2018

28-30 JUNE

VIENNA, AUSTRIA

SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

MASCC/ISOO

ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER

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SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

Neurocognitive Deficits in Older Cancer Patients

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Conflicts of Interest

- None

Background

- By 2030 close to 70% of cancer patients will be 65 years of age and older
- Age-related diseases include cognitive impairment and dementia, osteoporosis, diabetes, frailty, and sarcopenia
- The effect of chemotherapy on cognitive processes will be superimposed on age-related mild cognitive impairment (MCI) and dementia
- Given that many cancer patients have received cancer therapy, they may exhibit cognitive impairment and neurocognitive deficits earlier in life.
- Cultural and societal concerns

Definition

- Dementia is a general term for a “gradual decline in cognitive capacity severe enough to interfere with daily life”.

- The prevalence of dementia increases with age, from 15.0% of those aged 71–79 years to 37.4% of those aged 90 and older

- **Up to 74% of primary care physicians may not recognize cognitive impairment and when they do, the patient is in the moderate to severe stage of dementia**

DNA damage

Chemotherapy

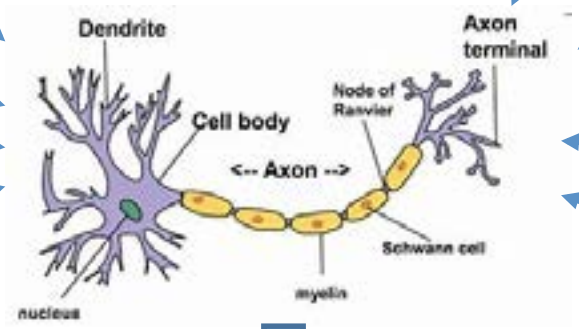
Androgen deprivation therapy

Mitochondrial Damage

Chronic inflammation

Depression

Metastatic cancer



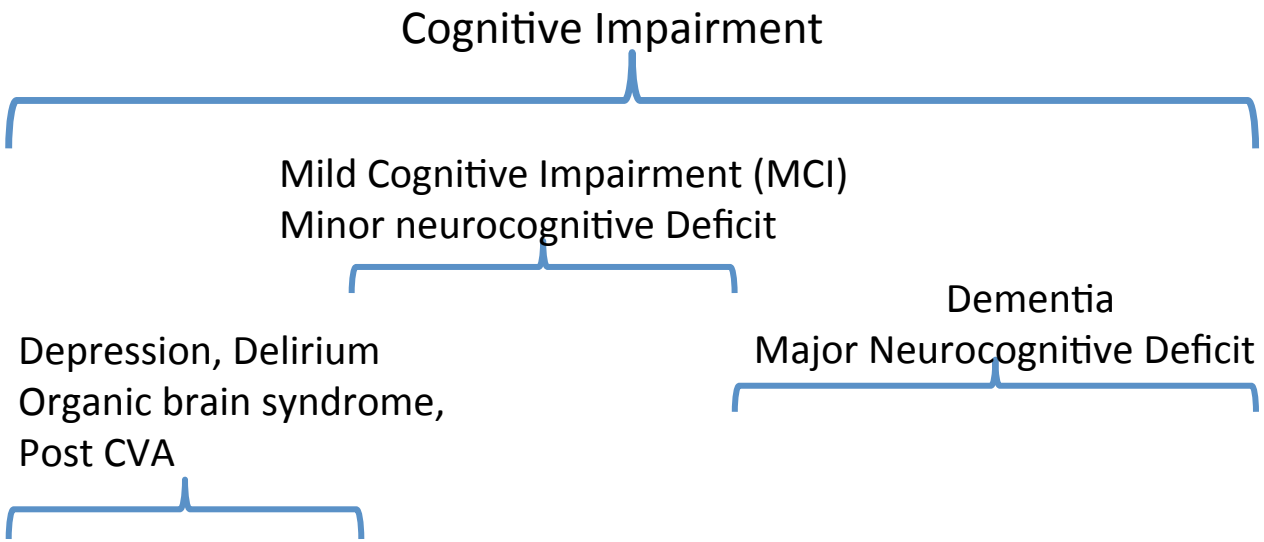
Strokes

Comorbidity

NEUROCOGNITIVE DEFICIT

Cognitive Impairment and Neurocognitive Deficits

Chemotherapy induced cognitive impairment (CCI) may develop in any of the 3 groups listed above.

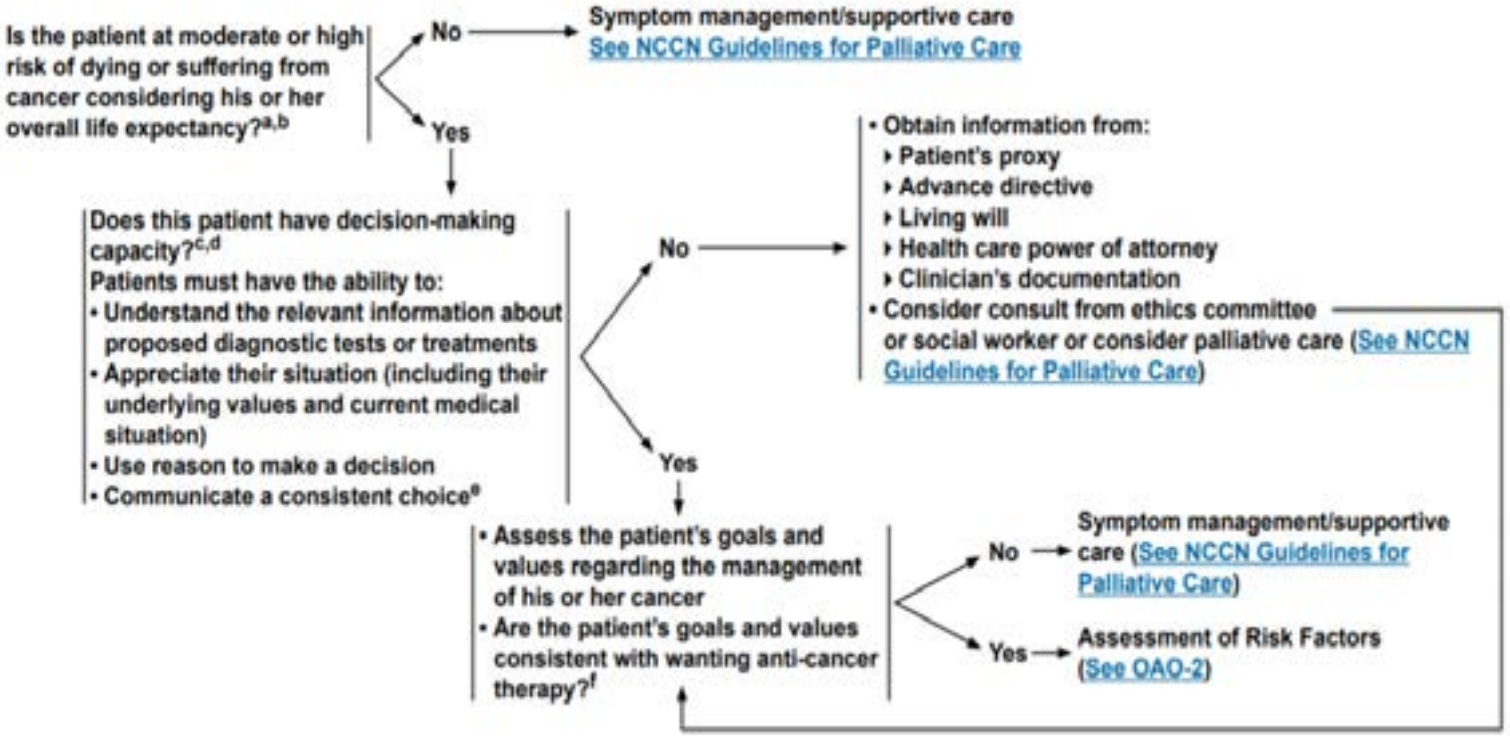


Criteria for Diagnosis

	CRITERIA FOR DIAGNOSIS		
	Oncology	National Institute of Aging	DSM V
Abnormal MoCA	Cognitive Impairment		
Abnormal MoCA + Loss of ≤ one IADL		Mild Cognitive Impairment (MCI)	Minor neurocognitive deficit
Abnormal MoCA + Loss of 2 or more IADLs*		Dementia	Major neurocognitive deficit

MoCa = Montreal cognitive assessment, IADL = independent activity of daily living, DSM = Diagnostic and statistical manual of mental disorders version V, Abnormal MoCA= < 26 or <20 if ethnic minority. Folstein Mini mental state exam (MMSE) has also been used in the literature.
* Deficits in 2 or more cognitive domains such as executive function, antegrade amnesia, aphasia, attention, abstraction, orientation, acalculia, apraxia, among others.

APPROACH TO DECISION MAKING IN THE OLDER ADULT[e]



ASSESSMENT OF COGNITIVE FUNCTION[1,2]

WHEN TO ASSESS FOR COGNITIVE FUNCTION	RECOMMENDATIONS
Would impaired cognitive function affect the planning or delivery of care? (eg, impact life expectancy or risk/benefit, impact adherence to treatment plan)	No (to all) → Reassess periodically or when considering treatment plan changes
Is the medical team concerned about decision-making capacity? See OAO-1	Yes (to any) → Consult with a clinician experienced in cognitive evaluation (ie, geriatrician, neurologist, geriatric psychiatrist, neuropsychologist, occupational therapist) OR Initiate the evaluation yourself See OAO-F (2 of 2)
Does the patient have a history of recent delirium or late onset of depression?	
Does the medical team suspect impaired cognitive function?	
Has the patient or patient's family suggested that the patient has impaired cognitive function?	

Instrumental Activities of Daily Living

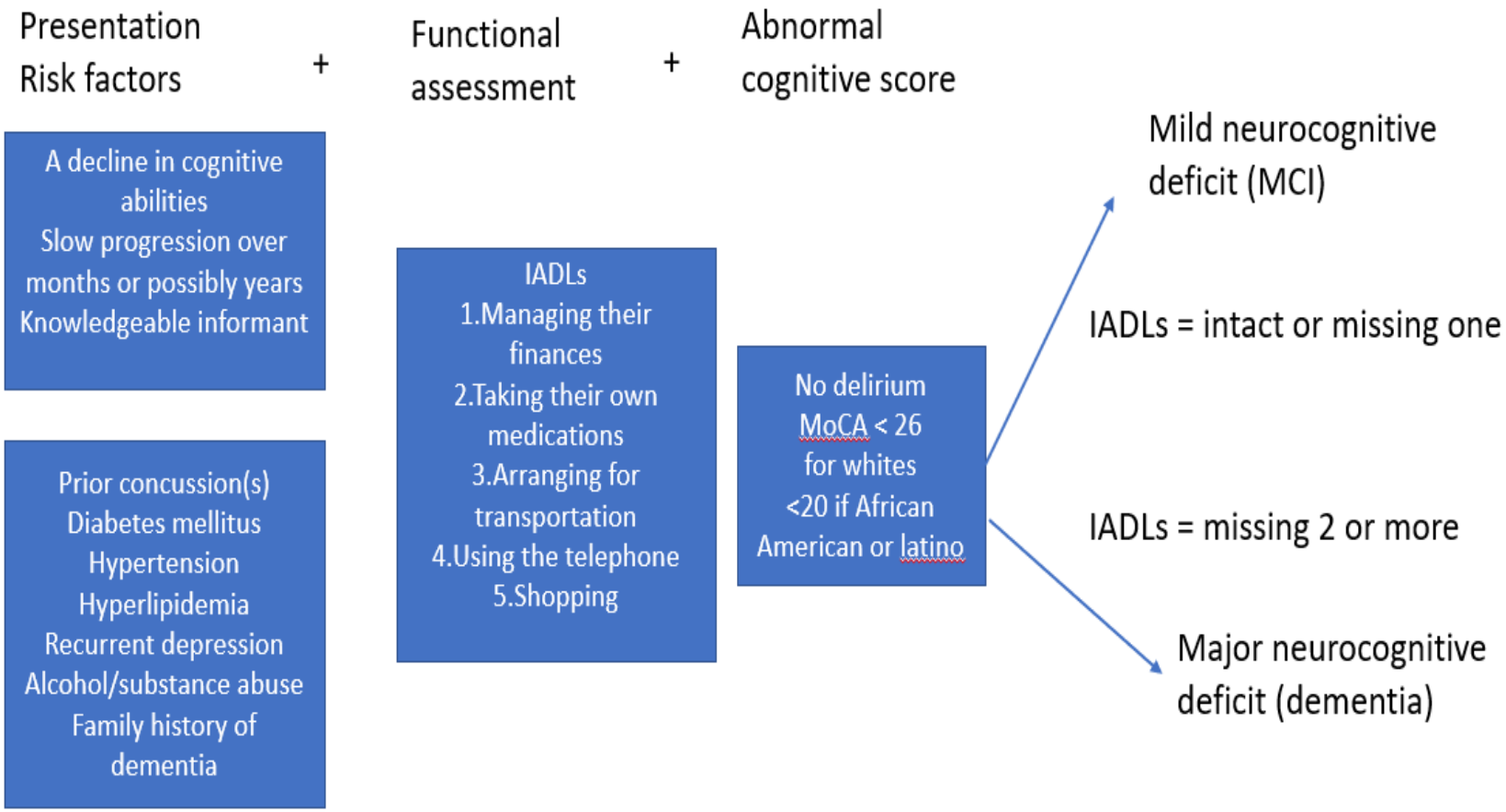
- **Original IADLS**
- Heavy housekeeping
- Laundry
- Cooking
- Financial Management
- Taking own medications
- Using the telephone
- Arranging for transportation
- Shopping

- GENDER BIAS

- **Brody's Adaptation**
- Financial management
- Taking own medications
- Using the telephone
- Arranging for transportation
- Shopping

- NO GENDER BIAS

STEPS IN DIAGNOSING NEUROCOGNITIVE DEFICITS



MCI=mild cognitive impairment; IADL= independent activities of daily living; ADL = activities of daily living

HISTORY

- **MAJOR NEUROCOGNITIVE DEFICIT**

- Cognitive deficits precede cancer diagnosis
- Cognitive deficits date back years
- Families will not recognize cognitive impairment, inquire about finances, driving, MVA, taking own medicines. etc
- Interpret findings in the setting of educational, occupational level, and ethnicity

- **CHEMOTHERAPY INDUCED COGNITIVE IMPAIRMENT**

- Cognitive deficits follow cancer care (months)
- Patient and/or families recognize a recent change in cognition

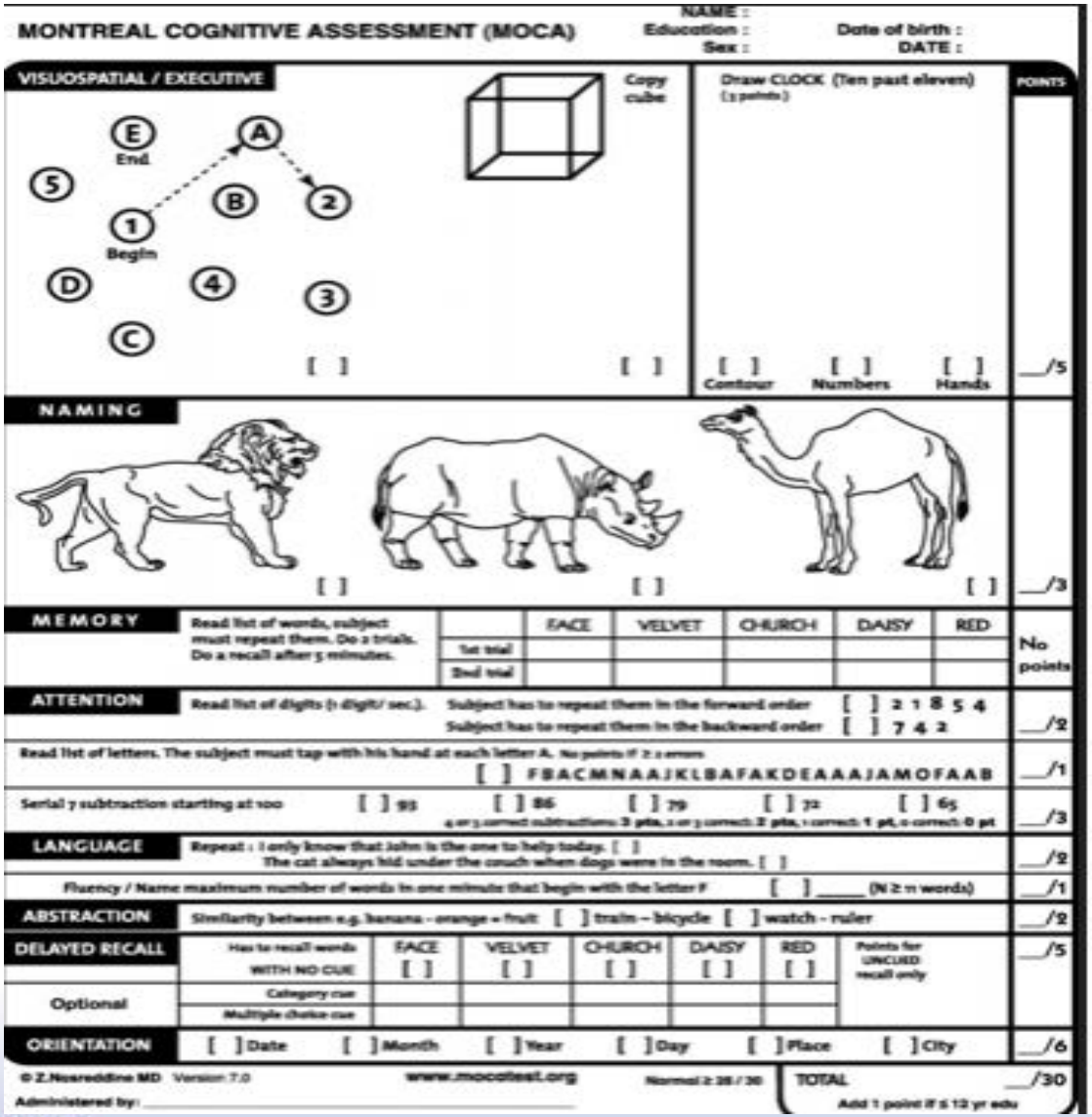
Mini Cog

- 4 items
- Clock drawing
- 3 item recall

- Comprehensive lit review 3 studies n= 1620
- Sens 99% spec 93%
- Sens 76% spec 89%
- Sens 99% spec 83%

Cochrane Database Syst Rev. 2015 Feb 3;(2):CD010860. doi: 10.1002/14651858.CD010860.pub2.

Montreal Cognitive Assessment (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands /5

NAMING

[ ] [ ] [ ] /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4 /2

Subject has to repeat them in the backward order [ ] 7 4 2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F S A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt /3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) /1

ABSTRACTION — Similarity between e.g. banana – orange = fruit [ ] train – bicycle [ ] watch – ruler /2

DELAYED RECALL

	Has to recall words	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
	WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30

Administered by:

TOTAL /30

Add 1 point if ≤ 12 yr edu

Cognitive Testing in African Americans

- Mini Mental State Examination (MMSE)
- Blessed Orientation Memory Concentration Test (BOMC)
- Neurobehavior Cognitive Status Examination (NCSE)
- Cambridge Cognitive Examination (CAMCOG)

- Montreal Cognitive Assessment (MoCA)

Lampley Dallas, JNMA 2001: 93:9

Folstein Mini Mental State Exam

- Ethnic bias
- In spite of education-adjustment, bias continues
- Does not detect early dementia
- Some studies suggest that 21 would be a better threshold for African Americans and possibly down to 18.
- Bias results in higher false positive rates for African Americans as compared to whites. Specificity of MMSE is lower in African Americans
- specific questions that are biased: WORLD spelling
  - No ifs ands or buts

Lampley Dallas, JNMA 2001: 93:9

Blessed Orientation Memory Concentration Test

- It tests Orientation, Memory and Concentration
- 6 Item scale, takes 2-3 min and has a total score of 28.
- Normal score 0 to 6 or 0 to 8; 9 questionable, 10 + dementia
- BOMC and MMSE misclassified more African Americans than whites
- BOMC 62% MMSE 42% misclassification for African Americans

- Short Portable Mental Status Questionnaire (SPMSQ), BOMC identifies patients at earlier stage than SPMSQ.
- BOMC apparently misclassified African Americans twice as often as SPMSQ

Welsh, Neurology 1995 45: 2207-2215

Lampley Dallas, JNMA 2001: 93:9

Montreal Cognitive Assessment

- MoCA was developed in Quebec, Canada among whites with a mean 13.3 ± 3.6 years of education.
- It is the scale best designed to identify Mild cognitive Impairment
- Scores may be lower in ethnic minorities (Score = 20)
- Scores may be lower in ethnic minorities. In a community of African Americans the mean MoCA 19.8 ± 3.8. If 26 is set as a cutoff for impairment, 93.5% of subjects would be considered impaired.
- Among AA with HS education, participants who were
- < 55 years MoCA 20.5
- 55 – 60 years 19.8 ± 3.8
- 65 + years of age MoCA 18.7
- In Latinos with low education (< 5 years of school) add 5 points

Dementia and geriatric cognitive disorders extra. 2015;5(1):85-95.

Journal of Aging Research. 2015;2015:872018.

MD Anderson Cohort

N=455, mean age 86 +/- 8; MoCA screen and exam, MCI 30%, dementia 33%

Prevalence of dementia is 2- fold higher than in non-cancer patients

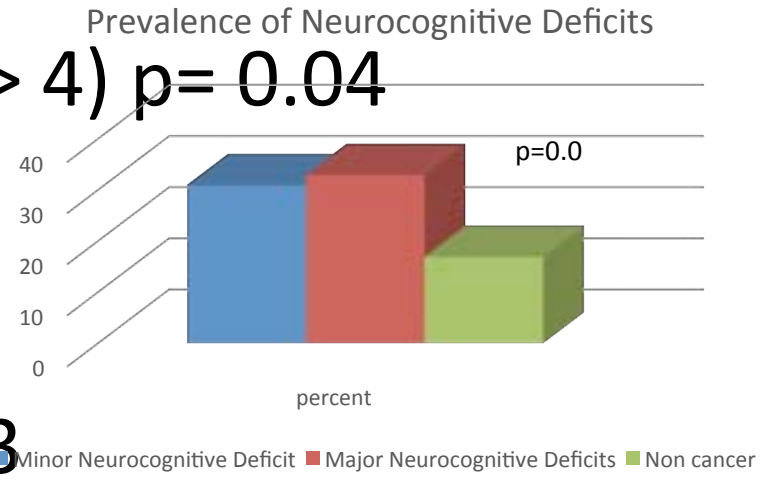
A) Previously received chemotherapy and adjuvant therapy
RCHOP, imatinib, capecitabine, folfox, bendamustine, rituximab, carboplatin, taxol, androgen deprivation therapy, aromatase inhibitors, tamoxifen, cisplatin, cyclophosphamide, clofarabine, decitabine, faslodex, cyclophosphamide, lenalidomide, prednisone, dexamethasone, doxorubicin, 5 fluorouracil, fulvestrant
B) Current chemotherapy and adjuvant therapy
Bladder cancer: cisplatin, trastuzumab, paclitaxel, doxorubicin, decitabine, sorafenib, cisplatin, trastuzumab, paclitaxel, sorafenib
Leukemias: cladribine, gleevec, clofarabine, mylotarg, Ara C, cyclosporine, fludarabine, CPX 351
Myelodysplastic syndrome: azacitidine, birinipart, decitabine, novolumab, cladribine, cytarabine, decitabine
Myeloma: lenalidomide, prednisone, zoledronic acid, bendamustine,
Lymphoma: RCHOP, bendamustine, rituximab
Breast cancer: taxol, taxotere, doxorubicin, cyclophosphamide, fulvestrant
Prostate cancer: leuprolide, abiraterone, trastuzumab, doxorubicin, decitabine, sorafenib

Edwards BJ https://doi.org/10.1016/j.jgo 2018.02.010

Factors Associated with Neurocognitive Deficits

- NCD: 33% Major NCD; 31% Minor NCD

- Multimorbidity (CCI > 4) p= 0.04
- Prior stroke p = 0.03
- Metastases p = 0.04
- Warfarin use p = 0.03



Edwards BJ https://doi.org/10.1016/j.jgo 2018.02.010

Caveats on Interpretation

- MoCA created on white HS graduates (threshold 26) in Canada
- Ethnic minorities: MoCA 20 (African Americans and Latinos)
- If you use a cut-off of 26, you miss 90% of African Americans
- Latinos with less than 5 years of education, you can add 5 points
- Repeat testing should be no closer than 6 months

DELIRIUM

- Definition :
- Acute or subacute onset of attention and cognitive changes associated with fluctuating sensorium. It may be accompanied by hyper- or hypoactivity.
- Predisposing factors: cognitive or sensory impairment, advanced age, male gender, Parkinson's disease, depression,
- Precipitating factors: infections, SIRS, strokes, myocardial infarction, heart failure, acidosis, hepatic failure, dehydration, advanced cancer, corticosteroids.

Delirium

The Confusion Assessment Method (CAM) Diagnostic Algorithm

Feature 1: *Acute Onset or Fluctuating Course*
This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

Feature 2: *Inattention*
This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3: *Disorganized thinking*
This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4: *Altered Level of consciousness*
This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

DEPRESSION

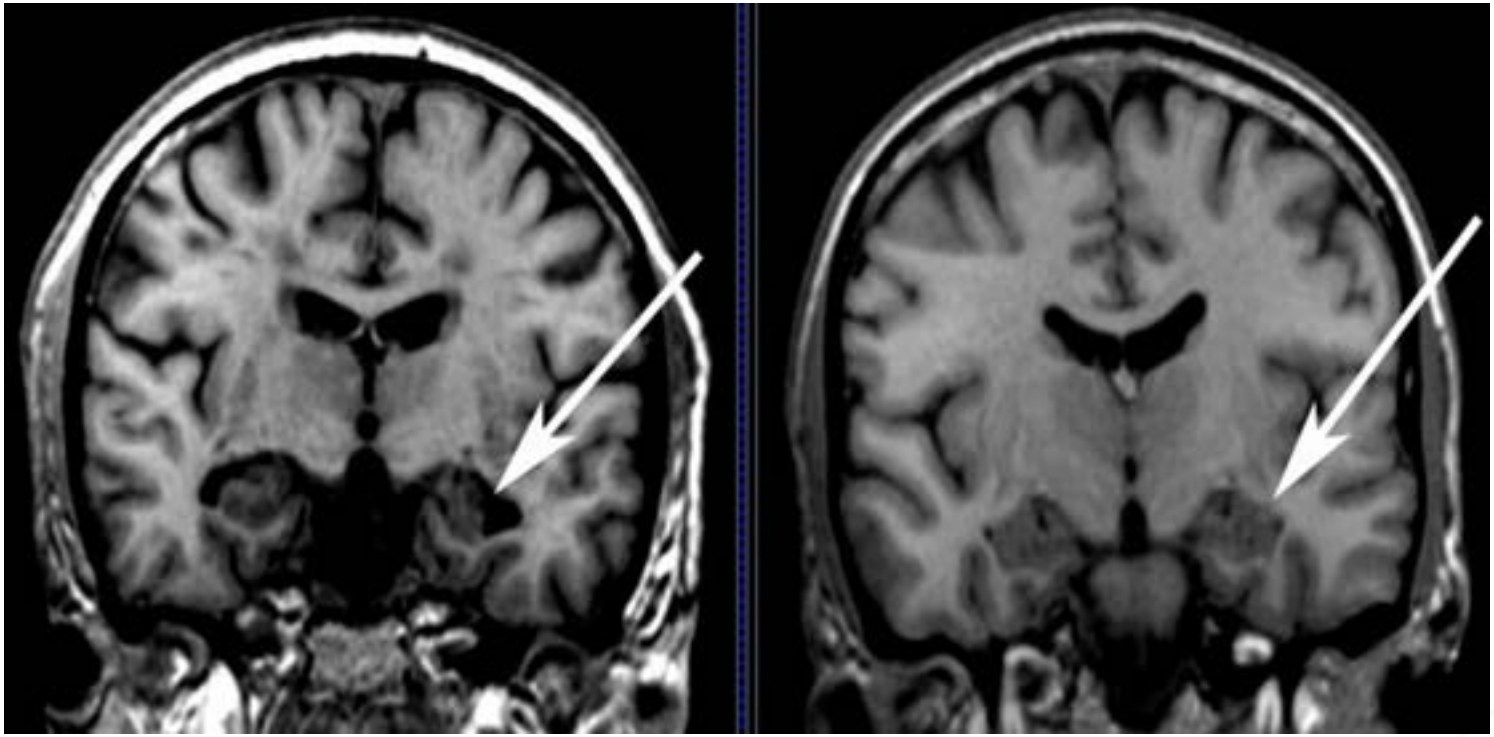
- Depression as a cause or risk factor for dementia
- Depression as a consequence of dementia
- Depression as a coincidental finding in dementia

Bennett, Maturitas 2014 Oct;79(2):184-90

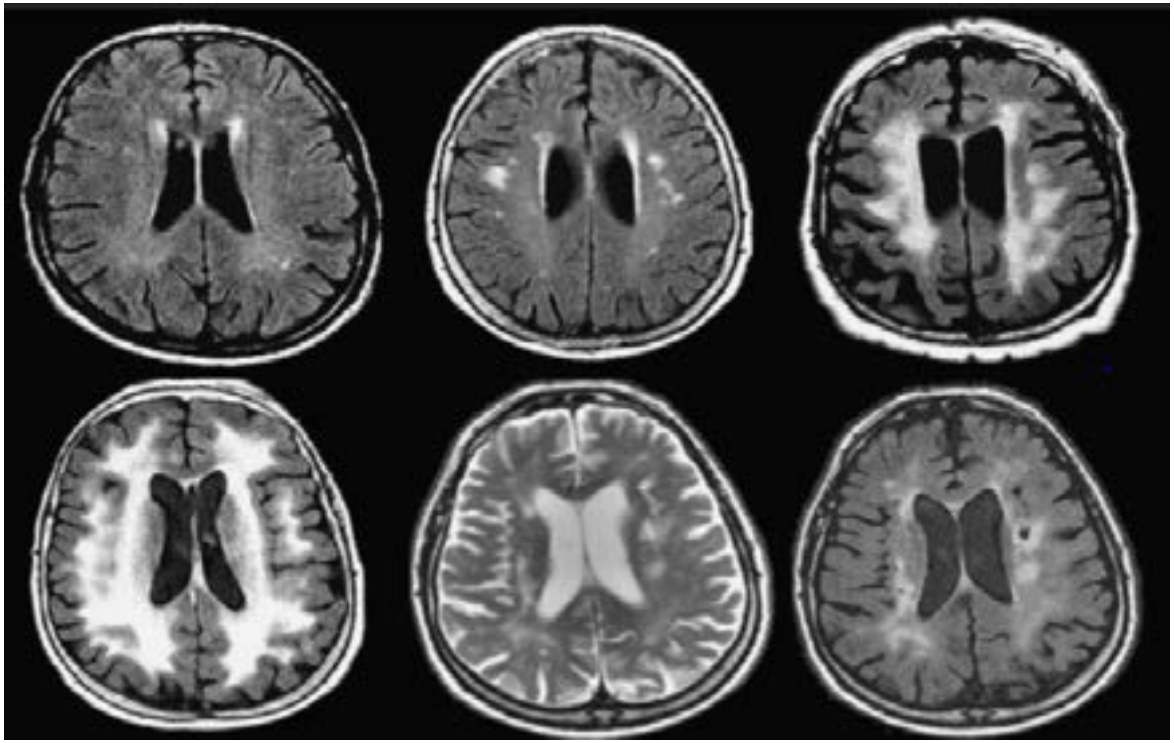
Hypothesis	Evidence for		Evidence against	
Depression being an independent risk factor in developing dementia	Ownby et al. [17]	Systematic review, meta-analysis, and metaregression analysis concluding a history of depression may confer an increased risk for later developing AD	Becker et al. [35]	Community based cohort finding no strong evidence to support the hypothesis that mood disturbance was linked with the development of dementia
	Diniz et al. [21]	Systematic review and meta-analysis of community-based cohort studies concluding late-life depression is associated with an increased risk for all-cause dementia	Luppa et al. [36]	An 8-year population-based prospective study finding no clear significant associations of depression and incident dementia
	Gao et al. [22]	Meta-analysis of longitudinal studies showing that depression was a major risk factor for incidence of dementia (including AD, VaD, and any dementia)	Li et al. [37]	Cohort study with 15 year follow up concluding that late-life depression may be an early manifestation of dementia rather than increasing risk for dementia
	Da Silva et al. [23]	Systematic review concluding affective disorders appear to be associated with an increased risk of developing dementia	Brommelhoff et al. [38]	Case control study finding depression earlier in life was not associated with dementia risk but that late-life depression may be a prodrome rather than a risk factor for dementia
	Saczynski et al. [24]	Cohort study with 17 year follow up period showing depression to be associated with increased risk of dementia		
	Geerling et al. [25]	Cohort study showing history of depression, and particularly an early onset increased risk of AD		
	Dotson et al. [41]	Cohort study with median 24 year follow up period supporting the hypothesis that depression is a risk factor for dementia and that recurrent depression increases risk		
	Chen et al. [42]	Cohort study showing the most severe syndromes and cases of depression are a risk factor for dementia		
	Barnes et al. [28]	Retrospective cohort showing recurrent depression may be etiologically associated with increased risk of VaD		
	Fernández Martínez et al. [1]	A two phase, door-to-door population-based study showing depression to be one of the risk factors for dementia		
Depression affecting the threshold for manifesting dementia	Butters et al. [2]	Narrative review formulating the link between depression and dementia		
Dementia or cognitive impairment being a feature of depression	Rapp et al. [15]	Cohort study showing that in dementia the presence of depression corresponds to accelerated cognitive decline	Bhalla et al. [16]	Cohort study showing most older individuals who are cognitively impaired during a depressive episode remain impaired when their depression remits
Depression being a prodrome of dementia	Gatz et al. [44]	Cohort study with 5-year follow-up depressive symptoms at baseline predict the development of AD and dementia	Becker et al. [35]	Community based cohort finding no strong evidence to support the hypothesis that mood disturbance was linked with the development of dementia
	Li et al. [37]	Cohort study with up to 15 year follow up concluding that late-life depression may be an early manifestation of dementia	Geerling et al. [25]	Cohort study with an average 6 year follow up showing only history of depression, and particularly an early onset, but not presence of depressive symptoms at baseline increased the risk for Alzheimer disease
	Lenoir et al. [29]	Cohort study showing high level of depressive symptoms is predictive of vascular dementia within a few years		
	Barnes et al. [28]	Retrospective cohort showing that depression that begins in late life may be part of the AD prodrome.		
	Brommelhoff et al. [38]	Case control study finding late-life depression may be a prodrome rather than a risk factor for dementia		
Depression being a reaction to cognitive decline	Jajodia and Borders [45]	A biannual longitudinal study finding that memory performance predicted change in depressive symptoms 2 years later but depressive symptoms did not predict later change in memory.	Carpenter et al. [46]	Study with a pre/post survey design finding no significant changes in depression, regardless of diagnostic outcome or dementia severity.
Dementia and depression simply sharing common risk factors	Mathers et al. [50] World Health Organisation and Alzheimer's Disease International [52]	Reports on incidence and prevalence of both depression and dementia.	Köhler et al. [27] Lenoir et al. [29]	Cohort studies showing that even controlling for shared risk factors, in particular vascular disease, depression still remained an independent risk factor for developing Alzheimer's disease
	Heun and Hein al. [54]	Prospective follow up study showing risk factors for depression in the elderly	Enache et al. [8]	
	Yip et al. [55]	Case control study showing risk factors for dementia	Savva et al. [53]	

Maturitas 2014 Oct;79(2):184-90

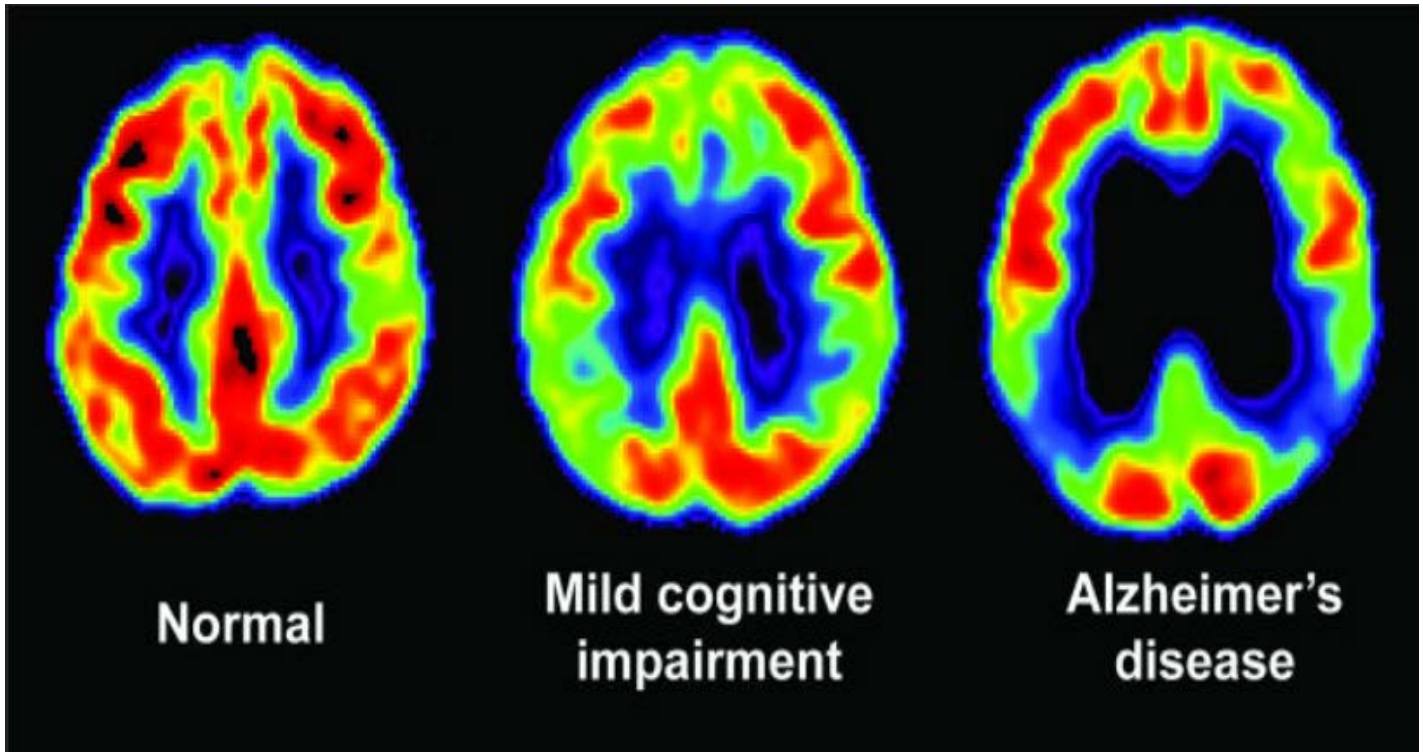
IMAGING IN ALZHEIMERS DISEASE



IMAGING IN VASCULAR DEMENTIAS



PET IMAGES IN ALZHEIMERS DISEASE



Neurobiol Aging.

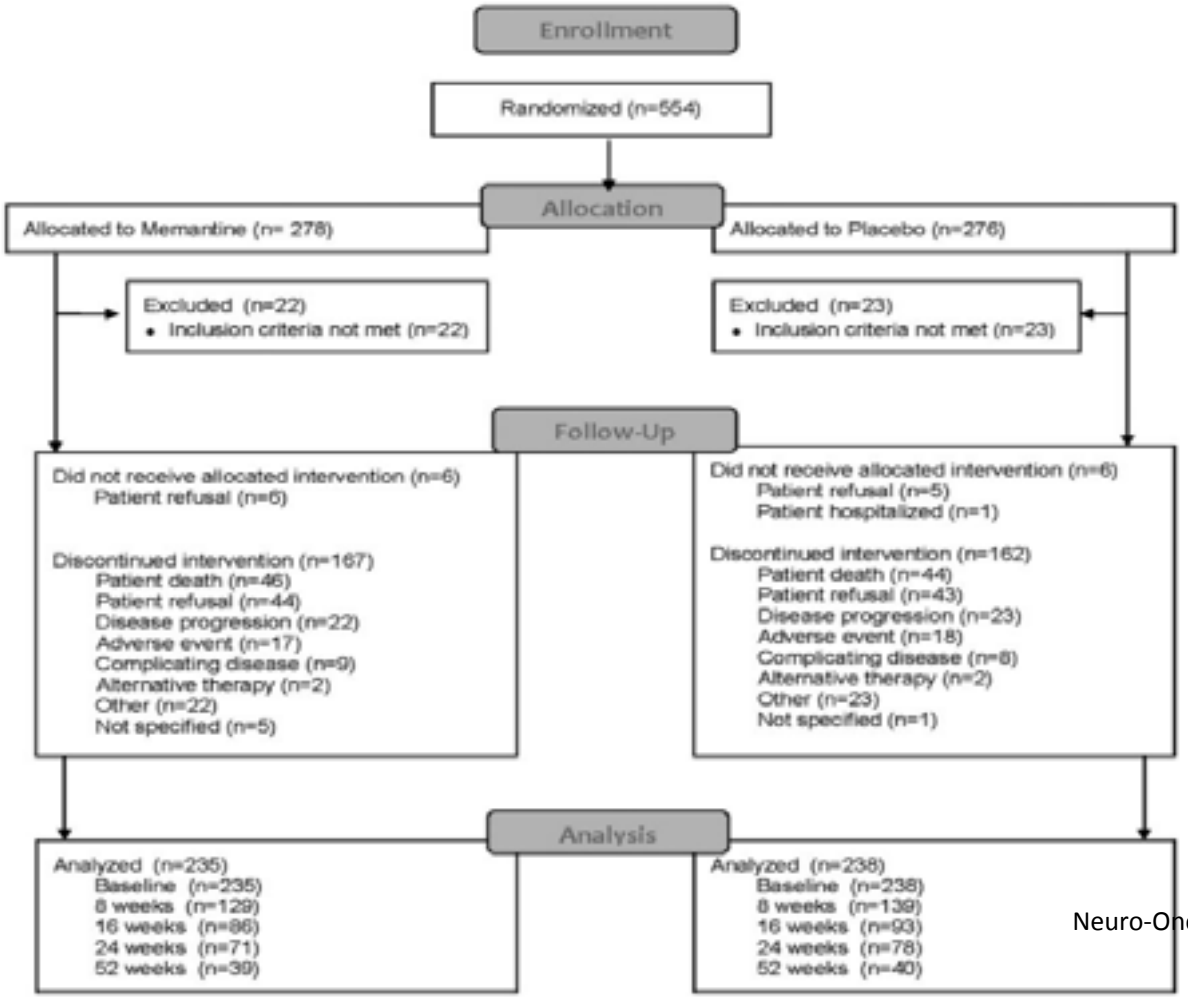
RESULTS

- MCI and dementia are commonly encountered in older cancer patients
- Issues to consider:
- Chemotherapy induced cognitive impairment- is there a greater decline with cancer care if NCD is present at baseline
- Decisional capacity- of concern when patient is in moderate stage dementia (Major NCD)
- Memantine has been successful preventing Cranial XRT cognitive impairment
- Major NCD will exert an effect on clinical outcomes

Operationalizing Cognitive Assessment

- Self- administer ADL, IADL, and Patient Health questionnaire (PHQ-9). Social support MOS
- History of concussions, strokes, T2DM, HTN, hyperlipidemia, substance abuse, family hx dementia. Assess for delirium
- Testing: quick screen Mini Cog, MoCA
- Testing: B12, VDRL, TSH/T4
- Imaging: CT brain, MRI, PET Scan
- Discussion about Rx.

RCT of Memantine to prevent XRT related cognitive impairment



Neuro-Oncology 15(10):1429–1437, 2013

Methods

- Patients received 37.5 Gy of WBRT (15 fractions of 2.5 Gy). Study drug administration was to commence no later than the third day of WBRT.
- Patients were randomly assigned to receive memantine or placebo orally for 24 weeks and escalating doses over the first 4 weeks.
- Memantine was slowly titrated to the maintenance dose of 10 mg BID.
- The dose was lowered to 5 mg orally twice daily if creatinine clearance fell below 30 mL/min and was held if the creatinine clearance was less than 5 mL/min with a weekly recheck of laboratory values.

Neuro-Oncology 15(10):1429–1437, 2013

	Memantine	Placebo	P*
Week 8			
HVLT-R Total Recall	−0.465	−0.62	.3805
HVLT-R Delayed Recall	−0.36	−0.72	.0692
HVLT-R Delayed recognition	0	−0.71	.0762
TMT-A	0	−0.1	.0848
TMT-B	0	−0.35	.2886
COWA	−0.11	−0.31	.0513
CTB Composite	−0.29	−0.48	.2157
Week 16			
HVLT-R Total Recall	−0.62	−0.615	.3854
HVLT-R Delayed Recall	−0.915	−0.71	.4109
HVLT-R Delayed Recognition	0	0	.4541
TMT-A	−0.2	−0.285	.4375
TMT-B	−0.39	−0.59	.2470
COWA	−0.05	−0.42	.0380
CTB Composite	−0.335	−0.45	.1926
Week 24			
HVLT-R Total Recall	−0.23	−0.415	.2093
HVLT-R Delayed Recall	0	−0.895	.0587
HVLT-R Delayed Recognition	0	−0.715	.0115
TMT-A	0.075	−0.365	.0237
TMT-B	−0.45	−0.49	.2966
COWA	−0.1	−0.16	.3080
CTB Composite	−0.03	−0.41	.0212

Abbreviations: HVLT-R, Hopkins Verbal Learning Test-Revised; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; COWA, Controlled Oral Word Association; CTB, Clinical Trial Battery.
*Wilcoxon rank-sum test (one-sided).

At 24 weeks there is
Less decline in delayed recall (p=0.0587)

Longer time to cognitive decline (hazard ratio 0.78, 95% CI 0.62–0.99, $p < 0.01$);

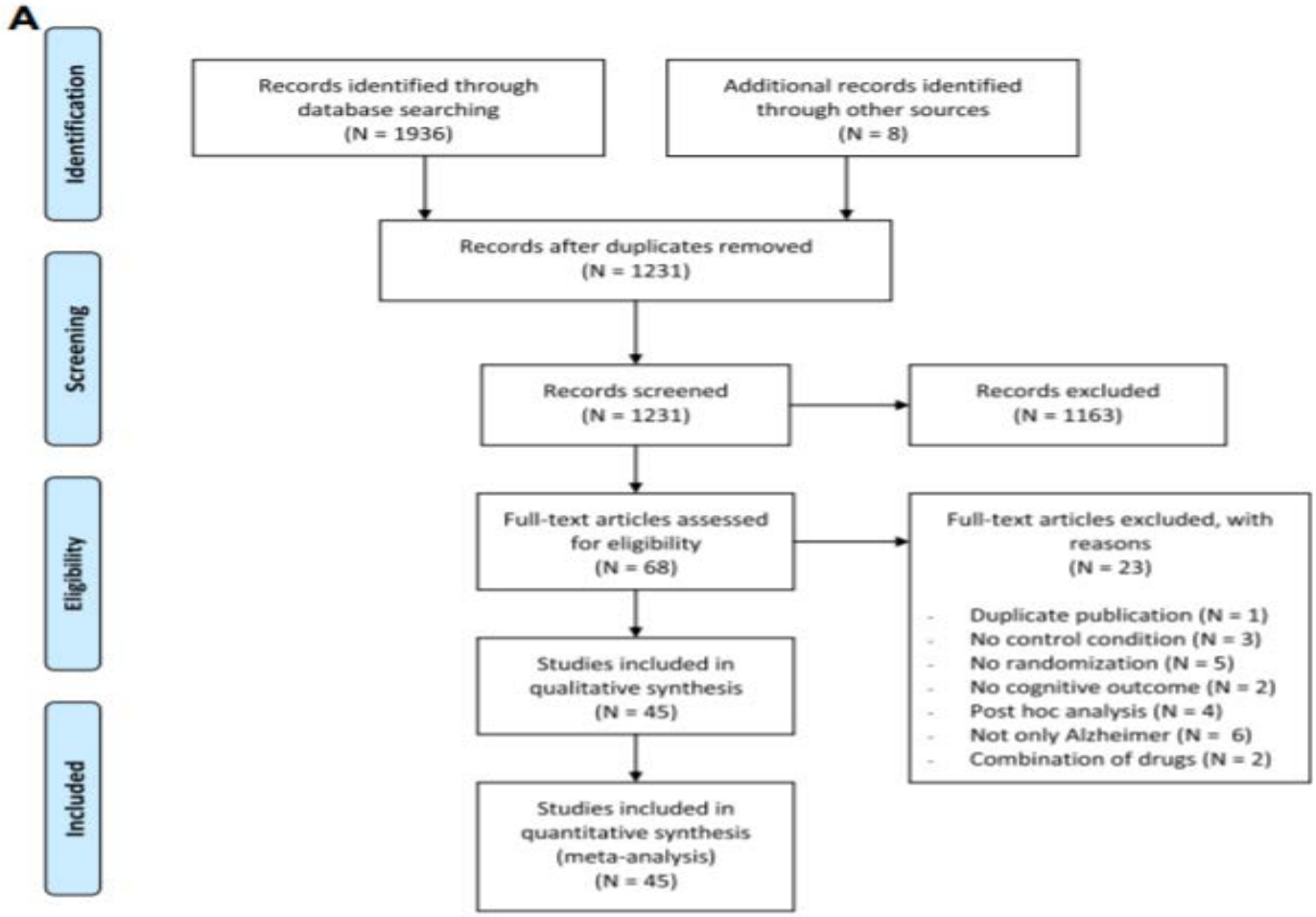
Superior executive function at 8 ($p < 0.008$) and 16 weeks ($p < 0.004$) and

Superior processing speed ($p < 0.024$)

Neuro-Oncology 15(10):1429–1437, 2013

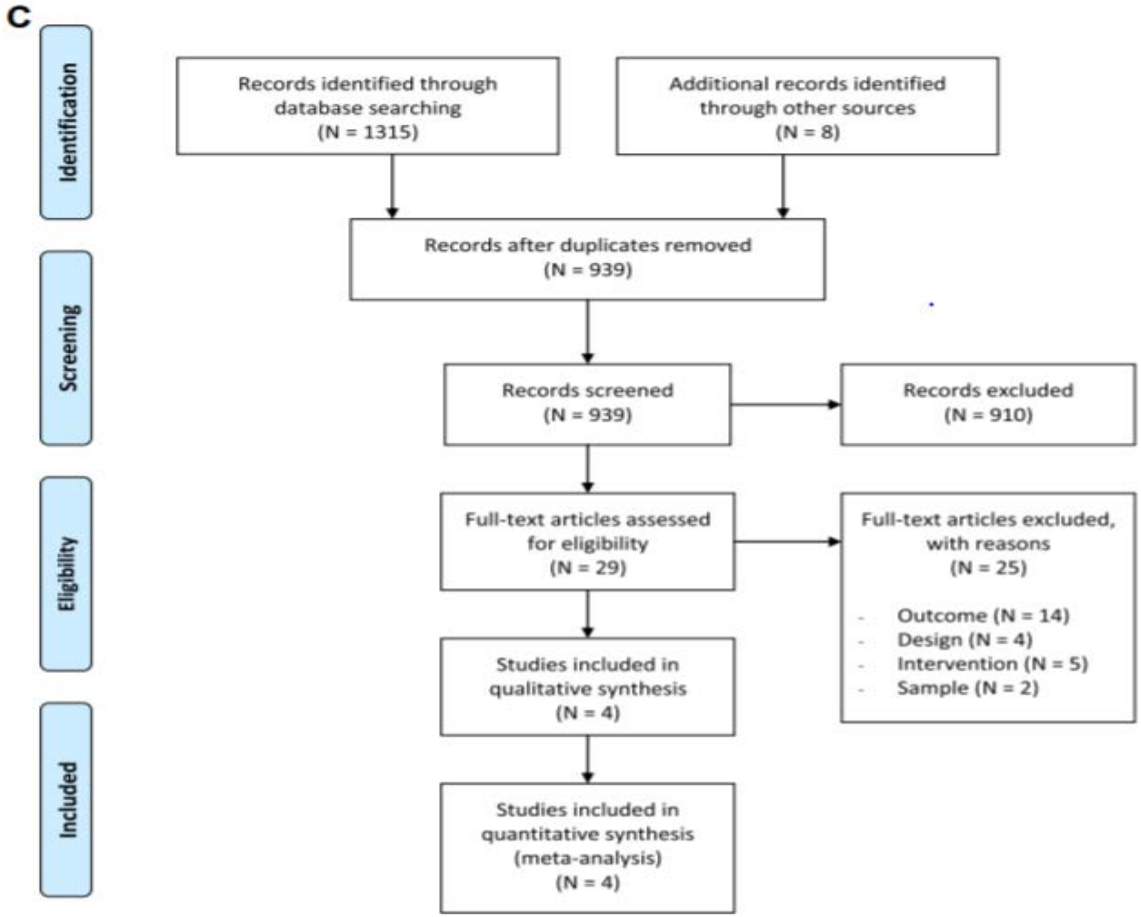
Superior delayed recognition ($p < 0.012$) at 24 weeks.

Meta-Analyses of Efficacy of Acetyl cholinesterase inhibitors on Major NCD



Strohle, Am J Geriatr Psychiatry 23:12, December 2015

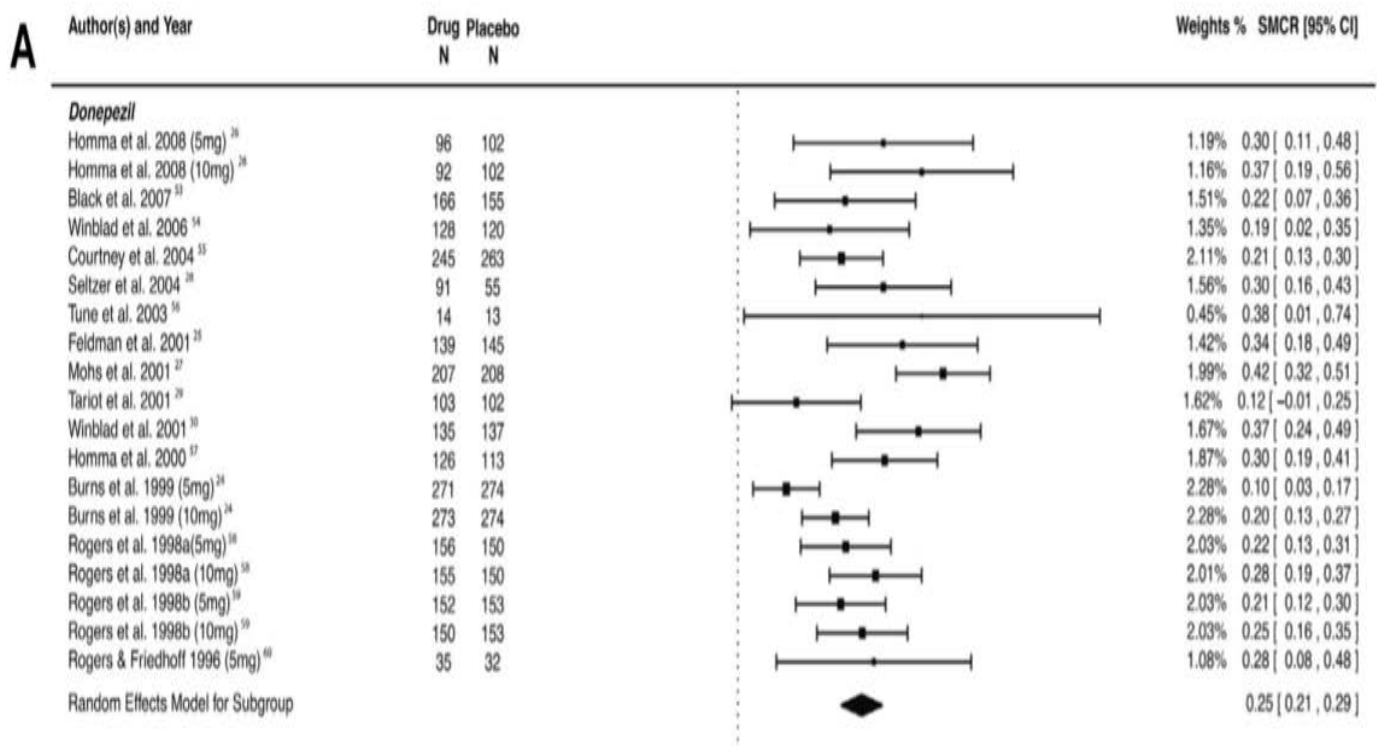
Meta analyses to assess the Efficacy of Exercise on Minor Neurocognitive Deficit



J Geriatr Psychiatry 23:12, December 2015

Forest Plot Donepezil

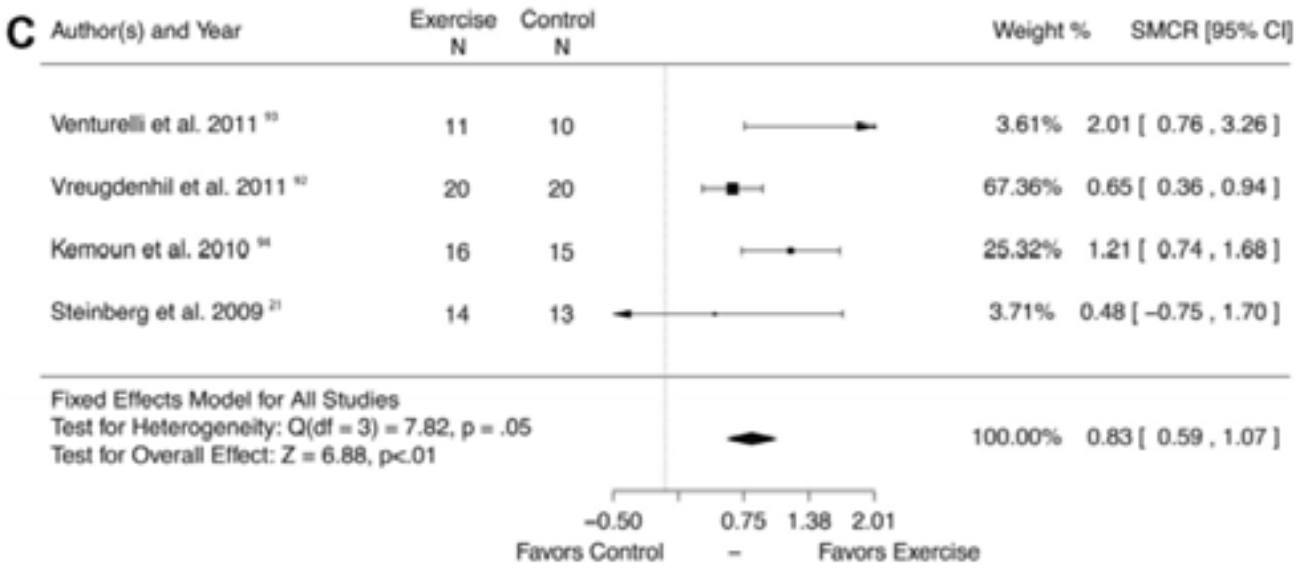
FIGURE 2. Forest plots for drug treatment in AD [A] and MCI [B] or exercise treatment in AD [C] and MCI [D].



Drug treatments resulted in a small pooled effect on cognition (SMCR: 0.23, 95% CI: 0.20 to 0.25) in AD studies (N = 45, 18,434 patients) and no effect in any of the MCI studies (N = 5, 3,693 patients; SMCR: 0.03, 95% CI: 0.00 to 0.005).

Strohle, Am J Geriatr Psychiatry 23:12, December 2015

Exercise and Major Neurocognitive Deficit



Exercise interventions had a moderate to strong pooled effect size (SMCR: 0.83, 95% CI: 0.59, 1.07)

Strohle, Am J Geriatr Psychiatry

Conclusion

- Neurocognitive deficits are common in older cancer patients
- Dementia is 2-fold higher in cancer patients than in patients without cancer
- Identification is critically important for decision making
- Management is possible
- Prevention of CCI ?
- Exercise is beneficial