

CIAN

PRIMER CURSO INTERAMERICANO DE
ACTUALIZACIÓN EN NEUROLOGÍA



Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

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Disclosures

- Dr. Ortega has no disclosures to report.



Learning Objective 1

Examine the relationship between MS and cognitive dysfunction.



Learning Objective 2

Identify psychiatric comorbidities most associated with patients with MS.



Multiple Sclerosis and Psychiatric Comorbidities

Multiple Sclerosis

- Multiple Sclerosis
 - Immune-mediated inflammatory demyelinating disorder of the central nervous system (brain, spinal cord, and optic nerves) **AND**
 - Neurodegenerative disease with axonal loss
- It derives its name from multiple “scleroses” (plaques, scars, or lesions) seen in the white matter (myelin covered axons) in pathology sections.

Epidemiology of Multiple Sclerosis

- Worldwide over 2.3 million people have MS.
- In the US, it is estimated that over 400,000 people have MS.
- It is a leading cause of disability among younger people.
- It is often diagnosed between 20 to 50 but very young pediatric patients and the elderly can also develop it.
- It is 3 times more common in women than in men, but it may be more aggressive in men.

National Multiple Sclerosis Society. Available at <http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS>. Accessed March 9, 2017.

Epidemiology of Multiple Sclerosis

- MS is more common among Caucasians (particularly those of northern European ancestry) than other ethnic groups, but people of African, Asian, and Hispanic ancestry also develop the disease.
- In fact African-Americans may have more aggressive disease.

Causes of Multiple Sclerosis

- Exact cause is unknown—likely a combination of genetics and environmental factors
 - The concordance for MS in identical twins is 20% to 30% and in fraternal twins or siblings, it is 2% to 5%. This suggest genetics plays a partial role in developing MS.
 - The strongest genetic factor in MS susceptibility is a gene located within the major histocompatibility complex (MHC) on chromosome 6p21: HLA-DRB1*1501.
 - 55% of MS patients have at least one allele compared to 24% of general population.
 - Therefore, this gene is important but only a small part of the genetic influence on MS.

Tullman MJ. *Am J Manag Care*. 2013;19:S15-S20.

Goodin DS. *BMC Neurol*. 2010;10:101.

Environmental Factors in MS

- MS is more common above 40° latitude than closer to the equator.
- This has led to speculation that sunlight or vitamin D is playing a role in MS development.
- However, many people in areas close to the equator have low vitamin D levels despite their geography and they do NOT develop MS.
- Infection is another theory. The prevailing pathogen that is believed to trigger MS is Epstein-Barr (EBV). Infectious mononucleosis is considered a risk factor.
- However, there is no unequivocal proof that EBV infected lymphocytes have ever been found in pathological sections of MS patients.

Multiple Sclerosis Immunopathology

- The basics of the immune cascade in MS are the following:
 - Antigens, either from the nervous system or antigens that resemble those from the nervous system, are presented to T cells.
 - T cells then become activated and cross the blood brain barrier.
 - They then induce inflammation via altering the production of cytokines. This inflammation is mainly directed at the myelin of neurons.
 - Initially the oligodendrocytes may remyelinate and neurons form new connections.
 - Over time, oligodendrocytes are destroyed as well and the brain loses more neurons and has less ability to repair or reconnect.

Multiple Sclerosis Immunopathology

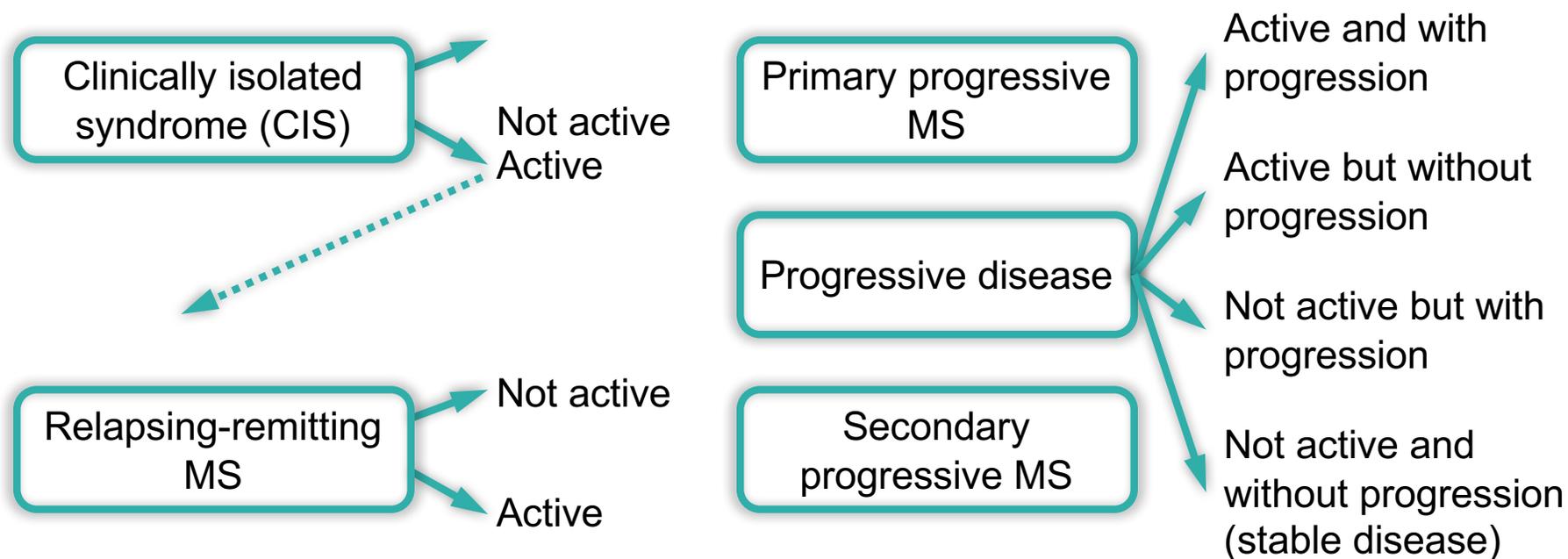
- The hallmark lesion is that of a white matter demyelinating plaque; however, even early on there is also axonal degeneration and cortical demyelination.
- Therefore there is an active inflammatory component and a neurodegenerative component.
- It is hypothesized that the inflammatory reactions lead to the neurodegenerative process likely by altering cellular metabolism in neurons and their axons.

Multiple Sclerosis

- About 90% of patients have relapsing and remitting neurological symptoms at the beginning of their disease = Relapsing-Remitting MS (RRMS)
 - Relapses are characterized by “attacks /relapses /flares /exacerbations” which are episodes of neurological symptoms in the CNS that last at least 24 hours that are due to demyelination.
- About 10% have disease that is characterized by insidious progression without relapses throughout their disease course = Primary Progressive MS (PPMS)
 - There is insidious degeneration
- Most patients with RRMS eventually stop having relapses and slowly have progressive neurological deficits = Secondary Progressive MS (SPMS)

Dendrou CA, et al. *Nat Rev Immunol.* 2015;15:545-558.

MS Disease Subtypes



Active = inflammatory activity measured by clinical relapses and/or MRI activity.

Progression = measured by clinical evaluation.

Lublin FD, et al. *Neurology*. 2014;83(3):278-286.

Multiple Sclerosis Clinical Aspects

- Some of the more common presentations:
 - Vision loss
 - Myelopathy
 - Brain stem syndromes
 - Cerebellar symptoms
 - Cerebral white matter symptoms
 - Pain syndromes
 - Neuropsychiatric presentations

Multiple Sclerosis Clinical Aspects

- Vision loss due to optic neuritis
- Transverse myelitis refers to inflammation of the spinal cord often with asymmetric sensory and motor deficits often accompanied by bowel and bladder dysfunction.
- Brainstem syndromes
 - Double vision
 - Trigeminal neuralgia with sharp pains on one side of the face in certain divisions of the trigeminal nerve.
 - Ataxia
 - Vertigo

Multiple Sclerosis Clinical Aspects

- Cerebellar relapses with Ataxia, Dysarthria, Tremor
- Cerebral white matter relapses
Hemiparesis/Hemisensory symptoms
- Pain Syndromes
 - Lhermitte's sign {Described by Jean Lhermitte (1877-1959)}: Shooting pains down neck and back with neck flexion due to lesions in the posterior column. Not specific for MS, but commonly seen in MS.
 - Paroxysmal spasms (sometimes painful, involuntary muscle contractions): Often in legs, but can occur in arms. Often due to spinal cord disease. Often worse at night.

Gelfand JM, et al. *Handb Clin Neurol*. 2014;122:269-290.



Neuropsychiatric Syndromes

Prevalence of Cognitive Dysfunction in Multiple Sclerosis

- 45% to 65% of people with MS will have some sort of cognitive problem.
- Cognitive dysfunction can be seen early in the disease course and ranges from mild to severe. It affects quality of life significantly.
- Frank dementia is seen more rarely in about 10% of patients usually in advanced progressive disease.

Rahn K, et al. *Cerebrum*. 2012;14; Newsome SD, et al. *Int J MS Care*. 2017;19(1):42-56; National Multiple Sclerosis Society. Available at https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical_Bulletin_Assessment-and-Management-of-Cognitive-Impairment-in-MS.pdf. Accessed March 6, 2017.

Cognition and Multiple Sclerosis

- There is a small subgroup of MS patients that present primarily with cognitive dysfunction.
- These patients presented with initial neuropsychiatric presentations with cognitive deficits. Imaging revealed typical demyelinating lesions and they subsequently developed typical MS relapses.

Zarei M, et al. *J Neurol Neurosurg Psychiatry*. 2003;74(7):872-877.

Staff NP, et al. *Arch Neurol*. 2009;66(9):1139-1143.

Cognitive Domains Affected by Multiple Sclerosis

- Most affected cognitive domains in MS are
 - Recent memory: retrieval of information, especially episodic memory (memory of autobiographical events)
 - Attention: difficulty with multi-tasking
 - Information processing speed: slowed thinking and responses
 - Executive functions: planning and decision making
 - Visuospatial abilities
- Intellectual functions and language skills generally remain preserved.

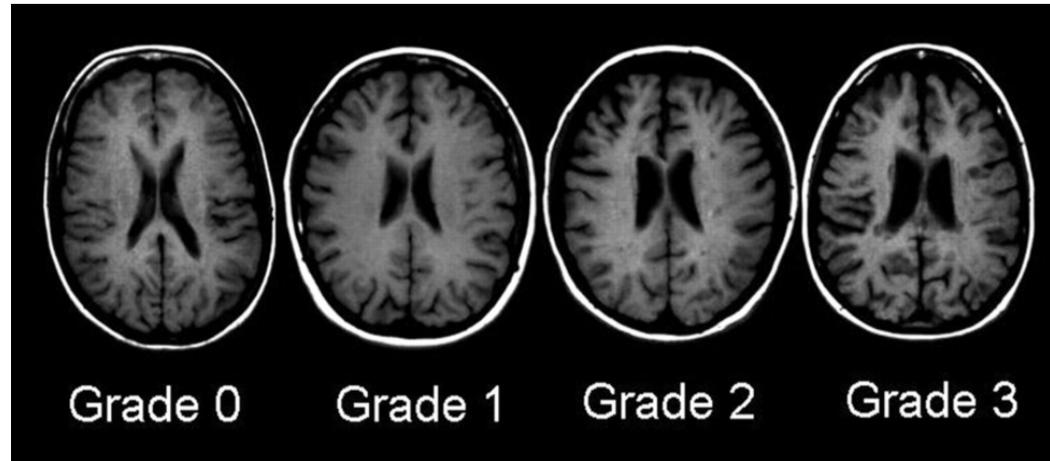
National Multiple Sclerosis Society. Available at https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical_Bulletin_Assessment-and-Management-of-Cognitive-Impairment-in-MS.pdf. Accessed March 6, 2017

MRI Findings and Cognitive Dysfunction

- Initially cognitive dysfunction was believed to be a subcortical “white matter” process, but T2 lesion volume alone does not explain
 - e.g., the cognitive dysfunction seen in PPMS where there can be minimal white matter lesion burden with severe cognitive dysfunction.
- Cortical lesions and cortical atrophy correlate better with cognitive dysfunction than the amount of white matter demyelination.

Calabrese M, et al . *Arch Neurol*. 2009;66(9):1144-1150.

Frontal Cortex Atrophy and Cognitive Impairment



Representative T1-weighted images showing all 4 grades of cortical atrophy in the superior frontal region in 4 MS patients. Atrophy was defined as enlargement of subarachnoid spaces (sulci/fissures) in relation to age-matched control subjects in a given region. The degree of atrophy was rated according to the % of loss of tissue volume, as shown on all axial slices from a given region, as normal (grade 0), mild (<10%, grade 1), moderate (10%—25%, grade 2), or severe (>25%, grade 3), according to the percentage of volume loss of parenchyma in the entire region as shown on all axial slices from that region.

Benedict RH, et al. *J Neuropsychiatry Clin Neurosci*. 2002;14(1):44-51.

Evaluation of Cognition Dysfunction

- Screening patients for cognitive dysfunction by simply asking them and family members is of value.
- After screening, patients can be referred for detailed neuropsychological testing which can better identify an individual's deficits. This can be very helpful if a patient is having difficulties at work or school.

Spanish Battery to Assess Cognitive Dysfunction

- Recently validated Spanish battery for assessment of cognitive dysfunction in MS patients.
- The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) comprised of:
 - Symbol Digit Modalities Test
 - Simple substitution task requiring less than 5 minutes to administer
 - Detects changes in cognitive dysfunction over time and in response to treatment
 - California Verbal Learning Test - Second Edition
 - Assesses episodic verbal learning and memory, encoding, recall and recognition
 - Requires 15– 30 minutes to administer
 - Brief Visuospatial Memory Test – Revised
 - Visual-graphic memory test that can document change in neurocognitive skills over time
 - Requires 45 minutes to administer, with 25 minute delay

Vanotti S, et al. *Clin Neuropsychol*. 2016;30(7):1023-1031.

Global Impact of Cognition Dysfunction

- Cognitive disorders do not occur in isolation so it is important to treat underlying mood disorders such as depression or anxiety and to address fatigue as all these can contribute to cognitive dysfunction.
- Evaluate for medical causes of cognitive dysfunction such as thyroid dysfunction B12 deficiency, sleep apnea.
- Evaluate concomitant use of medications that can affect cognition such as baclofen, benzodiazepines, or anticholinergics.
- It is important to involve the family and caregivers in discussions about cognitive dysfunction and the management plan.

Impact of Disease Modifying Therapies on Improving Cognitive Dysfunction

- There is no FDA approved medical treatment for cognitive dysfunction in MS.
- There is not much data with disease modifying treatments (DMT) as cognitive measures were not evaluated in many of the trials.
- Cognitive testing (California Computerized Assessment Package; Ruff Figural Fluency Test; California Verbal Learning Test) at wk 104 of treatment with interferon beta-1a (30 μ g weekly) or placebo noted that patients on treatment performed better than placebo.¹
- In the 5 year data from the BENEFIT trial of interferon beta-1b, PASAT (Paced Auditory Serial Addition Test) scores improved after 5 years and patients who were started on early treatment improved the most compared to the delayed treatment group.²

¹Fischer JS, et al. *Ann Neurol.* 2000;48(6):885-892; ²Kappos L, et al. *Lancet Neurol.* 2009;8(11):987-997;

Impact of Disease Modifying Therapies on Improving Cognitive Dysfunction

- Open-label use of natalizumab in patients with disease of at least 3 years found improvements in some measures of attention, memory, mood, and well-being after being on drug for 6 months.¹
- In a sample of patients with relapsing-remitting multiple sclerosis (RRMS) taking daclizumab high-yield process (DAC HYP) 150 mg subcutaneous every 4 weeks or interferon (IFN) beta-1a 30 mcg IM once weekly, DAC HYP improved SDMT scores and reduced clinically meaningful cognitive decline in RRMS versus IM IFN beta-1a over 96 weeks.²

¹Lang C, et al. *Eur Neurol.* 2012;67(3):162-166; ²Benedict R, et al. *Neurology.* 2016;86(16):P3.090.

Cognition Dysfunction is a Sign of Active Disease

“Like other clinical manifestations of MS, cognitive impairment—and especially worsening cognitive impairment as indicated by cognitive testing—is a sign of active disease, and should be viewed as justification for using disease modifying therapy or changing to a different immunomodulator, as well as other medications that may address cognitive symptoms.”

National Multiple Sclerosis Society. Available at https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical_Bulletin_Assessment-and-Management-of-Cognitive-Impairment-in-MS.pdf. Accessed March 6, 2017

Cognitive Rehabilitation

- **Compensatory Rehab**
 - Goal is not to improve cognitive abilities but rather to improve patients' everyday functions with compensatory strategies.
- **Restorative Rehab**
 - Goal is to improve impaired functions such as memory or attention using exercises and practice drills.
- There may be overlap between the two

Strategies to Improve Cognitive Dysfunction

- Focusing on one task at a time
- Memory strategies (e.g., lists and mnemonics)
- Assistive technology (e.g., hand held computers, electronic calendars and memory logs)
- Conducting conversations and activities in quiet places to minimize distraction
- Encouraging family, friend, and caregiver conversations as they may need to adjust their expectations to reflect the MS patient's deficits.

Multiple Sclerosis and Psychiatric Comorbidities

- Fatigue
- Depression
- Anxiety
- Emotional lability
- Pseudobulbar affect
- Psychosis
- Mania
- Substance Abuse
- Personality changes

Fatigue and Multiple Sclerosis

- Fatigue is the most common MS symptom¹
- Rule out any additional factors that may be contributing to fatigue
 - Iron deficiency, sleep apnea and other sleep disorders, urinary tract infections
- Exercise²
 - Consistency more important than length of session
- Drugs
 - Amantadine*
 - Modafinil/Armodafinil*

*Not FDA-approved for fatigue

¹Minden SL, et al. *Mult Scler.* 2006;12:24–38; ²Heine M, et al. *Cochrane Database of Syst Rev.* 2015;Sept 11(9):CD009956.

Relationships Between Multiple Sclerosis and Psychiatric Comorbidities

- The relationship between MS and psychiatric comorbidities is complex.
- The lifetime prevalence of many disorders is increased compared to general population.
- Stress due to illness,¹ structural abnormalities due to disease,² and inflammatory or immunological factors³ may all play a role.

¹Patten SB, et al. *Mult Scler.* 2000;6:115–120.

²Feinstein A. et al. *Mult Scler.* 2011;17:1276–1281.

³Irwin MR, et al. *Brain Behav Immunity.* 2007;21:374–383.

Psychiatric Comorbidities Negatively Impact Quality of Life of Patients with MS

- Recently a Canadian group came to the following conclusion:
 - MS patients with physical health problems are more likely to have depression, anxiety, or fatigue.
 - All have a negative impact on quality of life.

Depression and Multiple Sclerosis

- Depression
 - Point prevalence in the general population is 16%¹
 - Lifetime risk in MS is as high as 50%²
 - Up to 66% of people with MS with comorbid depression may not receive treatment³
 - People with MS are at greatest risk for depression¹
 - Following their initial diagnosis
 - Following significant loss of function and/or departure from workforce

¹Patten SB, et al. *Neurol.* 2003;61:1524-152; ²Goldman Consensus Group. *Mult Scler.* 2005;11:328–337;

³Mohr DC, et al. *Mult Scler.* 2006;12(2):204-208.

Screening for Psychiatric Comorbidities in MS

- There is no consensus for screening for mental health disorders in MS patients.
- Mental health disorders negatively impact quality of life in all people.
- They may impact medication compliance.

Screening for Psychiatric Comorbidities in MS

- For depression, one can consider the Beck Depression Inventory as a screening tool in the office.
 - 21-item, multiple-choice self-report inventory
 - Takes ~ 10 minutes to complete
- Spanish version is validated.

Treatment of Depression in Patients with MS

- If patient is suicidal, consider emergent hospitalization and referral to psychiatry.
- For patients who are not suicidal, may try a trial of antidepressant.
- Monitor liver enzymes and electrolytes especially sodium as many are associated with hyponatremia.
- Typically if patient does not respond or responds suboptimally to adequate dose, refer to psychiatry.

Additional Recommendations for Management of Comorbid Depression in MS

- Psychotherapy - often cost prohibitive
- Meditation including mindfulness based stress reduction¹
 - Mindfulness is the practice of paying attention, on purpose, in the present moment without judgment
- Patient Support Groups
- Discussions among neurologist with patient, family and support network

¹Simpson R, et al. *BMC Neurol.* 2014;14:15.

Anxiety and Multiple Sclerosis

- Lifetime prevalence in MS is as high as 22%.¹
- Anxiety has been shown to be a strong predictor of depression, explaining 48% of the variance of depression²
- Anxiety may reduce adherence to DMTs³

¹Boeschoten RE, et al. *J Neurol Sci.* 2017;372:331-341; ²Gay MC, et al. *BMC Neurol.* 2017;17:43; Bruce JM, et al. *J Behav Med.* 2010;33(3):219-227.

Screening Tools for Anxiety

- Beck Anxiety Inventory (BAI)
 - Brief, 21-item scale of subjective, somatic, or pain-related symptoms of anxiety
 - Available in Spanish
- 7-item Generalized Anxiety Disorder Scale (GAD-7)
 - Self-report inventory of seven items measuring severity of various signs of GAD
- Hospital Anxiety and Depression Scale-Anxiety (HADS-A)
 - Comprised of 14 questions to measure anxiety and depression in both the hospital and community settings
 - Available in Spanish
 - Demonstrated higher measures of sensitivity and specificity than the BAI and GAD-7

Litster B, et al. *Int J MS Care*. 2016;18(6):273-281.

Management of Anxiety in People with MS

- Trial of antidepressant
- Avoid benzodiazepines due to high addictive potential
- Refer to psychiatry for refractory anxiety
- Psychotherapy
- Meditation including mindfulness based stress reduction
- Patient support groups
- Discussions among neurologist with patient, family and support network

Other Psychiatric Comorbidities in MS

- Pseudobulbar affect (PBA) is usually seen in patients with more advanced MS
 - Prevalence of approximately 10% of patients with MS
 - Patients suddenly start to laugh or cry without feeling the associated happy or sad emotions
 - Dextromethorphan and quinidine combination FDA-approved for treatment of PBA in MS

Other Psychiatric Comorbidities (cont.)

- Psychosis
 - Prevalence of 2% - 3%¹
- Mania
 - Urgent referral to psychiatry for management with antipsychotics and mood stabilizers
- Bipolar disorder
 - Prevalence of ~6%²
- Substance abuse
 - Occurs in ~ 3% of people with MS²
 - Urgent referral to psychiatry for management with antipsychotics and mood stabilizers
 - Referral to substance abuse programs

¹Hausleiter IS, et al. *Ther Adv Neurol Disord*. 2009; 2(1): 13–29;

²Marrie RA, et al. *Mult Scler*. 2015;21(3):305-317.

Personality Changes Associated with MS

- Often related to frontal lobe dysfunction
 - Disinhibition
 - Decreased empathy
 - Lack of initiative
- Discussions among neurologist with patient, family and support network
- Factors affecting group discussions are related to patients level of insight.
- Sometimes, caregivers need mental health counseling to help cope with their increased burdens.

Smart Goals

- Assess cognitive dysfunction in patients with MS.
- Use evidence-based screening tools to assess psychiatric comorbidities in patients with MS. If present, implement treatment.
- Engage caregivers in the assessment of cognitive dysfunction and psychiatric comorbidities.



Questions & Answers



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