Management of Cognitive Dysfunction After Cancer Treatment

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Lafayette Family Cancer Center
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Summary of Cancer and Cognition

* Neuropsychological findings are supported by imaging and preclinical studies

* Chemotherapy-related cognitive dysfunction: 13-78%
  - Memory, Executive Function/Attention, Processing Speed
  - Persists in a subgroup of patients
  - Mild, tend not to be progressive impairments

* Risk factors for cognitive impairment:
  - Age, education, depression, anxiety, cognitive status, menopausal status, HRT history, disease stage, time since chemo, radiation therapy, hormonal therapy, anemia….

* Cognitive dysfunction before treatment:
  Age associated with pre-Rx cognitive dysfunction in some studies, not others
  Possibly: pre-Rx cognitive function, cognitive reserve, anemia

* Does not appear to be due to a main effect of: mood, treatment induced menopause (Hermelink et al, 2008), fatigue (Schagen et al., 2006)

* Many methodological differences between studies. Remedies suggested by the ICCTF
  - Incidence, nature and course needs to be more well defined

* Studies on mechanisms, intervention needed
• Questions

- How to manage the problem?

- What are the proposed treatment approaches?

  • Behavioral/Cognitive Behavioral
  • Rehabilitation
  • Pharmacological
Rehabilitation: Parallel Worlds?

**Compensatory Strategies:**
- Learning adaptive strategies with retained cognitive skills and functional re-organization of the brain
- Enhance performance on everyday tasks that require remembering (Rohling, et al., 2010; Wilson, 2005)

**Cognitive Retraining:**
- Directly retrain cognitive processes to promote repair of damaged circuitry or development of new circuitry with repetitive practice (Rohling, et al., 2010; Roberston & Murre, 1999)
Adjusted Z-transformed domain scores for chemotherapy vs. local therapy groups.
Normal neuropsych testing scores?
What Impairment?!
Their experiences fell into several categories:

:: Having to shift or relinquish employment:
   – inability to function in a work environment,
   – going on disability,
   – premature retirement,
   – downsizing to a job with fewer responsibilities and less pay.

:: Being overwhelmed by tasks assigned, unable to multi-task, or organize daily work load.
At home respondents report:

- Being teased, criticized, or ‘supervised’ by family members.
- Children prematurely taking on increased responsibility.
- Spouses who feel the cancer patient is acting irresponsibly.
- Respondents won’t go to social functions due to embarrassment.
- Inability to maintain personal responsibility for household or financial tasks.
Diathesis Stress Model

1-back > 0-back
2-back > 0-back
3-back > 0-back

Chemotherapy-treated Twin-Twin A

Non-cancer Twin-Twin B

Diathesis Stress Model
Memory and Attention Adaptation Training (MAAT): A Brief Behavioral Skills Program for Cancer Survivors with Attention and Memory Problems Associated with Chemotherapy

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Behavioral Medicine Section
Dartmouth Medical School

RUNNING HEAD: Memory and Attention Training

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Cognitive-Behavioral Approach to Management of Cognitive Problems

- Education and “memory failure reattribution”
- Self-awareness training
- Self-regulation and stress management
- Cognitive Compensatory strategies
Table 3
Comparisons of Mean Number of Premorbid and Reported Post-Injury Symptoms Among Head Injured and Non-Head Injured Athletes

<table>
<thead>
<tr>
<th>Time of Symptom Report</th>
<th>Group</th>
<th>Premorbid</th>
<th>Post-Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head Injured</td>
<td>3.4 (4.4)a</td>
<td>5.4 (5.5)b</td>
</tr>
<tr>
<td></td>
<td>Non-Head Injured Controls</td>
<td>6.7 (6.5)b</td>
<td>13.6 (8.3)ab</td>
</tr>
</tbody>
</table>

Note: Means with different subscripts indicate statistically significant differences.

Ferguson, Robert J.; Mittenberg, Wiley; Barone, David F.; Schneider, Barry
### Brief Cognitive-Behavioral Treatment Schedule

<table>
<thead>
<tr>
<th>VISIT</th>
<th>CONTENT</th>
</tr>
</thead>
</table>
| 1     | - TREATMENT OVERVIEW & PROVISION OF BOOKLET  
       | - EDUCATION ON MEMORY AND ATTENTION AND EFFECTS OF CHEMOTHERAPY  
       | - SELF-MONITORING INSTRUCTION  
       | - RELAXATION TRAINING  
       | - HOMEWORK |
| PHONE CONTACT 1 | - REVIEW HOMEWORK, PROBLEM SOLVE |
| 2     | - HOMEWORK REVIEW  
       | - COMPENSATORY STRATEGY(IES) SELECTION, INSTRUCTION, AND REHEARSAL  
       | - HOMEWORK |
| PHONE CONTACT 2 | - REVIEW HOMEWORK, PROBLEM SOLVE |
| 3     | - HOMEWORK REVIEW  
       | - COMPENSATORY STRATEGY SELECTION, INSTRUCTION, AND REHEARSAL  
       | - ACTIVITY PACING AND SCHEDULING  
       | - HOMEWORK  
       | - OVERVIEW |
| PHONE CONTACT 3 | - REVIEW HOMEWORK, PROBLEM SOLVE |
| 4     | - HOMEWORK REVIEW  
       | - COMPENSATORY STRATEGY REVIEW  
       | - ACTIVITY PACING AND SCHEDULING REVIEW  
       | - PLAN FOR RELAPSE PREVENTION  
       | - WRAP-UP |
To Do:

• Buy fresh lime for the fiesta tonight
• Pick up the cat’s medicine at vet’s
• Buy a new bike helmet for Jr.
“Levels of Evidence” and CBT Development

1. One-group pilot study
2. Waitlist Control RCT (absolute efficacy)
   - (No longer recommended, Herbert, 2003)
3. RCT with active control condition
4. Component Analysis
Cognitive-Behavioral Treatment of Chemotherapy-Related Attention and Memory Problems Among Breast Cancer Survivors: A Pilot Study

PI: Ferguson, R. J. Co-PI: Ahles, T.A.
NCI: 1 R03 CA090151-02; Lance Armstrong Foundation

• One group pilot design (feasibility, satisfaction)
• Baseline, post-treatment, 2-month follow-up
• N = 29, Stage I, II BCA, no CNS tx, intrathecal tx, or psychiatric, substance abuse, neurologic
• Mean Age = 56 (7.81), mean IQ, est: 112.82, 15 yrs edu
• Years-post chemotherapy: 8.2 (4.4)
• OUTCOMES:
  - Improved Multiple Abilities Self-report Questionnaire (MASQ)
  - Improved CVLT-II Total Score (54, 55, 61, 59)
  - Digit Symbol, Stroop, Trail-making improvements
  - High Satisfaction 7.14 (1.09) 0-8 rating
“Behavioral Management of Cognitive Impairment Associated with Chemotherapy”

Lance Armstrong Foundation
R. Ferguson, PI
INCLUSION

• diagnosis of stage I and II breast cancer;
• at least 18 months post-treatment currently disease free (not excluding individuals on hormonal therapies such as selective estrogen receptor modulators);
• treatment involved standard dose adjuvant chemotherapy;
• complaint of memory and attention following chemotherapy;
• able to speak read English;
• at least 18 years of age at diagnosis and able to provide informed written consent.

EXCLUSION

• history of CNS disease;
• history of CNS radiation, intrathecal therapy or CNS-involved surgery;
• neuro-behavioral risk factors such as traumatic brain injury, history of neurological disorder, learning disability or substance addiction;
• current psychiatric disorder.
Outcome Measures

- **Multiple Abilities Self-Report Questionnaire (MASQ)**
  (Seidenberg, Haltiner, Taylor, Hermann, & Wyler, 1994)
  - 48 items, 5 pt Likert scale, almost always/never
  - Language, visual-perceptual, visual memory, attention, verbal memory

- **Quality of Life-Cancer Survivor Scale (QOL-CS)**
  (Ferrell, Dow, & Grant, 1995)
  - 41 items, physical, psychological, social, spiritual scales
  - 0-10 Likert scale

- **CES-D-State-Trait Anxiety**
Outcome Measures

Satisfaction

- General (0 = not at all satisfied; 8 = completely satisfied)

- *Improving* or helping to *compensate for* problems of memory and attention (0 = not at all helpful; 8 = completely helpful)
Outcome Measures

Neuropsychological

Verbal Domain
CVLT-2 Total Score

Processing Speed
Trail Making Number-Letter Switching
Stroop Color-Word
Stroop Color-Word Switching
Digit Symbol
Figure 1. Study flowchart. Note: MAAT = Memory and Attention Adaptation Training
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 40)</th>
<th>MAAT (n = 19)</th>
<th>Waitlist (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.28 (6.4)</td>
<td>51.21 (7.3)</td>
<td>49.43 (5.1)</td>
</tr>
<tr>
<td>Education (in years)</td>
<td>16.38 (2.4)</td>
<td>16.95 (1.9)</td>
<td>15.86 (2.7)</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>114.72 (4.2)</td>
<td>115.61 (4.1)</td>
<td>113.92 (4.1)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently married</td>
<td></td>
<td>76.2%</td>
<td>63.2%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>97.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: No factor was significantly different between groups (p > 0.05).
<table>
<thead>
<tr>
<th>Table 2. Group comparisons of principal outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Mean (SD)</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Functional/quality of life outcomes</strong></td>
</tr>
<tr>
<td>MASQ total score*</td>
</tr>
<tr>
<td>Treatment n = 19</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
<tr>
<td>Quality of life—CS psychological well-being</td>
</tr>
<tr>
<td>Treatment n = 19</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
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<td>Treatment-control difference</td>
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<td>Quality of life—CS social well-being</td>
</tr>
<tr>
<td>Treatment n = 19</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
<tr>
<td><strong>Neuropsychological outcomes</strong></td>
</tr>
<tr>
<td>CVLT-II Total (T-score)</td>
</tr>
<tr>
<td>Treatment n = 19</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
<tr>
<td>Digit symbol-coding</td>
</tr>
<tr>
<td>Treatment n = 19</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
<tr>
<td>Color word trial*</td>
</tr>
<tr>
<td>Treatment n = 19</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
<tr>
<td>Color word* switching trial</td>
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<tr>
<td>Treatment n = 19</td>
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<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
<tr>
<td>Trail making number-letter trial*</td>
</tr>
<tr>
<td>Treatment n = 9</td>
</tr>
<tr>
<td>Waitlist n = 21</td>
</tr>
<tr>
<td>Treatment-control difference</td>
</tr>
</tbody>
</table>

Note: d = Cohen’s d. Each d in the table is the within group size of effect reflecting change from baseline to post-treatment, and 2-month follow-up, respectively. The treatment-control difference in effect size is the control group effect size subtracted from the treatment group effect size. Negative or positive signs in front of effect sizes do not affect magnitude of effect (larger integer = greater effect).

*Lower MASQ scores indicate fewer cognitive problems and lower scores for both Color-Word Interference and Trail Making Tests indicate better performance. By contrast, higher QOL-CS scores, CVLT-II, and Digit Symbol-Coding scores indicate clinical improvement.
Satisfaction

- Mean General Satisfaction rating
  - 7.0 (SD = 1.05; 0 = not at all satisfied; 8 = completely satisfied)
  - *compensating* for daily memory failures
    ($M = 6.7; SD = 1.54$)
  - *improving* memory ($M = 5.2; SD = 1.59$)

( 0 = not at all helpful; 8 = completely helpful)
5 Top-rated strategies included:
0 = Not at all helpful; 4 = Completely helpful

1. applied relaxation methods (self-regulation, arousal reduction) 3.6
2. using a schedule or day planner/organizer
3. verbal rehearsal methods
4. activity pacing and scheduling
5. self-instructional training 3.0
Conclusions and Limitations

• It appears that MAAT (CBT) may be effective to help improve *coping and self-management* of chemotherapy cognitive change

• Some evidence of verbal recall improvement

• Participants are satisfied

• Effect sizes are comparable, if not larger, than many cognitive rehabilitation interventions (fair comparison?)
Conclusions and Limitations

• The study was small, underpowered and required linear interpolation
• No active treatment control
• One clinician completed all treatment (RF)
• More precise outcome measures:
  – Improved measures of QOL impact: FACT-Cog; MIA-Anxiety
  – Neuropsychological measures, secondary
  – Memory self-efficacy?
What were the 3 items you were assigned to remember?
Medications

- dexmethylphenidate (d-MPH; Focalin)
  - N = 152 double-blind placebo control
  - 27.7 mg/day, patients with various cancers (non-CNS; n = 77 d-MPH; 7 placebo) > 2 months post-chemo
  - 8 weeks d-MPH or placebo
  - Improvements in fatigue (FACIT-Fatigue)
  - and memory (High Sensitivity Cog. Screen)
  - 40.8% headaches; 27.6% nausea

(Lower, et al., 2005)
Medications

- modafinil (Provigil)
  - N = 68 Breast cancer survivors double-blind placebo control
  - 22.8 months after chemotherapy
  - Improvements in speed of memory, continuity of attention, and quality of episodic secondary memory on computerized neurocognitive measure vs. placebo
  - (Cognitive Drug Research computerized assessment)

(Kohli, et al., 2007)
Most appreciated components of Strategy Training and C-Car:

• Organizational strategies,
• education and acceptance of cog. problems,
• acceptance of use of strategies,
• education on interrelations of various cog. functions

Future Directions for MAAT CBT

- Increase MAAT “dosing” 8 visits

- An active treatment RCT is needed with larger numbers and multiple clinicians
  - MAAT vs. Supportive Psychotherapy (Borkovec) or POSIT-Science

- FACT-Cog (QOL impact), MIA-A as the principal outcomes
  - This will also aid inclusion criteria

- Applied to –
  - Other cancer treatments that contribute to cognitive impairment
  - CNS disease-related cognitive impairment
  - MTBI

- MAAT – electronic? on line, iPad or iPhone based, Video conference
  - 1R21CA143619-01A1
Videoconference CBT for Rural Breast Cancer Survivors with Cognitive Complaints

Ferguson, RJ, PI; Sigmon, S., Co-PI

- RCT of MAAT vs. Supportive Therapy (N = 48)
- Utilizing videoconference infrastructure in Maine—33,000 square miles, 7 sites committed to the project
- Stage, I, II, IIIa BCA survivors, 6-months post-chemotherapy
- Telephone based self-report measures and modified Telephone Based Assessment of Neuropsychological Status (TBANS; Underzagt, 200?)
- Will use the FACT-Cog and MIA-A as primary PRO’s
Memory and Attention Adaptation Training (MAAT)

A Brief Behavioral Skills Program for Cancer Survivors with Attention and Memory Problems Associated with Cancer Treatment

Clinician Manual

Robert J. Ferguson, Ph.D.
Karen Gillock, Ph.D.
<table>
<thead>
<tr>
<th>VISIT</th>
<th>CONTENT</th>
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</table>
| 1 | • INTRODUCTION AND MAAT OVERVIEW  
• EDUCATION ON MEMORY AND ATTENTION AND EFFECTS OF CHEMOTHERAPY  
• MEMORY FAILURE RE-ATTRIBUTION: NOT ALL MEMORY FAILURES ARE CHEMO-RELATED  
• SELF-AWARENESS AND MONITORING MEMORY PROBLEMS  
• PROGRESSIVE MUSCLE RELAXATION  
• HOMEWORK |
| 2 | • REVIEW MAAT READING, RELAXATION AND QUICK RELAXATION REVIEW, REHEARSAL  
• REVIEW SELF-MONITORING, EFFECTS OF CONTEXT, SENSES AND MEMORY PROBLEMS  
• “INTERNAL STRATEGY”: SELF-INSTRUCTIONAL TRAINING (SIT)  
• HOMEWORK |
| 3 | • QUICK RELAXATION REVIEW  
• REVIEW APPLICATION OF SELF-INSTRUCTIONAL TRAINING (SIT)  
• “INTERNAL STRATEGY.” VERBAL REHEARSAL STRATEGIES (VERBAL REHEARSAL, SPACED REHEARSAL, CHUNKING AND RHYMES)  
• COGNITIVE RESTRUCTURING: REALISTIC PROBABILITIES AND DECATASTROPHIZING  
• HOMEWORK |
| 4 | • REVIEW OF VERBAL REHEARSAL STRATEGIES  
• REVIEW REALISTIC PROBABILITIES AND DECATASTROPHIZING  
• “EXTERNAL STRATEGY:” KEEPING A SCHEDULE AND MEMORY ROUTINES  
• HOMEWORK |
| 5 | • REVIEW OF KEEPING A SCHEDULE AND MEMORY ROUTINES  
• “EXTERNAL STRATEGIES:” EXTERNAL CUEING AND DISTRACTION REDUCTION  
• ACTIVITY SCHEDULING AND PACING  
• HOMEWORK |
| 6 | • REVIEW OF EXTERNAL CUEING, DISTRACTION REDUCTION AND ACTIVITY SCHEDULING AND PACING  
• “INTERNAL AND EXTERNAL STRATEGY:” ACTIVE LISTENING, VERBAL REHEARSAL FOR SOCIALIZING  
• FATIGUE MANAGEMENT AND SLEEP IMPROVEMENT  
• HOMEWORK |
| 7 | • REVIEW ACTIVE LISTENING, VERBAL REHEARSAL FOR SOCIALIZING  
• REVIEW FATIGUE MANAGEMENT AND SLEEP QUALITY IMPROVEMENT  
• “INTERNAL STRATEGY:” VISUALIZATION STRATEGIES  
• HOMEWORK |
| 8 | • REVIEW VISUALIZATION STRATEGIES  
• TYING IT TOGETHER AND CONTINUED QUALITY OF LIFE IMPROVEMENT IN SURVIVORSHIP  
• DISCUSSION AND WRAP-UP |
“I have had a moment a week ago where I just drew a blank on a person—like a curtain had been dropped. But I said, ‘_______, just relax. These memory lapses will happen. Relax and it will come.’ I went to the back of the store and did my relaxation and 10 minutes later, I remembered. I am not as upset by problems. I am more aware now and I walk into other rooms and rarely do I ask why I am there—that’s gone way down.”

- 73 years old, rt-sided ER+PR- bca
- Local radiotherapy completed 12/10.
- Arimidex since 11/2010- 5 year schedule
When in doubt, more cowbell