


# Sleep, Fatigue and Circadian Rhythms in Cancer

Sonia Ancoli-Israel, Ph.D.  
Professor Emeritus of Psychiatry  
Professor of Research  
Center for Circadian Biology  
University of California San Diego




1



SaFE - Light  
Sleep and Fatigue - Effect of Light

## Overview



Chem - brain  
SaFE - C  
Sleep and Fatigue - Effect of Chemotherapy

- Fatigue and sleep relationship
  - Before, during and after chemotherapy
- Effect of light treatment on sleep and fatigue
- Circadian activity rhythms during chemotherapy
- Changes in sleep/fatigue/circadian rhythms over time
- (Sleep, fatigue, circadian rhythms and cognition)

2

## Cancer-Related Fatigue

- Fatigue is one of the most frequent complaints of cancer patients
  - >75% undergoing chemotherapy or radiation therapy report feeling tired and weak
  - Symptom about which they express most concern



Richardson European J Cancer Care 1995, 4:20-32; Smets et al. Brit J Cancer 1996, 73:241-245; Stein et al., Cancer Practice 1988, 6:143-152; Winningham et al., ; Oncology Nursing Forum 1994, 21:23-36

3

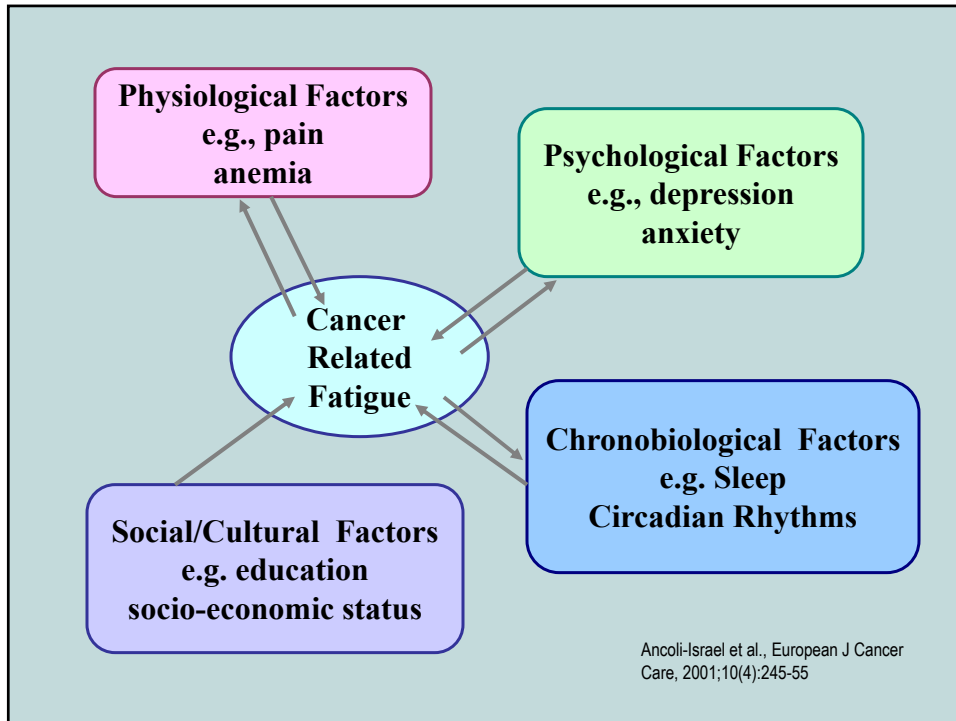
## Cancer-Related Fatigue

- *Cancer-related fatigue is a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning.*
  - Differs from fatigue of everyday life
    - Temporary and relieved by rest
  - More severe, more distressing, not relieved by rest

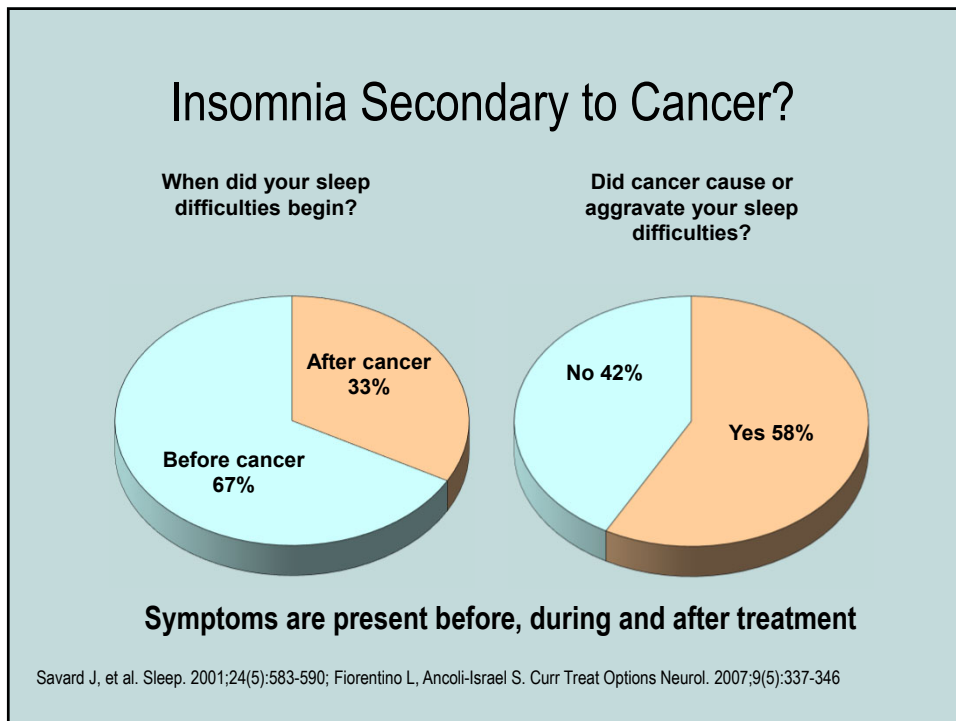


Mock et al, Oncology 2000; 14:151-161; Mock et al.  
[http://www.nccn.org/professionals/physician\\_gls/PDF/fatigue.pdf](http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf); accessed April 9, 2007

4



5



6

## Night and Day Actigraphy Studies at Baseline (n=86)

	Mean	SD	range
<u>NIGHT:</u> Total Sleep Time (hrs)	6.3	1.4	2.4-9.6
% sleep	74.6%	14%	26-97%
Wake After Sleep Onset (hrs)	2.2	1.3	0.24-7.1
<u>DAY:</u> Total nap time (hrs)	1.6	1.4	0.04-8.7
% sleep during day	10%	9%	0-59%
Mean duration of naps (min)	7.7	4.1	1.6-26.9

Ancoli-Israel et al. Supportive Care in Cancer, 2006,14: 201-209

8

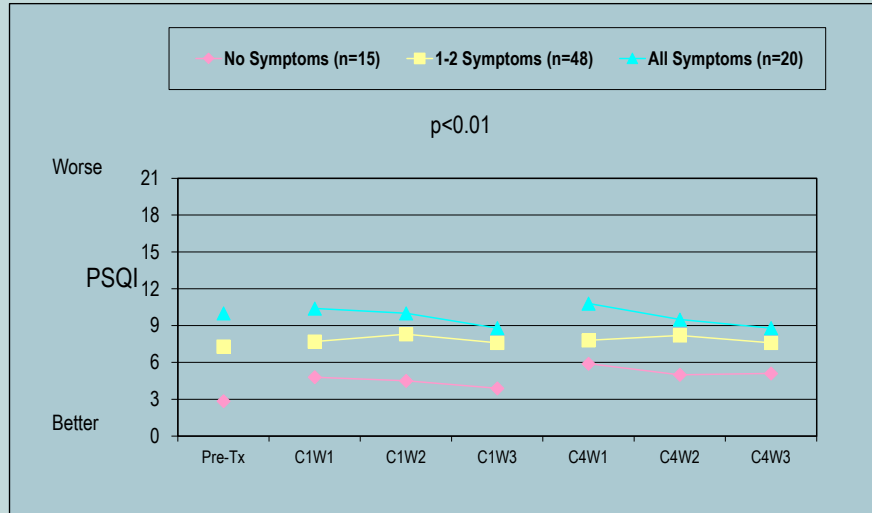
## Relationship between Pre-Treatment Symptoms and Symptoms during Treatment

- 3 groups were formed based on
  - Sleep quality (PSQI)
  - Fatigue (MFSI-SF)
  - Depression (CES-D)
- All symptoms got *significantly worse during chemotherapy* (all  $p < 0.01$ )
- Group with all 3 symptoms pre-chemotherapy had *significantly worse symptoms during chemotherapy*

Liu, L., et al. *Psycho-oncology* 2009, 18(2):187-94

11

## Poor Sleep, Fatigue and Depression Pre-Chemotherapy ⇒ Poor Sleep during Treatment



Liu, L., et al. *Psycho-oncology* 2009, 18(2):187-94

12

## Circadian Activity Rhythms

- Prior cross-sectional studies have shown that cancer patients have sleep-wake activity cycles that show little distinction between daytime and nighttime, a pattern indicative of circadian disruption.
- One of our goals was to assess the longitudinal course of sleep-wake activity rhythms before and during chemotherapy for breast cancer.

Berger et al. *J Cancer Surviv* 2012 6(3):305-14; Berger et al, *Support Care Cancer* 2010 Jan;18(1):105-14; Savard, J., Liu, L., Natajaran, L., Neikrug, A.B., He, F., Dimsdale, J.E., Mills, P.J., Parker, B.A., Sadler, G.R., and Ancoli-Israel, S. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. *Sleep* 32:1155-1160, 2009.

14

## Circadian Activity Rhythms during Chemotherapy - Results

- Compared to baseline, all circadian activity rhythm variables (except acrophase), were significantly impaired on the first week of both chemotherapy cycles (C1, C4)
  - amplitude, mesor and rhythmicity
- During Cycle 1
  - Rhythm variables approached baseline values during W2 and W3
- During Cycle 4
  - most remained significantly more impaired during W2 and W3

Savard, J., Liu, L., Natajaran, L., Neikrug, A.B., He, F., Dimsdale, J.E., Mills, P.J., Parker, B.A., Sadler, G.R., and Ancoli-Israel, S. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. *Sleep* 32:1155-1160, 2009.

15

## Rhythmicity Over Time with Chemotherapy



N=95; For comparisons between each time point vs. baseline: \*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ ; \*\*\*\*  $p < .0001$

Savard, J. et al. *Sleep* 32:1155-1160, 2009.

16

## Circadian Rhythms during Chemotherapy

- These data suggest that
  - the first administration of chemotherapy is associated with transient circadian disruption
  - repeated administration of chemotherapy results in progressively worse and more enduring rhythm impairments.

Savard, J. et al. *Sleep* 32:1155-1160, 2009.

17

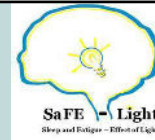
## Consequences of Disrupted Circadian Rhythms

- Increased risk of mortality
  - In older patients with dementia
  - In patients with metastatic colorectal cancer
  - In older men and older women
    - increased risk of CVD events
    - increased risk of cardiovascular disease-related mortality
    - higher all-cause mortality

Mormont MC, et al. *Clin. Cancer Res.* 2000, 6:3038–3045. Gehrman P, et al *J. Gerontol. A Biol. Sci. Med. Sci.*; 59:1050–1055; Tranah G et al, *JAGS*, 2010, 58:282-91; Paudel et al, *Chronobiology International*, 27(2): 363–377, (2010); Paudel et al, *Chronobiology International*, 2011

18

# Fatigue and Light

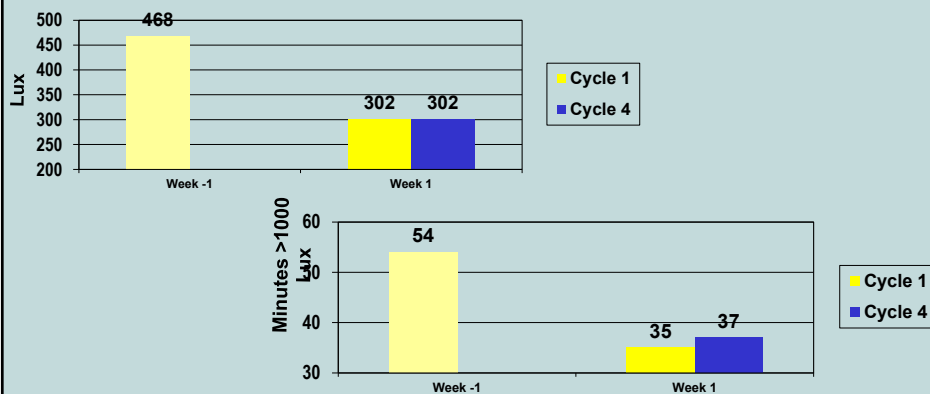
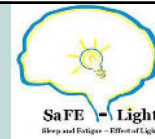


- Bright light has an alerting effect
- Bright light treatment has been shown to be effective for seasonal and non-seasonal depression, circadian disruption (delayed and advanced sleep phase syndromes, jet lag syndrome, and shift work syndrome)
- Fatigue has also been associated with these same disorders, but little is known about the association between bright light and fatigue.



19

## Daytime Light Exposure - Lux (n=85)



During treatment more fatigue ( $p < 0.01$ ) associated with lower light intensity & shorter duration of bright light exposure

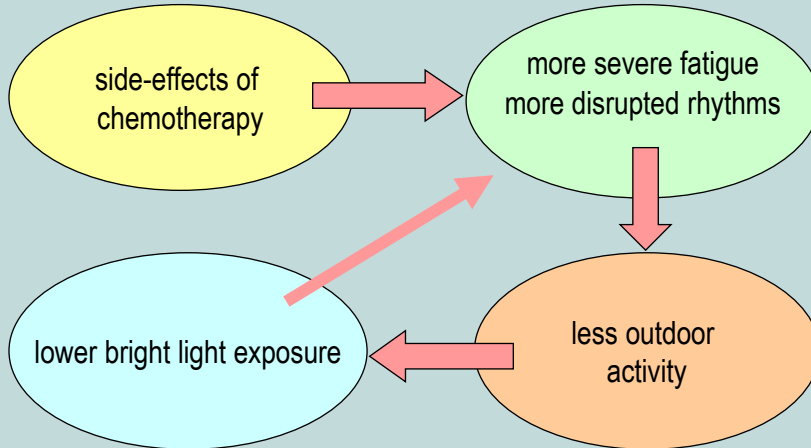
Negative correlation between change in fatigue and change in light exposure suggesting that **as amount of light decreased, amount of fatigue increased**

Liu et al. *Support. Care Cancer* 13(12):1010-1017, 2005

20



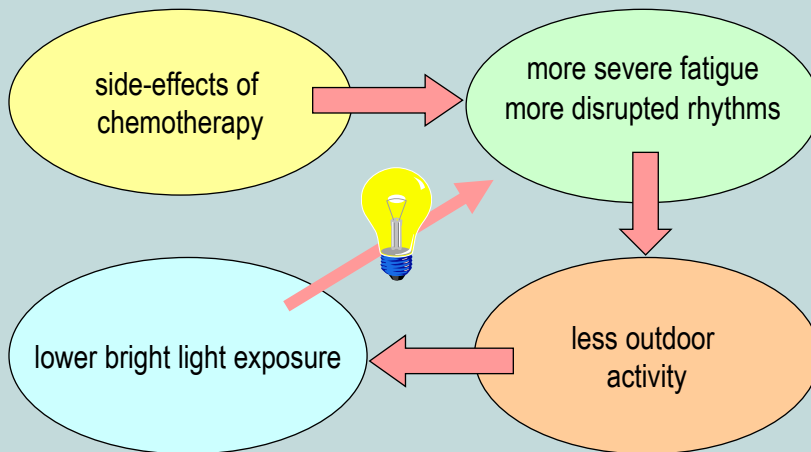
# Will Light Therapy Help? Negative feedback loop for light and fatigue



Ancoli-Israel et al. Support Care Cancer. 2011

21

# Light and Fatigue: Will light therapy break the loop?



Ancoli-Israel et al. Support Care Cancer. 2011

22

## Methods



- 40 women
  - mean age=53.4, SD=9.2, range=32-69 yrs
  - diagnosed with stage I–III breast cancer
  - scheduled to receive at least 4 cycles of chemotherapy
- Participants randomized into two treatment groups
  - bright white light (BWL; n=19)
  - dim red light (DRL; n=15)
- Treatment: sitting in front of the light box (Litebook, Ltd.) for 30 min each morning

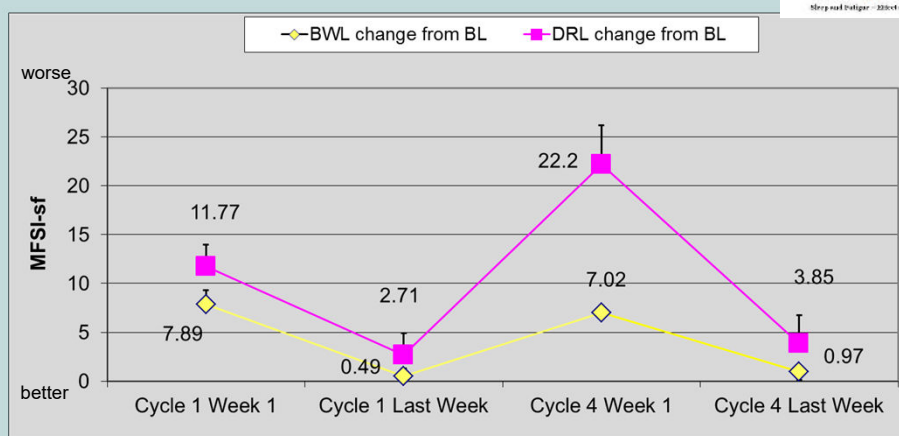
Permission obtained  
for photo



Ancoli-Israel et al. Support Care Cancer. 2011;  
Neikrug et al BSM 2012 2012;10(3):202-16;  
Jeste et al. Qual Life Res 2013;22(3):1239-44

23

## Change in Fatigue Scores from Pre-Treatment Baseline



DRL (n=16) group reported increased fatigue at C1 W1 ( $p=0.003$ ) and C4 W1 ( $p<0.001$ )

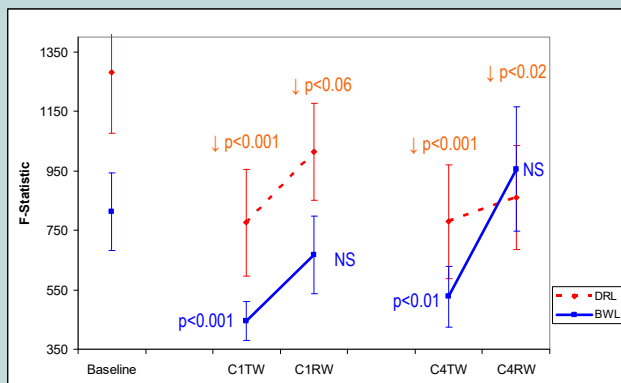
BWL (n=22) group reported no change in fatigue during the same time points

Group x Time Interaction: at C4W1 ( $p=0.021$ )

Ancoli-Israel et al. Support Care Cancer. 2011

24

## Light's Effect on Circadian Rhythms in Breast Cancer



- Both groups had worse circadian rhythms during chemotherapy.
- But the BWL group returned to baseline levels during the recovery weeks while the DRL did not, remaining disturbed

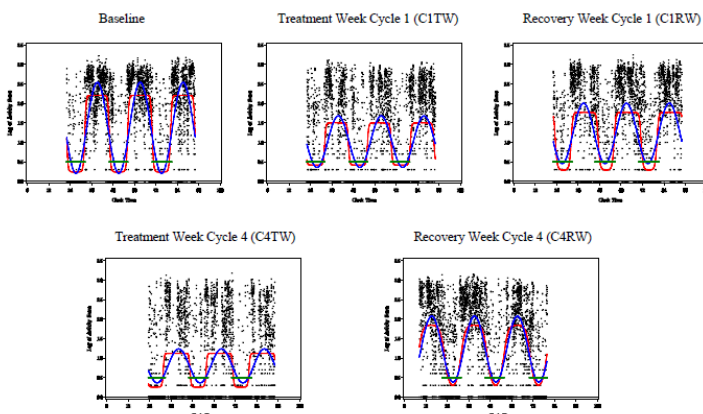
Neikrug et al BSM 2011 2012;10(3):202-16

25

## Circadian Rhythm of one DRL patient



Figure 2(a)

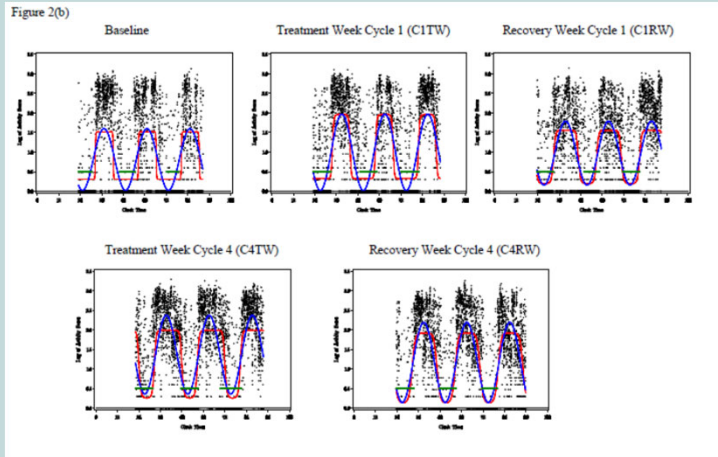


This DRL patient shows robust sleep-wake rhythm at baseline indicated by clear contrast between daytime and nighttime activity. The rhythm then became disrupted at C1TW and remained disrupted for the duration of chemotherapy, as indicated by lower amplitude and less contrast between bedtime and wake time

X-axis is clock time. Y-axis is log value.  
 Black dots = log of activity scores calculated by the actigraphy.  
 Blue line = best-fitting traditional cosine curve. Red line = extended cosine curve.  
 Green line = in-bed time.

26

# Circadian Rhythm of one BWL patient

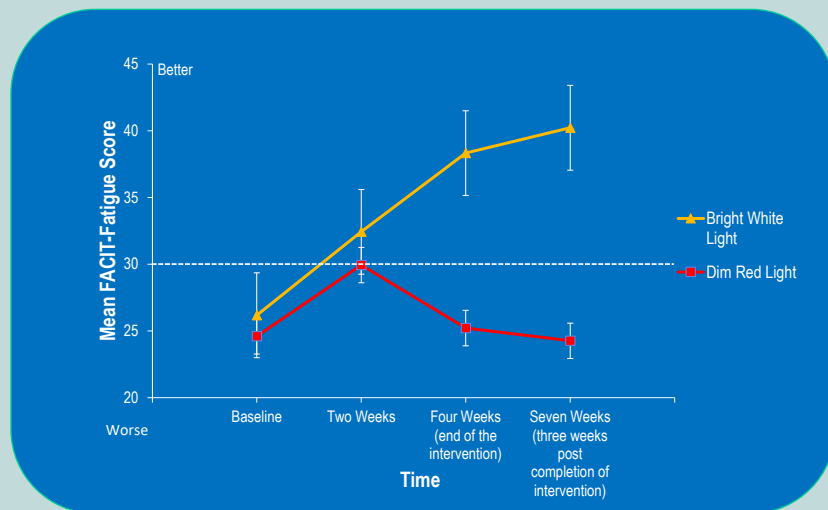


This BWL patient shows overall robust sleep-wake rhythm at baseline indicated by clear contrast between daytime and night time activity. This patient's rhythm remained overall stable and robust throughout chemotherapy.

X-axis is clock time. Y-axis is log value.  
 Black dots = log of activity scores calculated by the actigraphy.  
 Blue line = best-fitting traditional cosine curve. Red line = extended cosine curve.  
 Green line = in-bed time.

27

# Fatigue Scores over Time (mixed cancer survivors; n=31)



Redd et al, Psychooncology. 2014 Dec;23(12):1431-4.

28

# Light Therapy in Breast Cancer: Summary of Results

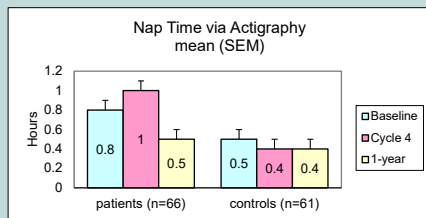


- Results suggest that bright white light prevents deterioration during chemotherapy and results in improvements in cancer survivors in:
  - Fatigue
  - Sleep
  - Mood
  - Quality of life
  - Circadian rhythm disruption

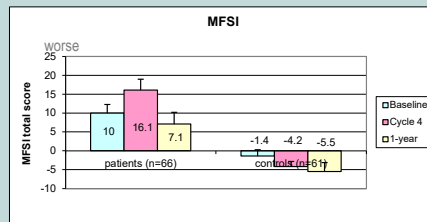
Ancoli-Israel et al. Support Care Cancer. 2011;  
Neikrug et al BSM 2012 2012;10(3):202-16;  
Jeste et al. Qual Life Res 2013;22(3):1239-44

29

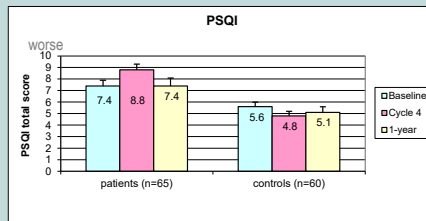
## Sleep/Fatigue/Circadian Rhythms Over Time (n=75; Breast cancer vs. Non-cancer)



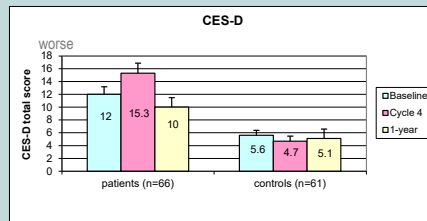
Within groups: Patients: BL-Y1 p=0.004; C4-Y1 p=0.001  
Between groups: Baseline p=0.006; Cycle 4 p=0.0002; Year one p=0.202



Within groups: Patients: BL-C4 p=0.011; C4-Y1 p=0.0004  
Between groups: Baseline p=0.0001; Cycle 4 p<0.0001; Year one p=0.002



Within groups: Patients: BL-C4 p=0.004; C4-Y1 p=0.013  
Between groups: Baseline p=0.004; Cycle 4 p<0.001; Year one p=0.006

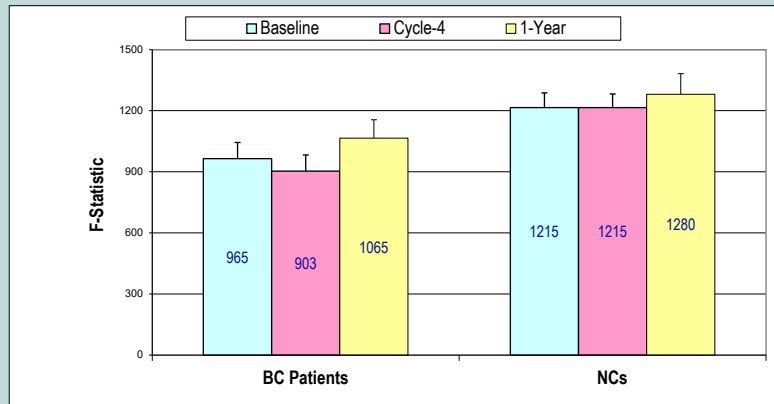


Within groups: Patients: BL-C4 p=0.0017; C4-Y1 p=0.0003  
Between groups: Baseline p<0.001; Cycle 4 p<0.001; Year one p=0.028

Ancoli-Israel S et al. Support Care Cancer. 2014 Sep;22(9):2535-45

30

## Circadian Rhythm Robustness



Baseline group difference ( $p=0.027$ );  
Overall group effect ( $p=0.011$ ).

31

## Summary (con't)

- Circadian activity rhythms become more desynchronized during chemotherapy
  - repeated administration of chemotherapy results in progressively worse and more enduring rhythm impairments
- During chemotherapy, women have very little bright light exposure, which is related to increased fatigue
  - Increasing bright light exposure prevents deterioration of fatigue, circadian activity rhythms, sleep and QOL during chemotherapy and improves these symptoms in survivors

32

## “Chemobrain” – What patients say

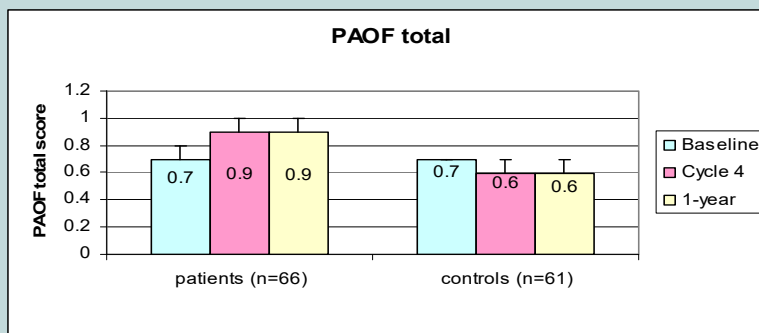
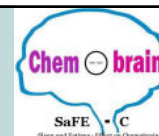
- “It’s a fuzzy feeling, like trying to think through a fog. Throw in a little bit of exhaustion and fatigue, and it doesn’t leave you at your cognitive best. It’s hard to concentrate. It’s a little bit like the feeling you get when you’ve had one or two or drinks too many, and you don’t want to be drunk.”
  - Leroy Siever
- “... 7 years out of chemo treatments. I have been telling my oncologist for years that I am still foggy. I am terrified that I might make a terrible mistake at my job, so I live in constant fear and stress.”
  - Carolyn S. 10-15-2007
- “Having just surpassed my 38 year old wife’s two year anniversary of discovering her cancer, we have found that her chemo brain actually worsened as the time from her treatments lengthened
  - Rick L. 11-06-2006



33

## Subjective Report of Cognition

PAOF = Patient’s Assessment of Own Function

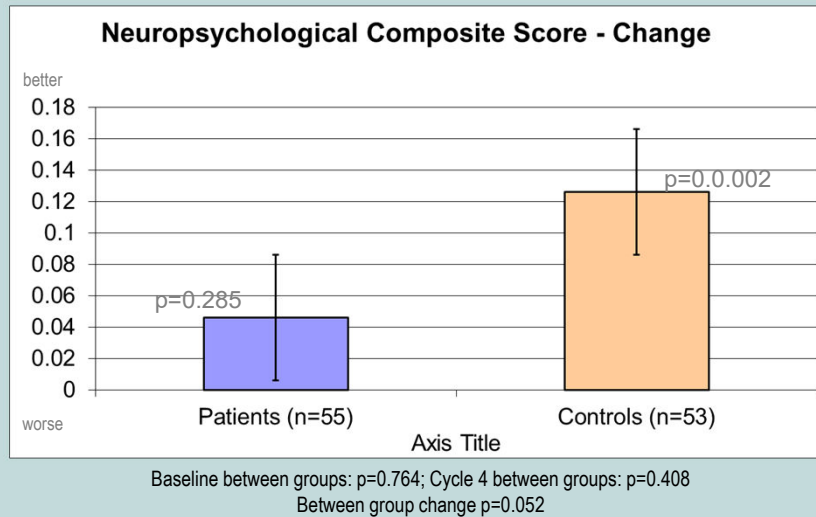
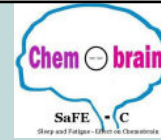


Baseline differences: NS;

Group-x-time interaction ( $p < 0.03$ ) with BC showing larger increases at C4 and 1Y

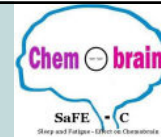
34

## Neuropsychological Composite Score Change Score BL vs. Cycle 4 [means (SEM)]



35

## Cognitive Ability Over Time

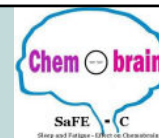


- At baseline:
  - no differences between patients and controls
    - objective or subjective
- Cycle 4:
  - Self Report –
    - Patients reported more deterioration of language and overall cognitive function vs baseline and vs. controls (who had no change)
  - NP scores at cycle 4 compared to baseline - No significant changes in patients (except for attention) BUT controls who got better
- 1-Year
  - Self Report - Patients reported more deterioration of language and overall cognitive function compared to BL, but no change from Cycle 4 to 1-Y; controls had no change
  - NP scores increased and matched levels in controls

36



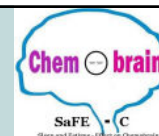
## Changes over Time Cognition



- Findings suggest that breast cancer patients undergoing chemotherapy
  - Subjective measures of cognitive function
    - No different than controls at baseline
    - Worse at Cycle 4 and 1-Year than at baseline and than controls
- NP measures of cognitive function
  - No change in patients at cycle 4; BUT controls improved
    - Except for attention
  - Match control levels at 1-Year
- ? Light improves chemobrain

37

## Predictors of Changes in Cognition – Composite Score



	Baseline–Cycle 4		Cycle 4–One Year		Baseline–One Year	
	R <sup>2</sup>	p-value	R <sup>2</sup>	p-value	R <sup>2</sup>	p-value
Rhythm Robustness (f-statistic)	0.15	0.03	0.18	0.03	0.09	0.02
Sleep quality (PSQI)	0.17	0.04	0.27	0.003	-	-
Night time sleep duration	0.16	0.02	-	-	-	-
PAOF Total	0.25	0.015	-	-	-	-
PAOF Memory	0.25	0.015	-	-	-	-
PAOF Language	0.31	0.0016	-	-	-	-

NS: Fatigue, depressive symptoms, napping

All models adjusted for age, college and BL composite NP score

Ancoli-Israel, in preparation

38

## Summary

- Women with breast cancer experience fatigue and poor sleep before the start of chemotherapy
  - Poor sleep is related to fatigue before and during chemotherapy
- All symptoms get worse with chemotherapy
  - Women who start out with more symptoms also have the worse symptoms during treatment
  - At one year, symptoms return to baseline levels, but remain worse than controls

39

## Collaborators

- Joel Dimsdale, MD
- Lianqi Liu, MD
- Paul Mills, PhD
- Loki Natarajan, PhD
- Barton Palmer, PhD
- Barbara A. Parker, MD
- William Redd, PhD
- Georgia Robins Sadler, PhD
- Niama Covassin, PhD
- Lavinia Fiorentino, PhD.
- Ariel Neikrug, PhD
- Michelle Rissling, PhD
- Vera Trofimenko, MD

Supported by NCI CA85264,  
CA112035, CBCRP 11IB-0034,  
Litebook, Inc., CESAMH



40

## Four Cardinal Rules for Good Sleep

- Reduce your time in bed
  - You should only be in bed about 30 minutes more than your total sleep time.
- Get up at the same time every day of the week, no matter how much you slept the night before - SEVEN DAYS A WEEK
- Don't go to bed unless you're sleepy
  - Do not go to bed to read, watch TV, play on your phone or computer etc etc. Only go to bed when you are sleepy and ready to go to sleep
- Don't stay in bed unless you're asleep
  - If you are awake in bed and start getting tense and anxious about not sleeping, get out of bed, leave the bedroom and do something relaxing until you feel sleepy. Then return to bed. Do this all night long if necessary until you can get into bed and fall asleep. Be sure to stick to rule 2.