Approach to Early Cognitive Impairment in the Office

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DISCLOSURES

- I have received speakers' honoraria from the following pharmaceutical companies
  - Astellas, Eisai, Pfizer
- *These potential conflicts of interest are not related to the the topic I will be talking about*
- *My presenation is strictly scientific and is not influenced by any commercial interests*

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Objectives

- *Describe the general clinical approach to early cognitive impairment*
- *List the practical tools and relevant investigations indicated for early cognitive impairment*
- *Discuss the updated criteria of Mild Cognitive Impairment and how they differ from the criteria of Dementia.*
- *Determine the best management and treatment approach in a patient with Mild Cognitive Impairment and Dementia.*

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INTRODUCTION

Should We Screen for Cognitive Impairment ?

- ***NO*** systematic screening
- Subjective complaint
- Caregiver complaint
- ***Case-Finding***
  - Age ≥ 80
  - Delirium
  - De novo (or recurrent) depression
  - Multiple vascular risk factors
  - Other clinical indices
    - Unexplained weight loss
    - Doubt about medication compliance
    - Frequent calls or medical visits (to the ER)
    - Forgetting appointments
    - « Bad historian » - Inconsistent history, etc.

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CLINICAL CASE 1

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Clinical Case 1

- You see a 81 y/o man on yearly follow-up.
- Well-controlled DM, HBP, and CAD. Recovered from a TIA in the past.
- Independent in ADLs and IADLs - Drives his car without difficulty.
- More difficulty organising his documents for tax returns in the previous year.
- Mild forgetfulness (names of actors, distant family members, rarely misplaces items, etc.).
- General physical examination is normal
- ***M***ini-***M***ental ***S***tatus ***E***xamination (Folstein) = 28/30

What other clinical evaluation would you recommend ?

Do you recommend further work-up ?

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Clinical Case 1
Clinical Evaluation

- History: r/o secondary cause
  - Medication side effects
  - Anxiety or depression
  - Sleep apnea
  - Uncontrolled chronic disease: COPD, CRF, heart failure, etc.
  - Metabolic disorder: thyroid disorder, diabetes
- General physical examination + Neurological Examination
- MOCA = 22/30 (normal 26)

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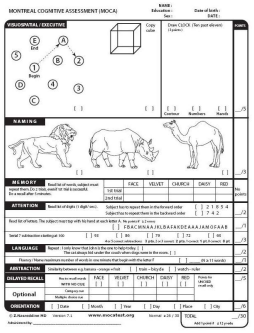
Montreal Cognitive Assessment (MOCA)



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Clinical Case 1
Work-Up

- CBC, electrolytes, Ca, BUN, creatinine, TSH (B12 / folate)
- Brain Imaging ?

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TABLE 4.
Recommendations from CCCDTD2 about CT scan needed if:

- age less than 60 years
- rapid (e.g., 1 or 2 months) unexplained decline in cognition or function
- "short" duration of dementia (less than 2 years)
- recent and significant head trauma
- unexplained neurological symptoms (e.g. new onset of severe headache or seizures)
- history of cancer (especially in sites and types that metastasize to the brain)
- use of anticoagulants or history of bleeding disorder
- history of urinary incontinence and gait disorder early in the course of dementia (as may be found in normal pressure hydrocephalus)
- any new localizing sign (e.g., hemiparesis or a Babinski reflex)
- unusual or atypical cognitive symptoms or presentation (e.g. progressive aphasia)
- gait disturbance

Gauthier S, Can Geriatr J 2012

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What is your diagnosis ?

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Clinical Case 1
Clinical Diagnosis

- Mild Cognitive Impairment (*Mild Neurocognitive Disorder*)

- Why is this not early Alzheimer's Disease?
  - Mild symptoms
  - Don't seem to be progressive
  - No repercussions on functional autonomy

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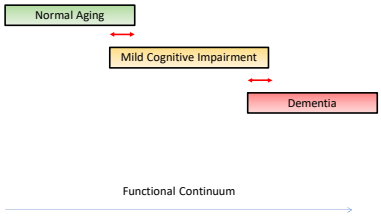
Cognitive Continuum



Petersen RC et al, Neurologia 2000

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Normal Cognitive Aging

- Slowing in reaction time
- Mild impairment in executive function (7th decade)
  - Initiation, planning, organisation (mental flexibility)
  - Capacity to evaluate and accommodate new learning
- Mild impairment in short-term memory (6th decade)
  - ↓ working memory
  - Immediate memory intact
  - Long-term memory intact
- ↓ divided attention (7th decade)
- Mild word-finding difficulty
- Typically
  - Changes are mild
  - Little/not progressive
  - Little/no functional repercussions

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Terminology

- *Cognitive Impairment Not Dementia* (CIND) (Can Study of Health and Aging, 1995)
- *Mild Cognitive Impairment* (amnestic) (MCI) (1999)
- *Mild Cognitive Impairment* (multi-domain) (2004)
  - Memory impaired (amnestic): alone or multi-domain
  - Memory spared: other cognitive fct alone or multi-domain
- Prodromal AD (Dubois, 2010)
- *Mild Cognitive Impairment due to AD* (NIA-AA, 2011)
- *Mild Neurocognitive Disorder* (DSM 5) (2013)

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Common Elements to All Definitions

- Subjective complaint – Confirmed by caregiver
- Objective evidence of decline (cognitive testing)
- Preservation of functional autonomy (mild impairment or decrease in efficiency accepted)
- Do not meet criteria for dementia
- At risk for progression ("conversion")
- Gray zone …

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Neurocognitive Disorder
DSM 5

- Change in terminology
- ***Dementia***: association with diseases of aging, stigma.
- Proposed Approach
  - Determine the affected cognitive domains
  - Determine severity of impairment / functional repercussions: mild vs major
  - Determine etiology (AD, vascular, Lewy Body, etc.)
    - Probable: typical clinical picture, supported by imaging or other biomarkers
    - Possible

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Mild Neurocognitive Disorder
DSM 5

- ***Modest Decline*** *in* ≥ ***1*** cognitive domain
  - On history
  - On objective evaluation
- No functional repercussions
- Exclusion: delirium or psychiatric condition

- Comparable to Dx criteria of MCI (Mayo, IWG, NIA-AA, etc.)

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Mild Cognitive Impairment
Progression (« conversion »)

Table 3. Rates of Progression

Source	Study Location	No. of Participants	Participant Age, y	Reported Rate of Progression	Annual Crude Progression Rate, %[a]
Solfrizzi et al.[42] 2004	Italy	1524	≥65	3.8/100 person-years	3.8
Busse et al.[70] 2006	Leipzig, Germany	863	≥75	44% per 4.3 y	10.2
Tschanz et al.[71] 2006	Cache County, Utah	3266	≥65	46% per 3 y	15.3
Fischer et al.[72] 2007	Vienna, Austria	476	75-76	33.9% per 30 mo	13.6
Ravaglia et al.[73] 2005	Italy	937	≥65	14% per 1 yr	14.0
Farias et al.[20] 2009	California	111	>60	3% per 1 yr[b]	3.0[b]
Petersen et al, unpublished data, 2009	Rochester, MN	1969	70-89	7.5% per 1 y	7.5

[a] Reported or crude rate estimated from data.
[b] Progression rate for clinic cohort reported as 13% per 1 year.

- Variable between studies
- Specialized clinics: 10%-15% per year
- Community: 6%-10% per year
- Reversibility: 25% - 30%

Petersen RC et al, Arch Neurol 2009

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Predictors of Progression

- Clinical
  - Age, education, scores on screening tests, (MMSE, MOCA, clock drawing)
  - Behavioral changes (anxiety, depression, etc.) – *Mild Behavioral Impairment, MBI*
  - Neuropsychology
- Biochemical
  - ApoE4
  - Protein τ / Aβ42 (CSF)
- Neuroimaging
  - Structural (MRI)
  - Functional (SPECT, PET)
  - Molecular (PET-PIB)

Not recommended for usual clinical management

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Mild Cognitive Impairment
Recommendations (CCCDT 2006)

- There is inadequate evidence to consider this state as equivalent to early dementia, and to treat it as such **(C, II)**
- Regular follow-up is recommended **(B, II)**
- If the MMSE is within normal limits, other ***tests such as the MOCA***, or the DemTect, or the CMC can be used **(B, II)**
- Full ***Neuropsychological*** evaluation can be used to support the diagnosis **(A, I)**

Chertkow H et al, Alzheimer's and Dementia 2007

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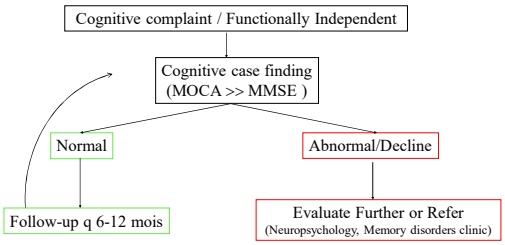
Mild Cognitive Impairment
Practical Recommendation



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Clinical Case
Counseling / Management

- Your patient is very worried about his memory
- He is worried it might be early Alzheimer's disease, and wants to inform his family about the diagnosis.
- He plans on updating his will and on making a power of attorney.
- He wants medication to slow progression of her memory loss.

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Mild Cognitive Impairment
General Management

- Counseling about the uncertainty of diagnosis and progression
- Insist on regular follow-up
- Opportunity to discuss medico-legal issues (will, power of attorney)
- Driving
  - Look for red flags (getting lost, tickets, difficulty with road signs, etc.)
  - Formal evaluation as needed

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Mild Cognitive Impairment
General Management

- ***Optimal management of comorbidities***
  - Chronic diseases
    - COPD, heart failure, DM, etc.
  - Metabolic disorders
    - Thyroid disease, etc.
  - Depression / anxiety
  - Hearing Impairment
  - Sleep disorder (Sleep apnea)
- ***Vascular prevention***
  - Optimal treatment of HBP (evidence-based data)
  - Dyslipidemia (non evidence-based data)
  - Healthy (Mediterranean) diet
  - D/C smoking
  - ***NOT*** Moderate alcohol consumption ???
- ***Rationalise medication***
  - Psychotropic medications, anticholinergic Rx, etc.

Ismail Z et al, 5th CCCDTD, Alzheimers & Dementia 2020

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Mild Cognitive Disorder
Non-Pharmacological Management

- Stay Active
  - Physically : aerobic physical exercise according to individual capacity and other medical conditions
  - Intellectually: reading, cross-word puzzles / sudoku, puzzles, solitaire, etc.
  - Socially: movies, theatre, volunteering, etc.
- Structured Programs of Cognitive Stimulation
  - Beneficial but limited and inconsistent access
- Cognitive Stimulation Software or Apps
  - Temporarily improve specific performances (task being stimulated)
  - Little or no data showing they prevent progression
- Multi-dimensional Approach
  - FINGER study (Lancet, 2015): vascular prevention / diet / physical exercise / intellectual and social stimulation.
  - Prevents cognitive deterioration in a normal population.

Ismail Z et al, 5th CCCDTD, Alzheimers & Dementia 2020

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Mild Cognitive Impairment
Pharmacological Management – CCCDT 2006

- Data is insufficient to recommend use of ***ChEI*** in MCI **(C, I)**
- Recommend ***against*** the use of the following in MCI **(D, I):**
  - NSAIDs
  - Estrogens
  - Vitamin E
  - Ginkgo Biloba
- BUT, many potentially disease-modifying drugs under study

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CLINICAL CASE 2

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Clinical Case 2

- A patient's daughter calls you because she is worried about her 78 y/o mother's memory and driving.
- Got lost for several hours in a familiar district on two recent occasions, and was unable to find her way back. She called her in panic, and she had to explain how to get back.
- Repeating herself - forgot to pays a couple of bills recently. Symptoms started about 12 months ago and are getting worse.
- Minimizes difficulties and keeps on repeating that she hasn't gotten a ticket in 20 years. She blames getting lost on road wok !!!
- "Head-Turning Sign"
- MMSE score is 22/30: misses the date by several days, forgets 2/3 words, and has difficulty with copying the pentagons.

What other clinical evaluation would you recommend ?

Do you recommend further work-up ?

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Clinical Case 2
Clinical Evaluation

- History: r/o secondary cause
  - Medication side effects
  - Anxiety or depression
  - Sleep apnea
  - Chronic disease: COPD, CRF, heart failure, etc.
  - Metabolic disorder: thyroid disorder, diabetes
- General Physical Examination + Neurological Examination
- MOCA = 18 (normal 26)

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Clinical Case 2
Work-Up

- CBC, electrolytes, Ca, BUN, creatinine, TSH (B12 / folate)
- Brain Imaging ?

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What is your diagnosis ?

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Clinical Case 2
Clinical Diagnosis

- Dementia (*Major Neurocognitive Disorder*) – Probable Alzheimer's Disease
  - Mild: impairment in IADLs
  - Moderate: impairment in ADLs
  - Severe: impairment in all ADLs (+ incontinence)
- Why is this not Mild Cognitive Impairment?
  - Progressive symptoms
  - Significant repercussions on IADLs (driving and managing $)

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MAJOR NEUROCOGNITIVE DISORDER
DSM 5

- ***Significant*** cognitive decline in ≥ ***1*** cognitive domain
  - On history
  - On physical examination
- ***Functional repercussions***
- Exclusion: delirium ou psychiatric illness
- With / without behavioral manifestations

- Significative decline in a single domain possible
- Memory decline not essential

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Mild Dementia
Non-Pharmacological Management

- **Disclose and discuss diagnosis**
- **Refer to community resources**
- **Insure home security issues**
  - *Risks*: fire, medication compliance / medication toxicity, wandering, falls, neglecting hygiene, malnutrition / food poisoning, etc.
- **Medico-Legal Dispositions** :
  - Will
  - Power of attorney
  - Competency issues
  - Driving

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Mild Dementia
General Management

- ***Optimal management of comorbidities***
  - Chronic diseases
    - COPD, heart failure, DM, etc.
  - Metabolic disorders
    - Thyroid disease, etc.
  - Depression / anxiety
- ***Vascular prevention***
  - Optimal treatment of HBP (evidence-based data)
    - Eventually, adapt Tx targets to disease stage (same for DM)
  - Dyslipidemia (non evidence-based data)
  - Healthy (Mediterranean) diet
  - D/C smoking
- ***Rationalise medication***
  - Psychotropic medications, anticholinergic Rx, etc.

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Mild Alzheimer's Disease
Standard Symptomatic Treatment

- Cholinesterase Inhibitors
  - ***Donepezil (Aricept):*** mild-severe AD
  - ***Rivastigmine (Exelon):*** mild-severe AD, parkinsonian dementia, patch approved
  - ***Galantamine (Reminyl ER):*** mild-sev AD
  - Restricted reimbursment (In Qc, exception medications → MMSE: 10-26)
- Glutamate NMDA-Receptor Antagonist
  - ***Memantine (Ebixa)*** : mod-sev
  - Restricted reimbursment (In Qc, exception medications → MMSE: 3-14)

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Standard Symptomatic Treatment
Efficacy

Cholinesterase Inhibitors

- Modest improvement or stabilisation of cognition (12 months on average)
- Stabilisation of functional impairment (6-12 months)
- May delay onset of certain behavioral symptoms
- *The three ChEI have shown efficacy in mild-severe AD. We recommend un trial with a ChEI in the majority of patients with AD (1, A)(CCCDTD 2012)*

Memantine

- Added benefit to ChEI unclear
- *Combined treatment is rational and seems safe. However, there is no sufficient data to recommend for or against this approach (2,B) (CCCDTD 2012)*

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Standard Symptomatic Treatment
Managing Expectations

- Benefits are mild and symptomatic
- There is no modification of disease progression
- Pharmacoeconomic benefits are controversial
  - Recent date (DOMINO trial) suggest
    - Decreasing Caregiver burden
    - Delaying NH placement
    - Decreasing disease cost

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Role of Primary Care Physician

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Neurocognitive Impairment
Role of PCP

- Quebec Alzheimer Plan (H Bergman et al, 2009)
- Central role for the PCP
  - Interdisciplinary support
  - Nurse / Social Workers / pharmacist, etc.
- Diligent support from secondary / tertiary specialized clinics

- Dementia Strategy for Canada (2019)

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Neurocognitive Impairment
Role of PCP

- Prevention
  - Vascular prevention
  - Non-Rx: physical / intellectual / social stimulation
- Case-finding
- Early diagnosis
- Non-pharmacological management
- Pharmacological management

Referral to Specialized ressources PRN

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Indications for Referral

- Continuing ***uncertainty*** about the diagnosis after initial assessment and follow-up
  - Atypical symptoms
  - Early onset
  - Rapidly progressive
- ***Request*** by the patient or the family for another opinion
- Presence of significant ***depression***, especially if there is no response to treatment
- ***Treatment problems*** or failure with specific medications for AD;
- Need for additional help in patient ***management*** (e.g., behavioural problems, functional impairments, medico-legal issues, driving..) or caregiver support;
- ***Genetic*** counseling when indicated
- Interest in either diagnostic or therapeutic ***research***

Third Canadian Consensus on Diagnsosis And Treatment of Dementia, 2007

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CONCLUSIONS

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Mild Cognitive Impairment
Conclusions

Mild Neurocognitive Disorder

- Intermediate state between normal aging and maj NCD
- At risk for progression to maj NCD
- Optimal management of comorbidities / Vascular prevention / Rationalise medication
- Healthy lifestyle
- No specific pharmacological treatment
- Regular follow-up

Major Neurocognitive Disorder

- Early diagnosis
- Non pharmacological interventions
- Pharmacological interventions
  - ChEI
  - Memantine
  - Modest benefits
- Future: Disease-Modifying Treatments

Central role for PCP in case-finding / early diagnosis / management

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