

A mysterious loss of memory

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Mrs. K develops depressive symptoms and memory loss while being successfully treated for multiple sclerosis and migraines. How would you address her cognitive decline?



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CASE Worsening memory

Mrs. K, age 46, is being treated by a neurologist for stable relapsing-remitting multiple sclerosis (MS) and migraine headaches when she complains of worsening memory over the past 5 years. She reports having difficulty recalling details of recent events and conversations. She describes occasional word-finding difficulties and problems maintaining her train of thought. She forgets where she places things and has gotten lost while driving, even on familiar routes. Her husband reports she takes more time to process things in general.

Mrs. K's cognitive decline has affected her daily life and ability to work. For 4 years, she has been an office assistant at a campground, where she takes phone reservations and keeps a site schedule. Formerly simple tasks—such as taking a phone number—have become increasingly difficult, and she cannot recall a list of 3 things to buy at the supermarket without writing them down.

Her psychiatric history is unremarkable for inpatient or outpatient treatment. She denies a history of head trauma or seizure disorder. Her medical history includes allergic rhinitis, hypothyroidism, mitral valve prolapse, fibrocystic breasts, endometriosis, and tem-

poromandibular joint disorder. Mrs. K had a hysterectomy in 2006. She denies current alcohol or tobacco use.

As a teenager, Mrs. K suffered migraines but did not seek treatment, and her headaches remitted for about 10 years. At age 29, she started to experience tunnel vision. Three years later she reported bilateral foot numbness and was diagnosed with MS. She responded well to interferon beta-1b but her migraines returned, occurring several times a week. Her migraines are successfully treated with topiramate, 75 mg/d, for prophylactic therapy and rizatriptan, 10 mg, as needed for abortive therapy. Her medication regimen also includes:

- eszopiclone, 2 mg/d, and amitriptyline, 10 mg/d, for insomnia
- butalbital/aspirin/caffeine, 50/325/40 mg, as needed for tension headaches
- fexofenadine, 12 mg/d, and budesonide, 32 mcg, 4 sprays/d, for allergy symptoms
- esomeprazole, 80 mg/d, and famotidine, 20 mg/d, as needed for dyspepsia
- propranolol, 120 mg/d, for hypertension
- levothyroxine, 75 mcg/d, for hypothyroidism
- conjugated estrogens, 0.45 mg/d, for hypoestrogenemia
- alprazolam, 0.25 mg/d, aspirin, 81 mg/d, vitamin E, 800 IU/d, and a multivitamin.

Her family history is remarkable for signs of neurocognitive degeneration in her father,

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Table**Neuropsychiatric conditions associated with MS**

Disorder	Prevalence
Major depression	Lifetime prevalence: 50%
Bipolar disorder	Estimated prevalence is 10%, twice that of the general population
Euphoria	25%
Pseudobulbar affect	Pathological laughing or crying, emotional incontinence; affects 10% of patients
Psychosis	2% to 3% vs 0.5% to 1% in general population
Cognitive impairment	40% to 60%
Source: Reference 1	

Clinical Point

MS patients might have deficiencies in information processing speed, attention, memory, and executive functions

age 75. She has 3 siblings with no known neurologic or neuropsychological symptoms.

The neurologist orders neuropsychological testing. Mrs. K demonstrates some depressive symptoms but is within normal limits across all aspects of neurocognition, including basic and complex attention, memory, bilateral motor functioning, expressive and receptive language, visuospatial/constructional function, and self-regulatory/executive functioning. The neurologist refers Mrs. K for psychiatric evaluation of her depressive symptoms.

What is the likely cause of Mrs. K's cognitive difficulties?

- early-onset Alzheimer's disease
- MS
- major depressive disorder
- side effect of topiramate
- side effect of interferon beta-1b

The author's observations

Many neuropsychiatric abnormalities may accompany MS (*Table*).¹ These can be classified as cognitive dysfunction or disturbances in mood, affect, and behavior.

Although the cause of cognitive impairment in patients with MS is unclear, its extent and profound impact on functioning has become widely recognized over the past 20 years.²

An estimated 40% to 65% of patients with MS suffer from cognitive dysfunction.^{1,3} Testing indicates deficiencies most often in:

- attention
- information processing speed
- working memory
- verbal memory
- visuospatial function
- executive functions.⁴

Although in neuropsychological testing Mrs. K had scored within normal limits on memory, attention, and executive and visuospatial function, at the time of her psychiatric evaluation she is experiencing difficulties in all of these areas. Cognitive decline can occur early in the course of MS, but Mrs. K's cognitive symptoms began approximately 10 years after she was diagnosed. The extent of the cognitive deficits commonly expands as the disease progresses.¹ Cognitive dysfunction is the primary cause of MS patients' withdrawal from the workplace⁵ and often leads to:

- reduced social interactions
- increased sexual dysfunction
- greater difficulty with household tasks.⁶

When she first complained of memory loss, Mrs. K was taking topiramate for migraine prophylaxis. Multiple studies have demonstrated adverse cognitive effects from topiramate;⁷ however, Mrs. K had noticed substantial memory changes at least 2 years before starting topiramate. She denied experiencing worsening memory after starting topiramate and did not recall any major change after her dosage was increased to 75 mg/d. She chose to continue

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memantine

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topiramate because it effectively prevented migraines and, in her mind, was unlikely related to her memory problems.

Long-term interferon beta-1b treatment prevents MS relapses, but a recent study found that interferon beta-1b had a negative impact on patients' mental health composite score and in most quality-of-life subscales over 2 years.⁸ Nevertheless, Mrs. K received interferon beta-1b therapy for at least 9 years without noticing cognitive decline.

EVALUATION **Dysthymia**

Mrs. K reports memory problems as her chief complaint. She also complains of a depressed mood, irritability, distractibility, and insomnia since her memory problems began, and admits being readily tearful. Mrs. K has difficulty "turning off her thinking" at night, which leads to delayed sleep onset, but denies sleeplessness, racing thoughts, or feelings of euphoria.

During the mental status exam, she is cooperative, alert, and oriented to person, place, and time, but distractible. She is hypokinetic throughout the interview. Her speech is normal. She describes her mood as "empty" and scores 3 on a 1-to-5-point scale for depression severity. She demonstrates a constricted affect.

Her thought process is coherent and goal-directed, and she denies having auditory or visual hallucinations or active or passive suicidal or homicidal ideation. She scores 29/30 on the Mini-Mental State Exam, but by interview she appears to have impaired remote memory. Mrs. K demonstrates unimpaired judgment and good insight.

What is the lifetime prevalence of major depression in patients with MS?

- a) 10%
- b) 30%
- c) 50%
- d) 70%

continued

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The primary cause of MS patients' withdrawal from the workplace is cognitive dysfunction

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Clinical Point

Memantine blocks effects of abnormal glutamate activity but preserves receptor activity needed for learning and memory

Box

Memantine's mechanism of action in dementia

Memantine was FDA-approved in 2003 to treat moderate-to-severe Alzheimer's disease dementia. The drug also has been used off-label to treat vascular dementia, dementia of Wernicke-Korsakoff syndrome, and acquired pendular nystagmus.¹¹

Although the neurobiologic basis for memantine's therapeutic activity in patients with dementia is not fully understood, it is thought to reduce glutamatergic excitotoxicity. The mechanism of action is voltage-dependent, uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonism with low-to-moderate affinity and fast blocking/unblocking kinetics.¹² Its kinetic profile is beneficial because it allows memantine to occupy the receptor for a sufficient time to prevent pathologic activation of glutamate receptors. However, it dissociates when the physiologic activation of glutamate receptors is necessary, thus preserving normal NMDA receptor activity required for learning and memory. By blocking the effects of abnormal glutamate activity, memantine may prevent abnormal neuronal cell death and cognitive dysfunction.

The author's observations

Mrs. K meets DSM-IV-TR criteria for dysthymic disorder and agrees to start mirtazapine, 15 mg at bedtime. I chose this antidepressant because Mrs. K continues to complain of difficulty falling asleep, and mirtazapine is known to significantly decrease sleep latency and increase total sleep time. Approximately one-half of patients with MS will experience depression.¹⁹ In a recent study of 245 MS patients followed in a neurology clinic, two-thirds of those who met criteria for major depressive disorder did not receive antidepressants.¹⁰

TREATMENT A new strategy

Mrs. K returns 2 months after starting mirtazapine and reports she is "doing the same." Her mood is improved but still dysthymic. She again demonstrates irritability during

her mental status examination and continues to complain of persistent memory problems. I titrate mirtazapine up to 30 mg/d.

After 2 more months Mrs. K's mood is euthymic and she demonstrates a bright affect, but she experiences continued decline in short- and long-term memory and reports increasing frustration with simple tasks. The rest of her mental status exam is unremarkable. I instruct her to reduce the mirtazapine dosage to 15 mg/d.

At the next visit 10 weeks later, she again presents with a euthymic mood and a bright affect. She says she attempted to decrease mirtazapine but experienced increased irritability so she remained on the 30-mg dose, with a positive effect on her mood and reduced irritability. Unfortunately, her memory problems persist.

Approximately 2 years after Mrs. K's first visit, I devise a new pharmacologic strategy. Mrs. K believes that she no longer is depressed and that her only problem is her inability to recall events. To address this, I decide to try memantine, which has been shown to cause modest improvement in clinical symptoms in severe stages of Alzheimer's disease¹¹ and also has been reported to be useful in the treatment of cognitive impairment in some bipolar disorder patients.¹² I start memantine at 10 mg/d and titrate up to 20 mg/d in 3 months.

At 3 months, Mrs. K reports improvement that she describes as "life-changing." She experiences improved memory in almost every aspect of daily functioning. She remembers daytime events and has stronger short-term memory. She can recall up to 4 items on a list several hours later, and no longer relies upon written lists to complete daily activities. Her husband and children also comment on her "remarkable" improvement.

What is memantine's mechanism of action?

- cholinesterase inhibitor
- serotonin reuptake inhibitor
- GABA receptor agonist
- N*-methyl-D-aspartate (NMDA) receptor antagonist

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The author's observations

Mrs. K's substantial memory improvement while receiving memantine warrants considering the drug for patients with cognitive dysfunction attributable to MS. Memantine is an uncompetitive NMDA receptor antagonist that the FDA approved in 2003 to treat moderate-to-severe Alzheimer's disease (*Box, page 58*).^{11,13} It is generally well tolerated and safe, with a low potential for drug-drug interactions. In clinical trials of patients receiving memantine for Alzheimer's disease and vascular dementia, the most commonly reported side effects were dizziness, headache, constipation, and confusion.¹⁴

A recent trial of memantine therapy for MS at the University of Navarra was suspended for reversible mild-to-moderate neurologic side effects.¹⁵ A phase II/phase III double-blind placebo-controlled trial at the University of Oregon designed to determine whether memantine is an effective treatment for memory and cognitive problems associated with MS is recruiting participants.¹⁶

Memantine has been reported to successfully treat other MS symptoms. A 1997 retrospective study found that 11 patients with acquired pendular nystagmus (APN) secondary to MS experienced complete resolution of APN when given memantine.¹⁷

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Related Resource

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Drug Brand Names

Alprazolam • Xanax	Famotidine • Pepcid
Amitriptyline • Elavil	Fexofenadine • Allegra
Budesonide • Rhinocort	Interferon beta-1b • Betaseron
Butalbital/Aspirin/ Caffeine • Fiorinal	Levothyroxine • Synthroid
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Disclosure

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Clinical Point

Memantine resolved acquired pendular nystagmus (APN) in 11 patients with APN secondary to MS

Bottom Line

Patients with multiple sclerosis (MS) are likely to experience depression, which may unmask or exacerbate cognitive dysfunction. Consider memantine for MS patients with cognitive dysfunction that persists despite adequate depression treatment.