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Mild Cognitive Impairment

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The past decade has seen a clear move towards clinical characterization of patients with mild cognitive concerns who appear to fall in the “grey zone” between cognitive normality and dementia.

While dementia represents cognitive deterioration causing loss of daytime functional independence, the diagnosis of “Mild Cognitive Impairment” (MCI) can be made earlier, in the presence of cognitive deterioration (confirmed by objective cognitive testing) without any clear loss of daytime functional independence^{1,2}.

Case Example: *A 67 year-old man living with his wife has had a one-year history of increasing forgetfulness for details from recent conversations. On one occasion 2-3 months ago, the patient was clearly told to pick up his wife at the store, but he never did, not recalling he was asked to do so. The patient is fully independent for all daytime functioning such as taking medications and going shopping, and he drives safely without accidents. His past history is notable for hypertension, for which he is treated with ramipril. Family history is negative for any neurologic disease. Physical examination is normal, as is bloodwork and a CT scan of the head. Mini-Mental State Examination (MMSE) is 28 out of 30, but the Montreal Cognitive Assessment (MoCA) score is 24/30 with 0/5 words recalled after a delay. Neuropsychological testing revealed delayed memory scores below the 8th percentile for age and gender. As the patient has cognitive symptoms which are verified by formalized cognitive testing, but daytime functioning is intact, a diagnosis of Mild Cognitive Impairment (MCI) is made.*

A diagnosis of MCI indicates a “warning state” which carries an increased risk of further cognitive deterioration towards dementia (MCI patients have a ~10-15% per year conversion to dementia, while a normal population has ~1-2% per year conversion to dementia^{1,3}). MCI patients and their loved ones can be informed of this increased risk, and increased clinical follow-up can be arranged. Furthermore, patients with MCI represent an ideal target population for testing of novel “disease-modifying” therapeutics designed to slow the neurodegenerative processes of conditions such as Alzheimer’s disease.

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Indeed, the most common form of MCI is one in which memory is primarily affected (i.e. amnesic MCI), which has an increased risk of progressing to the dementia of Alzheimer's disease. However, MCI involving other cognitive domains such as language, visuospatial, attention, or executive functioning (i.e. non-amnesic MCI), may progress to dementias due to other conditions, such as vascular disease, Lewy body disease, or Frontotemporal lobar degeneration^{4,5}.

The diagnosis of MCI involves careful clinical judgment regarding the nature and severity of cognitive symptoms, focusing on the presence or absence of clear-cut daytime functional impairment. Investigations such as routine bloodwork screening along with thyroid function and vitamin B12 levels, as well as a CT or MRI scan of the brain, are routinely indicated.

Neuropsychological testing is very helpful in detecting the objective cognitive deterioration required to make a diagnosis of MCI. However, office testing involving the Montreal Cognitive Assessment (MoCA) can also find evidence of cognitive impairment if the score is less than 26/30⁶. Referral to a cognitive specialty clinic can provide assistance in obtaining in-depth cognitive testing.

No pharmaceutical agent has been approved for the treatment of MCI, as clinical trials involving the cholinesterase inhibitors donepezil, rivastigmine, and galantamine have been negative^{7,8,9}. However, in one trial, use of donepezil did delay conversion of MCI to Alzheimer's dementia by 6-12 months⁷, though there was no sustained delay in conversion by the end of the trial at 3 years. Therefore, treatment of MCI with donepezil or other cholinesterase inhibitors is not routinely recommended unless patients are highly motivated to begin treatment, or there appears to be imminent conversion to the dementia stage, at which treatment with cholinesterase inhibitor therapy is indicated. Management of vascular risk factors is likely of benefit in the prevention of decline in patients with MCI, as is the maintenance of mental, physical, and social activities in daily life¹⁰.

Mild Cognitive Impairment (MCI) represents a clinical diagnostic framework in which patients with mild cognitive symptoms can be characterized. The diagnosis of MCI carries an increased risk of future worsening of symptoms, and represents an ideal target population in which future disease-modifying therapies may be most beneficial.

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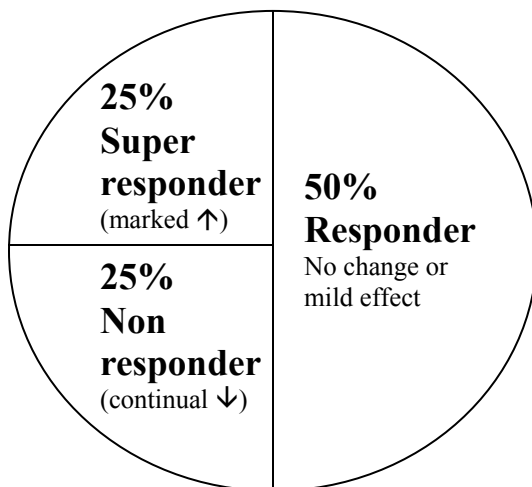
Monitoring Patient Response to Cognitive Enhancers (Cholinesterase Inhibitors and Memantine)



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1. Currently in Canada, only 25% of persons with dementia get a trial of a Cholinesterase Inhibitor (Aricept, Reminyl ER, Exelon) or Memantine. Everyone should receive a three month trial of one drug and if non-responsive/not tolerated, a trial with a second drug. Of course, consideration needs to be given to side effects and compliance issues. By the moderate stage of dementia, optimum therapy would include a trial of a CI and a trial of Memantine, either alone or in combination.
2. Monitor benefit at three months. This has been shown by studies to be generally the timeframe for optimum response. (If you're unsure, go on to six months.)
3. Response is best judged by caregiver/patient impression, not MMSE. The expected MMSE decline in untreated AD for one year is only 1 – 2 points; therefore only 1/2 point maximum change at three months. But the MMSE test-retest variability is two points. Therefore, obviously unless there is a big change (super responder: 25%) with > 2 point MMSE improvement, MMSE scores are not that helpful.
4. Patient /caregiver feedback is critically driven by (1) expectations, (2) global impression, and (3) a target symptom checklist approach.
 - i) Expectations. No change in the person at three months is a POSITIVE response to drug therapy because untreated dementia progressively worsens over time. The average patient response to CI therapy is NO deterioration one year post treatment. (In terms of “clinical meaningfulness”, think of this in cancer terms. “I have a drug that in one year, your cancer (dementia) on average will be no worse.”

Expected Response at Three Months:



A non responder should be switched to a different CI or Memantine for a second three month trial.

It is very important when starting therapy to explain these expectations so patient/caregivers understand that no change is a positive treatment response, demonstrating stabilization of the condition.

Monitoring Patient Response to Cognitive Enhancers (... continued from page 4)

ii) Global impression by patient/caregiver is just a ‘seat of the pants’: same, better or worse. Five areas factor into global impression:

| | Same | Better | Worse |
|----------------------------|------|--------|-------|
| Global Impression | | | |
| 1. Cognition | | | |
| 2. ADL’s (function) | | | |
| 3. Behaviour | | | |
| 4. Caregiver stress/burden | | | |
| 5. Interactiveness | | | |

iii) A Target Symptom Checklist approach identifies those specific symptoms of dementia which are a “problem” and have changed in the last 6 –12 months (therefore more likely to be affected by drug treatment). We use the same approach in other diseases: depression, arthritis, etc. In my opinion, the most responsive domains are interactiveness, caregiver stress/burden, global impression and behaviour. On the following checklist, pre treatment ask the patient and family to identify four to five target symptoms relevant to the individual, then to monitor and report these back to you at three months.

| <u>Cognition</u> | <u>ADL’s (function)</u> | <u>Behaviour</u> | <u>Caregiver</u> | <u>Interactiveness</u> |
|-------------------|-----------------------------|------------------|------------------|----------------------------------|
| Forgetfulness | Telephone use | Apathy | Stress | Can’t focus |
| Repetitiveness | Set/clear table | Anxiety | Burden | ↓ interaction |
| Orientation | Hygiene | Irritability | Overwhelmed | “Tuned in vs out” |
| Word finding | Bathing | Agitation | Frustration | ↓ participation |
| Getting lost | Dressing | Restlessness | Impact on job | ↓ interest |
| Misplacing things | Appliances use | Outbursts | Fatigue | ↓ initiative |
| Planning problems | Finances | Depression | Depression | More “like her/ his own self” |

THANK YOU

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