

# SYMPTOM MANAGEMENT IN MULTIPLE SCLEROSIS: NEUROPSYCHOLOGICAL ISSUES

Donna Graves, M.D.

Assistant Professor

University of Texas Southwestern

Multiple Sclerosis Clinic

# DISCLOSURES

- I have received honoraria from Teva pharmaceuticals, Novartis, and Bayer pharmaceuticals.

# Obtaining CME Credit

- If you would like to receive CME credit for this activity, please visit:

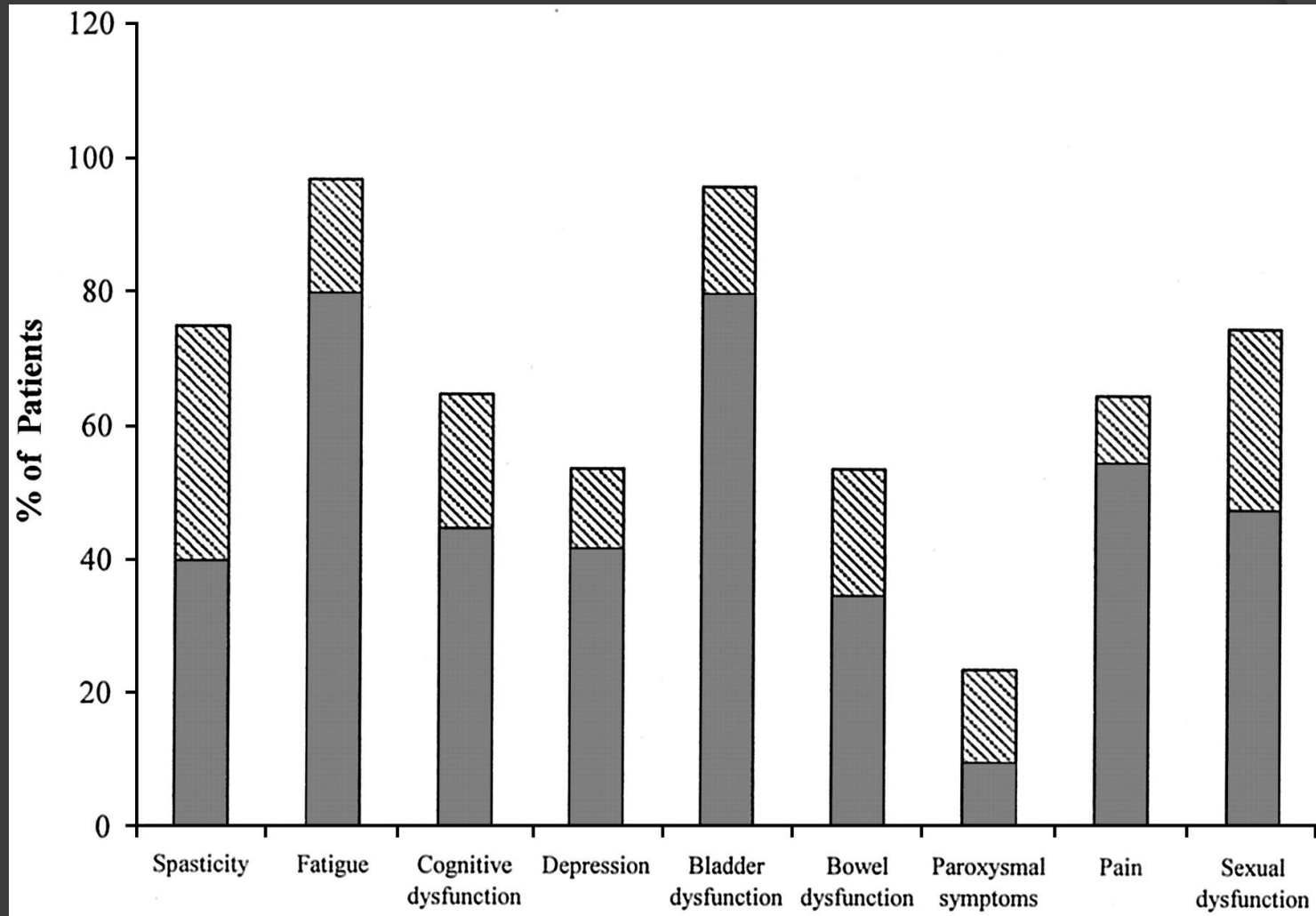
<http://www.pesgce.com/PVAsummit2011/>

- This information can also be found in the Summit 2011 Program on page 8.

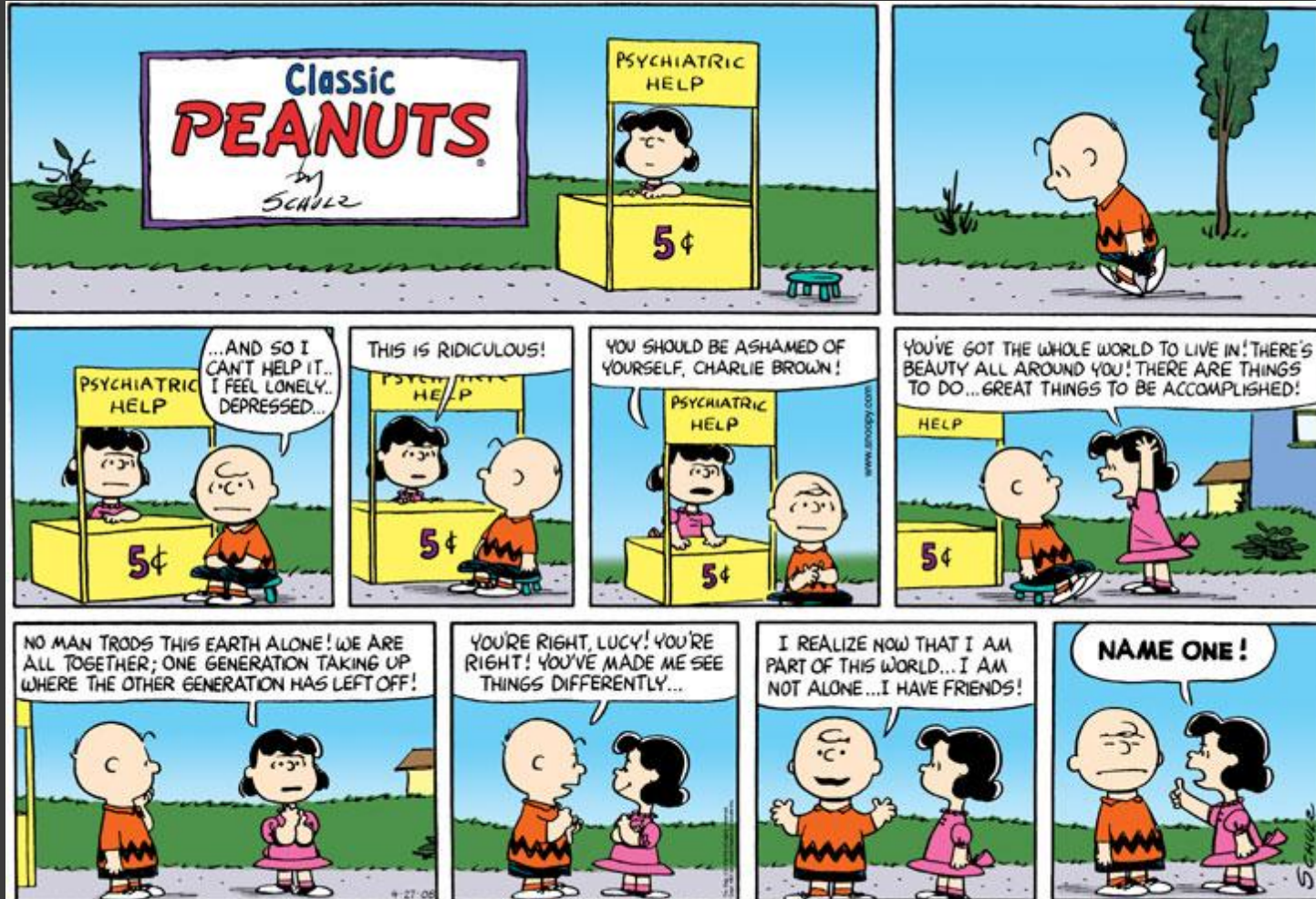
# Objectives:

- Identify common psychiatric issues in MS
- Discuss the impact of cognitive dysfunction in MS and management of these symptoms
- Examine the impact of fatigue in MS
- Recognize the interdependence of the “cycle of symptoms” in MS

# Common multiple sclerosis symptoms



# Psychiatric Implications of MS



# Psychiatric disorders in MS

**TABLE 1. Prevalence of Psychiatric Disorders in Patients With MS**

<b>Psychiatric Disorder</b>	<b>Prevalence in MS (%)</b>	<b>Reference</b>
Depression	22.8–54.0	Joffe et al, 1987 <sup>9</sup> ; Minden et al, 1987 <sup>4</sup> ; Patten et al, 2000 <sup>10</sup>
Bipolar disorder	13	Joffe et al, 1987 <sup>9</sup>
Pseudobulbar affect	10	Feinstein et al, 1997 <sup>42</sup>
Anxiety	25	Feinstein et al, 1999 <sup>38</sup>

MS indicates multiple sclerosis.

# Depression

- ⦿ Occurs in more than 50% of MS patients
  - May occur in very mild cases
  - Mixed results on correlation with degree of disability and duration of disease
- ⦿ 30% of MS patients will have thoughts of self harm or suicide.
- ⦿ Rates of suicide are 7 times higher than in the general population.

• Feinstein, A. Can J Psychiatry 2003;49:157-163

# Causes of depression in MS:

---

**TABLE 2.** Suspected Causes of Depression in Patients With MS

---

Neuroanatomic location of brain lesions

Immune dysregulation

Neuroendocrine abnormalities

Psychological reaction to the effects of disease on work, social, and family relationships

History of depressive disorder

Fatigue or other somatic complaints (eg, sleep disturbances)

Unrealistic expectations from disease-modifying treatment

Lack of social support

Social stress

Disease exacerbation or activity

MS-related cognitive dysfunction

---

MS indicates multiple sclerosis.

---

# Localization

**TABLE 3. Correlation Between Depression and MS-Related Lesions and Atrophy**

Study	Depression Measure	MRI Correlate
Pujol et al, 1997 <sup>18</sup>	BDI	Left suprainular white matter brain lesions
Berg et al, 2000 <sup>19</sup>	HDS, MADRS, BDI, GHQ	Right temporal brain lesions
Di Legge et al, 2003 <sup>20</sup>	BDI, STAI	Right temporal brain lesions
Bakshi et al, 2000 <sup>21</sup>	BDI, HDI	Frontal and parietal white matter lesions; atrophy
Rabins et al, 1986 <sup>5</sup>	GHQ	Atrophy

MS indicates multiple sclerosis; MRI, magnetic resonance imaging; BDI, Beck Depression Inventory; HDS, Hamilton Depression Scale; MADRS, Montgomery and Asberg Depression Scale; GHQ, General Health Questionnaire; STAI, State-Trait Anxiety Inventory; HDI, Hamilton Depression Inventory.

# Medications associated with depression

- ⦿ Interferons
  - Conflicting results, but overall appears to have shown no increased risk of depression with interferons.
- ⦿ Corticosteroids
  - Increased energy, insomnia, mood lability, euphoria, depression, psychosis, delirium
    - Occurs in 5-8% of patients
  - Mania/hypomania more common with acute use but long term use more commonly associated with depression
- ⦿ Anti-cholinergics
  - Reports of cognitive dysfunction, anxiety and hallucinations
- ⦿ Anti-spasmodics
  - Confusion, euphoria or depression, anxiety, somnolence

# Bipolar Disorder

- ⦿ Prevalence in MS varies from 0.3 to 32%
- ⦿ Multifactorial
  - Lesion burden
    - Temporal lesions and diffuse white matter changes
  - Genetics
    - Similarities between HLA class II genes
  - Medications such as corticosteroids, baclofen, dantrolene, tizanidine have been implicated to cause hypomanic or manic episodes.

# Anxiety

- ⦿ Estimated prevalence of 36%
  - Generalized anxiety disorder most common
  - Increased prevalence of panic disorder and obsessive compulsive disorder
- ⦿ More suggestion that anxiety is a reactive response
- ⦿ Localization is less clear

# Anxiety Disorders in MS

**Table 1** Prevalences of DSM-IV anxiety disorders in subjects ( $n = 140$ ) with MS and the general population

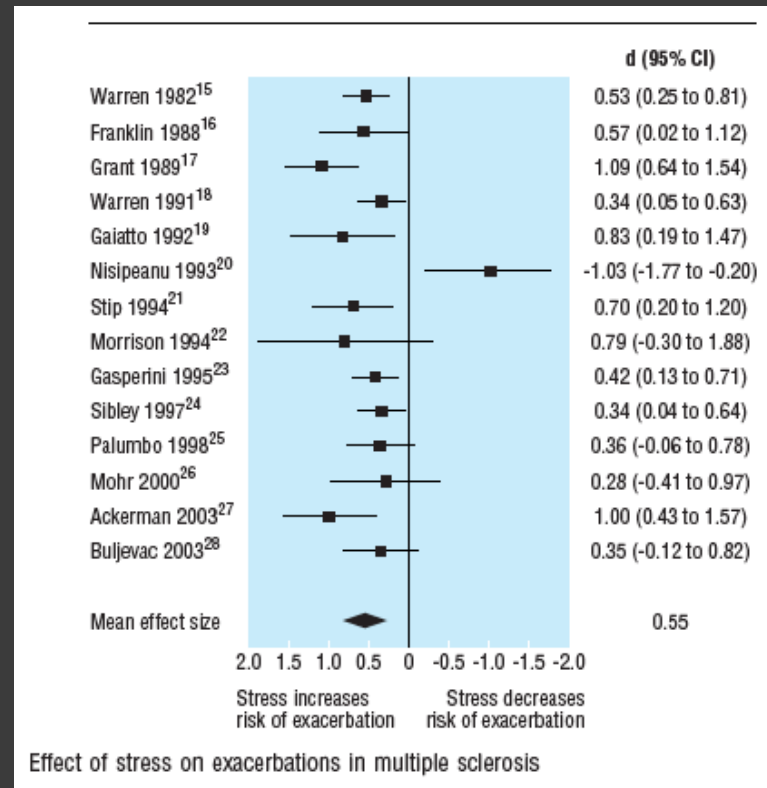
	Lifetime prevalence in MS (% ( $n$ ))	Point prevalence in MS (% ( $n$ ))	Lifetime prevalence in general population [23] (%)
Panic disorder	10.0 (14)	2.1 (3)	3.5
Social phobia	7.8 (11)	2.1 (3)	13.3
Specific phobia	10.8 (15)	2.9 (4)	11.0
Obsessive compulsive disorder	8.6 (12)	5.7 (8)	2.5
Generalized anxiety disorder	18.6 (26)	10.0 (14)	5.1

# Stressful life events and exacerbations

- A prospective study of 36 MS patients followed with monthly MRIs found that stress increased the risk of developing a new Gd+ enhancing MRI lesion.
  - Mohr, et al. Neurology 2000;55:55-61.
- A prospective study of 26 females with MS found:
  - Experiencing 3 or more stressful life events was associated with a 5-fold increase in relapse rate.
  - At least one long term stressful life event was associated with a 3-fold increase in the risk of relapse.
    - Charalampos, et al. European Psychiatry 2008;23:497-504.

# Stressful life events and Exacerbations

- Meta-analysis evaluating the association between stressful life events and exacerbations
- Included 14 publications
- Mean effect size was 0.53



# Pseudobulbar affect

- Occurs in up to 10% of MS patients
- Sudden episodes of laughing or crying that occur spontaneously or out of proportion to the stimuli
- Thought to be due to loss of cortical inhibition of brainstem centers involved in activation of laughing and crying

# PBA: Management

- ◎ Dextromethorphan/Quinidine (Neudexta)
  - First FDA approved therapy for PBA
  - MOA: DM modulates glutamate by inhibiting its release and acting as a NMDA antagonist
    - Quinidine needed to prevent the metabolism
  - Randomized , double blinded trial involving 150 MS patients to investigate the use of DM/Q in PBA

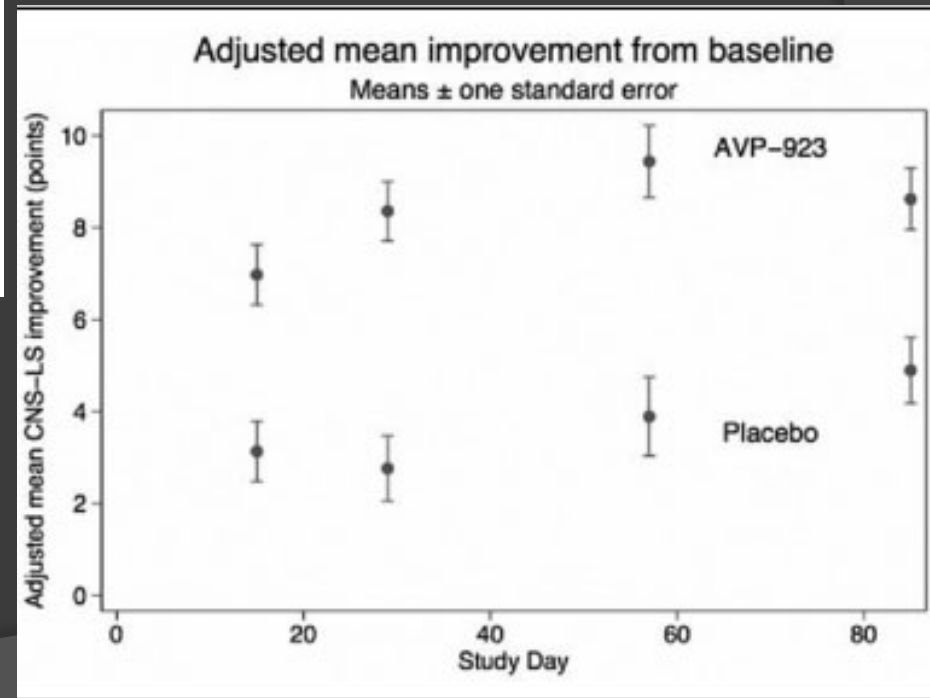
# Dextromethorphan/Quinidine (DM/Q)

## Center for Neurologic Study-Lability Scale (CNS-LS) for pseudobulbar affect (PBA)

Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time
1	2	3	4	5

Assessment questions	Answers
1 There are times when I feel fine 1 minute, and then I'll become tearful the next over something small or for no reason at all.	
2 Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny.	
3 I find myself crying very easily.	
4 I find that even when I try to control my laughter, I am often unable to do so.	
5 There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.	
6 I find that even when I try to control my crying, I am often unable to do so.	
7 I find that I am easily overcome by laughter.	

Total Score: \_\_\_\_\_

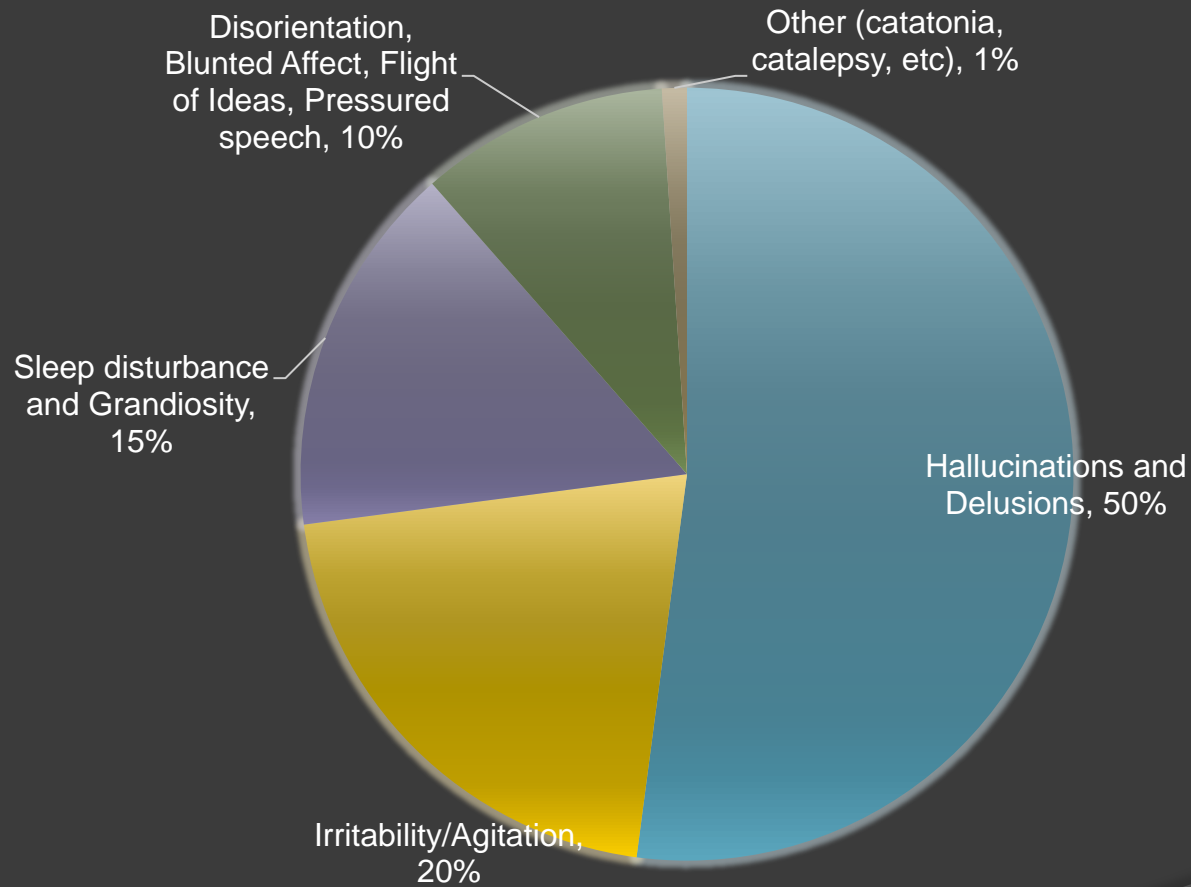


# Psychotic features in MS

Table I. Studies reporting the frequency of psychotic features in large samples of multiple sclerosis patients.

Authors	Country of study	Number of patients with MS	% MS patients with psychotic features	Psychotic features/diagnosis	Neuroimaging findings
Brinar & Zadro (2007)	Croatia	250	2.4%	Hallucinations, paranoid symptoms	Lesion in left temporal lobe
Harel et al. (2007)	Israel	651	2.61%	Dysregulation of affect with no insight	
Patten et al. (2005)	Canada	10367	2.0–4.0%	Non-organic psychotic disorders (schizophrenia spectrum and delusional disorders), organic psychosis	
Diaz-Olavarrieta et al. (1999)	Mexico	44	17.0%	Hallucinations, delusions	Moderately severe frontotemporal abnormalities
Ron & Logsdail (1989)	UK	110	6.3%	Delusional disorders, atypical psychosis	Temporal lobe pathology
Joffe et al. (1987)	Canada	100	0.0%		
Schiffer & Babigian (1984)	USA	368	4.6%	Psychosis	
Surridge (1969)	UK	108	0.9%	Schizophreniform psychosis and manic-depressive mood swings	

# Psychotic Features in MS



# Cognitive Dysfunction in MS



# Cognitive dysfunction in MS

- ⦿ Occurs in up to 70% of patients
  - Including early MS, CIS and pediatric MS patients
- ⦿ The most important factor associated with loss of work for MS patients
- ⦿ May disrupt social life, impair ability to live independently irrespective of physical disability, impedes participation in rehabilitation, and impair ability to follow more complex treatment regimens.

# Areas of cognition affected

<b>Cognitive Domains Affected by MS</b>	
<b>Impaired</b>	<b>Not Impaired</b>
<b>Long-term memory</b>	<b>Long-term memory</b>
<b>Explicit memory</b>	<b>Semantic memory</b>
<b>Episodic memory</b>	<b>Implicit memory</b>
<b>Working memory</b>	<b>Language</b>
<b>Attention</b>	<b>IQ</b>
<b>Complex attention tasks - selective, divided or alternating attention</b>	
<b>Processing speed</b>	
<b>Executive Function</b>	
<b>Abstract reasoning</b>	
<b>Problem solving</b>	
<b>Planning</b>	
<b>Visual spatial tasks</b>	

# MRI and Cognitive Dysfunction

## ◎ Diffusion tensor imaging

- Quantitative MR techniques allowing for the study of normal appearing brain tissue allows for more specific localization

## ◎ Double inversion recovery

- Allows for superior detection of cortical lesions
- Studies have shown strong correlation between cortical lesion volume and cognitive impairment
  - Calabrese, et al. Arch Neurol 2009;66:114-1150.

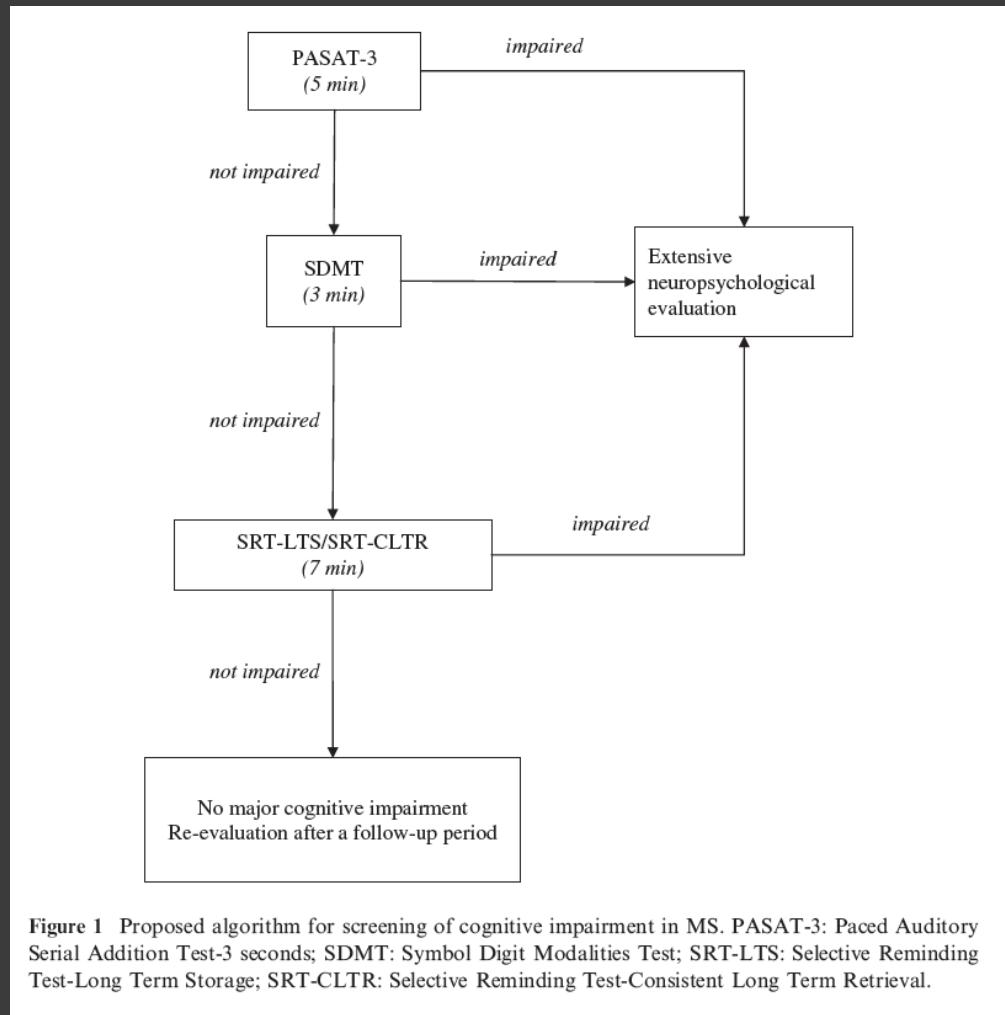
## ◎ fMRI

- Allows for mapping of brain activity
- Studies show increased activation in MS patients compared with controls but for patients that had poorer performance on cognitive tests there was less extensive brain activation.
  - Mainero et al. Neuroimage 2004;21(3):858-867.

# Assessment of Cognitive Function

- ⦿ MMSE is not an appropriate screening tool for cognitive dysfunction in MS
  - Sensitivity is only 30%
- ⦿ Brief Repeatable Battery is the most widely used
  - Selective Reminding Test – verbal memory and delayed recall
  - 10/36 Spatial Recall Test – visual memory and delayed recall
  - PASAT - attention, concentration and processing speed
  - SDMT attention, concentration and processing speed
  - Word List Generation – verbal fluency

# Brief Cognitive Screen



# Management of Cognitive Dysfunction

- Prevention
- Non-Pharmacologic
- Pharmacologic

# Non-Pharmacologic

- ◎ Lifestyle changes
  - Smoking cessation
  - Restful sleep
  - Management of fatigue
- ◎ Computer based programs
  - BrainStim
    - 3 modules
      - City Map – spatial orientation
      - Find Pairs – working memory and visual memory
      - Memorize Numbers – working memory
  - AIXTENT
    - Training of attention across 4 domains (alertness, divided attention, selective attention and vigilance)

# Pharmacologic

## ⊙ AchE Inhibitors

### • Donepezil

#### ○ 69 MS treated for 24 weeks

- showed improvement in verbal learning and memory test.
- Treatment group reported improvement in cognitive function

• Krupp, et al. Neurology 2004;63:1579-1585

### • Rivastigmine

#### ○ 12-week trial of 60 cognitively impaired patients showed no improvement with rivastigmine

• Shaygannejab, et al. Canadian Journal of Neurological Sciences 2007;35:476-481.

# Pharmacologic

## ⦿ Memantine

- 1 year, randomized trial suggests that high dose (30mg/day) memantine may induce reversible neurologic impairments
  - Villoslada, et al. *Neuro* 2009;72:1630-1633.
- 16 week trial showed no improvement on the CVLT-II or PASAT
  - Lovera, et al. *Mult Sci* 2010; 16 (6):715-723.

# Pharmacologic treatments

**Table 1** Symptomatic agents of cognitive impairment in MS: literature studies

Study	Drug	No. of patients	Study design	Outcome
Geisler et al. [17]	Amantadine/ pemoline	45, MS-severe fatigue	Placebo-controlled trial for 6 weeks	No effects
Krupp et al. [11]	Donezepil	69-Memory-impaired (RAVLT) (67 completed the trial)	Parallel groups, RCT, intention-to-treat analysis, 24 weeks of treatment	Improvement SRT, patient- and physician-reported cognition
Lovera et al. [18]	Ginkgo biloba	43, a score between 0.5 and 2.5 SD below PASAT/ CVLT-II	RCT, 120 mg twice a day or placebo for 12 weeks	No effects
Villoslada et al. [16]	Memantine	19, MS- cognitive impaired (1.5 SD below in at least two tests BRBN)	1-year crossover RCT, 30 mg daily	Trial halted after nine patients reported neurological worsening
Krupp et al. [13]	Donezepil	120-memory- and cognitive impaired ( $\leq 0.5$ SD below in RAVLT)	Multicenter RCT, 10 mg daily	No effects

*RCT* Randomized controlled trial, *PASAT* paced auditory serial addition test, *RAVLT* rey auditory verbal learning test, *SRT* selective reminding test, *CLVT II* California verbal learning test-II, *BRBN* brief repeatable battery-neuropsychology

# L-Amphetamine sulfate

- Effects of L-amphetamine sulfate (Adderall) on cognition
  - 151 MS patients
  - Primary outcome – SDMT
    - Not significant improvement
  - Secondary outcomes:
    - PASAT – not significant
    - CVLT II – DR and BVMTR showed significant improvements
  - Patients' self report showed no improvement

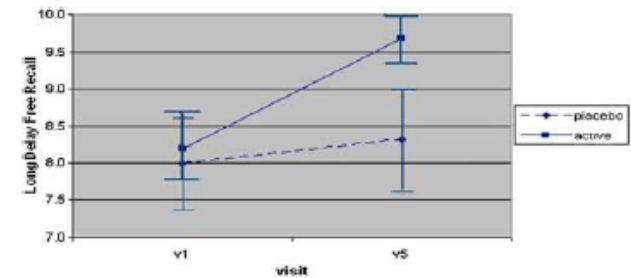


Fig. 2 Mean California Verbal Learning Test 2nd edition delayed free recall (CVLT2-DR) by treatment condition and visit

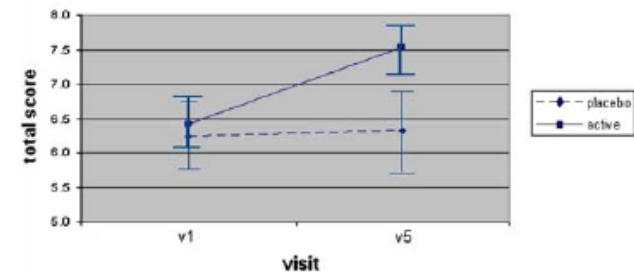
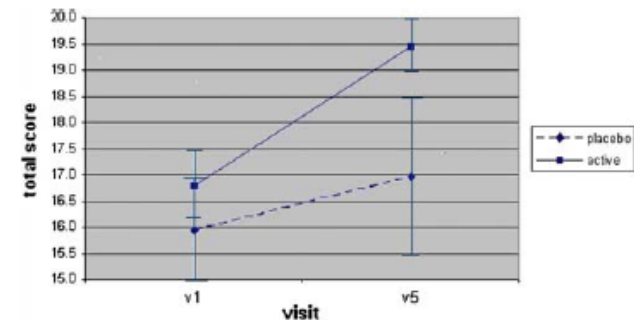


Fig. 3 a Mean Brief Visual Memory Test Revised Total Learning (BVMTR-TL) by treatment condition and visit. b Mean Brief Visual Memory Test Revised Delayed Recall (BMVTR-DR) by treatment and visit

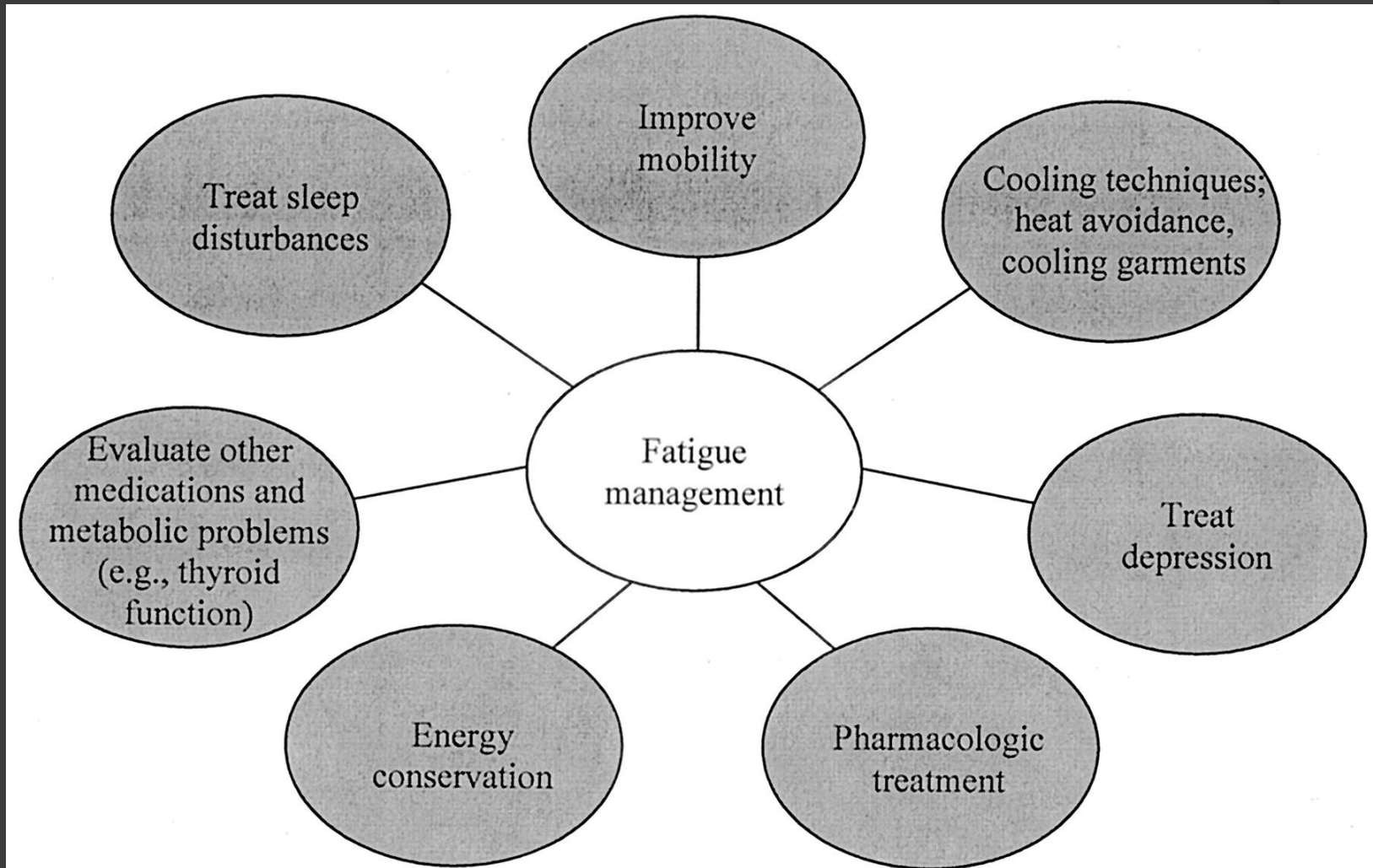
# Fatigue

- ⦿ The most common symptoms in MS
  - Reported in up to 87% of patients
- ⦿ May exacerbate other symptoms of MS such as mood disturbance, cognitive dysfunction, and sexual dysfunction.
- ⦿ May refer to mental or physical energy

# Fatigue: Assessment

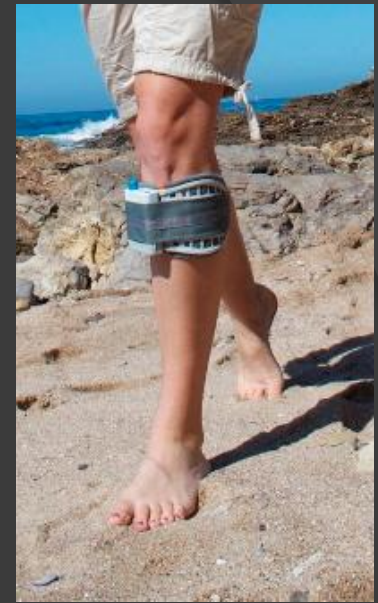
- ⊙ Assess for other MS related issues that may contribute:
  - Depression
  - Sleep disturbance
    - Sleep apnea, PLMD, pain, nocturia
- ⊙ Assess for other exacerbating factors:
  - Metabolic
    - Thyroid disease, vitamin B12 deficiency, anemia
  - Infections
  - Medication side effect
    - Anti-spasmodics, analgesics, sedative-hypnotics, anti-convulsants, IFN

# Fatigue management.



# Non-pharmacologic treatments

- ⦿ Exercise
- ⦿ Rehabilitation
  - Energy conservation strategies
  - Gait dysfunction
    - AFO
    - Bioness or Walk-Aid
- ⦿ Cooling devices



# Fatigue: Pharmacologic Treatments

**Table 1.** Medications used to treat multiple sclerosis-related fatigue.

Medication	Effects in improving fatigue	Mechanism of action	Side effects
Amantadine	Widely used and moderately effective	Effect on fatigue is unclear, but known to have monoaminergic, cholinergic and glutaminergic effects	Neuromalignant syndrome Nausea Dizziness Sleep disturbance
Modafinil	Evaluated in several studies with varying results [Lapierre and Hum, 2007]. Although it is commonly used in clinical settings with good results	$\alpha$ -1 adrenergic properties It is widely used as a wake-promoting agent for the treatment of narcolepsy	Headache Nausea Dizziness Elevated blood pressures Tachycardia Sleep disturbance
Acetyl L-carnitine	Recently evaluated in a small study by Tomassini and colleagues who found it to be better tolerated and more effective than amantadine [Tomassini <i>et al.</i> 2004]	Carnitine is a cellular component involved in energy metabolism	Abdominal discomfort
Dalfampridine	Has been shown to be effective in reducing fatigue and may also improve weakness and heat sensitivity.	Potassium channel blocker intended to improve conduction in demyelinated pathways	May increase serum potassium level ECG changes were observed in clinical trials but were not felt to be significant Seizures

# Social impact of MS

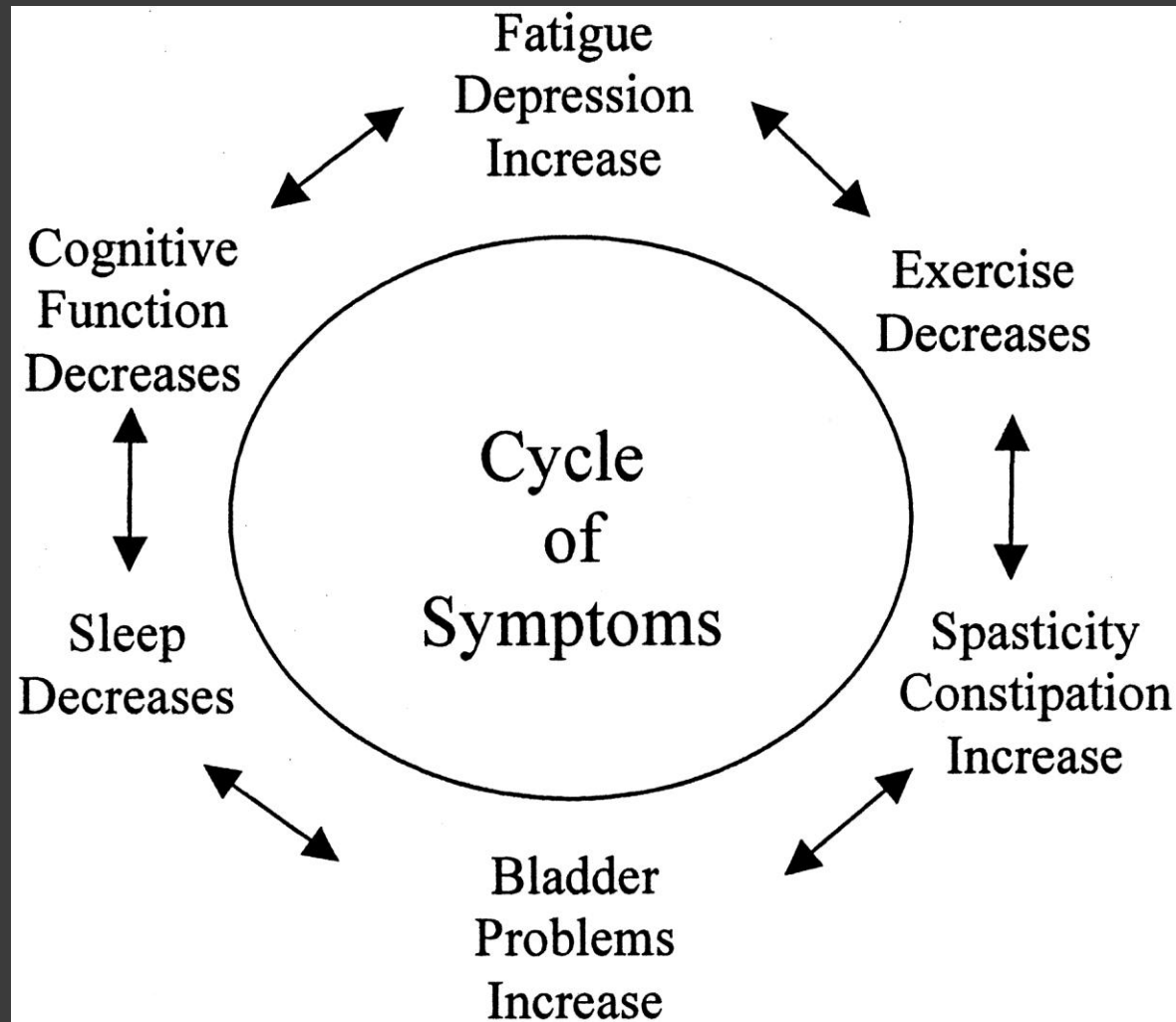
## ⦿ Financial burden

- One of the most costly neurological disease due to early onset, chronicity and loss of employment
- The annual cost of living with MS is greater than \$57,000 per year.

## ⦿ Family burden

- Psychiatric symptoms as well as physical disability place a burden on the family/caregiver
- Varying reports on divorce rate
  - 6-fold increase in divorce when patient is female
- Children may feel fear and anxiety surrounding the diagnosis, a sense of burden, or anger
  - Children who are better informed about their parents disease have fewer problems

## Multiple sclerosis symptoms can be related and interdependent



Questions?