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AN OVERVIEW OF COGNITIVE-BEHAVIORAL MANAGEMENT OF MEMORY DYSFUNCTION ASSOCIATED WITH CHEMOTHERAPY

PANORAMA DEL MANEJO COGNITIVO CONDUCTUAL DE LA DISFUNCIÓN DE LA MEMORIA ASOCIADA A LA QUIMIOTERAPIA

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Abstract

Objective: **This article summarizes current empirical support for Memory and Attention Adaptation Training (MAAT), a cognitive-behavioral treatment program that uses a compensatory strategy approach for management of late cognitive effects of chemotherapy among cancer survivors. A description of MAAT, in addition to other treatment approaches, is presented.** ***Results:*** **Current methods of assessing treatment gains among cancer survivors with cognitive problems who have completed programs such as MAAT need to be expanded. As such, a table of patient reported outcome (PRO) measures that may be better suited for future outcome research is proposed.** ***Conclusions:*** **Identifying outcome measures that accurately assess the clinical targets of MAAT and other behavioral treatments is of prime importance, as certain variables (e.g., quality of life, role strain) are not detected by neuropsychological testing in isolation. The PRO table presented in this article is intended to aid future researchers in identifying measures that can reflect quality of life improvement in response to treatments such as MAAT.**

Keywords: Chemotherapy, cognitive dysfunction, cancer survivorship, cognitive-behavioral therapy.

Resumen

Objetivo*: El presente artículo resume el apoyo empírico actual para el Entrenamiento de la Adaptación de la Memoria y la Atención (MAAT), un programa de tratamiento cognitivo-conductual que utiliza un enfoque de estrategia compensatoria para el manejo de los efectos cognitivos tardíos de la quimioterapia en los supervivientes del cáncer. Se presenta una descripción del MAAT, además de otros enfoques de tratamiento.** ***Resultados: **Es necesario ampliar los métodos actuales de evaluación de las mejorías del tratamiento en los supervivientes de cáncer con problemas cognitivos que han completado programas como el MAAT. En este sentido, se propone una tabla de medidas de resultado informadas (PRO) por el paciente que puede ser más adecuada para la investigación de resultados futuros.** ***Conclusiones:*** **Identificar medidas de de resultado que evalúen con precisión los objetivos clínicos del MAAT y otros tratamientos conductuales es de vital importancia, ya que algunas variables (ej., calidad de vida, estrés de rol), no son detectados por pruebas neuropsicológicas de modo aislado. La tabla de PRO presentada en este artículo tiene el propósito de ayudar a los futuros investigadores a identificar las medidas que pueden reflejar la mejoría en calidad de vida en respuesta a tratamientos como el MAAT.**

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Palabras claves: Quimioterapia, disfunción cognitiva, supervivencia al cáncer, terapia cognitivo-conductual.

INTRODUCTION

Cognitive impairment associated with chemotherapy and its impact on cancer survivor quality of life has gained increased interest among clinical research investigators over the last 2 decades[1-3]. One of the most feared health problems among members of the general public is cognitive decline[4-5]. With growing numbers of individuals living longer with a cancer diagnosis (estimated at 11.7 million and growing in the United States)[6-7], research on the neuropsychological impact of chemotherapy has gained in importance. The discussion to follow outlines development and research of a cognitive-behavioral treatment approach to help mitigate the health-related quality of life impact of chemotherapy-related cognitive dysfunction. First, a summary of the empirical literature to date regarding the impact of chemotherapy on cognitive function and quality of life will be provided, followed by an overview of Memory and Attention Adaptation Training (MAAT) and the research on this treatment approach. Last, we will summarize recommended steps in future research and other treatment approaches in this area.

NEUROPSYCHOLOGICAL IMPACT OF CHEMOTHERAPY

Research on the neuropsychological impact of cancer treatment dates back to the early 1980s with studies suggesting patients treated with chemotherapy experience measurable cognitive deficits on standard neuropsychological tests[8]. Historically, the largest body of research with the highest quality designs has been conducted in children[9-11] but interest grew with adult populations. Initially, smaller studies with cross-sectional designs compared groups of individuals who had the same cancer diagnosis but differed in treatment approach –that is, chemotherapy vs. nonchemotherapy recipients–. One example was an early study by Wieneke and Dienst[12] that evaluated 28 women with a standardized neuropsychological test battery an average of 6 months post-treatment with CAF (cyclophosphamide, doxorubicin and 5-fluorouracil) and/or CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). Seventy-five percent of patients scored greater than 2 standard deviations below published norms on one or more of neuropsychological measures, lending preliminary support to the notion that chemotherapy can negatively affect an individual's later cognitive abilities.

In a larger study, Ahles et al.[13] compared long-term breast cancer and lymphoma survivors (> 5 years post-treatment) who completed chemotherapy or local therapy (e.g., localized radiation therapy). Survivors were matched on age, education, IQ, menopausal status and were excluded if they had histories of neurologic, substance abuse or severe psychiatric illness. Multivariate analyses demonstrated between group differences in Verbal Memory ($p<0.01$) and Psychomotor Processing Speed ($p<0.03$). Using a definition of low neuropsychological performance similar to that used in other studies (lower 25th percentile), 39% of chemotherapy patients compared to 14% of local therapy patients scored within the low performance range ($p<0.002$). In short, Ahles et al. demonstrated cognitive effects of chemotherapy could be long-

term and not attributable to previous brain injury, age, education, gender, menopausal status or IQ. However, Ahles and colleagues did not report differences between types of chemotherapy received, and to date it is unclear which anti-neoplastic agents are more likely to spawn cognitive impairments[14-17]. In addition to the examples of cross-sectional studies cited above, longitudinal studies were undertaken. In two examples, researchers assessed breast cancer patients with standardized neuropsychological tests prior to chemotherapy and 6-months post-treatment[18,19]. Comparison groups either involved healthy controls or breast cancer patients on experimental therapies. In one of these studies, Shilling and et al.[19] identified 34% of chemotherapy recipients with cognitive impairment at 6 months post-treatment in comparison with 18.6 % of control participants. These and other longitudinal studies appear consistent with previous cross-sectional designs suggesting that for a subset of survivors who receive adjuvant chemotherapy, there are detectable neuropsychological declines. In summary, the body of evidence supports the hypothesis that chemotherapy can lead to long-standing cognitive change for some survivors[20,21]. Overall, three principal conclusions that can be drawn from this literature are:

1) A subset of individuals (ranging from about 20 to 40%) experience mild to moderate cognitive decline in comparison to matched controls[21];
2) Cognitive declines do not appear to be associated with age, education, neurologic history, psychiatric history, stress or menopausal status as the bulk of studies have controlled for these factors[17]; and
3) Mild cognitive decline appears long term and in domains of verbal memory, working memory and visual motor processing speed[16,21]. These declines are believed to be static and not progressive; that is, there is little evidence that cognitive decline after chemotherapy is progressive such as that seen in serious forms of dementia.

QUALITY OF LIFE AND FUNCTIONAL IMPACT OF COGNITIVE DYSFUNCTION

The research cited above is primarily concerned with identifying rates of neuropsychological impairment in chemotherapy recipients using standardized neuropsychological tests; it is less focused on quality of life impact cognitive problems can produce[21,22]. By contrast, a recent online survey of 453 cancer survivors evaluated functional and quality of life impact (www.hurricanevoices.org/today/cognition). This survey was overseen by Ian Tannock MD, PhD, FRCPC and Janette Vardy PhD, MEd, FRACP, who are well known for their investigations in the area of chemotherapy-related cognitive dysfunction. Of survivors responding, 62% noted cognitive problems affected role function in relationships at home and employment. Reports of home-related problems included being criticized or "supervised" by family members, avoiding social functions due to embarrassment with memory lapses (a common report in previous Memory and Attention Adaptation Training —MAAT— research) and change in family roles with children taking on more responsibility. Reports of work-related problems included shifting to jobs with fewer responsibilities and lower pay, inability to "multi-task" and handle pre-cancer work load, frustration exhibited by co-workers or supervisors and in some instances termination (another report in previous MAAT research). A controlled empirical study (cross-sectional design) reports similar quality of life effects [23]. Breast cancer and lymphoma survivors

who had chemotherapy found diminished social role function and less home activity than non-chemotherapy counterparts[23].

Finally, among surveyed survivors who report seeking help from their oncologists regarding the aforementioned problems, 55% reported their oncologist as understanding. However, only 10% reported they were offered assistance to deal with the problem(s). While this latter point appears negative, it is emphasized that the problem of chemotherapy-associated cognitive change is complex and treatment strategies are only beginning to be developed and evaluated. Therefore, oncology providers have few readily available options to help survivors at present. MAAT was developed in response to this void in survivor treatment offerings.

MAAT: BACKGROUND AND RATIONALE

MAAT was developed as a brief intervention to minimize the impact of cognitive change on quality of life and role function among adult cancer survivors. To date, no treatment is conclusively efficacious for adults who experience chemotherapy-related cognitive change. Historically, pediatric psychosocial oncology appeared more advanced in addressing cognitive problems among survivors. In particular, Butler and Copeland[24] developed a treatment program for children with central nervous system (CNS) disease and who have undergone a variety of cancer treatments that can adversely affect cognitive development and function (e.g., intracranial irradiation, surgery, systemic chemotherapies or intrathecal therapies). Results from their multi-site, waitlist randomized control trial (RCT) of the Cognitive Remediation Program (CRP)[25] suggest children improved on measures of academic achievement (as assessed by the Wide Range Achievement Test-3) and in parent ratings of inattention and hyperactivity (as assessed by Conner's Parent Rating Scales). Furthermore, CRP children also tended to report use of more meta-cognitive strategies in academic tasks than wait-list controls.

While these results are encouraging for children and adolescents, the CRP may not be suited to adult cancer survivors for several reasons. First, cognitive dysfunction observed in the Butler et al. sample may be more profound than the mild cognitive change commonly observed in adults after systemic chemotherapy with no CNS disease. Second, the CRP program can be lengthy with high time demand (up to 20 2-hour sessions) to accommodate complex cognitive developmental factors seen in pediatric cases (e.g., neurophysiological damage in a developing brain co-mingled with social/emotional development). The CRP may thus be too disruptive and costly in terms of time and expense for adult survivors who are resuming functional roles after cancer treatment.

THEORETICAL UNDERPINNINGS OF MAAT

In the cognitive rehabilitation literature, two broad approaches emerge: 1) A rehabilitation approach that emphasizes repetitive practice of cognitive tasks to promote neural circuitry repair or cortical reorganization[26,27]; and 2) A "compensatory strategy" approach. There is evidence that repetitive practice can enhance brain plasticity[28,29] and directly affect underlying neurocircuitry involved in cognitive function. By contrast, the compensatory strategy approach places emphasis on the acquisition of adaptive behavioral and cognitive skills to optimize cognitive task performance-presumably using retained or unaffected brain regions after neurophysiological insult[30,31]. This approach tends to directly address behavioral *memory-related disability*; that

is, improve performance on daily tasks *for which memory is used*[26] . Therefore, the primary outcomes of interest with a compensatory approach are not neuropsychological testing score gains per se, but rather measures that are sensitive to enhanced function and quality of life.

There is ongoing debate about the effectiveness of repetitive practice versus compensatory/adaptive strategy approaches. Although such a discussion is beyond the scope of this article, in general, the repetitive practice rehabilitation approach appears to have overall moderate effects on memory function among individuals with more severe neuropsychological impairment secondary to stroke or other acquired brain injury[26]. At the same time, there is evidence that compensatory strategy training may help individuals generalize (or "transfer") cognitive compensatory skills to daily life across multiple settings to promote adaptation to cognitive problems. Traditional repetitive practice may only improve performance on unitary tasks[26,31-34].

MAAT was designed by the primary author with the compensatory strategy approach in mind. A principal aim of MAAT is to improve self-management and coping with cognitive failures in daily life to enhance overall quality of life and function. MAAT is also consistent with a cognitive-behavioral therapy (CBT) model, where the over-arching goal is to enhance adaptive behavioral and cognitive responses to minimize the deleterious effects of symptoms on function. A parallel illustration of this approach is the cognitive-behavioral management of chronic pain[35]. In that literature, studies indicate CBT generally does not produce substantive reductions in overall report of pain intensity in many cases. CBT does, however, produce significant gains in various domains of life among pain sufferers, including improvements in social, emotional, occupational and physical function, despite persistent chronic pain[25-37]. Likewise, MAAT emphasizes quality of life gains through adaptive self-management skill acquisition despite persistence of some cognitive dysfunction[34,38-40].

On a final note of theoretical underpinnings, MAAT conceptualizes chemotherapy-related cognitive dysfunction from a "diathesis-stress" framework. That is, under times of low demand such as smooth work or home routines, cognitive dysfunction may not cause undue life interference. If memory problems arise under times of low demand/stress, they are readily handled or are of little consequence. By contrast, under times of high performance demand, such as sales presentations, dispensing dangerous medications, or making parenting decisions, cognitive failures may cause greater interference and distress. MAAT is not concerned with the neurobiological causes of memory and attention failures. Indeed, as reviewed previously, the mechanisms by which cancer chemotherapies disturb functions of memory and attention remain unknown. Therefore, MAAT is based on social learning principles common to other cognitive-behavioral approaches. The goals of treatment are to modify maladaptive cognitions (beliefs, attitudes) and behaviors in order to bring about optimal adaptation to living with newly acquired cognitive effects of cancer treatment. Although neuropsychological test performance may improve as an effect of MAAT, it is contended here that changes in neuropsychological test scores may not be as clinically meaningful as improvements in measures of daily function or quality of life for individual cancer survivors[17,22]. As it may not be fully possible to eliminate life experiences such as physical pain or anxiety, it is not possible to fully eliminate

daily cognitive failures of memory and attention as these are daily experiences in of healthy individuals[41,43].

MAAT COMPONENTS

MAAT draws from the CBT and rehabilitation evidence base related to mild traumatic brain injury, cerebral damage due to stroke or other trauma recovery[26,27,32,43-47]. There are four components to MAAT: 1) education (on chemotherapy and cancer-treatment related cognitive problems, cognitive symptom re-attribution, and other influences on attention and memory such as stress); 2) self-awareness training (self-monitoring to identify "at risk" conditions where cognitive failures occur); 3) self-regulation (emphasis on arousal self-regulation, relaxation and stress coping skills) and 4) compensatory strategies[39,40]. Each component is presented in serial fashion over the course of 8 weekly MAAT visits, ranging from 45 to 50 minutes in duration.

Education. The educational component of MAAT consists of reviewing the current understanding of how chemotherapies can influence memory function and how other cancer treatments, such as hormonal therapies, can affect cognitive function. Time is also devoted to reviewing basic memory and attention functions and illustrating how much of everyday memory failure is normal. The intent of the latter educational point is to help reduce misattribution of everyday memory failure to chemotherapy causes when it could be due to inattention, distraction, stress, emotional arousal, hunger, fatigue, etc. It is emphasized strongly to the survivor that this information is not intended to dismiss or minimize their cognitive complaints. Rather, the intent is to have the survivor recognize that while some daily cognitive failures may be due to cancer treatment, certainly not all are going to be. Some may be due to environmental factors (e.g., visual or auditory distractions) or internal states (excessive stress responding) that can be readily modified. This "re-attribution" element of MAAT is considered critical to starting a healthy cognitive self-appraisal process that can reduce distress about cognitive failures after cancer treatment. This sets the stage to enhance beliefs of self-efficacy in coping with the problems. Expectations about cognitive symptoms are associated with stronger perceptions of pre-to-post brain injury symptom change[43] and can lead to reduced neuropsychological test performance in a "self-fulfilling" prophecy fashion[48]. Therefore, by modifying survivors' self-appraisal of cognitive symptoms experienced from uncontrollable to more controllable causal attributions, this will likely lead to less distress about memory failures when they occur.

Self-awareness training. This component of MAAT refers to survivors using a brief self-monitoring form to record memory and attention failures. Obviously, given the common rates of daily memory failure in healthy individuals, survivors are not asked to record every memory failure but to gather a sample of those cognitive failures that produce distress and performance interference. Each "Memory and Attention Problem Record" evaluates the intensity of how much distress each failure causes, the nature of the cognitive failure (cognitive task demands), the environmental (e.g., ambient auditory or visual distractions), and internal (e.g., fatigue, emotional distress such as anxiety, hunger, etc.) antecedents. This information is reviewed with the clinician and helps identify the "at risk" situations where cognitive failures are more likely. Self-awareness also helps guide the selection of the most applicable cognitive compensatory strategies to either prevent cognitive failures or minimize their quality of life impact.

Self-regulation. Self-regulation refers to applied relaxation training methods of progressive muscle relaxation (PMR) and cue-controlled or "quick" relaxation. The intent is to enhance survivors' skills to regulate psychophysiological arousal that can interfere with cognitive processes such as attention, encoding and recall. An emphasis is placed on mindfulness or greater awareness of relaxing skeletal muscles and self-regulating breathing during everyday tasks to generalize the skill to daily life. In addition to relaxation, other self-regulation methods that emphasize stress management include activity scheduling and pacing, or the scheduling of pleasant or achievement oriented tasks to optimize mood management that can positively influence cognitive performance[49]. In the latest version of MAAT, methods of sleep quality improvement and managing fatigue with pacing and goal setting have been added to this component.

Compensatory Strategies. Compensatory strategies are defined as behavioral or cognitive skills and external devices (such as day-planners, electronic devices or visual or auditory prompts) that help prevent or mitigate adverse consequences of memory failures in daily life. Other compensatory strategies in MAAT includes verbal rehearsal methods such as repeating information to aid encoding or "holding" the information long enough to perform an action (such as dial a phone number or enter it into a computer data base). "Spaced rehearsal" is a form of verbal rehearsal where the interval of repeating information is gradually lengthened with each repetition— in a sense, a practical "exercise" for working memory and short-term or delayed recall. Self-instructional training (SIT) is another method of "talking to one's self" to aid focused attention during procedural task performance to reduce error in missing steps in the task[50,51]. In addition to these internal strategies, there are host of external strategies[52] such as using a day planner to keep a simplified, organized schedule, either paper or electronic device, establishment of memory routines at work or home, or using external visual or auditory cues (cell phone alert) to cue specific behavior. In each MAAT visit, the clinician reviews the rationale of the compensatory strategy, rehearses the strategy with the survivor, and identifies where and when the strategy will be applied in daily activity.

EMPIRICAL SUPPORT FOR MAAT

In initial development, MAAT was characterized as a "guided self-help" CBT in which the survivor uses a workbook in conjunction with clinician interactions. The brief format was intended to optimize wide spread use and reduce survivor office visit burden, particularly in rural regions where people live long distances from comprehensive cancer centers[53]. The initial edition of MAAT consisted of 4 individual office visits once every 4 weeks, with 3 phone contacts (1 between each visit) for support and to review daily homework. After two studies conducted on MAAT feasibility and preliminary efficacy, however, MAAT has been modified to 8 weekly, 45-50 minute visits.

Pilot research points to support of MAAT feasibility and positive impact on quality of life gains. In a single-arm pilot study[38], 29 breast cancer survivors (average 8.2 years post-chemotherapy; SD = 4.4 years) completed MAAT. Principal outcome measures included self-reported cognitive function in daily life as assessed by The Multiple Ability Self-Report Questionnaire (MASQ)[54], The Quality of Life- Cancer Survivors scale (QOL-CS[55]), satisfaction ratings and a brief neuropsychological test battery. Testing occurred at 4 time points: baseline, post-treatment, 2-month and 6-month follow-

up. Survivors were excluded if they had any history of neurological problems such as prior traumatic brain injury or central nervous system disease, substance addiction, or severe psychiatric illness. Results indicated a significant reduction in self-reported daily cognitive complaints (MASQ), improved quality of life and high satisfaction ratings. Neuropsychological test score improvements were observed in verbal memory and processing speed. Although positive, neuropsychological results were interpreted with caution as there was no control group to rule out effects of practice with repeat testing. Nonetheless, the pilot results did support primary aims of the proposed study, helped to identify modifications to the MAAT format (such as placing visits 2 weeks apart rather than one month apart) and thus set the stage for further MAAT evaluation.

In the second study of MAAT, a small RCT utilizing a waitlist control design was completed[40]. The intent was to establish preliminary efficacy of MAAT and identify possible areas of treatment improvement. Forty women were enrolled and randomized to treatment (n = 19) or waitlist control (n = 21) conditions and assessed at baseline, post-treatment and 2 month follow-up time points. Participants were 18 months post-chemotherapy and the exclusionary criteria were identical to the one-group pilot study of MAAT (e.g., no neurological, psychiatric or substance addiction history). Of 53 individuals initially screened via telephone for participation, 40 were randomized to MAAT or waitlist control conditions. The mean age of the final sample was 50.3 years (SD = 6.4). Five participants did not complete the three assessment points and linear interpolation methods were used to account for missing data in this small trial. A 2 (MAAT vs. Waitlist control) X 3 (Baseline, post-treatment and follow-up) multivariate, repeated measures analysis of variance was employed for statistical analysis. Dependent measures included those used in the previous study: the MASQ total score, QOL-CS and a brief neuropsychological test battery. Within-group effect sizes (Cohen's *d*) were calculated to examine baseline to post-treatment and follow-up effects to detect magnitude of MAAT treatment effects. Subtracting waitlist control group effect size from MAAT effect size was completed to estimate "true" MAAT effect by accounting for study demand characteristics such as expectations of being enrolled in a research study and/or practice effects with repeat administration of neuropsychological tests. This method has been used in meta-analyses of cognitive rehabilitation approaches by Rohling et al.[26]

Correlation analyses demonstrated education (in years) and IQ (estimated by demographic factors[56]) were covariates. Accounting for these 2 variables, MAAT participants made significant improvements over waitlist control participants on the QOL-CS Spiritual Wellbeing subscale and on CVLT-2 total score-or verbal memory. The outcome of the QOL-CS Spiritual Wellbeing subscale is likely due to the item content of the 7-item scale; the items reflect general positivism and hopefulness in cancer survivorship. MAAT is aimed at enhancing self-management of and coping with cognitive symptoms. Therefore, participants likely made improvements in coping that may be reflected in the QOL-CS Spiritual Wellbeing subscale changes. The CVLT-2 total score gains suggest MAAT compensatory strategies may be relatively more helpful for the verbal memory domain than in domains of visual motor processing speed, although MAAT participants made some statistically non-significant gains in the digit-symbol subtest. In addition, MAAT participants did not differ significantly on self-report of daily cognitive complaints (as assessed by MASQ total score) from controls. However,

the pre-to-post-treatment effect size for the MASQ total score was .43 after subtracting control group size of effect. In addition, effect sizes in the QOL-CS Spiritual Wellbeing and CVLT-2 total score results were -.49 and -.50, respectively (note that the negative sign does not change the magnitude of effect; this reflects the fact that MAAT participant scores improved on both measures where higher scores indicate improvement). The CVLT-2 total score effect size was -.63 at 2-month follow-up. In summary, while the waitlist RCT was small and likely underpowered, MAAT participants appeared to improve more than controls in one quality of life measure and verbal memory performance with moderate to stronger effects. Overall, research on MAAT thus far encourages further development and investigation of MAAT as a treatment option for adult cancer survivors with post-cancer treatment memory problems.

CONTINUED MAAT DEVELOPMENT AND FUTURE DIRECTIONS

Several concerns about MAAT remain and should be addressed in continued research. First, a major weakness is that no MAAT research to date has used an active treatment control condition. One RCT is underway using a supportive therapy control condition vs. MAAT with the both treatment conditions being delivered via videoconference rather than face to face clinical delivery. However, this is another somewhat small trial (*N*=48; 24 participants per condition). While such research is a step in the right direction, clearly, a larger RCT using an active attention-treatment control design with multiple clinicians is necessary for a more rigorous evaluation of MAAT efficacy.

A related concern with MAAT research to date is power-either due to small sample sizes or the treatment "dosing." Because of this, we modified MAAT to an 8-visit format as described above. While expanding MAAT to 8 visits may add to cancer survivor burden (office visits, travel, etc.), MAAT still remains a brief CBT and retains its practical focus on quality of life improvement. We believe this modification is justified given results of preliminary research and makes good use of available data for treatment development. However, future research should continue to examine the efficacy of the 8-visit format of MAAT in larger samples.

Most notably, a final area of concern with MAAT research to date is identifying outcome measures that most accurately assess the clinical targets of MAAT. As stated above, neuropsychological testing scores can be considered secondary to quality of life and functional effects. Furthermore, neuropsychological tests may not be sensitive to many of the cognitive problems cancer survivors experience. The key is to identify patient reported outcome (PRO) measures that can reflect quality of life improvement when cognitive problems are hypothetically better managed. In previous MAAT studies, the quality of life measure used (i.e., the QOL-CS) has only one item on cognitive function. It is a broad measure of quality of life and does not directly assess the impact of cancer treatments on quality of life. Further, the other self-report measure used in previous studies, the MASQ, only assesses perceived cognitive symptoms, not *quality of life impact* of cognitive dysfunction. The MASQ also does not assess emotional impact of cognitive failures of daily life, such as anxiety about memory problems. In light of these findings, we propose using different PRO measures that reflect quality of life impact. For example, the Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog[57-59]) is a PRO measure that may be better suited for MAAT outcome research. The FACT-Cog

Table 1. **Patient Reported Outcome Measures Assessing Quality of Life Impact of Cognitive Dysfunction**

Measure	What it Measures	Description	Validity, Reliability	Pros, Cons	Primary Reference
Workplace Cognitive Failures Scale (WCFS)	Workplace cognitive failures	15 items; 5-point ratings (1= never; 5= very often)	neuroticism r= .38, role-overload r= .37 unsafe behavior r= .49 micro-accidents r= .24	***Pros:*** *Great utility in predicting safety behaviors & outcomes* ***Cons:*** *Limited to workplace*	Wallace & Chen (2005) [71]
Work Limitations Questionnaire (WLQ)	Impact of chronic health problems on productivity & work	25 items; 5-point scale (0=none of the time; 4= all of the time); 4 subscales (time, physical, mental-interpersonal & output demands); ref period 2 weeks	α ranges 0.89 to 0.91 for 4 subscales. Item-to-total = .40	***Pros:*** *Anchored to output; WLQ validated in cancer survivors with cognitive problems* ***Cons:*** *Standardization sample may not be generalizable to all occupations*	Lerner et al. (2001-3)[61,62] Calvio et al. (2010) [63]
Metamemory In Adulthood (MIA) Questionnaire	Personal memory functioning & general knowledge of memory processes	108 statements rated on a 5-point scale (1-5); 7 aspects of metamemory (strategy, task, capacity, change, anxiety, achievement, locus)	α = .71 to .93. Good discriminant validity	***Pros:*** *Several translations (e.g., Dutch, French)* ***Cons:*** *Complex instruction, lengthy*	Dixon & Hultsch (1983)[59] Dixon et al. (2008)[57]
Metamemory In Adulthood Questionnaire-Anxiety Subscale (MIA-A)	Anxiety about daily memory performance and anxiety-based memory interference	14 items; modified instructions; 5-point scale (1=strongly agree; 5=strongly disagree); ref period 2 weeks; higher score = more anxiety	α = .83 to .87 across 5 studies N = 108 to 348 (Dixon, 1988) Sensitivity to change: Healthy elderly with less education report more anxiety about cognitive ability	***Pros:*** *Short format 14 items, reduced participant burden* ***Cons:*** *Validity, reliability not established in cancer survivors*	Dixon & Hultsch (1983)[59] Dixon et al. (2008)[57]

Measure	What it Measures	Description	Validity, Reliability	Pros, Cons	Primary Reference
Cognitive Symptoms Checklist-Modified (CSC)	Cognitive symptoms in the context of work tasks	59 items; yes-no format	3 factors: working memory (α = .93) executive function (α = .91), and attention (α = .86)	***Pros:*** *Modified version reduced number of items from 100 to 59* ***Cons:*** *Limited to work setting, subjective rating of cog perform*	O'Hara et al. (1993)[72]
Functional Assessment of Cancer Therapy Cognitive Scale v.3 (FACT-Cog)	Perceived cognitive impairments, abilities, comments from others and impact of cognitive problems on quality of life in cancer survivors	50-item self-report; 5-point scale (0=never; 4=several times a day); 7 day ref period; higher scores = better QOL	α = .97 (total score) to α = .58 (concentration subscale).	***Pros:*** *Brief; norms based on cancer survivors; IQOL subscale is brief* ***Cons:*** *More data needed in broader cancer survivor samples*	Wagner, Cella, & Doninger (2003)[22]
European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 Cognitive Functioning scale (EORTC-CF)	QOL of a wide range of cancer populations on the following domains: Physical, role, cognitive, emotional, social, pain, fatigue, emesis, and QOL	2 items; 4-point scale (1-7 on health/QOL) Cognitive problems: concentration (Q20) and memory (Q25) Social interference Family (Q26) Social (Q27)	α = .69 for all scales except for the cognitive functioning scale (.28) and low correlation between the 2 scales r = .17); α = .77 for social function	***Pros:*** *Easy to administer and takes less than 2 minutes; studied in diverse populations.* *Social interference scale relevant to cancer-cog problems* ***Cons:*** *2 item subscales may limit validity, reliability*	Aaronson et al. (1993)[73]

Measure	What it Measures	Description	Validity, Reliability	Pros, Cons	Primary Reference
Brief Illness Perceptions Questionnaire (Brief IPQ)	Cognitive & emotional representation of illness	9 items (consequences, timeline, personal control, treatment control, identity, coherence, concern, emotional response, & causes); Single-item scale; Items rated 0-to-10 ; higher scores= increases in the dimension measured	Good test-retest: .42-.75 at 6 weeks; moderate to good associations between the Brief IPQ and the IPQ-R on all equivalent dimensions	***Pros:*** *Brevity, easy interpretation; Has open-ended causal questions* ***Cons:*** *The IPQ-R provides a more detailed analysis of the patient's identity beliefs, & provides info on cyclical timeline beliefs*	Broadbent, Petrie, Main & Weinman (2006)[74]
Memory Self-Efficacy Questionnaire- 4	Self-efficacy in memory performance for common cognitive tasks	20 items; 4 memory tasks with 5 0-100% ratings of confidence each; For each task, there are 5 memory performance items listed most to least difficult	$\alpha = .93$	***Pros:*** *Evaluates self-efficacy with memory in daily tasks* ***Cons:*** *Questionnaire burden--much reading for instructions; Those with greater impairment require assistance*	West (2001[75]; 2008)[76]
The Mayo-Portland Adaptability Inventory 4th Revision (MPAI-4)	Major obstacles people may encounter following acquired brain injury (ABI)	35 items; 5-point scale (0= None; 4= Severe problems, 75% of the time) 3 factors or indices: Ability, Adjustment and Social participation	Good internal consistency (r = .92; Item to total reliability= .96	***Pros:*** *Designed for completion by professional staff, people with ABI, and their significant others; offers the possibility for combined results of 2 or 3 rater groups; social participation relevant to cancer-cog problems* ***Cons:*** *Unstudied in cancer*	Malec (2005)[77]

Measure	What it Measures	Description	Validity, Reliability	Pros, Cons	Primary Reference
Memory Self-Efficacy Questionnaire- 4	Self-efficacy in memory performance for common cognitive tasks	20 items; 4 memory tasks with 5 0-100% ratings of confidence each; For each task, there are 5 memory performance items listed most to least difficult	α = .93	***Pros:*** *Evaluates self-efficacy with memory in daily tasks* ***Cons:*** *Questionnaire burden--much reading for instructions; Those with greater impairment require assistance*	West (2001[75]; 2008)[76]
The Mayo-Portland Adaptability Inventory 4th Revision (MPAI-4)	Major obstacles people may encounter following acquired brain injury (ABI)	35 items; 5-point scale (0= None; 4= Severe problems, 75% of the time) 3 factors or indices: Ability, Adjustment and Social participation	Good internal consistency (r = .92; Item to total reliability= .96	***Pros:*** *Designed for completion by professional staff, people with ABI, and their significant others; offers the possibility for combined results of 2 or 3 rater groups; social participation relevant to cancer-cog problems* ***Cons:*** *Unstudied in cancer*	Malec (2005)[77]
Medical Outcomes Study, Cognitive Functioning Scale (MOS COG)	6 domains of cognitive function: reasoning, concentration, thinking, confusion, memory, attention & psychomotor	6 items; 5-point scale(1 = all of the time; 5=none of the time); higher scores = better function	α = .93; 4-months re-test = .68	***Pros:*** *Brief & easy to administer* ***Cons:*** *Confusing items and the measure has been revised; research pending*	Stewart et al. (1992)[78]
Cognitive Failures Questionnaire (CFQ)	4 domains of cognitive problems in daily life (memory, distractibility, blunders, memory of names)	25 items; 5-item scale (0= never; 4=very often); Scores range 0 to 100, higher scores = more cognitive failures	Test-retest reliability of the CFQ was 0.82 over 21 weeks and 0.80 over 64 weeks. Internal consistency of this scale was α = 0.93 CFQ total post-treatment *d* =.31	***Pros:*** *Ecologically valid; responsive to treatment* ***Cons:*** *It is self-report with cognitive symptoms, not impact on QOL/function*	Broadbent et al. (1982)[79]

measures subjective cognitive complaints, cognitive abilities, comments on cognitive function from others and the impact of cognitive problems on quality of life[22-60]. We are primarily interested in the Impact on Quality of Life subscale in the current research as a primary depended variable. At the time of early MAAT development and the studies cited above, the FACT-Cog was not available. However, it is now ready for research use and we strongly encourage other investigators to use this measure.

The other outcome measure we believe to better reflect MAAT's treatment effects, the MIA-Anxiety scale, is a measure of anxiety about cognitive function and symptoms. This 14-item scale evaluates anxiety about perceived memory function (e.g., "I get anxious when I am asked to remember something") and thus provides an appropriate assessment of emotional coping with cognitive failures –a domain MAAT is designed to address–. In conclusion, it is believed these measures are better suited to the clinical targets of MAAT. There are also a number of other measures that evaluate quality of life or functional impact of cognitive problems, in addition to perceived cognitive symptoms in daily life. For example, the Work Limitations Questionnaire (WLQ) evaluates the impact that cognitive or other symptoms can have on work output[61,62] and has been used to assess the impact of cognitive problems on work among breast cancer survivors[63]. We have summarized these and other measures in Table 1 and encourage investigators to consider use of these measures in research on the cognitive effects of chemotherapy among cancer survivors.

OTHER TREATMENTS

Aside from MAAT, there are other behavioral and computer-based interventions that are being developed and studied among cancer survivors with cognitive complaints. One intervention, the Cognitive-Behavioral Model of Everyday Memory (CBMEM)[64] is a group intervention that consists of eight, 90-minute visits with four weekly, 2-hour follow-up or "booster visits." The intervention was principally designed for older adults but there is one published study with a small cancer survivorship sample consisting of 8 cancer survivors in the active treatment and 14 randomized to a health information/ education control condition. Results of this study suggest that CBMEM survivors tended to score better in memory self-efficacy and locus of control with regard to handling memory problems. CBMEM, similar to MAAT, consists of several components and emphasizes mastery of strategy training to promote self-efficacy in use of and application of memory strategies in daily life. While more rigorous study of CBMEM is necessary, the target of CBMEM on self-efficacy and mastery of self-management of daily cognitive performance is intriguing.

A computerized treatment program is currently being investigated as a treatment of chemotherapy-related cognitive dysfunction[65]. The intervention, the Brain Fitness Program by Posit Science of San Francisco, CA, utilizes a series of repetitive computer-based auditory processing speed exercises that provides performance feedback to the user. Continual adjustment by the computer to the user's performance is made to so the user is performing at about 85% success continuously. Training is based on forty 1-hour sessions (5 days per week of 1-hour sessions over 8 weeks). One RCT of older adults did produce moderate positive effects in neuropsychological test scores verbal-auditory immediate and delayed recall domains among those treated versus participants randomized to an educational control condition[66]. The authors interpreted results that the speed of processing improvements generalized

across neuropsychological domains. However, the neuropsychological test results were on tests that are presented in auditory fashion, so it remains in debate whether improved speed of processing will significantly affect daily behavioral performance in functional tasks or positively affect daily quality of life. Nevertheless, this computer-based method may hold promise for cancer survivors and investigations remain ongoing.

A final example of another intervention that has potential of helping cancer survivors with cognitive problems after cancer treatment is "C-Car and Strategy Training" by Gehring and colleagues[67]. This cognitive rehabilitation program actually combines a computerized training program with a compensatory strategy approach. C-Car was designed to treat individuals with moderate cognitive dysfunction secondary to gliomas. The overall program consists of 6 weekly, 2-hour training sessions. The computer-based component involves a computer display view of simulated automobile driving and an oncoming roadway. Hierarchically graded "driving" tasks that demand greater and faster attention are presented, and performance feedback is provided. Glioma survivors are also trained in psychoeducation sessions in compensatory strategy training. In a randomized, wait-list control trial, participants in C-Car improved in attention and verbal memory at 6 month follow-up. In addition, improvements were seen treated individuals in self-reported cognitive failures at post-treatment and 6-month follow-up that was significantly different from controls. It is not known if C-Car can help reduce anxiety about cognitive failures or reduce negative quality of life impact of cognitive symptoms among those treated. Further, C-Car has not been evaluated yet in an active control condition among individuals with cognitive dysfunction secondary to chemotherapy or other cancer treatment, and who do not have CNS disease. Nevertheless, the high quality of the waitlist RCT and the combination of computer-based processing speed training with compensatory strategies holds great promise for C-Car as an intervention for cancer survivors with chemotherapy-related cognitive problems.

PHARMACOTHERAPY

In addition to the behavioral and computer-based interventions described above, drug interventions for chemotherapy-related cognitive dysfunction have also been investigated. For example, an 8-week double-blind placebo control trial of dexmethylphenidate (d-MPH; Focalin; mean of 27.7mg/day) was conducted with 152 adult patients with various cancers (excluding patients with primary or metastatic CNS tumors) [68]. Improvements in fatigue and the memory score of the Highly Sensitive Cognitive Screen (HSCS) were observed among active medication participants vs. placebo. In another study, a sample of 68 breast cancer survivors with chemotherapy-cognitive complaints (mean of 22.8 months after last treatment) completed a trial of modafinil vs. placebo[69]. Participants were assessed with the Cognitive Drug Research (CDR) computerized neuropsychological assessment and the Brief Symptom Inventory at baseline and after 4 weeks. Significant improvements in the Speed of Memory Index ($p = .0002$) and Digit Vigilance sub-tests of the CDR were observed in the participants taking modafinil while no significant gains in the placebo group were observed. Taken together, these results suggest that there may be some clinical benefit for such medications, although more research is needed. Furthermore, cancer survivors may prefer effective non-drug alternatives after primary cancer treatment to either reduce the number of medications taken

or minimize side effects[7,70]. For instance, in the d-MPH trial cited above, 40.8% of participants reported mild/moderate headache, in addition to 27.6% reporting nausea. In light of our poor understanding of the etiology of cognitive effects of chemotherapy and potential for medication side effects and interactions, continued development of non-pharmacological approaches to cognitive dysfunction can offer survivors lower risk treatment alternatives.

DISCUSSION

Much research on the causality and treatment of cognitive effects of cancer chemotherapies remains to be done. Despite growing recognition of cognitive disturbance following chemotherapy among cancer survivors, research on effective treatments is still developing. This article has summarized some of the empirical support to date regarding MAAT as one of the emerging treatment approaches and high-lighted limitations in the research to date. In addition, we outlined the importance of identifying patient reported outcome measures that may be better suited for evaluating the quality of life and functional impact of late cognitive effects of cancer treatment— the clinical targets that MAAT is designed to affect, perhaps more so than neuropsychological test performance. Regardless of current knowledge of the etiology of chemotherapy-related cognitive problems, continued development and refinement MAAT or similar treatments is strongly encouraged especially in light of the large and growing numbers of cancer survivors.

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