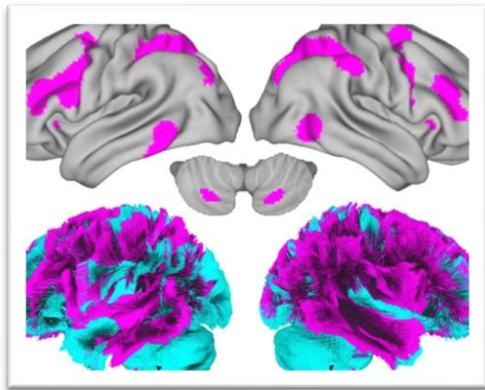


Neuropsychiatry of Multiple Sclerosis

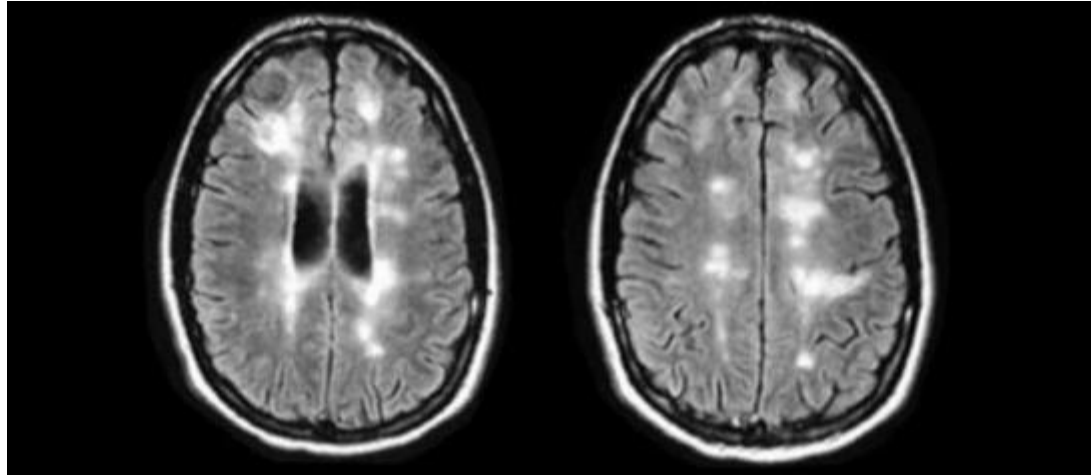
Laura T. Safar, MD



Neuropsychiatry: A Comprehensive Update

MGH Psychiatry Academy

October 23, 2026



Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose.

This talk includes discussion of off-label use of psychiatric medications and neuromodulation treatments.

Neuropsychiatry of MS

General Review

Multiple Sclerosis

Neuropsychiatric disorders in MS



Specific Neuropsychiatric Disorders in MS

Depression

Mood
Disorders

Cognitive
Disorder

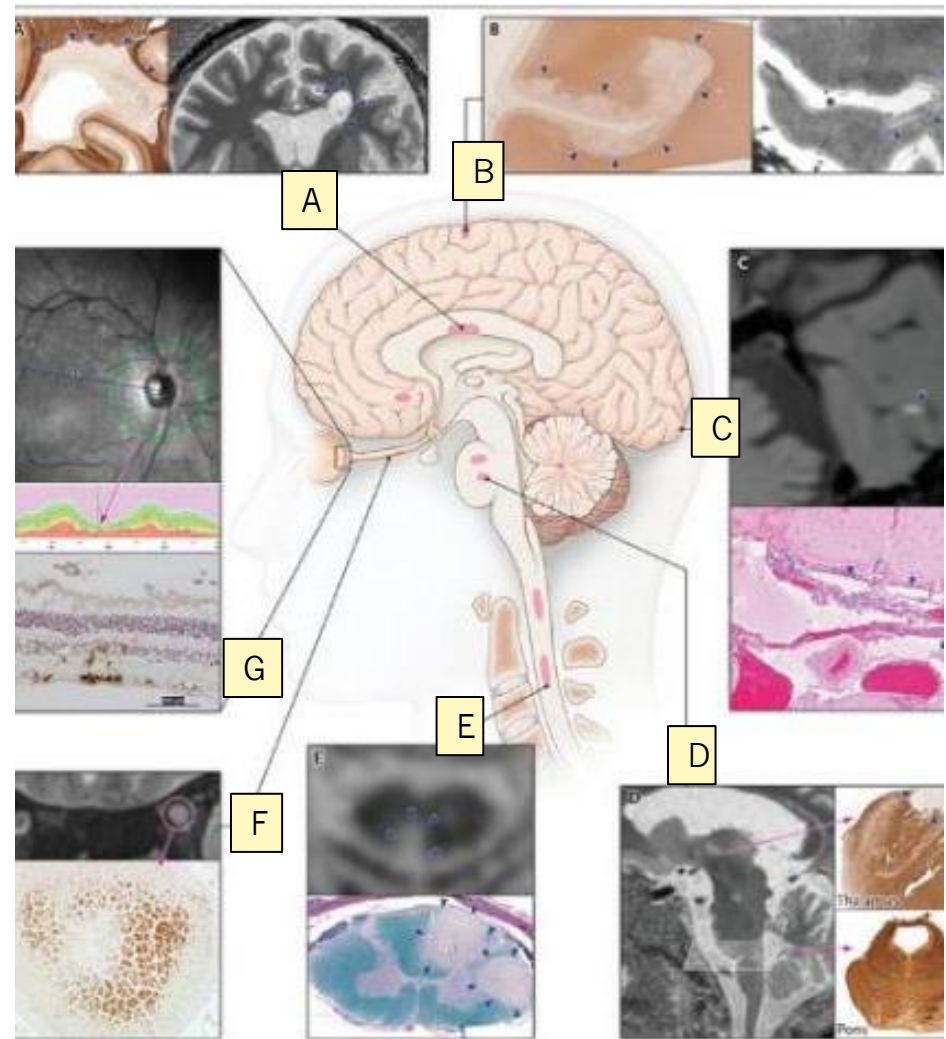
Anxiety

Psychosis

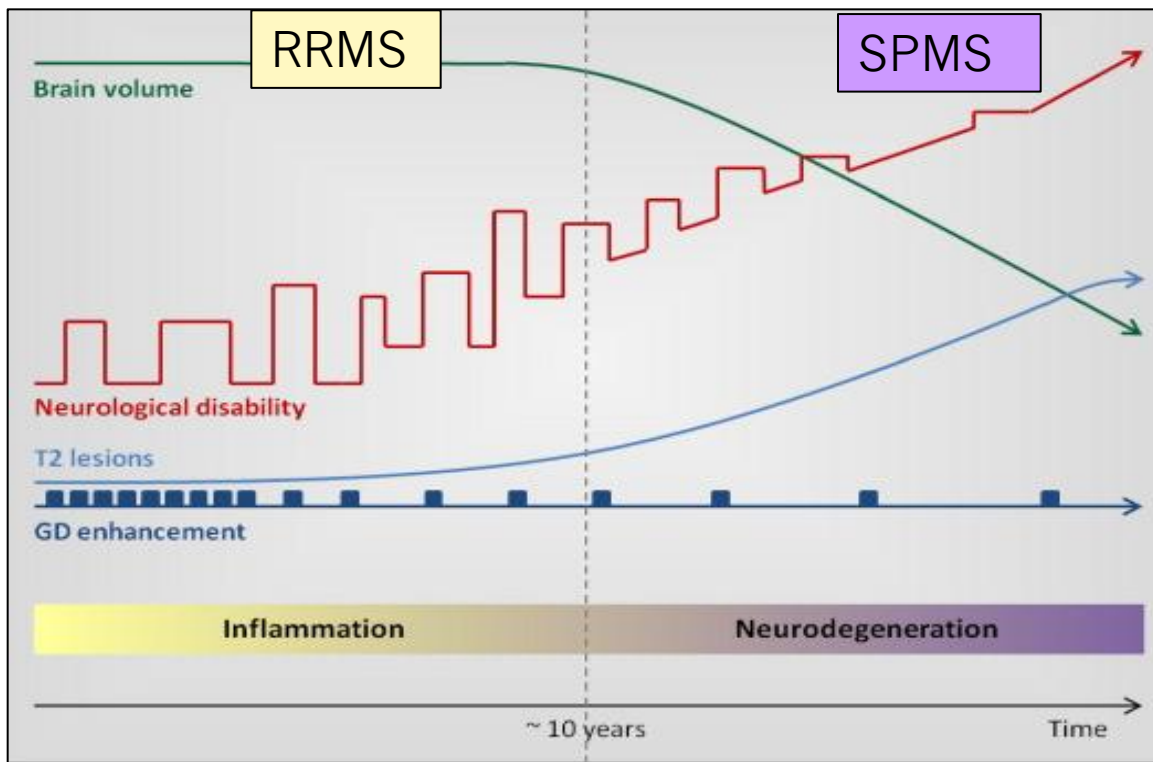
Other
Disorders

Multiple Sclerosis

- Complex immune- mediated CNS disease.
- Pathological mechanisms include inflammation, demyelination and neurodegeneration.
- Lesions in white matter, cortical and subcortical gray matter
- About 85% of individuals first present with a relapsing remitting course (RRMS).
- Majority develop Secondary Progressive MS (SPMS)
- A minority: progressive course at onset (PPMS).



Lesions Topography: (A) periventricular WM; (B) subpial cortex; (C) leptomeninges; (D) thalamus and pons; (E) spinal cord; (F) optic nerve; and (G) retina.



Graphic: Multiple Sclerosis – An overview. ScienceDirect Topics.

Neurodegenerative mechanisms include:

- Dysfunction of the innate immune system and B cells, may start early.
- Oxidative stress, microglial activation, increased metabolic demand of demyelinating axons.
- Remyelination failure, iron accumulation.
- Mitochondrial damage with resultant hypoxia.
- Inflammation & tissue injury compartmentalized behind BBB.

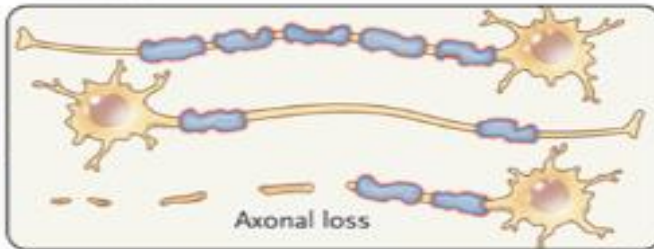
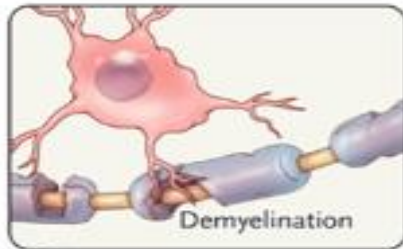
Inflammation: Main feature of RRMS. It gradually subsides with age, disease duration.

Neurodegeneration: Predominates in progressive MS.

Both mechanisms co-occur.

PIRA: Progression independent of relapse activity- drives disability;

EBV and mononucleosis
Other viruses
Risk genes
Temperate latitude
Fibrinogen
Toxins
Trauma
Low vitamin D
Smoking
Obesity
Early adulthood
Female sex



Low inflammation,
few spinal cord lesions,
good endogenous repair,
preserved axons and synapses,
early treatment,
younger age

VS.

High or chronic inflammation,
many spinal cord and cortical lesions,
poor endogenous repair,
mitochondrial dysfunction,
extensive axon and synapse loss,
delayed treatment,
older age

Low

Intermediate

High

Chance of progression

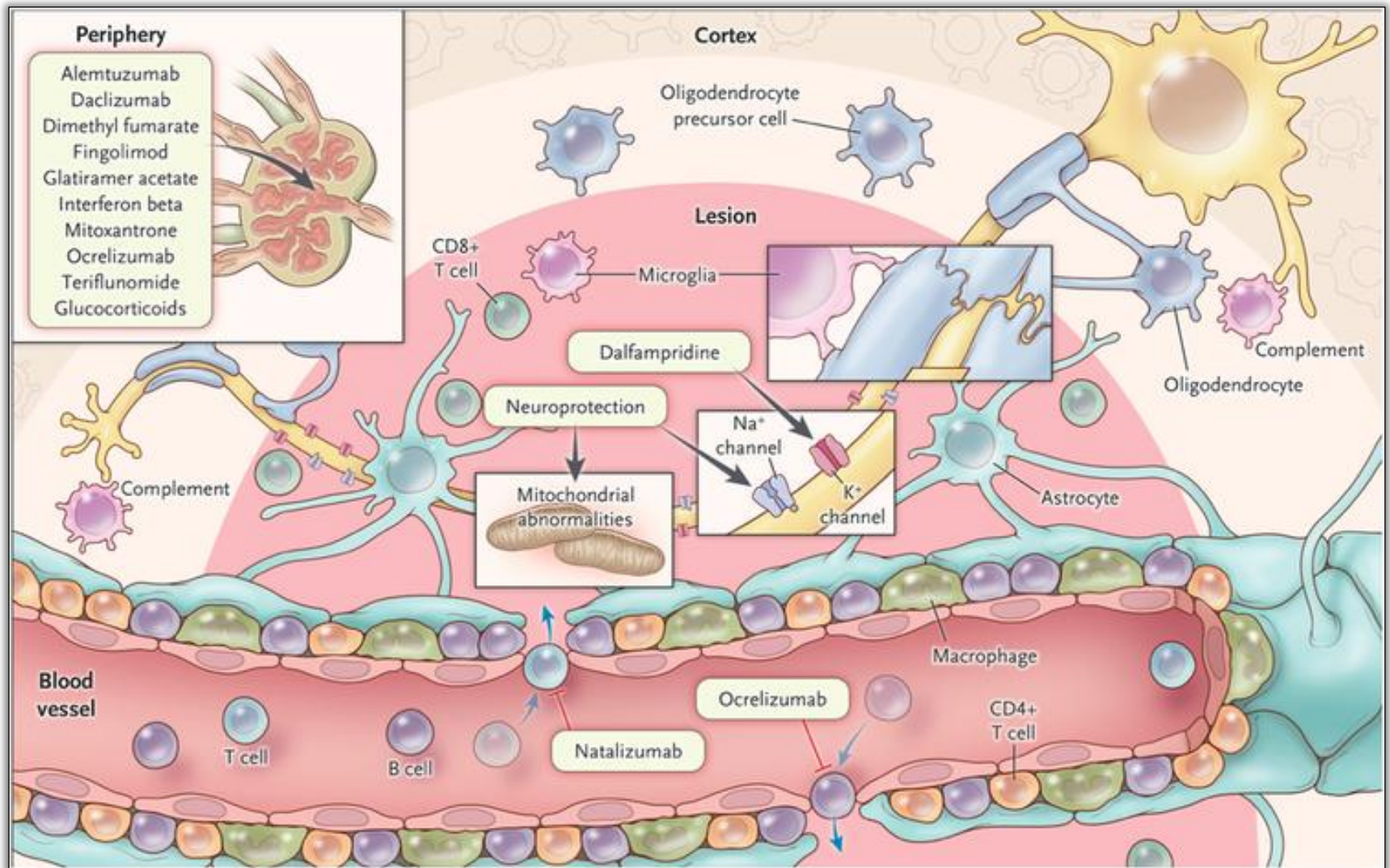
Genetic, environmental, and lifestyle factors affect risk for MS and disease course.

Multiple genetic risk factors identified.

Other risk factors:

- Female sex
- Low vitamin D level
- H/o Epstein-Barr virus infection
- Cigarette smoking
- Obesity (esp childhood)
- Gut microbiome abn (3).

Ward & Goldman; MS & Rel Disorders 2022
Reich et al. NEJM 2018
Dunalska et al. Cells 2023



Reich DS, Lucchinetti CF, Calabresi PA. N Engl J Med. 2018

Interplay - Immune system, glia, neurons. Adaptive Immunity (T Cells; B cells; antibodies) & Innate Immunity (macrophages, microglia). Glutamate & Inflammatory cytokines excess.

MS Diagnosis

Typical presentations

- ◆ Acute unilateral optic neuritis
- ◆ Double vision due to an internuclear ophthalmoplegia or sixth nerve palsy^b
- ◆ Facial sensory loss or trigeminal neuralgia^b
- ◆ Cerebellar ataxia and nystagmus
- ◆ Partial myelopathy
- ◆ Sensory symptoms in a central nervous system pattern
- ◆ Lhermitte symptom
- ◆ Asymmetric limb weakness
- ◆ Urge incontinence or erectile dysfunction

Atypical or red flag presentations that may suggest an alternative diagnosis

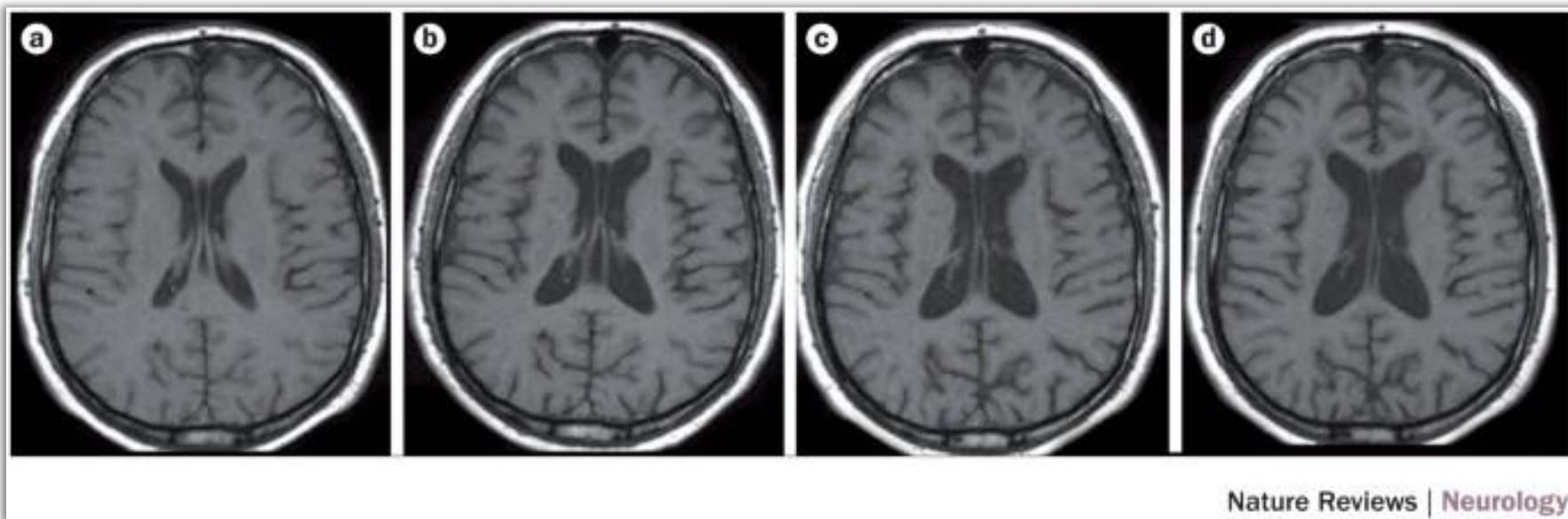
- ◆ Bilateral optic neuritis or unilateral optic neuritis with a poor visual recovery
- ◆ Complete gaze palsy or fluctuating ophthalmoparesis
- ◆ Intractable nausea, vomiting, or hiccups
- ◆ Complete transverse myelopathy with bilateral motor and sensory involvement
- ◆ Encephalopathy
- ◆ Subacute cognitive decline
- ◆ Headache or meningism
- ◆ Isolated fatigue or asthenia
- ◆ Constitutional symptoms

Neuropsychiatric symptoms (mood, psychosis, cognition) may present at onset.

Brain MRI & CSF-specific oligoclonal bands: Reach diagnosis, minimize misdiagnosis.

Jiwon Oh- Mult Sclerosis and related disorders 2022

MS - MRI Lesions	Pathological / Clinical correlation
T2-Hyperintense lesions	<u>Helpful</u> for dx (dissemination in space). <u>Central vein sign</u>: more specific for MS. <u>Non-specific</u> (inflammation, demyelination, edema, gliosis, axon damage). Unreliable correlation with clinical status, disability.
T1-Hypointense lesions or “black holes”	Axonal injury. May be <u>transient</u> (repair of BBB & remyelination). <u>Chronic</u> (>6-12 months): <u>axonal loss</u>; better correlation with <u>disability</u>.
Gadolinium-enhancing lesions	Inflammation > Disruption of BBB > contrast extravasation. Disease <u>activity</u>.
Brain atrophy	Neuronal and axonal loss. Affects WM, GM. Decreased tissue volume, cortical thickness. Correlates with <u>physical and cognitive disability</u>. Mech: Inflammation; iron deposits; mitochondrial damage; microglia activation
Cortical lesions (3T and 7T MRI)	Cortical demyelination; neuronal apoptosis; axonal loss; microglial activation. Present in <u>RRMS</u> and <u>Progressive MS</u>. <u>Common in early MS</u>. <u>Accumulation</u>: Associated with MS <u>duration</u>, <u>GM atrophy</u>, <u>cogn/ physical disability</u>.



Serial T1-weighted MRI scans in a patient with MS, over a 6-year period. Brain volume loss over time indicates progressive neurodegeneration.

Treatment of MS

Three aspects:

- Disease- modifying therapy (DMT)
- Relapse management (IV corticosteroids)
- Symptomatic treatments (psychiatric, urological, sleep, other problems).
 - Treatment is interdisciplinary.

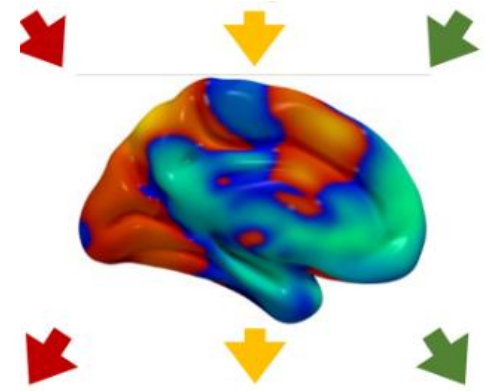
DMT:

- Immune-modulating & immune-suppressing agents.
- Reduction of: Relapse frequency; disability progression; new/enlarging MRI lesions.

Treatment of MS. Cross A & Riley C. MS & related Disorders 2022. Montague T et al. Advancements in MS. Intern Med J. 2025.

Neuropsychiatric Disorders in MS- General Concepts

- Highly prevalent
- Impact QOL, functional status, prognosis
- They may be the initial MS presentation
 - They may signal MS relapse
- MS physical symptoms (fatigue, pain) contribute to psychiatric presentation



Lifetime prevalence

- Mood / Affect Disorders:
 - Major Depression: 25- 45%
 - Bipolar Disorder: 6%
 - Pathological Laughing and Crying: 10%
- Cognitive Disorders: 43-70%
- Anxiety Disorders: 25%
- Psychosis: 4.3%
- Substance- Related Disorders:
 - Alcohol (AUD): 18.8%
 - Substances (SUD): 2.5-7.4%
 - Cannabis use: ~43%
- Syndromes:
 - Apathy: 10-20%
 - Disinhibition: 10-15%
- Comorbid disorders:
 - Sleep: RLS 14-57%; OSA 7-58%
 - Pain: ~65%

Assessment: Screening tools

Screen widely, then focus the evaluation:

- PHQ-9, HADS, or BDI: Depression
 - GAD-7: Anxiety
 - C-SSRS: Suicide Risk
 - CNS-LS: Pathological Affect
 - MDQ: Bipolar Disorder & symptoms in bipolar spectrum
 - MFIS or FSS: Fatigue: Physical, cognitive, social (60-80% of pts.)
 - Audit-C or other: Alcohol, substances
 - MoCA, SDMT: Cognition
-

Progressive MS with higher disability:

- ADLs & IADLs
- Risks: Medication errors, suicide/ access to weapons, falls, abuse/ exploitation, driving, etc.

Suicide Risk in MS

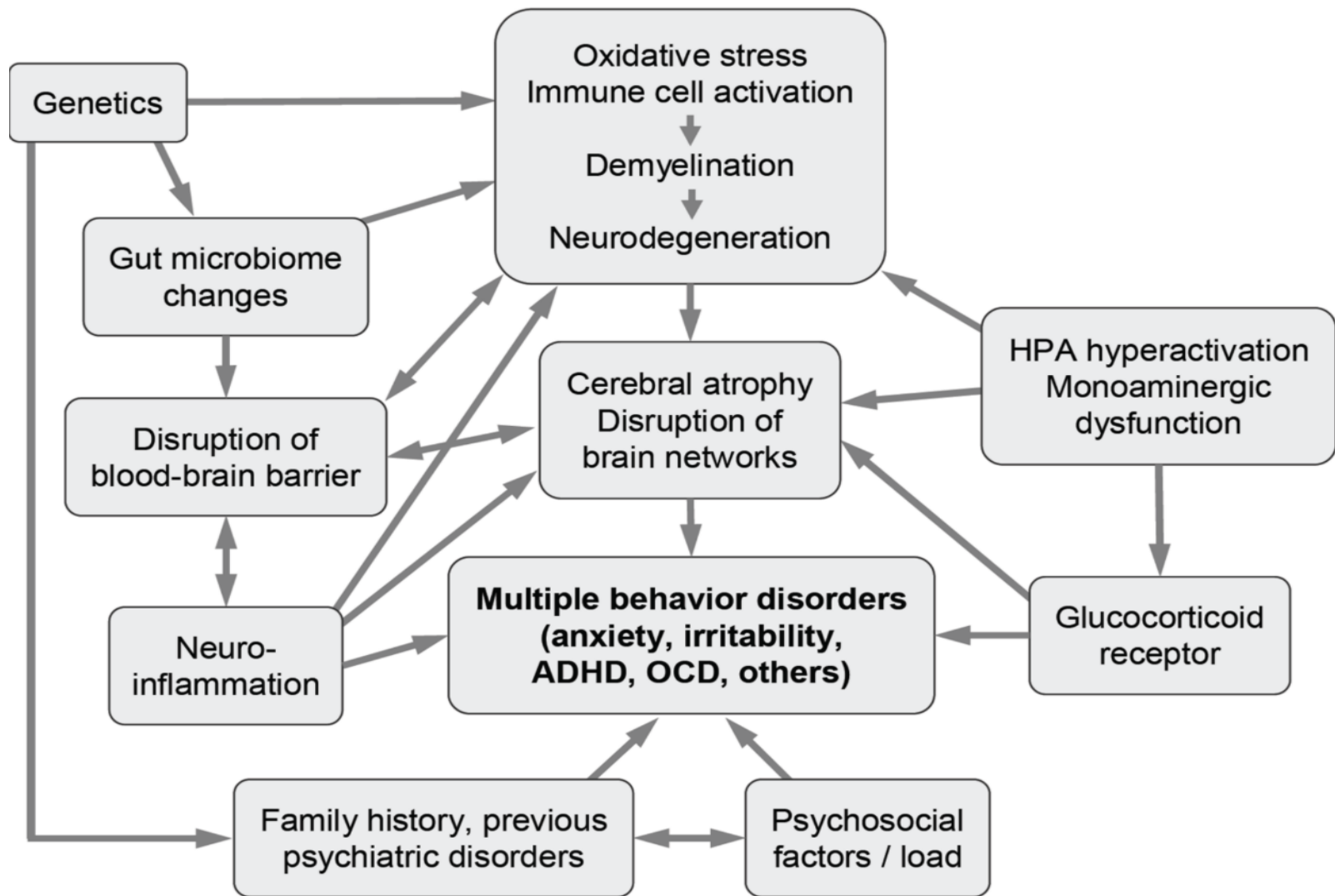
Increased rate of suicide ideation and attempts compared to GP and other neurological d/o

Risk factors for suicide intent in MS:

- Major depression or anxiety disorder
- Alcohol use disorder
- Social isolation
- High level of stress
- Demographic: Younger age; lower income
- Illness factors: Higher disability; progressive illness.

Pathophysiology: Neuropsychiatric D/o in MS

- Primary psychiatric illness
 - Higher depression genetic burden: Increased odds of depression in pwMS Kowalec et al Neurology 2023
- Direct physiological consequence of MS
 - Inflammatory/ autoimmune
 - Brain lesions: type (inflammatory, atrophy); load; localization, network disruption. Fiore et al Mol Psychiatry 2023
 - Serotonergic, dopaminergic, other receptors abnormalities (2)
- Medications & substances
 - Steroids, symptomatic treatments
 - Cannabis, substances of abuse
- Secondary to MS symptoms (fatigue, pain)
- Medical comorbidities (OSA, other sleep d/o, SZ, other)
- Psychosocial: High stress/ low support; coping style.
 - Intimate partner violence correlates with disability (3) Patil, Glanz, Safar et al 2023
- Factors above combined and interacting



Some factors contributing to pathogenesis of behavioral disorders in MS

DMTs - Psychiatric Notes

Comprehensive review did not find an increased risk of adverse psychiatric effects with DMTs.

Some studies: DMTs may reduce incidence of depressive symptoms - mechanism is unclear (immune modulation, positive effect on MS, other).

Fingolimod may cause QTc prolongation. Avoid psychotropics with similar s/e.

Interferon beta-1b: Early trials suggested higher frequency of depression. Not replicated in subsequent studies. Monitor patients with h/o depression when initiating interferon treatment.

Adverse psychiatric effects of DMTs in MS: A systematic review. Gasim et al. Mult Scler Rel Disord 2018.

Risk of Depression Across DMTs. Longinetti et al. MS Journal 2021.

Symptomatic treatments

- Spasticity

- Baclofen
- Diazepam
- Tizanidine
- Cannabinoids

- Pain Treatment

- Phenytoin
- Carbamazepine
- Ami/ Nortriptyline
- Gabapentin
- Pregabalin
- Duloxetine
- Opioids

- Corticosteroids

- Bowel and Bladder

- Oxybutynin
- Tolterodine
- Amitriptyline
- Darifenacin
- Trospium

- Insomnia

- Antihistaminics
- Hypnotics

- Fatigue

- Amantadine
- Modafinil/ Armodafinil
- Stimulants

- Dalfampridine

Treatment of Psychiatric Disorders in MS

- Bio-psycho-social
 - Individualized: Preferences & values
 - Support higher functioning, adaptive skills
 - **Longitudinal:** Needs vary along the lifespan and according to illness course
- Interdisciplinary:**
- Mental Health (Psychopharmacologist; Psychotherapist, Neuropsychologist)
 - Neurology team
 - Rehab: PT, OT, CRT, Driving Evaluation
 - PCP, specialists (pain, sleep, urologist, etc.)
 - Patient & caregivers
 - MS society, online/ community resources
 - Attorney (disability/ labor, estate planning)
 - Case manager

Neuropsychiatric Disorders in MS

- Depression
- Bipolar Disorder
- Cognitive Disorders
- Anxiety Disorders
- Psychosis

- Pathological Laughing and Crying (PLC)
- Syndromes:
 - Apathy
 - Disinhibition
- Substance- Related Disorders

Depression

- Clinical Presentation:
 - Typical depressive syndrome
 - Hypoactive (psychomotor retardation, apathy, fatigue, latency)
 - Labile (irritable, mood lability/ heightened reactivity, disinhibition)
 - Combinations of above
- Comorbid MS/ medical symptoms: Fatigue, pain, sleep disturbances
- Comorbid psychiatric symptoms/ syndromes:
 - Irritability, disinhibition, mood lability
 - Pathological Laughing and Crying (PLC)
 - Apathy
 - Anxiety
 - Cognitive dysfunction

Depression Pathophysiology: Lesion studies (load, type, localization) insufficient explanation

Feinstein A et al. *Nat. Rev. Neurol.* 2014

Table 1 Multiple sclerosis and depression: brain imaging studies					
Study	Number of participants	Assessment tools	Imaging modality	Imaging findings associated with depression	Laterality of findings
Sabatini <i>et al.</i> ⁸⁰	20 (10 depressed, 10 nondepressed)	DSM-III*	Single-photon emission CT	Increased perfusion in limbic areas	Left
Pujol <i>et al.</i> ^{67,68}	45	BDI-II*	T2-weighted MRI	Increased lesion load in the arcuate fasciculus associated with somatic and affective symptoms	Left
Fassbender <i>et al.</i> ⁷⁸	73 (23 with RRMS, 50 healthy controls)	DSM-III-R,* HRSD, ZSRDS	Gadolinium-enhanced MRI	Increased lesion load linked to increased cortisol and a positive dexamethasone suppression test	None reported
Bakshi <i>et al.</i> ⁶⁹	48 (19 depressed, 29 nondepressed)	DSM-IV,* HRSD, BDI	T1-weighted MRI	Superior frontal, superior parietal and temporal lesions; enlargement of lateral and third ventricles; frontal atrophy	Left
Berg <i>et al.</i> ⁷²	78	DSM-IV*	T2-weighted MRI	Increased lesion load in temporal lobe	Right
Zorzon <i>et al.</i> ⁷¹	90	DSM-IV,* HDRS	MRI	Atrophy in the left frontal lobe; severity of depressive symptoms associated with reduced right temporal lobe volume	Bilateral
Feinstein <i>et al.</i> ⁷⁰	40 (21 depressed, 19 nondepressed)	DSM-IV*	T1-weighted and T2-weighted MRI	Increased lesion volume in medial inferior prefrontal cortex; anterior temporal atrophy	Left
Passamonti <i>et al.</i> ⁸¹	24 (12 with MS, 12 healthy controls)	CMDI, HAM-A*	Functional MRI	Reduced functional connectivity between ventrolateral prefrontal cortex and amygdala	Bilateral
Gold <i>et al.</i> ⁷⁵	49 (20 with RRMS, 29 healthy controls)	BDI-II*	MRI	Hippocampal atrophy, particularly in CA2, CA3 and dentate gyrus, linked to increased cortisol	Bilateral
Feinstein <i>et al.</i> ⁷³	62 (30 depressed, 32 nondepressed)	BDI-II*	T1-weighted MRI plus diffusion tensor imaging	Increased lesion volume in right medial inferior frontal region; atrophy of left superior frontal region; reduced fractional anisotropy; higher mean diffusivity in left anterior temporal normal-appearing white and grey matter; higher mean diffusivity in right inferior frontal hyperintense lesions	Bilateral
Kiy <i>et al.</i> ⁶¹	88 (72 with MS, 16 healthy controls)	BDI-II*	MRI	Increased temporal horn volume correlated with mood-related aspects of the BDI-II, but not with somatic items	Left
Gold <i>et al.</i> ⁷⁹	109 women with MS	CES-D*	MRI	Reduced hippocampal thickness	Right

- ❖ Lower Deep Gray Matter Volume (caudate, putamen, accumbens, other): Higher odds of depression.
- ❖ 3, 844 participants with MS, of whom 1,905 experienced depression.

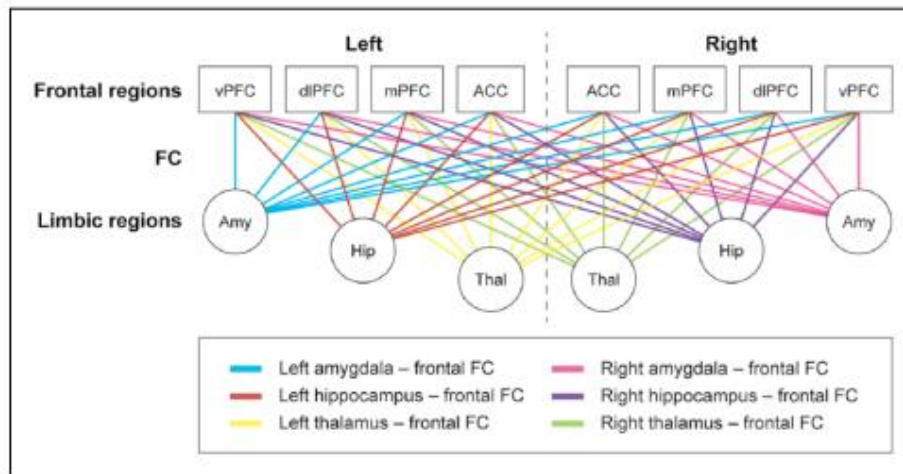
Hu et al. *Mult Scler* 2023

Fronto-Limbic disconnection in pwMS and depression

Small retrospective study.

22 patients with MS & Depression.
21 non depressed MS patients.

Depressed MS pts had lower WM volume, decreased fractional anisotropy of uncinated fasciculus, and lower functional connectivity between the amygdala and frontal regions.



Depressed patients w MS: More pronounced structural damage & functional changes in frontal-temporal regions compared to non-depressed MS patients.

Schematic overview of functional connectivity
between limbic and frontal regions

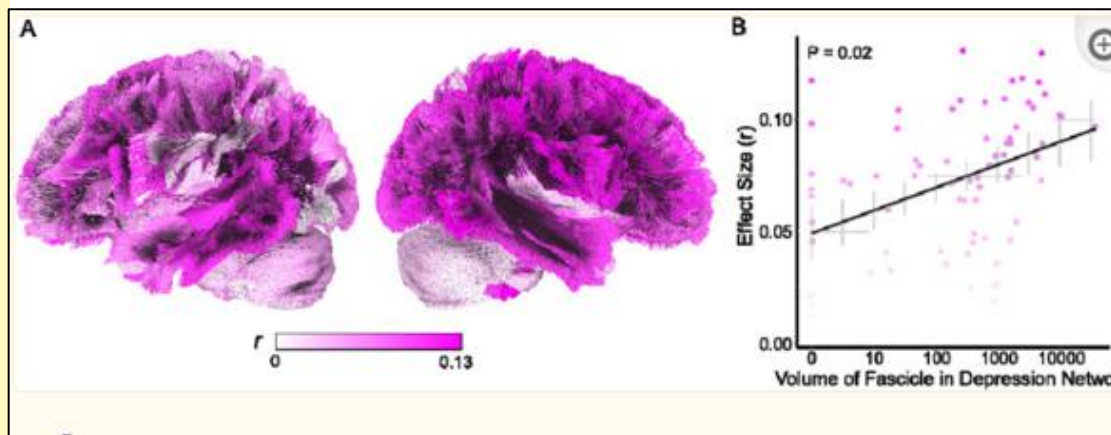
Van Geest et al. MS Journal 2019.

PwMS: Greater disease burden in the WM depression network: may create vulnerability to depression in MS.

PwMS + Depression:

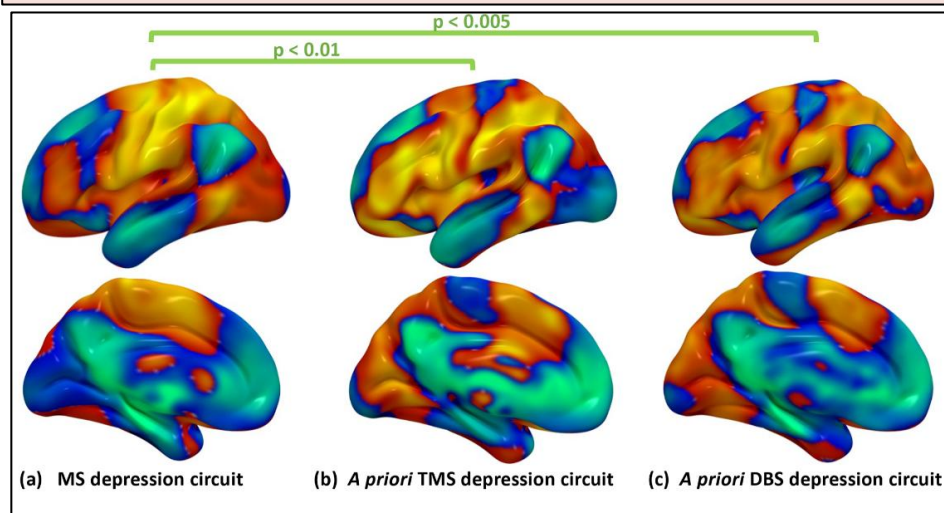
- Higher disease burden across the whole brain
- Greater burden in fascicles with more overlap with the depression network

-A data-driven circuit for MS depression : similar topography to *a priori* depression circuit.



Functional depression network includes:

- Frontoparietal network
- Dorsal attention network



Baller EB et al. Mapping the Relationship of WM Lesions to Depression in MS-Biol Psychiatry. 2024

Siddiqi SH et al. Lesion network localization of depression in multiple sclerosis. Nat Ment Health. 2023

Depression in MS: Treatment

- Antidepressants
- Psychotherapy: CBT, M-BT, Computer-based CBT, iCBT, ACT, Positive Psychology
- Neuromodulation: ECT (Severe, TRD); rTMS, tDCS (case reports; small, limited trials)
- Exercise: Possible effect
- Treat MS
- Treat MS symptoms: Fatigue, pain, etc
- Treat comorbidities (OSA, RLS, etc)
- Reduce CNS-depressant medications

Antidepressants trials in MS

Drug Class	Drug	RCT (n; result)	Open Label (n; result)
SSRIs	Sertraline	63; effective	11; effective
	Paroxetine	42; marginal benefit	
	Fluvoxamine		43; effective
SNRIs	Duloxetine		75; effective
TCAs	Desipramine	28; modest benefit	
MAOI	Moclobemide		10; effective

Safar, Singhal, et al. The Neuropsychiatry of MS. McGraw Hill- 2021

Antidepressant selection in MS

- Establish if major depression syndrome is present.
- Screen for bipolar d/o and psychosis.
- Personal or family h/o response.
- Consider specific symptoms; ADs therapeutic & S/E profile.
 - Insomnia and low appetite: Mirtazapine
 - Sexual dysfunction: Bupropion, Mirtazapine, Vilazodone.
- SNRIs may also benefit pain; NE activity may provide some benefit for fatigue.
- Vortioxetine may have cognitive benefits (1).

Antidepressant selection in MS

- Citalopram, escitalopram, others: may lengthen QTc interval- avoid with fingolimod.
- Bupropion may lower SZ threshold; MS increases SZ risk. However: It can be very helpful for MDD in MS. Use XL form; titrate cautiously; avoid if h/o SZ.
 - It may alleviate Sexual Dysfunction in females w MS (1)
- TCAs: Not a good choice. Anticholinergic (cognition); sedating; increase SZ risk. May have a role for PwMS and pain, urinary incontinence, insomnia.

Bipolar Disorder & related symptoms

Clinical Presentation:

- Full manic/ hypomanic syndrome
- Sub- syndromal: Irritability, emotional lability, agitation, disinhibition.

Pathogenesis:

- Limited lesion localization studies:
 - Widespread lesions
 - Bilateral temporal horns lesions: Bipolar with psychosis
- Steroids, stimulants, modafinil, baclofen, may contribute

Bipolar Disorder in MS- Psychopharm guidelines

No published clinical trials. Use same agents as in BPAD without MS. Some adverse reactions may be more problematic for PwMS.

Lithium's polyuria- a concern in PwMS and bladder dysfunction. Cognitive S/E. Benefit: Protection against suicide.

Valproate: Cognitive S/E; weight gain.

Lamotrigine: relatively less cognitive s/e.

Antipsychotics (Effect and S/E profile vary widely between agents):

- Motor s/e, tremors, gait difficulties/ worsened balance (Typical AP; Risperidone).
- Fatigue/ Sedation (Quetiapine, Clozapine).
- Metabolic syndrome (OLZ, Quetiapine, Clozapine)
- QTc prolongation (Ziprasidone, Asenapine, Iloperidone).

❖ Corticosteroid-induced mania: Management and Prophylaxis: Lithium, atypical antipsychotics, or VPA - without need to discontinue steroids.

❖ Treat MS; discontinue agents that contribute to bipolar sx.

Cognitive Disorders in MS



Cognitive Disorders: Clinical Presentation

- **Symptoms:** Difficulty multitasking, organizing; things take longer; increased effort for same tasks
- **Functions commonly affected:**
 - Processing Speed
 - Episodic Memory: Encoding & retrieval
 - Executive function & Attention
 - Word retrieval/ verbal fluency
- Deficits may occur early. The profile broadens with MS progression; 10-25% of patients develop Major Neurocognitive Disorder (MND)
- Screening + Neuropsychological Assessment

Cognitive Phenotypes in MS

Multicenter crosssectional study. 1212 pwMS and 196 HC.

Five cognitive phenotypes identified:

- Preserved cognition [~20%]
- Mild-verbal memory/semantic fluency dysfunction [~30%]
- Mild-multidomain dysfunction [~20%]
- Severe-executive/attention [~14%]
- Severe-multidomain [17.5%]

De Meo et al. JAMA Neurology 2021

Cognition worsens w age, illness duration, progressive MS.

MRI:

- Mild-verbal memory/semantic fluency: decreased hippocampal volume
- Mild-multidomain: decreased cortical gray matter volume
- Severe-executive/attention: higher T2-hyperintense lesion volume.
- Severe-multidomain: extensive brain damage & decreased brain volume.

Cohort: 1281 pwMS; 3 MS Centers. At 1.5 SD threshold:

-73% intact. 14% single domain, 8.2% bi-domain, 5% multi-domain impairment.

-Most frequent impairments: 1) Processing speed; 2) Exect fct; 3) Memory.

Hancock et al. Mult Scler 2023

Cognitive Disorders: Treatment

- Treat MS. DMTs: Possible benefit for cognition.
- Treat medical comorbidities (OSA; DM, HTN- risk factors for cerebrovascular disease; thyroid disease; etc.)
- Treat depression, anxiety, insomnia, fatigue
- Reduce polypharmacy, esp. CNS depressants & anticholinergics. Review use of cannabis.
- Cognitive Rehabilitation Therapy
- Work and school accommodations
- Medications: Evidence is scarce; not approved medications. Stimulants, cholinesterase inhibitors, other agents may be tried in selected patients, carefully monitoring therapeutic & s/e.

Safar, Singhal, et al. The Neuropsychiatry of MS. McGraw Hill- 2021; De Meo et al. Update on treatment of cognitive dysfunction in patients with MS; Expert Review Neurotherapeutics 2025

Research Article

 Open Access

Treatment Effect on Brain Atrophy Correlates with Treatment Effect on Cognition in Multiple Sclerosis

Maria Pia Sormani PhD , Irene Schiavetti PhD, Marta Ponzano MSc, Elisa Colato PhD,
Nicola De Stefano MD, PhD

ANN NEUROL
2023

Fourteen DMT trials, more than **8,813** patients with MS.

Treatment effect on cognition: Strongly associated with treatment effect on brain atrophy ($p < 0.001$); not correlated with treatment effect on active MRI lesions.

Brain atrophy: may be used as main outcome for clinical trials targeting cognitive impairment.

DMTs included: Natalizumab, Ocrelizumab, Fingolimod, Interferon Beta 1-a, and others.

Cognitive Disorders in MS- Stimulants Trials

Medication	Study	Results	Article
Methylphenidate 10mg	Double blind RCT (n=26) @ 1hr	Improved attention- 1hr post dose	Harel 2009
l-amphetamine 15, 30, 45 mg	Within-subject design (n=19)	Improved processing speed, working memory (SDMT) (45mg) Trend toward improved memory	Benedict 2008
l-amphetamine 30mg	Double blind RCT (n=151); 1 mo	Improved total learning and delayed recall. No processing speed difference.	Morrow 2009
l-amphetamine 30mg	Double blind RCT (n=151); 1 mo	Improved memory for patients with baseline memory impairment	Sumowski 2011
Lis- dexamfetamine 30-70mg	Double blind RCT (n=63); 8 wks	Improved processing speed, working memory, learning	Morrow 2013

Acetylcholinesterase inhibitors trials

Medication	Study	Result	Article
Donepezil	RCT (n=69); 24 wks	Improved memory	Krupp 2004
Donepezil	RCT (n=120); 24 wks	No effect of treatment	Krupp 2011
Donepezil	OLT (n=17); 12 wks	Improved attention, memory, exect fct (small, OLT)	Greene 2000
Rivastigmine	RCT (n=60); 12 wks	No effect of treatment	Shaygannejad 2008
Rivastigmine	RCT (n=86); 16 wks	Trend toward improved memory	Maurer 2013
Rivastigmine Single dose	OLT (10 pwMS, 5 got single dose riv; 11 HC)	Stroop task and fMRI. pwMS & HC similar Stroop performance but different activation pattern. Relative normalization of brain activation post-riv	Parry 2003
Rivastigmine	CO SB (n=15); 4 wks	Riv altered functional connectivity assoc w tasks. No statistically sign change in task performance	Cader 2009

Anxiety Disorders in MS

- Adjustment: Post-diagnosis & post-relapses; post diagnosis of SPMS.
- Unpredictability- worries about MS course, disability
- Increases suicide risk
- Increased use of benzodiazepines, other sedatives, alcohol, cannabis
- Clinical presentation:
 - GAD
 - Somatic complaints; differential with MS physical symptoms
 - PD
 - OCD
- Treatment: Meds and psychotherapy as in primary anxiety disorders
- CBT, Stress-management counseling, ACT,

Anxiety Disorders in MS- Psychopharm guidelines

No published clinical trials. Follow guidelines used in general psychiatry.

SSRIs: typically the first line of treatment.

SNRIs: may be preferred when prominent fatigue or cognitive difficulties

- Duloxetine: consider for patients with comorbid pain

RLS: high prevalence in MS- serotonergic agents can worsen this; monitor.

Gabapentin & pregabalin: not first line treatment for anxiety. May help paresthesia and RLS. A larger evening dose may lessen S/E (fatigue, cognitive slowing).

Benzodiazepines: Avoid if possible. Occasional use (e.g., MRI anxiety), or severe anxiety and failure of psychotherapy (CBT) and other agents. May worsen fatigue, cognition, coordination; increased fall risk.

Psychosis in MS

- May be initial MS presentation
- Phenomenology: similar to primary psychotic disorders. Positive symptoms more common
- Pathophysiology:
 - Brain inflammation/ immunological process
 - Lesions: Temporal, temporoparietal, frontotemporal
 - Medication/ Substances: Steroids; Interferon B-1b & 1a; stimulants; modafinil; cannabis; baclofen
 - Delirium; mood disorder with psychosis
- Treat MS; remove offending agents; address delirium; antipsychotics. Little evidence that DMTs help treat psychotic symptoms in MS.
- Steroids may be therapeutic; esp acute inflammation, gadolinium-enhancing lesions

Asghar-Ali et al. Am. J. Psychiatry 2004; Ketata I et al. Psychoses onset in MS. Rev Neurol 2025; Camara-Lemarroy et al. *Mult Scler Relat Disord* 2017.

Psychosis in MS- management

Delirium w psychosis: Address contributing factors (metabolic, toxic, etc.).

Medication (stimulant, etc.) or substances: Remove if possible.

Both above: May also need symptomatic antipsychotic treatment.

Depression w psychosis: Antidepressant + antipsychotic.

- Consider ECT for non-responders (Corruble et al. *Am. J. Psychiatry* 2004).

Bipolar disorder w psychosis: Mood stabilizer + antipsychotic. Atypical antipsychotics may be used alone.

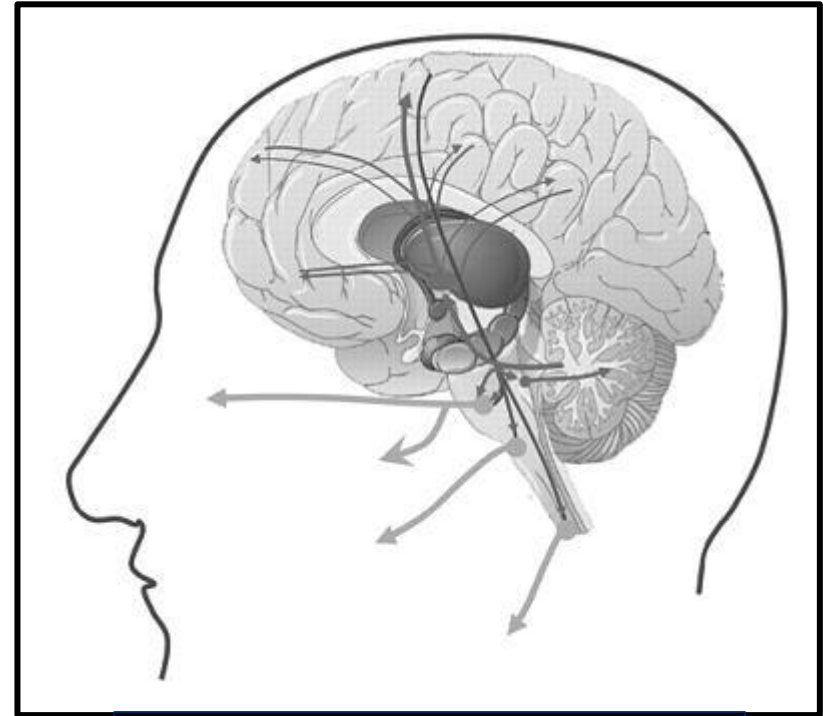
Enhancing MS lesions possibly causing the syndrome: May need combination of psychotropics & corticosteroids (Holtier et al. *Gen. Hosp. Psychiatry* 2015).

Selection of Antipsychotic: As in general psychiatry. Consider therapeutic and S/E profile of each agent. No data specifically for MS, beyond case reports.

Pathological Laughing and Crying (PLC)

Brief, intense, frequent episodes of crying or laughter

- Unprovoked or out of proportion to the stimulus
- Mood-incongruent
- May coexist with mood d/o



Parvizi et al. 2009

Pathophysiology: MS lesions disrupt neurocircuitry involved in emotional regulation and expression

PLC - Treatment

- **Dextromethorphan/ Quinidine (20/10):** Effective for PLC in MS & other conditions. Can also help irritability/ anger.
- D: NMDA receptor antagonist & sigma-1 receptor agonist.
- Q: inhibits (CYP2D6) metabolism of D.

DM/ Q	Study	Results	Article
30mg/30mg BID or placebo MS	Double-blind RCT (n=150); 12 weeks	Effective (CNS-LS; # episodes; QoL, relationships)	Panitch 2006
30mg/10mg or 20mg/10mg or placebo MS, ALS	Double-blind RCT (n=326); 12 weeks	Both doses effective	Pioro 2010

PLC - Treatment

- **SSRIs** (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline): Effective for PLC in MS, other neurological illnesses. (Case series; open label trials; small RCTs).
- **TCAs** (Nortriptyline, Amitriptyline, Imipramine): Effective- Most studies in PLC post-stroke.
 - Amitriptyline effective for PLC in MS: Small (n=12) study. Schiffer 1985
- Case reports: Venlafaxine, duloxetine, mirtazapine, lamotrigine, valproic acid, levodopa, amantadine, methylphenidate.

Other Neuropsychiatric syndromes in MS

Apathy

- Medial frontal and anterior cingulate lesions

Disinhibition

- Orbitofrontal lesions: Irritability, lability, disinhibition, socially inappropriate behavior

Alcohol Use Disorder

- Use correlates with severity of depressive symptoms.

Substance Use Disorder

- Patients may abuse medications prescribed for MS symptoms (BZD, tizanidine, opioids, modafinil, etc.).

Cannabis:

- Risks: psychosis, cognitive dysfunction, worsening of mood/anxiety d/o, fatigue, apathy, somnolence.

Cannabis in MS

- May help spasticity & perhaps pain in MS.
- Tetrahydrocannabinol (THC) and cannabidiol (CBD): Studies in MS used combinations in varying ratios, or stand-alone THC or CBD. The ideal ratio or doses are not clear.
- Certainty of evidence limited by short-term duration of studies.
- **Cannabis may increase risk of psychosis, cognitive dysfunction, anxiety, mood disorders, apathy, somnolence.**

1. Yadav et al *Neurology* 2014; 2. Hill KP *JAMA* 2015; 3. Gustavsen et al 2021; 4. Chohan et al *Curr Treat Options Neurol* 2016; 5. Nugent SM et al *Ann Intern Med* 2017; 6. Corey-Bloom et al *CMAJ* 2012; 7. Pavisian et al *Neurology* 2014; 8. Romero et al *NeuroImage: Clinical* 2015; 9. Filippini G et al. Cochrane systematic review 2022; 10. De Toffol et al *BMJ* 2023.

Neuropsychiatric disorders in MS

Conclusions

- Highly prevalent- especially Mood, Anxiety, Cognitive Disorders
- Screen periodically, diagnose, treat. Monitor Suicidal Risk.
- Understand pathophysiology, implement the most relevant treatments.

