Managing fatigue during cancer therapy

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Overview

- NCCN guidelines
- Psycho-social interventions
- Exercise
- Drug treatment
- Conclusions

Prevalence

- Fatigue affects 39% 90% of patients undergoing...
 - Surgery
 - Chemotherapy
 - Radiotherapy
 - Hormone therapy
 - Biological therapies

NCCN recommendations

- Screen using NRS (>3)
- Assess for treatable contributing factors
 - Pain, emotional distress, anaemia, insomnia, nutritional assessment, activity level, medication sideeffects, co-morbidities
- Patient /family education, general strategies
- Activity enhancement and/or psychological interventions
- Drug treatment

Psycho-social interventions

- At least three systematic reviews
 - Jacobsen 2007, Kangas 2008, Goedendorp 2009

Systematic reviews

 Goedendorp MM et al. Psychosocial interventions for reducing fatigue during cancer treatment in adults. Cochrane database of systematic reviews 2009; Issue 1

Goedendorp MM et al.

- RCTs
- Patients on treatment
- Types of interventions
 - Psychotherapy, psycho-education, cognitive restructuring, coping strategies, behavioural therapies, self-help, support groups, relaxation, energy conservation, stress management...
- Outcomes
 - Fatigue

Results

- On-going studies (n = 8)
 - Yoga, group education and support, self-help for insomnia, mindfulness relaxation, music relaxation, CBT and nursing intervention
- Included 29 publications (27 studies)
- Participants
 - Mostly breast cancer, mostly on-treatment
- Format of intervention
 - Extremely heterogeneous
 - Only 5 studies specifically focused on fatigue

Results

- Seven studies reported a significant effect of the intervention
 - Effect sizes varied between 0.17 to 1.07
- 20 studies reported no significant effect on fatigue
- Interventions specific for fatigue
 - 4/5 (80%) positive
- Interventions not specific for fatigue
 - -3/22 (14%) positive

Nature of fatigue specific interventions

- Brief
 - Three individual sessions (10-60 mins)
- Content
 - Education about fatigue
 - Taught self-care or coping techniques
 - Taught activity management
 - (emotional support)
- Administered
 - Trained oncology nurses

Exercise treatment

- At least 10 systematic reviews and metaanalyses!
 - Stevinson 2004, Schmitz 2005, Knols 2005, Conn 2006, McNeeley 2006, Markes 2006, Luctkar-Flude 2007, Jacobsen 2007, Cramp 2008, Kangas 2008
- New primary studies occurring all the time
 - Segal et al JCO 2009; 27:344 351
 - Prostate cancer, RT ± anti-androgren therapy
 - Usual care, resistance, aerobic exercise
 - Both forms of exercise beneficial

Exercise is effective

- Cramp F and Daniel J Cochrane Database of Systematic Reviews 2008, Issue 2
 - Patients on treatment, after treatment or receiving palliative care
 - Randomised controlled trials only (usual care, no treatment, alternative treatment)

Outcomes

- Fatigue
- Exercise maintenance and attrition
- Time spent exercising
- Aerobic capacity
- Quality of life
- Anxiety and depression
- Self-efficacy

Comparison 1. Fatigue: All data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise versus no exercise control. Post test means.	30	1662	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.33, -0.13]
2 Exercise versus no exercise control. Change data.	11	853	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.36, -0.09]

Comparison 2. Fatigue: Breast cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
1 Exercise versus No intervention control. Post test means.	18	977	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.49, -0.23]	

Comparison 3. Fatigue: During anti-cancer therapy

Outcome or subgroup title	studies participants	Statistical method	Effect size	
1 Exercise versus no exercise control. Post test means	15	929	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.32, -0.05]

Exercise is effective, but...

- More research is needed to identify...
 - Optimal type
 - Intensity
 - Timing
- More work needed...
 - To assess multi-modal approaches
- Improved methodology needed, including better...
 - Participant selection criteria
 - Concealment of allocation and blinding of assessors
 - Outcome endpoints
 - Inclusion of longer term follow-up assessments

Drug treatment

 Minton et al J Natl Cancer Inst 2008; 100: 1155 - 1166

Erythropoietin (SMD = -0.3)

Review: Drug therapy for the management of cancer related fatigue

Comparison: 01 Erythropoetin versus no intervention (subanalysis versus placebo)

Outcome: 01 Difference in fatigue score

Study	160	Erythropoetin		Control	SMD (random)		
or sub-category	N	Mean (SD)	N	Mean (SD)	95% CI		
01 All Trials					100		
Littlewood 2001	251	-3.30(13.20)	124	1.60(12.70)			
Osterborg 2002	170	-5.20(12.20)	173	-3.00(12.10)			
Boogaerts 2003	133	-5.50(13.83)	129	-1.25(9.08)	S =		
Glossmann 2003	22	18.90(18.10)	14	39.40(18.10)	——		
Iconomou 2003	57	-4.60(12.50)	55	1.00(12.80)	V		
Chang 2005	175	-1.85(10.52)	175	3.55(11.40)			
O'Shaughnessy 2005	47	3.00(11.90)	47	9.40(13.80)	10 mm		
Savonije 2005	211	-3.48(12.67)	104	1.67(11.61)			
Witzig 2005	154	3.00(23.22)	151	10.60(22.08)			
Wright 2007	14	-4.50(14.80)	20	-2.55(13.80)	77 2		
Subtotal (95% CI)	1234		992		•		
Test for heterogeneity: Chi2 =	9.48, df = 9 (P	= 0.39), I ² = 5.0%			2269		
Test for overall effect: Z = 8.	32 (P < 0.0000°	1)					

Darbepoetin (SMD = -0.13)

	Dar	bepoet	in	C	Control			Std. Mean Difference	Std. Mean Di	fference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random	, 95% CI
All Trials			\$							
Hedenus 2003	-3.33	17.38	176	-1.1	17.23	173	40.2%	-0.13 [-0.34, 0.08]		
Kotasek 2003	-3.4	12.6	189	-2.3	11.6	50	18.2%	-0.09 [-0.40, 0.22]		
Smith 2003	-4.15	12.35	46	-0.25	13.95	16	5.4%	-0.30 [-0.87, 0.27]		*******
Vansteenkiste 2002	-0.8	10	156	0.6	10.7	158	36.1%	-0.13 [-0.36, 0.09]	-	
Total (95% CI)			567			397	100.0%	-0.13 [-0.27, 0.00]		
Heterogeneity: Tau ² =	0.00° CF	$ni^2 = 0.4$	2000	3 (P = 0	94)- 12		160			——
Test for overall effect:				- (, -)		V /0			-1 -0.5 0 Favors treatment	0.5 Favors control

Berenstein 2009

Review: Megestrol acetate for treatment of anorexia-cachexia syndrome

Comparison: I Megestrol acetate vs placebo (ITT)

Outcome: I Appetite improvement

Study or subgroup	Megestrol acetate	placebo		Risk Ratio	Weight	Risk Ratio
	n/N	n/N	1	M-H,Random,95% Cl		M-H,Random,95% CI
I Cancer						
Batterham 2001	0/1	0/1	•		0.0 %	0.0 [0.0, 0.0]
Erkurt 2000	55/58	7/57			13.7 %	7.72 [3.85, 15.49]
Feliu 1992	30/76	8/74			13.5 %	3.65 [1.79, 7.44]
Gebbia 1996	0/1	0/1	*	*	0.0 %	0.0 [0.0, 0.0]
Lai 1994	11/20	4/19			11.2 %	2.61 [1.00, 6.80]
Loprinzi 1990b	24/67	16/66		-	15.3 %	1.48 [0.87, 2.52]
Schmoll 1992	37/63	6/28			13.3 %	2.74 [1.31, 5.74]
Zeca 1995	13/16	5/17			12.9 %	2.76 [1.28, 5.99]
Subtotal (95% CI)	302	263		-	79.9 %	3.03 [1.83, 5.01]
Total events: 170 (Megestrol	acetate), 46 (placebo)			12		
Heterogeneity: $Tau^2 = 0.26$;	$Chi^2 = 14.78$, $df = 5$ (P = 0.0	I); I ² =66%				
Test for overall effect: $Z = 4$.	30 (P = 0.000017)					
4						

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours placebo Favours MA

Berenstein 2009

Review: Megestrol acetate for treatment of anorexia-cachexia syndrome

Comparison: I Megestrol acetate vs placebo (ITT)

Outcome: 2 Weight gain

Megestrol acetat	Megestrol acetate Placebo			М	Mean Difference			
N	Mean(SD)	Mean(SD)		Mean(SD) IV,Random,95% CI			IV,Random,95% CI	
4	3 -1.71 (4.56)	40	-3.99 (5.52)		-	8.8 %	2.28 [0.14, 4.42]	
2	1.06 (1.95)	21	-0.34 (1.01)			11.6 %	1.40 [0.46, 2.34]	
5:	5 (6)	57	-5.9 (7)			→ 8.3 %	10.90 [8.52, 13.28]	
3	-0.8 (3.6)	32	-3.2 (3.2)			10.0 %	2.40 [0.73, 4.07]	
6	7 1.36 (4.99)	66	-0.22 (3.01)			10.7 %	1.58 [0.18, 2.98]	
2!	3 -1.22 (6.25)	29	-4.8 (4.8)			7.1 %	3.58 [0.68, 6.48]	
9; $Chi^2 = 55.13$, df		245 ; 1 ² =91%			•	56.5 %	3.56 [1.27, 5.85]	
3.03 (F - 0.0023)								
	N 48 2 58 32 65 28 254	N Mean(SD) 48 -1.71 (4.56) 21 1.06 (1.95) 58 5 (6) 32 -0.8 (3.6) 67 1.36 (4.99) 28 -1.22 (6.25) 254 9; Chi ² = 55.13, df = 5 (P<0.00001)	N Mean(SD) N 48 -1.71 (4.56) 40 21 1.06 (1.95) 21 58 5 (6) 57 32 -0.8 (3.6) 32 67 1.36 (4.99) 66 28 -1.22 (6.25) 29 254 245 9; Chi² = 55.13, df = 5 (P<0.00001); l² = 91%	N Mean(SD) N Mean(SD) 48 -1.71 (4.56) 40 -3.99 (5.52) 21 1.06 (1.95) 21 -0.34 (1.01) 58 5 (6) 57 -5.9 (7) 32 -0.8 (3.6) 32 -3.2 (3.2) 67 1.36 (4.99) 66 -0.22 (3.01) 28 -1.22 (6.25) 29 -4.8 (4.8) 254 245 9; Chi² = 55.13, df = 5 (P<0.00001); l² = 91%	N Mean(SD) N Mean(SD) IV,Rar 48 -1.71 (4.56) 40 -3.99 (5.52) 21 1.06 (1.95) 21 -0.34 (1.01) 58 5 (6) 57 -5.9 (7) 32 -0.8 (3.6) 32 -3.2 (3.2) 67 1.36 (4.99) 66 -0.22 (3.01) 28 -1.22 (6.25) 29 -4.8 (4.8) 254 245 9; Chi² = 55.13, df = 5 (P<0.00001); l² = 91%	N Mean(SD) N Mean(SD) IV,Random,95% CI 48 -1.71 (4.56) 40 -3.99 (5.52) 21 1.06 (1.95) 21 -0.34 (1.01) 58 5 (6) 57 -5.9 (7) 32 -0.8 (3.6) 32 -3.2 (3.2) 67 1.36 (4.99) 66 -0.22 (3.01) 28 -1.22 (6.25) 29 -4.8 (4.8) 254 245 9; Chi² = 55.13, df = 5 (P<0.00001); l² = 91%	N Mean(SD) N Mean(SD) IV,Random,95% CI 48 -1.71 (4.56) 40 -3.99 (5.52) 21 1.06 (1.95) 21 -0.34 (1.01) 58 5 (6) 57 -5.9 (7) 32 -0.8 (3.6) 32 -3.2 (3.2) 67 1.36 (4.99) 66 -0.22 (3.01) 28 -1.22 (6.25) 29 -4.8 (4.8) 254 245 9; Chi² = 55.13, df = 5 (P<0.00001); l² = 91%	

Progestational steroids

Study	Pr	ogestional steroid		Placebo		SI	MD (randor	m)	
or sub-category	N	Mean (SD)	N	Mean (SD)		95% CI		8.429	
01 Sub-category							10		
Simons 1996	103	3.60(19.60)	103	7.00(25.10)			-		
Bruera 1998	65	-0.40(1.50)	65	0.30(2.10)			-		
De Conno 1998	21	-2.00(3.00)	21	5.00(0.10)	4 =	-			
Westman 1999	128	1.30(4.50)	127	-3.90(2.20)				-	
Subtotal (95% CI)	317		316						
Test for heterogeneity: Ch	i ² = 146.61, df = 3	(P < 0.00001), P = 98.0%					Andrew Coloreda Color		
Test for overall effect: Z =	0.78 (P = 0.44)								
02 Megestrol acetate alone	9								
Bruera 1998	65	-0.40(1.50)	65	0.30(2.10)			-		
De Conno 1998	21	-2.00(3.00)	21	5.00(0.10)	4 =				
Westman 1999	128	1.30(4.50)	127	-3.90(2.20)				er a a	
Subtotal (95% CI)	214		213					3.5	
Test for heterogeneity: Ch	i ² = 130.94, df = 2	(P < 0.00001), F = 98.5%							
Test for overall effect: Z =	0.67 (P = 0.51)	THE ACCOUNT SHIPS			28	8		23	52
	177 741				-4	-2	0	2	4
					Favo	ours treatm	ent Fav	rours contr	rol

Anti-depressants

Review: Drug therapy for the management of cancer related fatigue

Comparison: 04 Antidepressants versus placebo

Outcome: 01 Fatigue score change

Study		ntidepressant Placebo			lom)				
or sub-category	N	Mean (SD)	N	Mean (SD)			95% C	Control of the Contro	
Morrow 2003	277	-4.80(21.30)	272	-3.40(20.30)					
Roscoe 2005	44	-5.00(6.60)	50	-2.50(17.80)		<u> </u>	•	<u>()</u> ;	
Total (95% CI)	321		322			£	-		
Test for heterogeneity: Ch	$hi^2 = 0.25$, $df = 1$ (F	9 = 0.61), I ² = 0%					200		
Test for overall effect: Z									
					-1	-0.5	0	0.5	1
					Fav	ours treatm	ent F	avours contr	ol

Psychostimulants (SMD = -0.3)

Review: Drug therapy for the management of cancer related fatigue

Comparison: 05 Psychostimulants versus placebo

Outcome: 01 Fatigue score change

Study		Psychostimulant		Placebo		SMD (random)				
or sub-category	N	Mean (SD)	N	Mean (SD)		95% CI				
Fleishman 2005	75	-11.80(12.60)	77	-7.10(12.60)			- 19			
Bruera 2006	56	-9.60(9.80)	56	-7.50(11.30)		3/2				
Total (95% CI)	131		133			-			10	
Test for heterogeneity: Ch	ni2 = 0.48, df = 1 (P = 0.49), I ² = 0%				₹ (\$7)				
Test for overall effect: Z =										
					-1	-0.5	0	0.5	1	
					Fav	ours treatm	ent Fa	vours contr	ol	

Drug treatment

- Minton et al 2008
 - Ibandronate
 - Etanercept
- New studies
 - Donepezil (Bruera et al JCO 2007; 25: 3475 3481)
 - -N = 142, 1 week, RCT, no effect
- On-going studies
 - Modafanil

Conclusions

- Fatigue is a major problem for cancer patients from diagnosis through to long-term survivorship
- Exercise, psychological interventions and drugs have all been shown to be effective
- The specific effects of nutritional interventions on fatigue have not been adequately researched
- More work is required to assess effectiveness of individual interventions and to assess the role of multi-modal therapy