

# ***Practical Considerations in the Management of Alzheimer's Disease***

*McGill Refresher Course – December 2019*

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# DISCLOSURES

- **No Conflicts of Interest to Disclose**

# Objectives

- *Discuss when and how to prescribe cholinesterase inhibitors and memantine*
- *Consider when and how to stop these medications*
- *Develop a structured approach to deprescribing of other medications as dementia progresses to the moderate-severe stages*

# Clinical Case

- A patient's wife calls you because she is worried about her husband's driving.
- He got lost for several hours in a familiar district on two recent occasions, and was unable to find his way back. He called her in panic, and she had to explain how to get back.
- During the visit, your 78 y/o patient minimizes his difficulties and keeps on repeating that he hasn't gotten a ticket in 20 years. He blames getting lost on road work !!!
- On history, his wife mentions that he's repeating himself, and forgot to pay a couple of bills recently. These symptoms started about 12-18 months ago and are getting worse.
- "Head-Turning Sign"
- On examination, his **MMSE** score is 24: he misses the date by several days, he forgets 2/3 words, and has difficulty with copying the pentagons.
- **MOCA** = 18/30

# Clinical Case

## 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
- Neurological Examination

# Clinical Case

## Work-Up

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

***What is your diagnosis ?***

# Major Neurocognitive Disorder DSM 5

- ***Decline*** in  $\geq 1$  cognitive domain
  - On history
  - On objective evaluation
- Functional Impairment
- Exclusion: delirium or psychiatric condition



# Clinical Case 1

## 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 \$)

# Neurocognitive Disorder- Alzheimer

## Severity/Staging

Stage	MMSE	Cognition	Function / Autonomy	Behaviour	Other
<b><i>MCI</i></b>	> 26	Mild ↓ short-term memory (subj/obj)	Autonomous	.Normal .Withdrawal .Anxiety / mild depressive symptoms	NA
<b><i>Mild</i></b>	20 -26	. Significant ↓ short-term memory .Word-finding difficulty .↓ executive fct	Impairment in IADLs	.Apathy .Irritability .Anxiety .Depression	NA
<b><i>Moderate</i></b>	10-19	.↓ v-spatial orientation .Apraxia	Impairment in ADLs (choice of clothing)	.Agitation .Agressiviy .Psychotic Sx	-Difficulty with balance / risk of falling
<b><i>Severe</i></b>	< 10	.↓orientation to person .Apraxia .Agnosia	-All ADLs impaired -Incontinence	.Agitation .Agressivity .Psychotic Sx .Wandering .etc	.Rigidity .Falls .Immobilisation .Dysphagia / aspiration

# Neurocognitive Disorder

## Stage / Severity → Management

- ***MCI***
  - Manage comorbidities / Vascular prevention
  - Optimise medications (avoid psychotropic and anticholinergic Rx)
  - Healthy lifestyle
  - Physical exercise, intellectual /social stimulation
- ***Mild***
  - Referral to community resources
  - Assessment of home safety
  - Driving evaluation
  - Medico-legal issues (power of attorney, mandate, will)
  - Pharmacological Tx(ChEI)
- ***Moderate***
  - Home safety / community resources
  - Competency evaluation (if relevant..)
  - Stop driving
  - Prepare for NH placement
  - Pharmacological Tx (ChEI / mémantine)
  - Manage BPSD PRN
- ***Severe***
  - NH placement
  - Pharmacological Tx (ChEI / mémantine / other)
  - Level of care / palliative care (includes stopping ChEI / mémantine)

# Mild Dementia

## Non-Pharmacological Management

- **Disclose and discuss diagnosis**
- **Refer to community resources**
- **Evaluate home safety 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

# 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 / DM (non evidence-based data)
  - Healthy (Mediterranean) diet
  - D/C smoking
- **Rationalise medication**
  - Psychotropic medications, anticholinergic Rx, etc.

# 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 reimbursement (In Qc, exception medications → MMSE: 10-26)

# 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 a trial with a ChEI in the majority of patients with AD (1, A)(CCCDTD 2012)*

# Standard Symptomatic Treatment

## Managing Expectations

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



# Clinical Case

- Your patient has been on a ChEI for 2 years.
- On FU:
  - MMSE = 19/30 ( $\leftarrow$  24) – MOCA = 14 ( $\leftarrow$  18)
  - He stopped driving, has help for medications and with meals
  - Needs supervision for choice of clothing
  - Independent in other ADLs

# Clinical Case

What would you do ?

1. Continue the ChEI
2. Add memantine
3. Substitute with memantine
4. Discontinue treatment

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# Neurocognitive Disorder

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  - Assessment of home safety
  - Driving evaluation
  - Medico-legal issues (power of attorney, mandate, will)
  - Évaluation de la conduite automobile
  - Pharmacological Tx(ChEI)
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# Memantine

## Benefits / Indications

- Glutamate NMDA-Receptor Antagonist
- Moderate to severe AD
  - Restricted reimbursement (In Qc, exception medications → MMSE: 3-14)
- Superior to placebo in mod-sev AD (Reisberg et al, N Engl J Med 2003)
- Added benefit when combined with ChEI ?
  - Contradictory data
  - Yes (Tariot et al, J Am Med Assoc 2004)
  - No (Howard et al, N Engl J Med 2012)
- May improve aggressivity

### CCCDTD 2012 Recommendation:

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

# Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses

Robert Howard, Rupert McShane, James Lindsay, Craig Ritchie, Ashley Baldwin, Robert Barber, Alistair Burns, Tom Dening, David Findlay, Clive Holmes, Robert Jones, Roy Jones, Ian McKeith, Ajay Macharouthu, John O'Brien, Bart Sheehan, Edmund Juszcak, Cornelius Katona, Robert Hills, Martin Knapp, Clive Ballard, Richard G Brown, Sube Banerjee, Jessica Adams, Tony Johnson, Peter Benthams, Patrick P J Phillips

- N = 295
- Mod-sev AD (MMSE:5-13)
- 4 arms
  - DPZ
  - DPZ + Mem
  - Mem
  - Pbo
- ↓ rsq of NH placement by 17% in the 1st yr (6 months delay) (NNT=5)

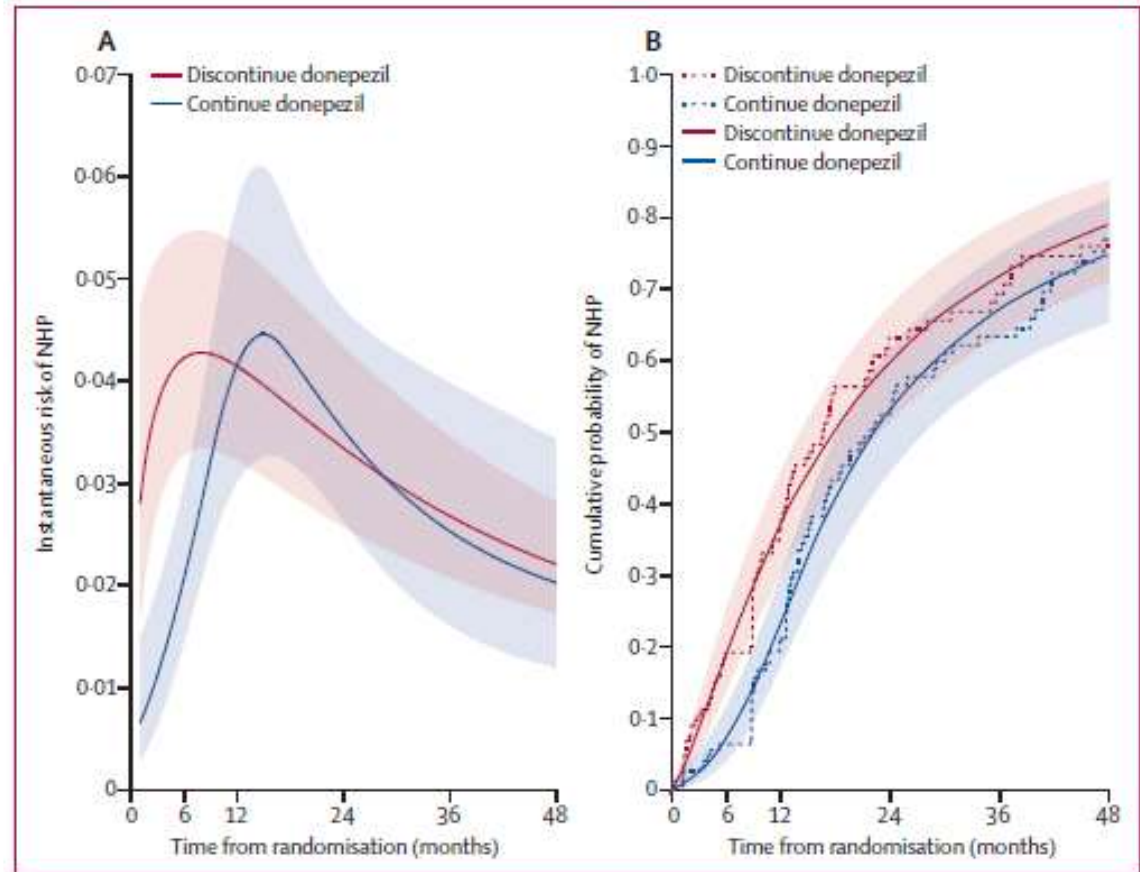


Figure 4: Change in risk of nursing home placement with time

# Clinical Case

- On FU 18 months later, he needs supervision or help for most ADLs
- He has urinary incontinence
- One episode of wandering out of the house
- Arrangements for NH placement ongoing
- MMSE = 12/30 (← 19)

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# Clinical Case

What would you do ?

1. Stop the ChEI
2. Continue the ChEI

# Discontinuing ChEI Treatment

- *Discontinuing cholinesterase inhibitors in patients with mod-sev AD may lead to worsening of cognitive/fct impairment (2B)*
- *This must be balanced with the risk for known side-effects and drug costs if therapy continues.*

# ChEI Discontinuation

## ***CCCDTD 2019***

- For individuals taking a ChEI for AD, PDD, LBD or VaD for >12 months, discontinuation should be considered if (98%):
  - a) There has been a clinically meaningful worsening of dementia as reflected in changes in cognition, functioning or global assessment over the past 6 months in the absence of other medical conditions (e.g. presence of delirium, significant concomitant medical illness) or environmental factors (e.g. recent transition in residence) that may have contributed significantly to the observed decline.
  - b) No clinically meaningful benefit was observed at any time during treatment (improvement, stabilization, decreased rate of decline)
  - c) The individual has severe or end-stage dementia (dependence in most basic activities of daily living, inability to respond to environment or limited life expectancy)
  - d) Development of intolerable side-effects (e.g. severe nausea, vomiting, weight loss, anorexia, falls)
  - e) Medication adherence is poor and precludes safe ongoing use of the medication or inability to assess the effectiveness of the medication.

# ChEI Discontinuation

## ***CCCDTD 2019***

- ChEI should ***not*** be discontinued in individuals who currently have clinically meaningful psychotic symptoms or agitation and aggression until these symptoms have stabilized unless these symptoms appear to have been worsened by the initiation or an increase in the dose of a ChEI (100%)
- Individuals who have had a clinically meaningful reduction in neuropsychiatric symptoms(e.g. psychosis) with cognitive enhancers should continue to be treated with the cognitive enhancer even if there is evidence of cognitive and functional decline (91%)
- ChEI and memantine should be deprescribed for individuals with mild cognitive impairment. (89%)

# Optimising Rx in AD

## General Principles

- Reduction of life expectancy with progression of dementia
  - Minimal duration to benefit from intervention (prevention)
  - « Time to Benefit »
- Progressive frailty with dementia - ↑ vulnerability to adverse events
  - Avoid complications of « aggressive » treatment
- Treatment Objectives
  - Tx Preventive → Curative → Symptomatic / palliative
  - Aim: quality of life, symptom control, short-term
- Adapt Tx objective to stage of the disease
- Other issues to consider
  - Correspondence with study populations
  - Cost / Socio-economic perspective
  - Ease of administration (dysphagia)

# Life Expectancy and Stages of AD

- **MCI (MMSE  $\geq 26$ )** 12 yrs
  - Subjective complaints
  - Objective decline
  - Independent
- **Mild AD (MMSE 16-26)** 6 yrs
  - Decline in memory, language, executive function
  - Impact on IADLs
- **Moderate AD (MMSE 10-15)** 4 yrs
  - Impact on ADLs
- **Severe AD (MMSE 0-10)** 2 yrs
  - Dependent on all ADLs / incontinence
- **Very severe AD (MMSE 0)** 1 yr
  - Mutism / Immobilisation

# Optimising Medication

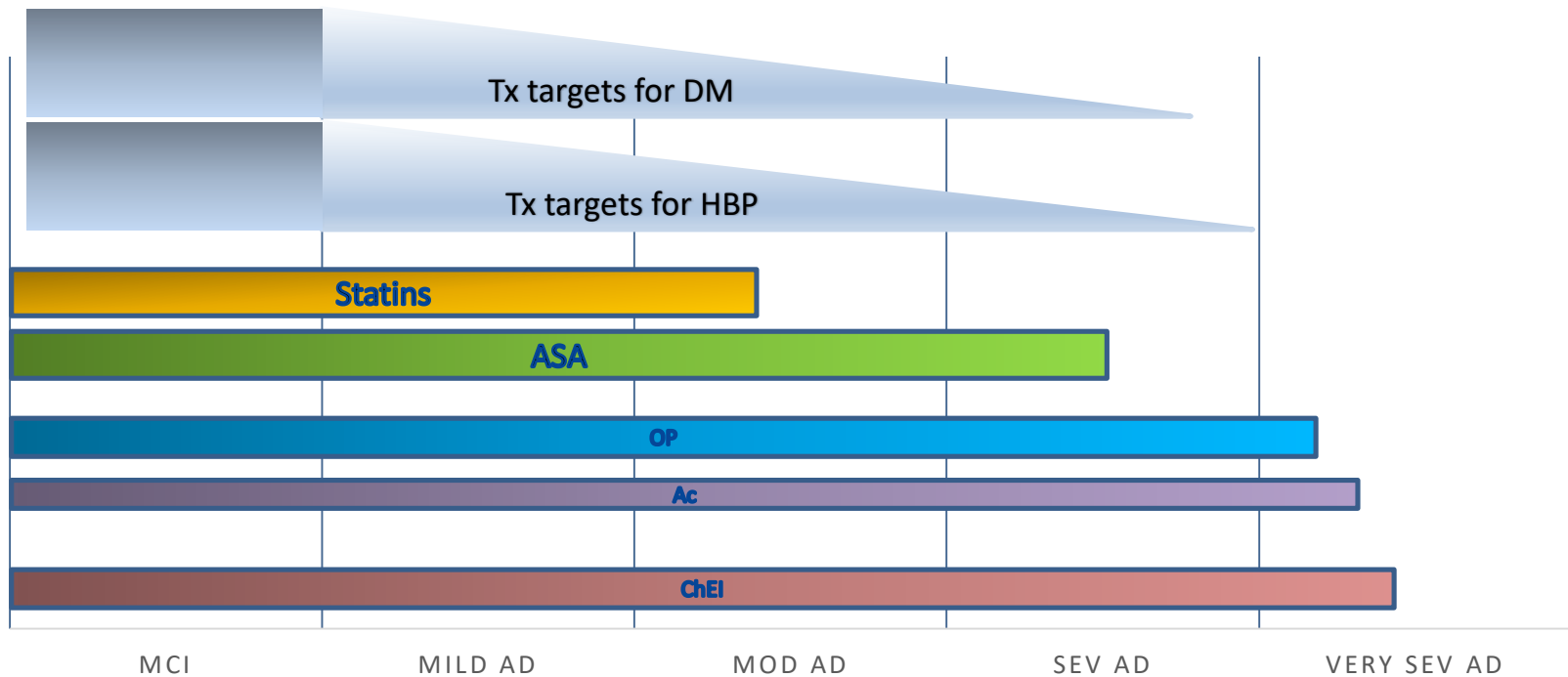
## According to Stage of AD

- **MCI (MMSE  $\geq$  26) (Life exp = 12 yrs)**
  - Avoid psychotropics / anticholinergics
  - Vasc Rsk Fct / Osteoporosis: same targets and Tx objectives as for normal older adults
- **Mild AD (MMSE 16-26) (Life exp = 6 yrs)**
  - Avoid psychotropics / anticholinergics
  - DM: Adapt therapeutic targets
  - HBP: Avoid orthostasis / “hypoperfusion” syndrome
- **Moderate AD (MMSE 10-15) (Life exp = 4 yrs)**
  - Same
  - Consider stopping statins
- **Severe AD (MMSE 0-10) (Life exp = 2 yrs)**
  - Same
  - Consider stopping ASA
  - Consider rationalizing HBP Tx
- **Very severe AD (MMSE 0) (Life exp = 1 yr)**
  - Consider stopping Tx for OP and anticoagulation in AF
  - Consider stopping ChEI
  - Consider stopping all medications that are not symptomatic



# Optimising Medication

## According to Stage of AD



# 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