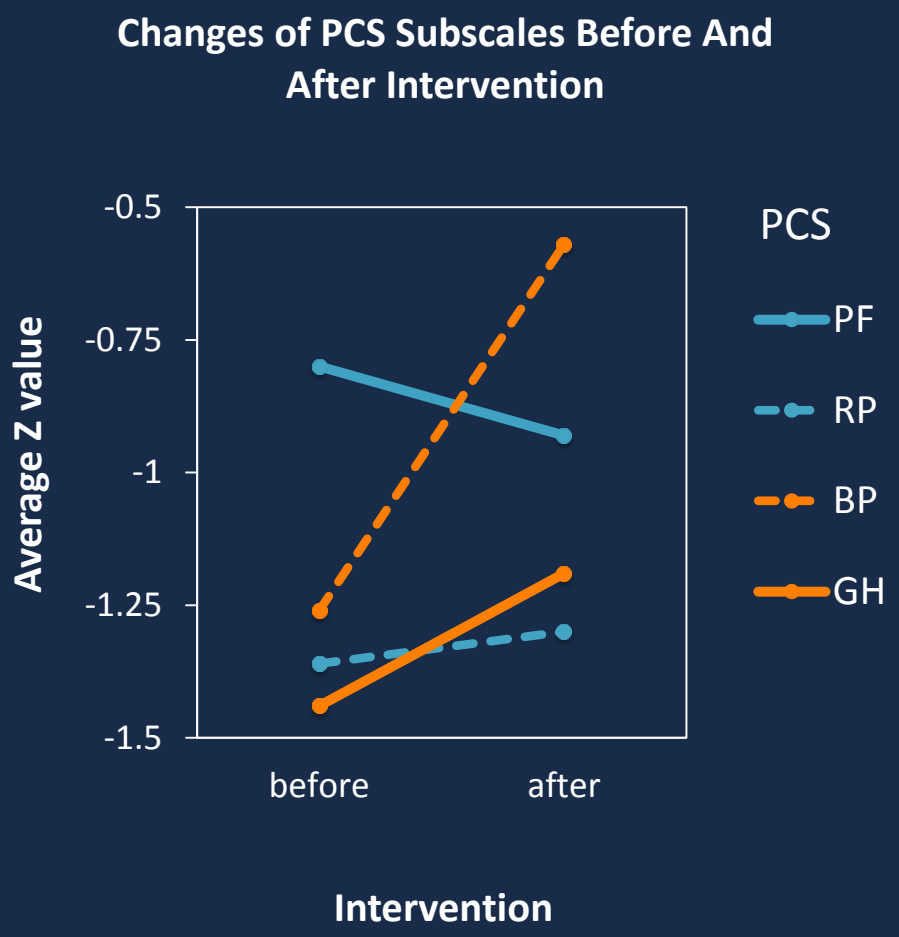
Department of Psychology, National Chengchi University, Taipei

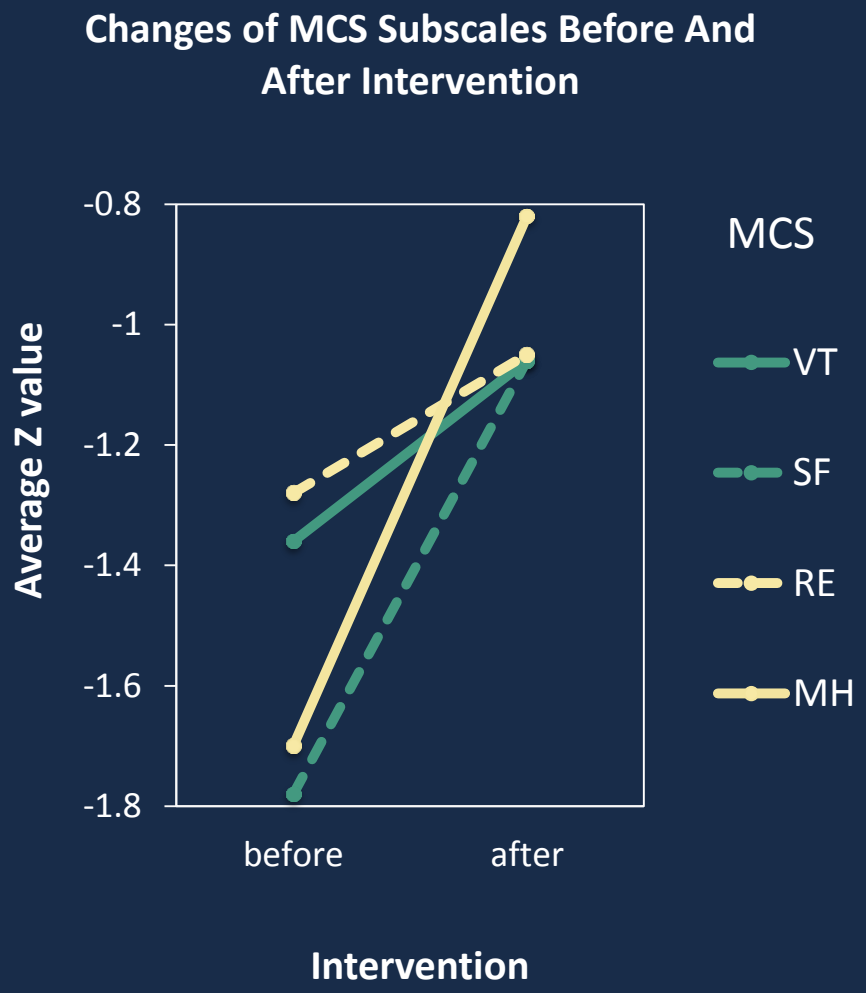
Results



Physical Health Component Score (PCS) and Mental Health Component Score (MCS).

Results

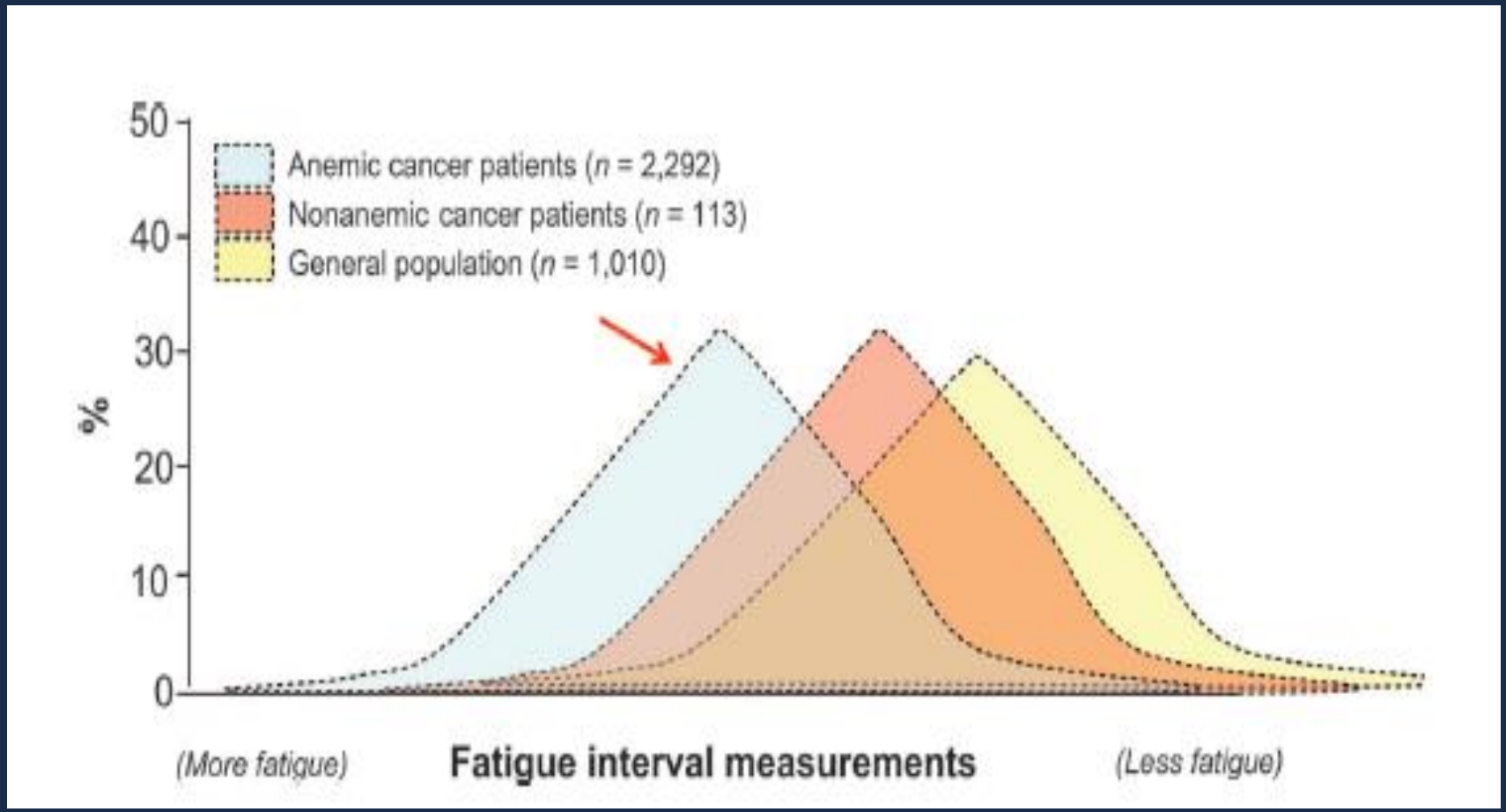

Changes of PCS Subscales Before And After Intervention
Average Z value
-0.5
-0.75
-1
-1.25
-1.5
before
after
Intervention
PCS
PF
RP
BP
GH


Changes of MCS Subscales Before And After Intervention
Average Z value
-0.8
-1
-1.2
-1.4
-1.6
-1.8
before
after
Intervention
MCS
VT
SF
RE
MH

CRF Management (Cont'd)

Pharmacological therapy	
Erythropoietin Treatment of Anemia-Related Fatigue	Hypothyroid conditions Thyroid replacement hormone
Psychostimulants Cancer-related fatigue • Methylphenidate • Dexmethylphenidate • Modafinil Fatigue in multiple sclerosis • Pemoline Insomnia • Sleep medications	植物新藥

Fatigue is worse in anemic cancer patients



Spivak, Gascón, Ludwig ***The Oncologist 2009;14(suppl 1):43–56***

Blood contaminants

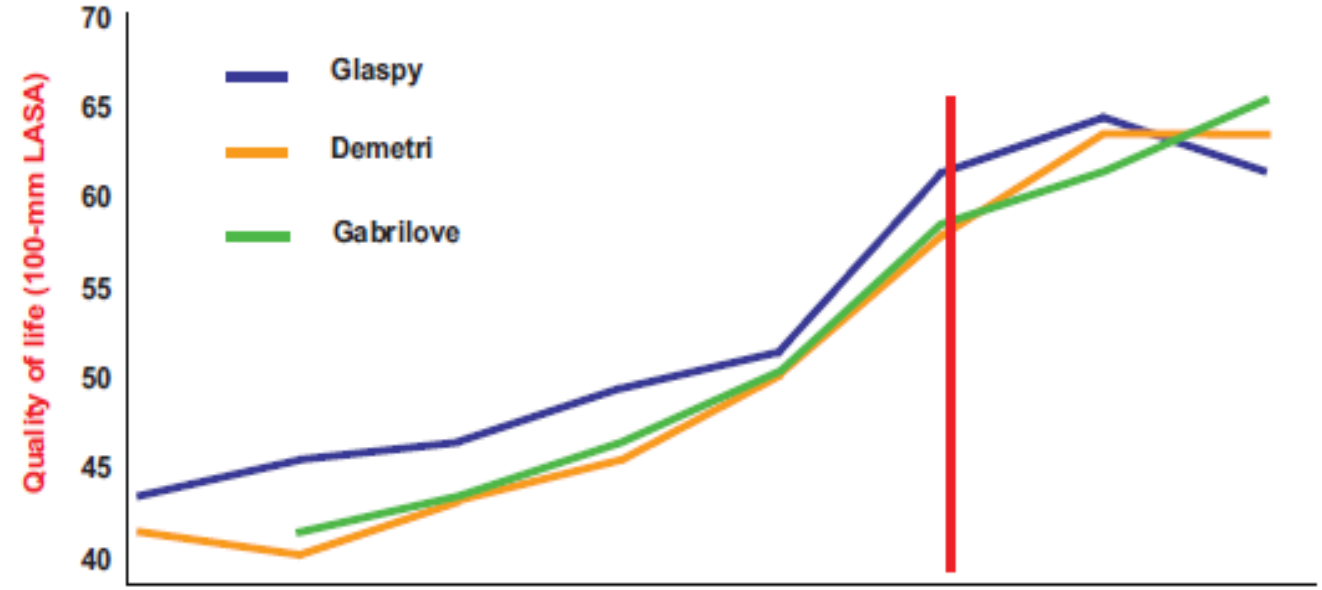
Table 4. Transfusion time window of selected viruses

Virus	Time taken to detect virus in stored blood
HIV	10 days[a]
HIV p24	16 days
HTLV	28 days
HBV	20 days[a]
HCV	12 days[a]

[a]These values are obtained by screening blood samples using genomic analysis (polymerase chain reaction). In conventional assays, the time windows were: HIV, 22 days; HBV, 21 days; HCV, 21 days.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T lymphotropic virus.

*Spivak, Gascón, Ludwig**The Oncologist 2009;14(suppl 1):43–56***

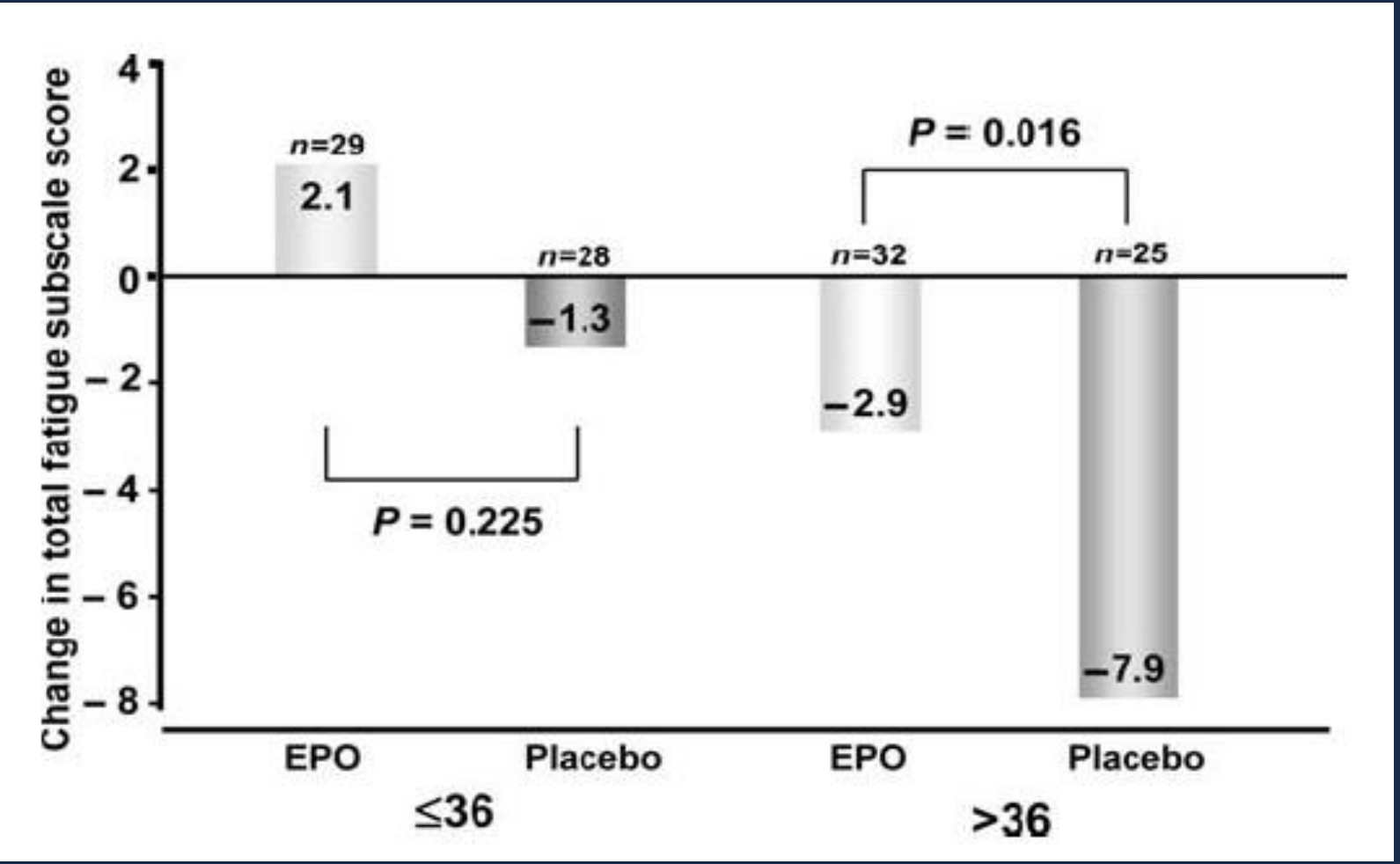
Epoetin alfa phase IV studies in tumor-associated anemia: Incremental increase in quality of life and hemoglobin (Hb) level



Glaspy	–	267	740	918	833	308	287	223
Demetri	59	352	770	753	547	391	313	160
Gabrilove	156	466	1134	1426	844	544	410	168

Spivak, Gascón, Ludwig, ***The Oncologist 2009;14(suppl 1):43–56***

Mean change in FACT-An total fatigue subscale score stratified by baseline total fatigue subscale score



Jpn J Clin Oncol 2009;39(3)163–168

Analyses of recombinant erythropoietin therapy in cancer patients

Table 2. Analyses of recombinant erythropoietin therapy in cancer patients

Type of analysis	*n* of patients
U.S. FDA approval (1993)	413 (3 studies)
ASH/ASCO meta-analysis (2002)	1,927 (22 studies)
Cochrane meta-analysis (2005)	3,287 (27 studies)
Cochrane meta-analysis (2006)	9,353 (57 studies)
ASH/ASCO meta-analysis (2007)	11,757 (59 studies)
Cochrane IPD meta-analysis (2008)	13,933 (53 studies)

Abbreviations: ASH/ASCO, American Society of Hematology/American Society of Clinical Oncology; FDA, Food and Drug Administration; IPD, individual patient data.

Spivak, Gascón, Ludwig ***The Oncologist 2009;14(suppl 1):43–56***

Three major concerns

- Tumor progression resulting from stimulation of tumor cell EPO receptors,
- Higher risk for TE events,
- Shorter survival duration because of recombinant EPO itself.

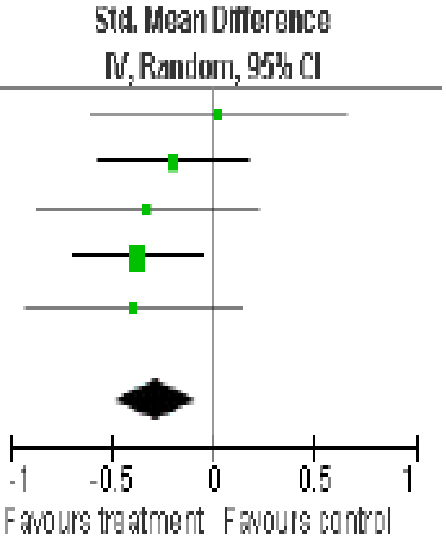
Psychostimulants versus placebo

Figure 1. Forest plot of comparison: 5 Psychostimulants versus placebo, outcome: 5.1 Fatigue score change.

Study or Subgroup	Psychostimulant Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Auret 2009	-1.07	1.85	21	-1.13	2.24	18	9.8%	0.03 [-0.60, 0.66]
Bruera 2006	-9.6	9.8	56	-7.5	11.3	56	27.5%	-0.20 [-0.57, 0.17]
Butler 2007	-3.8	9	26	-0.4	11.64	26	12.7%	-0.32 [-0.87, 0.23]
Lower 2009	-11.8	12.6	75	-7.1	12.6	77	36.9%	-0.37 [-0.69, -0.05]
Mar Fan 2008	-3.3	10	27	1	11.4	28	13.3%	-0.39 [-0.93, 0.14]
Total (95% CI)			205			205	100.0%	-0.28 [-0.48, -0.09]

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 4 (P = 0.80); I² = 0%

Test for overall effect: Z = 2.83 (P = 0.005)



Methylphenidate on CRF

- Methylphenidate, a stimulant drug that improves concentration, is effective for the management of cancer related fatigue but the small samples used in the available studies mean more research is needed to confirm its role.

Cochrane Database Syst Rev. 2010 Jul 7;(7):CD006704

Effects of Methylphenidate on Fatigue and Depression: A Randomized, Double-Blind, Placebo-Controlled Trial

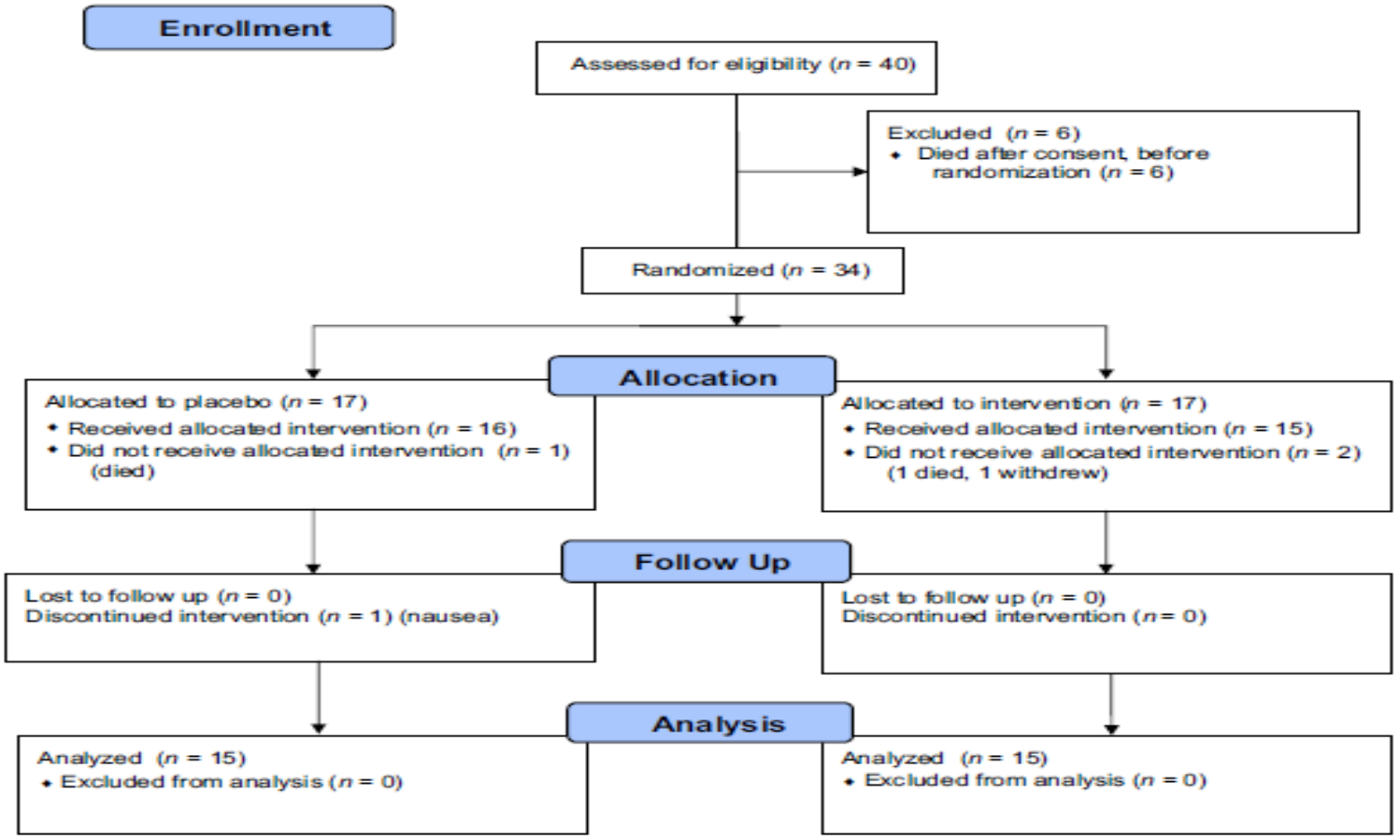


Fig. 1. Flow diagram of study phases.

Journal of Pain and Symptom Management Vol. 43 No. 1 January 2012

Effects of Methylphenidate on Fatigue and Depression: A Randomized, Double-Blind, Placebo-Controlled Trial

Table 2

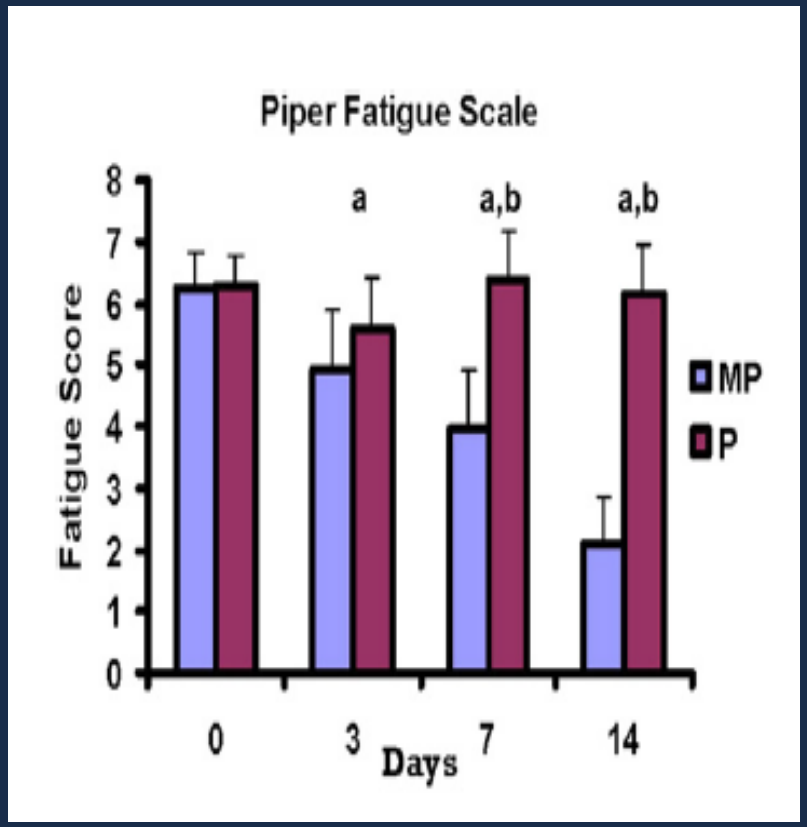
Comparison of Mean ESAS Scores for Placebo- and MP-Treated Groups at Baseline (Day 0) and Day 14

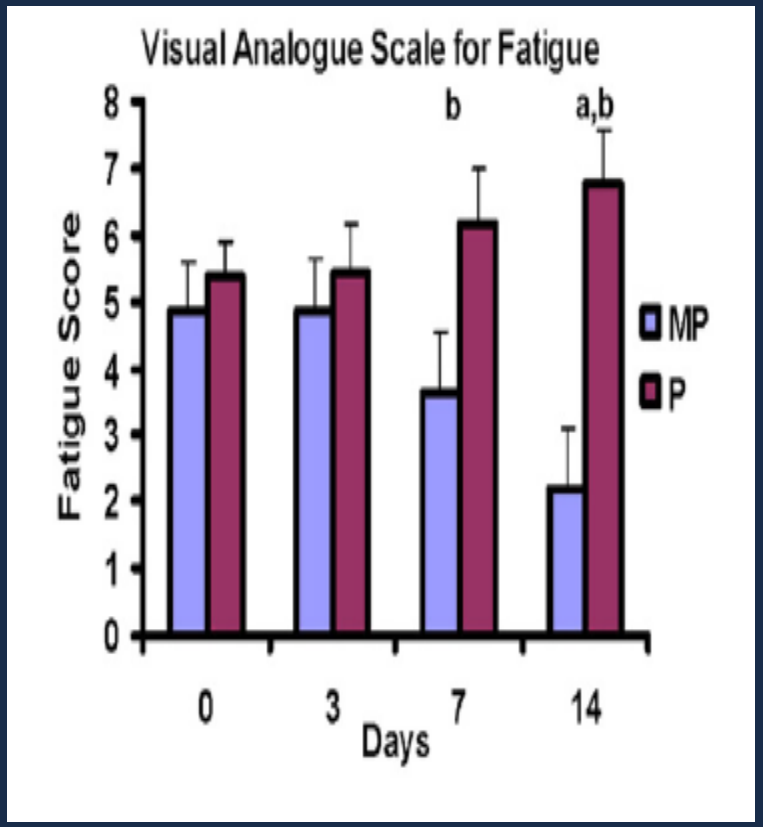
	Placebo		MP Treatment	
	Mean ± SD			
Variable	Day 0	Day 14	Day 0	Day 14
Fatigue	6.93 ± 2.37	6.58 ± 2.31	7.40 ± 2.03	2.69 ± 1.32
Depression	3.93 ± 3.06	3.58 ± 2.57	2.93 ± 3.12	1.92 ± 1.98
Well-Being	5.07 ± 1.77	4.82 ± 2.09	6.00 ± 2.04	3.67 ± 2.06
Anxiety	2.60 ± 2.20	3.42 ± 2.87	3.13 ± 2.33	1.69 ± 2.21
Pain	2.07 ± 1.44	1.75 ± 1.86	2.07 ± 2.15	1.08 ± 1.50
Appetite	3.13 ± 2.26	2.25 ± 2.34	4.13 ± 2.70	4.08 ± 3.40
Nausea	1.73 ± 2.81	1.67 ± 2.06	0.87 ± 0.99	1.54 ± 3.36

SD = standard deviation.
Scores: 0 = best; 10 = worst.

Journal of Pain and Symptom Management Vol. 43 No. 1 January 2012

Comparison of mean fatigue scores for placebo- and MP-treated groups





Journal of Pain and Symptom Management Vol. 43 No. 1 January 2012

Efficacy and Safety of Modafinil in CRF Treatment

Table 1. Summary of Clinical Trials

Reference	Pts. (N)/Malignancy	Cancer Treatment	Modafinil Regimen	Fatigue Rating (mean)		
				Baseline	Posttreatment	p Value
Morrow (2005)[1]	51/breast cancer	23.5 mo post unknown treatment	200 mg/day for 1 mo	6.9 (0-10 scale)	3.7	<0.1
Morrow (2006)[13]	82/breast cancer	22.8 mo post radiotherapy	200 mg/day for 1 mo	5.1 (BFI)	3.2	<0.001
Morrow (2006)[14]	30/cerebral tumors	post neurosurgical resection, radiotherapy, chemotherapy	200 or 400 mg-day for 3 wk; washout 1 wk; 8-wk open extension	5.2 (FSS) 50.2 (MFIS) 4.0 (VAFS)	3.5 28.9 6.7	0.0003 <0.0001 0.0005
Morrow (2008)[12]	888/unknown	concurrent chemotherapy	200 mg/day or placebo	numeric data/ scale not published	numeric data not published	0.03

BFI = Brief Fatigue Inventory; FSS = Fatigue Severity Scale; MFIS = Modified Fatigue Impact Scale; VAFS = Visual Analogue Fatigue Scale.

Ann Pharmacother 2009;43:721-5.

Bupropion/Paroxetine on CRF

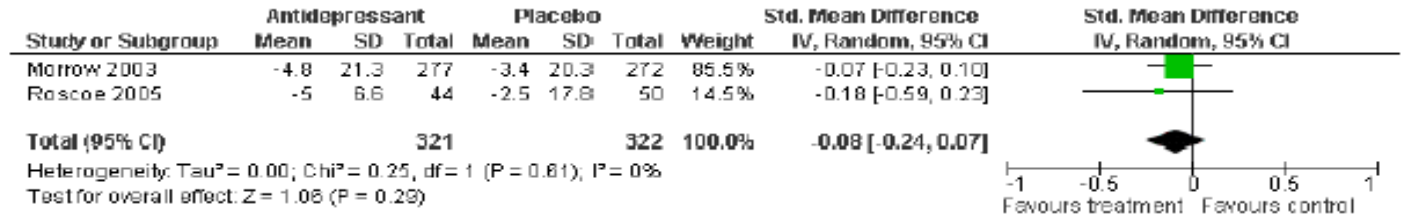
- **Bupropion**
- Bupropion SR can reduce fatigue in cancer patients.
- Further placebo-controlled studies are necessary.

The Oncologist 2007;12(suppl 1):43–51

- **Paroxetine**
- This indicated no difference between paroxetine and placebo for the treatment of CRF.

Cochrane Database Syst Rev. 2010 Jul 7;(7):CD006704

Figure 4. Forest plot of comparison: 4 Antidepressants versus placebo, outcome: 4.1 Fatigue score change.

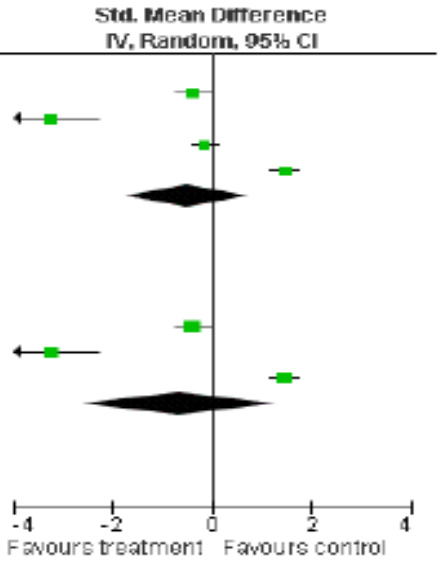


Others

Steroids on CRF

Figure 5. Forest plot of comparison: 3 Progestational steroids versus placebo, outcome: 3.1 Fatigue score change.

Study or Subgroup	Progestional steroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Sub-category								
Bruera 1998	-0.4	1.5	65	0.3	2.1	65	25.6%	-0.38 [-0.73, -0.03]
De Conno 1998	-2	3	21	5	0.1	21	22.7%	-3.24 [-4.18, -2.29]
Simons 1996	3.6	19.6	103	7	25.1	103	25.8%	-0.15 [-0.42, 0.12]
Westman 1999	1.3	4.5	128	-3.9	2.2	127	25.8%	1.46 [1.19, 1.74]
Subtotal (95% CI)			317			316	100.0%	**-0.49 [-1.74, 0.75]**
Heterogeneity: Tau² = 1.55; Chi² = 146.81, df = 3 (P < 0.000 01), I² = 98%								
Test for overall effect: Z = 0.78 (P = 0.44)								
3.1.2 Megestrol acetate alone								
Bruera 1998	-0.4	1.5	65	0.3	2.1	65	34.0%	-0.38 [-0.73, -0.03]
De Conno 1998	-2	3	21	5	0.1	21	31.8%	-3.24 [-4.18, -2.29]
Westman 1999	1.3	4.5	128	-3.9	2.2	127	34.2%	1.46 [1.19, 1.74]
Subtotal (95% CI)			214			213	100.0%	**-0.66 [-2.60, 1.28]**
Heterogeneity: Tau² = 2.85; Chi² = 130.94, df = 2 (P < 0.000 01), I² = 98%								
Test for overall effect: Z = 0.67 (P = 0.51)								



- This indicated no difference between progestational steroids and placebo for the treatment of CRF.

Cochrane Database Syst Rev. 2010 Jul 7;(7):CD006704

- Pain improvement by methylprednisolone.

The Oncologist, 2007

L-carnitine on CRF

Timing	Mean FACT-F (s.d.)		Mean Hb g dL^{-1} (s.d.)	
Baseline	19.7 (±6.4)		13.6 (±0.6)	
		$P<0.001$		$P>0.05$
After 1 week	34.9 (±5.4)		13.4 (±0.5)	
		$P>0.05$		$P>0.05$
After 2 weeks	35.7 (±5.5)		13.0 (±0.3)	
		$P>0.05$		$P>0.05$
After 3 weeks	36.5 (±5.1)		13.2 (±0.5)	

- Oral levocarnitine 4 g daily, for 7 days
- Levocarnitine supplementation may be effective in alleviating chemotherapy-induced fatigue
- This compound deserves further investigations in a randomised, placebo-controlled study

Br J Cancer, 2002

Guarana (Paullinia cupana) improves Fatigue in Breast Cancer Patients undergoing C/T

TABLE 2. COMPARISONS OF QUESTIONNAIRE SCORES WITHIN EACH GROUP

	Day	*Placebo–guarana*[a] ± *SD* (n)	p-*Value*	*Guarana-placebo*[b] ± *SD* (n)	p-*Value*
Primary outcome					
FACIT-F global score	1	93.5 ± 22.4 (43)	<0.01	93.3 ± 25.5 (32)	0.09
	21	85.4 ± 22.1 (43)		108.7 ± 26.1 (32)	
	49	110.2 ± 20.9 (35)		92.9 ± 22.6 (25)	
Secondary outcomes					
FACT-ES global score	1	115.6 ± 26.2 (43)	<0.01	111.3 ± 26.5 (32)	0.18
	21	105.5 ± 22.9 (43)		123.2 ± 31.0 (32)	
	49	131.3 ± 26.5 (35)		112.3 ± 27.0 (25)	
Pittsburg Sleep Quality Index	1	8.1 ± 3.6 (43)	0.18	8.7 ± 4.5 (32)	0.04
	21	8.9 ± 3.5 (43)		7.7 ± 3.6 (32)	
	49	7.4 ± 3.0 (35)		9.0 ± 2.6 (25)	
Chalder global score	1	12.2 ± 7.3 (43)	0.06	11.2 ± 7.9 (32)	<0.01
	21	15.9 ± 7.3 (43)		10.2 ± 7.3 (32)	
	49	11.9 ± 6.1 (35)		16.5 ± 6.7 (25)	

[a]The placebo–guarana group received placebo during the first phase and guarana after the crossover.
[b]The guarana–placebo group received guarana during the first phase and placebo after the crossover.
SD, standard deviation; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-ES, Functional Assessment of Chronic Illness Therapy–Endocrine Symptoms.

- Guarana 50 mg by mouth twice daily for 21 days
- Guarana is an effective, inexpensive, and nontoxic alternative for the short-term treatment of fatigue in BC patients receiving systemic chemotherapy fatigue.

Alternative and Complementary Medicine. June 2011, 17(6): 505-512.

PG2 Injection

- **An IV injectable extracted from *Astragalus membranaceus* (黃耆)**

  - Polysaccharide of *Astragalus membranaceus*

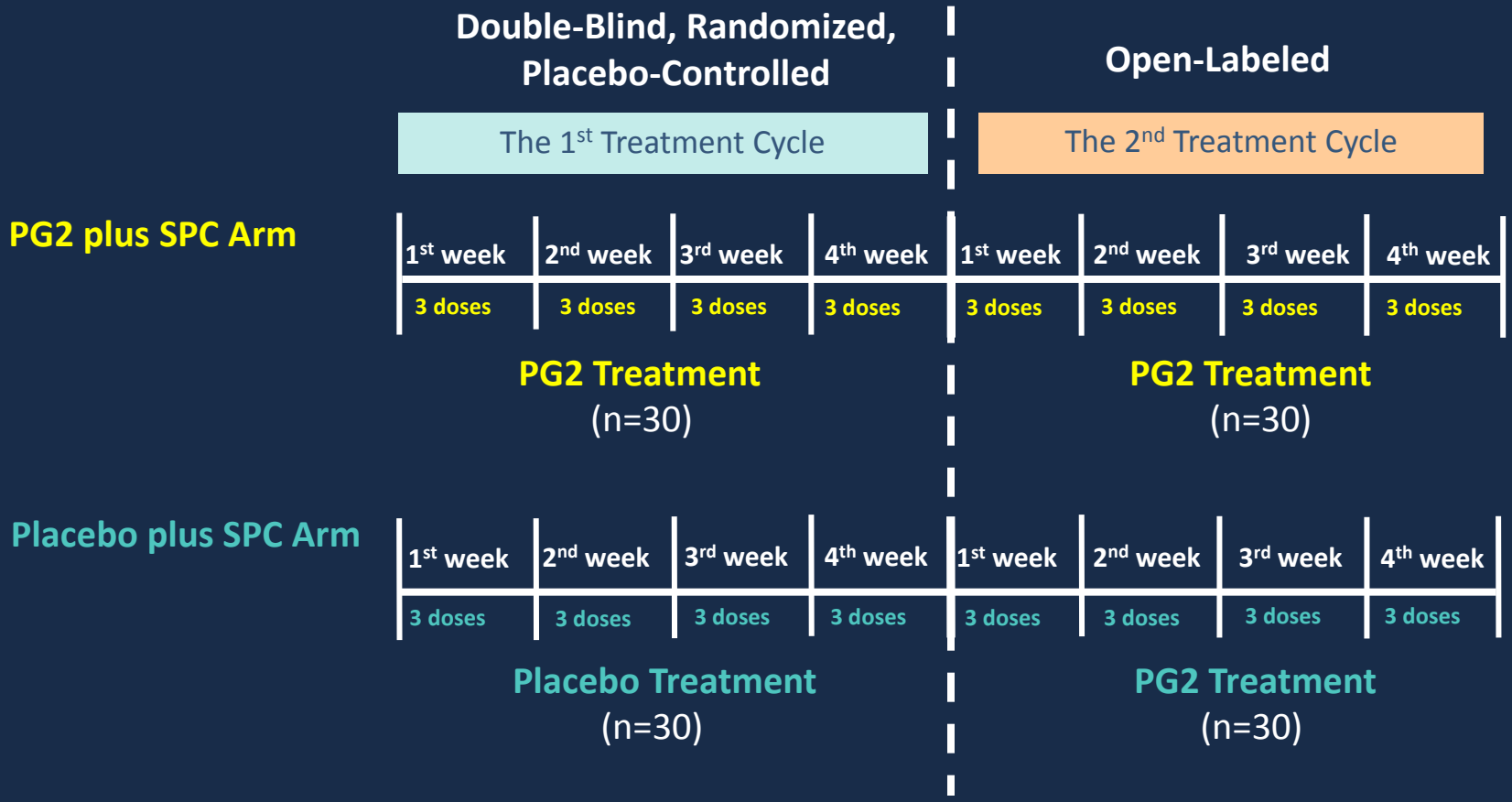
  - *One of the most popular TCM, and is said to benefit the deficiency of qi (vital energy) of the spleen that symptomatically presents with fatigue, diarrhea, and lack of appetite*

- **Indication:**

  Relieving moderate to severe cancer-related fatigue among advanced patients

- **The first NDA approved botanical new drug in Taiwan**

PG2 Pivotal study for CRF (I)

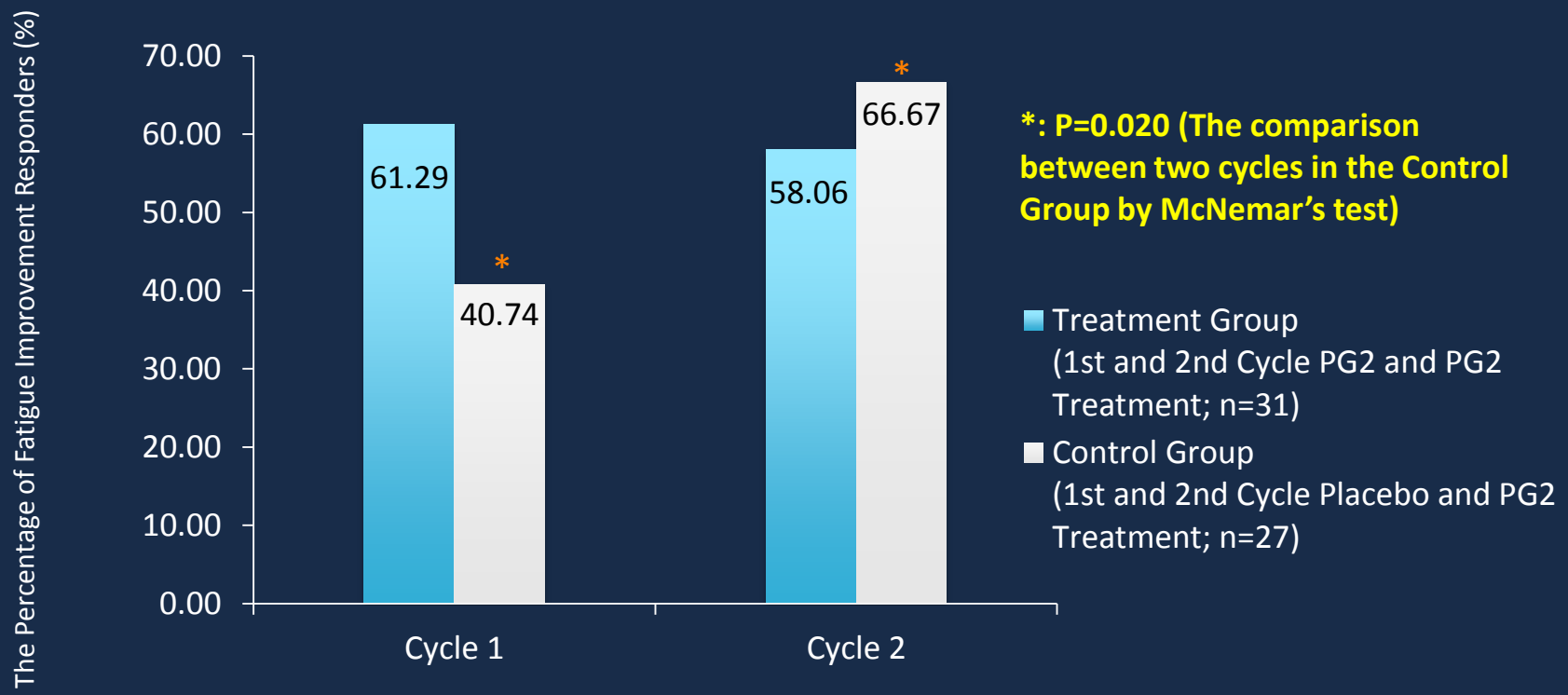


Population

- Advanced progressive cancer patients
- Under standard palliative care (SPC) at hospice setting
- Have no further curative options available

PG2 Pivotal study for CRF (II)

The Fatigue Improvment Rate Between Cydes in PP Population (Baseline: Visit 1 of Cyde 1)



- PG2 treatment significantly improved fatigue among cancer patients when compared with placebo treatment.
- The **improvement** of the fatigue status for the Treatment Group sustained for 8 weeks.

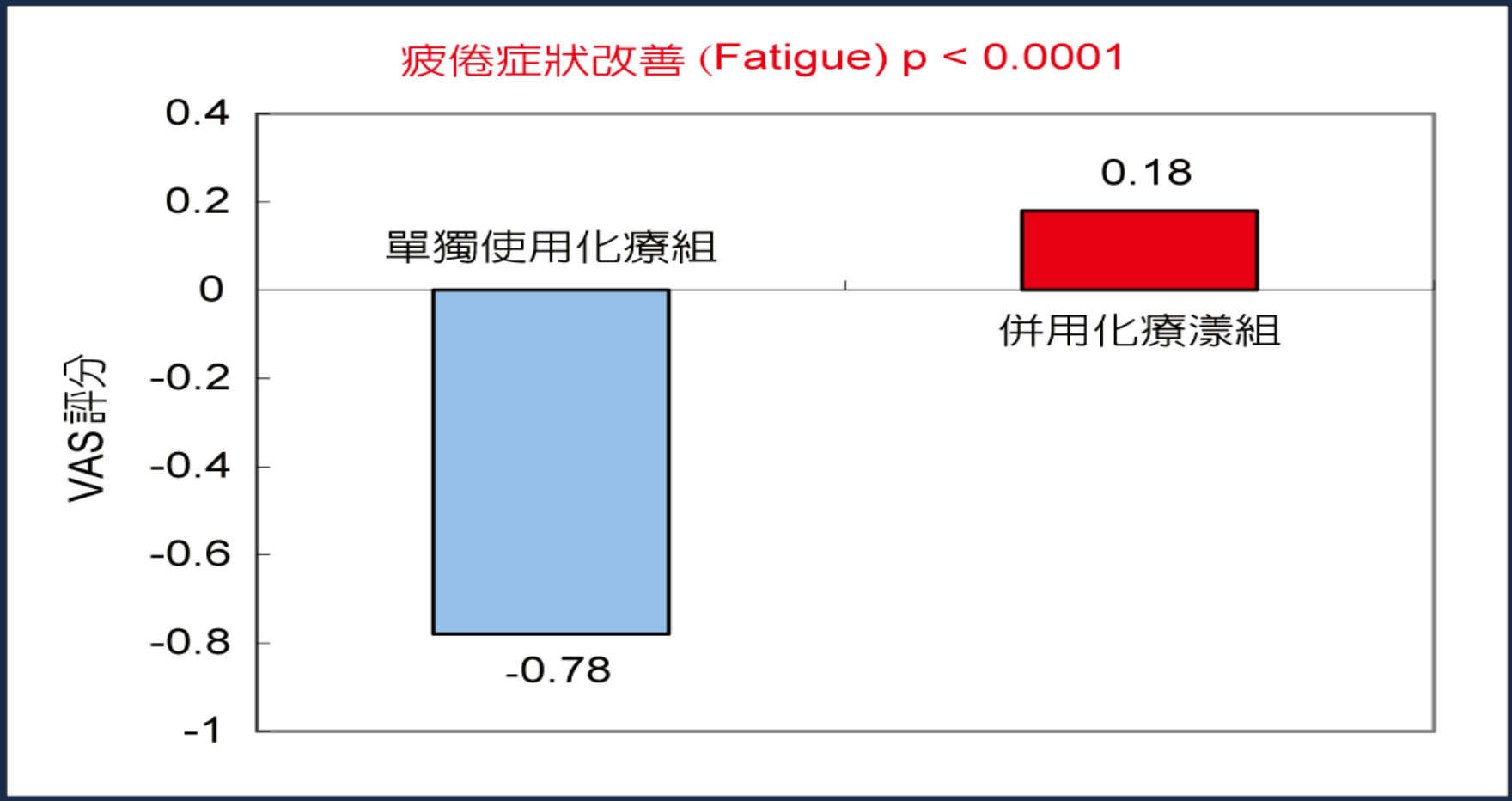
中天生技 化療漾

本藥品為利用微生物共生發酵有機非基改大豆後之代謝物質，經濃縮後製成，呈黑褐色液態。

癌症病人在接受化學藥物治療時，每日早、晚各服用一次，每次 4 c.c. 溫水稀釋後空腹服用。

化療漾核定適應症(一)

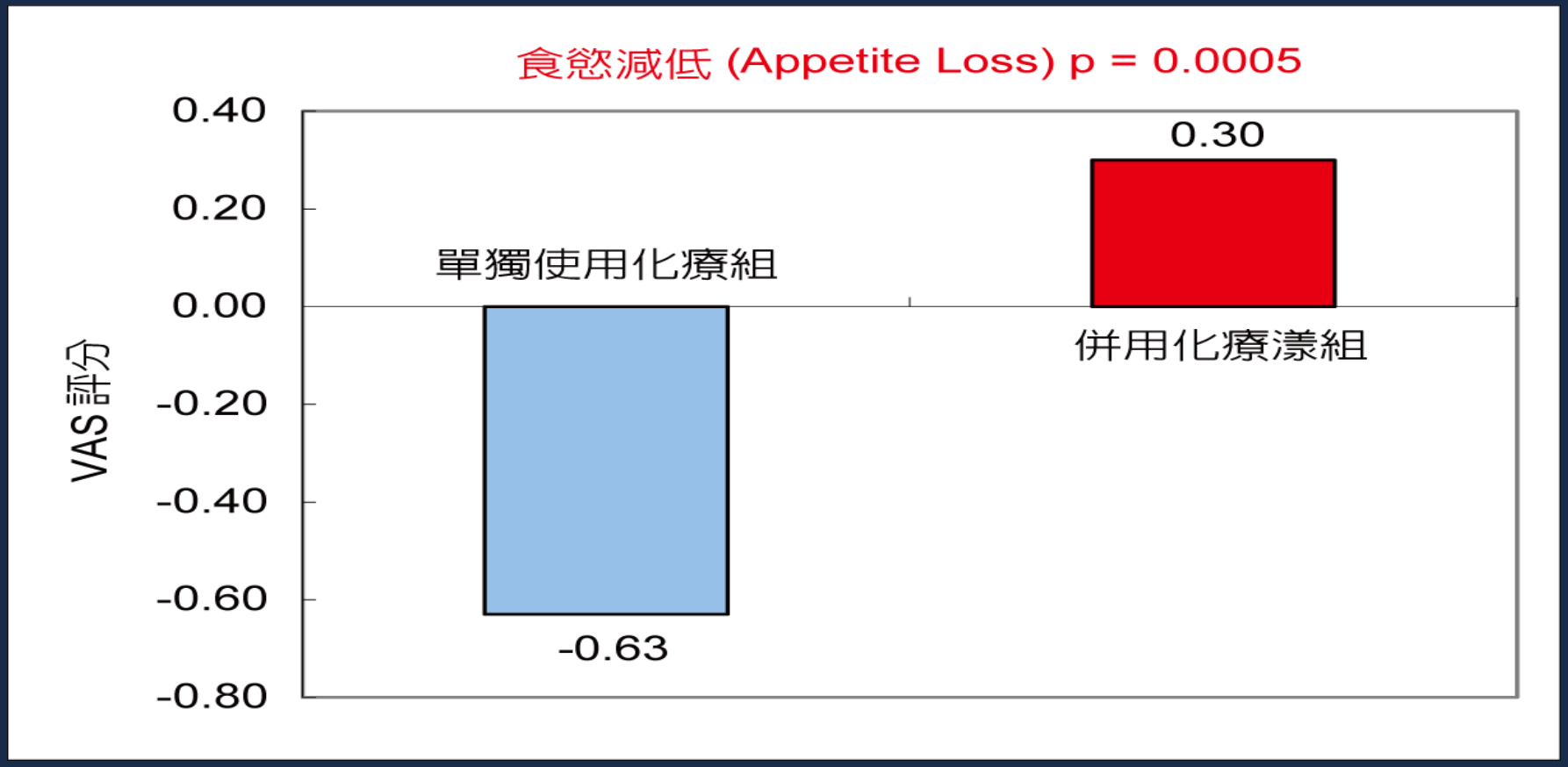
1、可顯著改善因化療造成之疲倦症狀



本試驗是以視覺模擬評分法(Visual Analogue Scale; VAS)針對癌症病患進行評估

化療漾核定適應症(二)

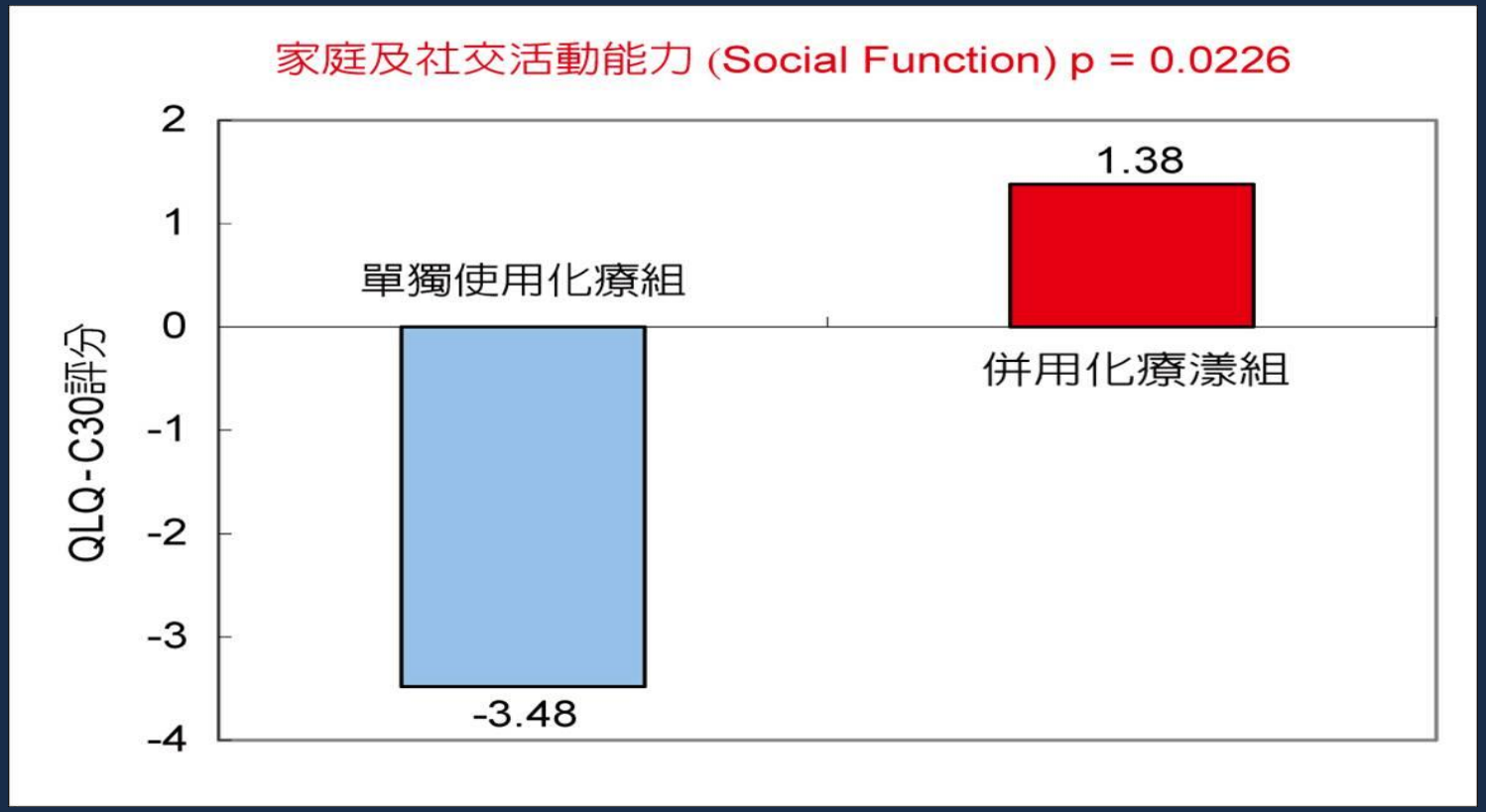
2、可顯著改善因化療造成之食慾不振



本試驗是以視覺模擬評分法(Visual Analogue Scale; VAS)針對癌症病患進行評估

化療漾核定適應症(三)

可顯著維持病患家庭及社交活動能力



本試驗是以癌症患者生活品質測定量表(EORTC QLQ-C30)，針對癌症病患於各項日常生活中，進行家庭與社交活動狀況做評估。

Therapeutic efficacy of traditional Chinese medicine, Shen-Mai San, in cancer patients undergoing chemotherapy or radiotherapy: study protocol for a randomized, double-blind, placebo-controlled trial

Trials 2012, ***13:232***

Acupuncture for cancer- related fatigue: a systemic review of randomized clinical trials

- The aim of the current SR was to critically evaluate the effectiveness of AT/EA for the treatment of CRF. Only seven RCTs were found: four of them favored AT in relieving CRF, whereas the remaining three showed no effect.
- The evidence from RCTs of AT for treating CRF is, thus, ambiguous and inconclusive.

Support Care Cancer 2013 Feb.

A Systematic Review of Complementary and Alternative Medicine Interventions for the Management of Cancer-Related Fatigue

Integrative Cancer Therapies
2013, XX(X) 1–15

Abstract

- Twenty studies were eligible for the review, of which 15 were RCTs.
- Forms of CAM interventions examined included acupuncture, massage, yoga, and relaxation training.
- The review identified some limited evidence suggesting hypnosis and ginseng may prevent rises in cancer-related fatigue in people undergoing treatment for cancer and acupuncture and that biofield healing may reduce cancer-related fatigue following cancer treatments.
- Evidence to date suggests that multivitamins are ineffective at reducing cancer-related fatigue.

Abstract

- However, trials incorporated within the review varied greatly in quality; most were methodologically weak and at high risk of bias.
- Consequently, there is currently insufficient evidence to conclude with certainty the effectiveness or otherwise of CAM in reducing cancer-related fatigue.
- The design and methods employed in future trials of CAM should be more rigorous; increasing the strength of evidence should be a priority.

Conclusion

- Current therapeutic options include the assessment and treatment of any underlying causes
- Several non-pharmacological and pharmacologic approaches have the potential to provide relief for patients suffering from CRF
- The non-pharmacological treatment shows to be promising with measures such as cognitive-behavioral therapies (ECAM), physical exercises and maybe sleep therapies.

Conclusion

- The pharmacological treatment has shown promising results that include the use of psycho-stimulants such as methylphenidate and dexmethylphenidate, modanafil (in patients with severe fatigue), 植物新藥 in advanced cancer patients and ESA in patients with CT-related anemia and hemoglobin < 10 mg/dL.

Thank you!