

# Pharmacotherapy of Major Depressive Disorder

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# Overview

- Biology of depression
- Effectiveness of pharmacotherapy for Major Depressive Disorder (MDD)
- MDD Pharmacotherapy trials in MS

# Location of brain lesions in MS depression

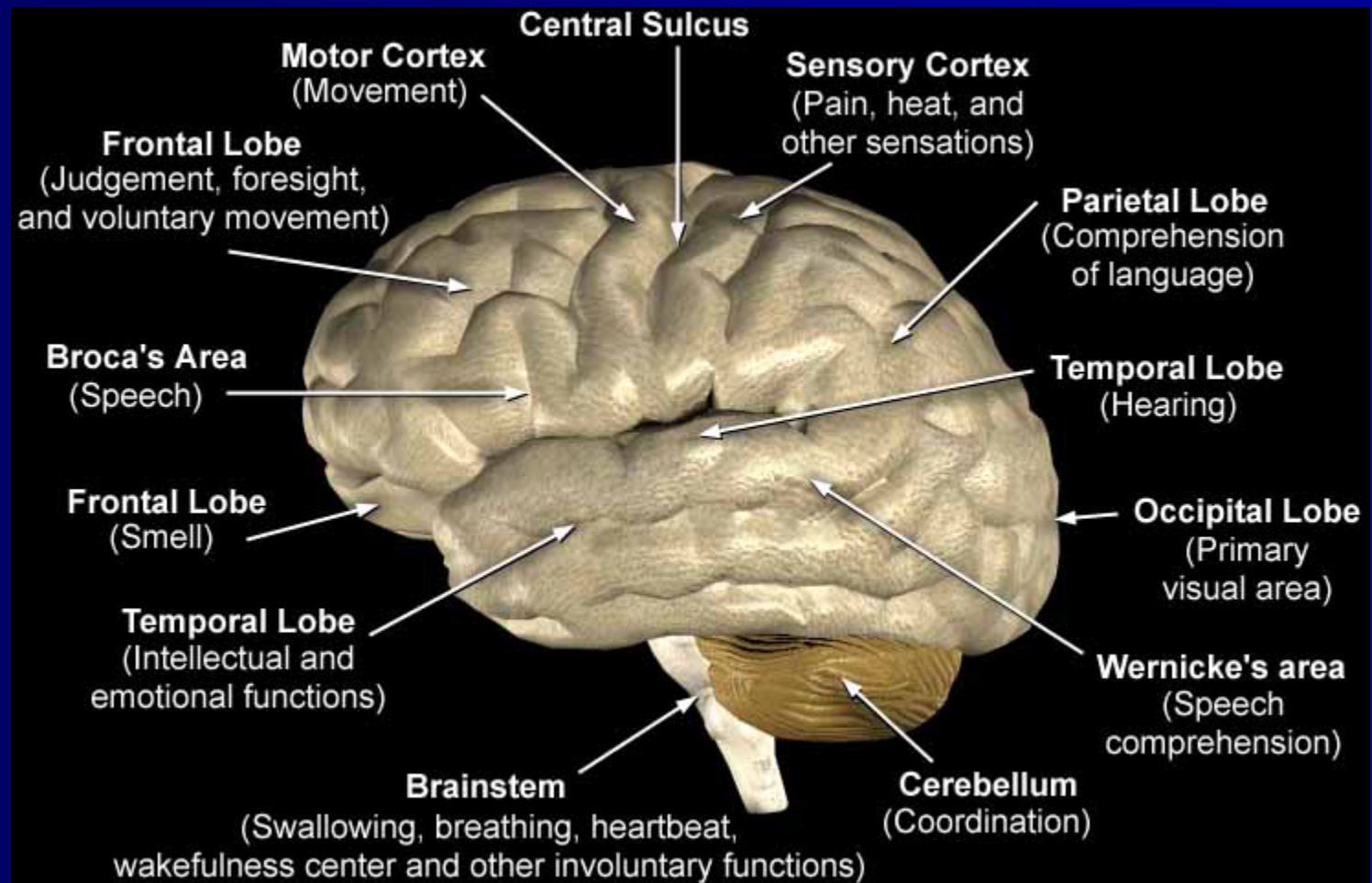
- No clear theoretical model of neuropathology
- No relation between total lesion volume and depression
- There is evidence of an association between depression and greater neuropathology in the left anterior temporal / parietal region

*Pujol J, et al. Neurology 1997; 49: 1105-1110*

*Zorzon, et al. J Neurol 2001; 248: 416-421*

*Feinstein A et al. Neurology 2004; 62: 586-590*

# Neuropathology of depression



# Interferon and Depression

- Interferon does not appear to increase incidence of depression in persons with MS
- Best predictor is pre-treatment depressed mood
- Depression increases risk of non-adherence to Interferon
  - Treatment of depression improves adherence
- Screening for depression and monitoring of mood should be part of medical management of all persons with MS

*Mohr DC et al. Arch Neurology 1997; 54: 531-533*

# Antidepressant Medications



# Use of Antidepressant Medications By Persons with MS

- 35% of persons with MS reported use of an antidepressant
- 43% of those with significant depressive symptoms reported antidepressant use

*Johnson et al., poster presented at CMSC, 2005*

# Inadequate Treatment of Depression

- 140 consecutive patients at MS clinic in Canada
  - 2/3 of MS patients with current major depression were not receiving medication
  - 1/3 of patients with suicidal ideation had not received any psychological assistance
- 260 patients treated by 35 neurologists, 25.8% met criteria for MDD
  - 65.6% received no antidepressant medication
  - 4.7% received sub-therapeutic doses

*Feinstein A. Neurology 2002; 59: 674-678*

*Mohr DC et al. Multiple Sclerosis 2006; 12: 204-208*

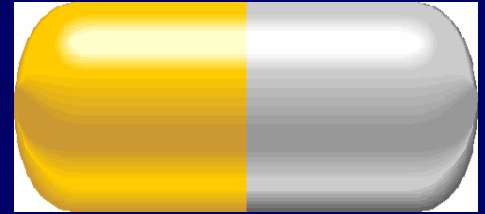
# Summary of evidence on treatment efficacy

- Antidepressant clearly indicated for MDD
- The probability of recovery is equal for pharmacotherapy or psychotherapy (50-70%)
- all available approved antidepressants are equal in clinical efficacy
- wide variation in clinical response
- follow-up is critical
- 9-12 months of treatment
- Maintenance treatment for 2 or more episodes

# Indications for pharmacotherapy (AHRQ)

- Major Depressive Episode
- Initial symptoms of moderate or greater severity
- milder symptoms that have persisted for two years or more
- milder symptoms that persist after 1-2 months of support and watchful waiting

# Medication selection



- Previous experience with specific drug or class
- Presenting symptom of anxiety or insomnia
- Decreased risk of medication interaction
  - escitalopram, mirtazapine

# Selective Serotonin Reuptake Inhibitors (SSRIs)

- Citalopram (Celexa) 10-60 mg qD
- Escitalopram (Lexapro) 5-20 mg qD
- Fluoxetine (Prozac) 10-80 mg qD
- Paroxetine (Paxil) 10-60 mg qD
- Sertraline (Zoloft) 25-200 mg qD

# Side effects of SSRIs

- dry mouth
- nausea
- tremor, restlessness
- insomnia
- headaches
- sexual dysfunction

# Other antidepressant medications

- bupropion (Wellbutrin) 75-300 mg qD
- mirtazapine (Remeron) 15-60 mg qD
- venlafaxine (Effexor) 37.5-225 mg qD
- duloxetine (Cymbalta) 20-60 mg qD
- trazodone (Desyrel)
- nefazodone (Serzone)

# Tricyclic antidepressants (TCAs)

- amitriptyline (Elavil)
- desipramine (Norpramin)
- imipramine (Tofranil)
- nortriptyline (Pamelor)

# Side effects of TCAs

- dry mouth
- blurred vision
- constipation
- urinary retention
- sedation

# Assessment of treatment

- Side effects
  - Sexual side effects
- Assess treatment response
  - Patient report
  - Validated instruments
- If inadequate response
  - Too low a dose, too short a course
  - Misdiagnosis
  - Co-morbidity

# Sexual side effects

- Wait for adaptation
- Reduce dose (side effects are dose-dependent)
- Drug holiday?
- Switch: bupropion, mirtazapine, escitalopram
- Pharmacologic antidotes
  - bupropion, buspirone, viagra, gingko, yohimbine, cyproheptadine

# Importance of follow-up

- Up to 50% of patients starting antidepressant will experience unsatisfactory outcome (side effect or inadequate response)
- 25-30% of patients discontinue medication within one month
- 40-50% discontinue within three months
- Follow-up every 2 weeks first 8 weeks (AHRQ)

# Treatment response rates

- STAR-D: 47% response rate
  - remission of MDD in 28-33%
- When one SSRI is ineffective, response rates to a second SSRI (or bupropion or venlafaxine) is 21-28%
  - response rate to augmentation with bupropion or buspirone is 30-39%

*Rush et.al. N Engl J Med 2006; 354: 1231-1242*

*Trivedi et al. N Engl J Med 2006; 354: 1243-1252*

# If initial treatment fails...

- Switch to alternative medication
- Augmentation (RCT)
  - psychotherapy
  - bupropion, buspirone
- Other pharmacologic augmentation options
  - TCA, lithium, thyroxine

# Continuation and maintenance treatment

- Continuation: treatment necessary to prevent return of index depressive episode or relapse
  - 9-12 months after remission
- Maintenance: treatment necessary to prevent recurrence or new episode
  - more than 6 months after remission

# Pharmacotherapy for MDD in MS

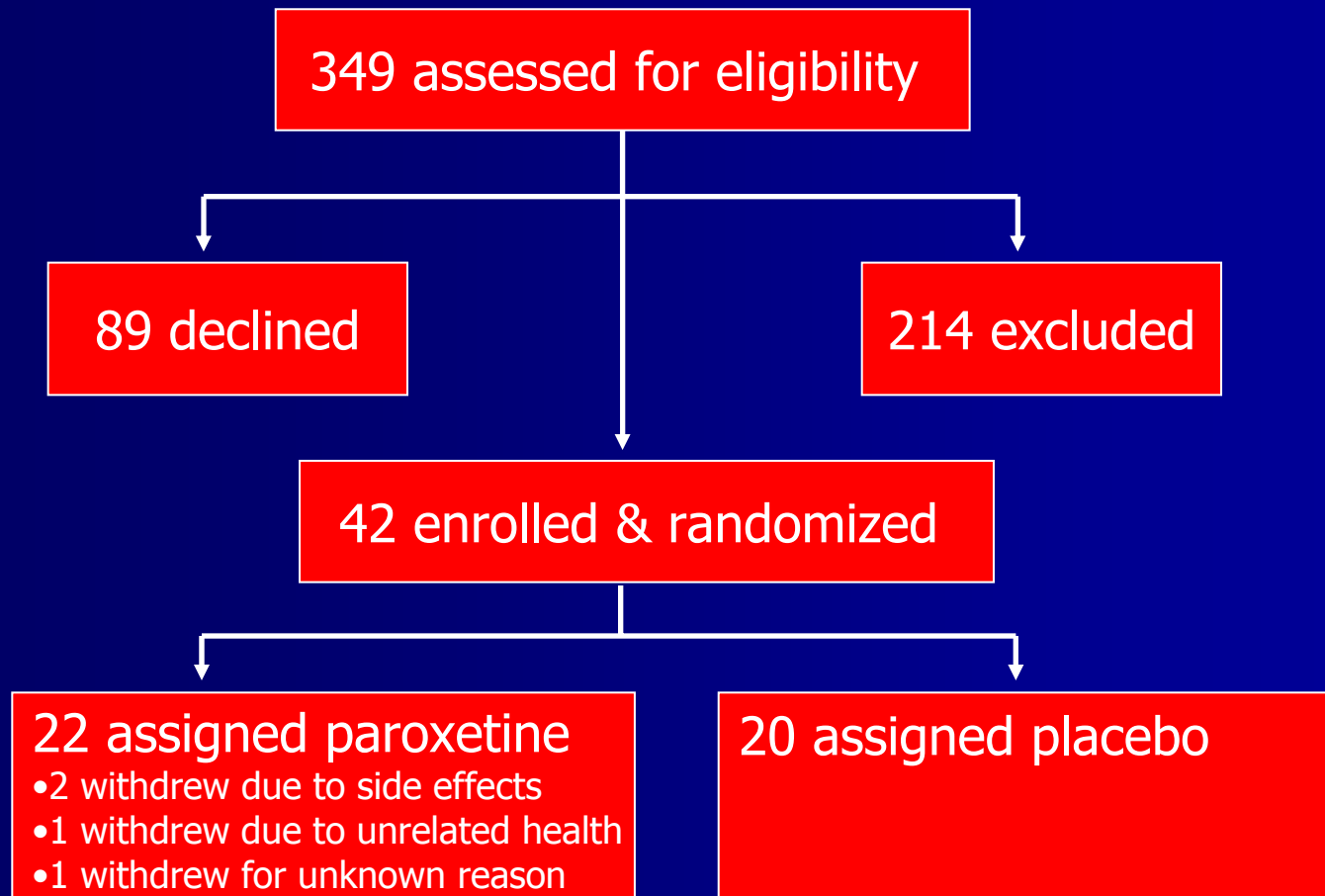
# Randomized Controlled Trials

Study	n	Treatment	Control	Outcome
Schiffer 1990	28	desipramine, 5 weeks (n=14)	placebo	BDI, Ham-D
Mohr 2001	63	sertraline, 16 weeks (n=21)	individual CBT, group SET	BDI, Ham-D
Ehde unpublished	42	paroxetine, 12 weeks (n=22)	placebo	Ham-D, SCID

# Response and attrition

Group	subjects with 50% ↓ in Ham-D	% Attrition
Individual CBT	50%	5%
Sertraline	24%	29%
Group therapy	14%	18%

# Paroxetine trial: Subject flow



# Exclusions

*108 were already taking antidepressant*

29 did not have MDD or dysthymia

6 had exclusionary psychiatric diagnosis

5 were in psychotherapy

4 were abusing drugs/alcohol

# Participant Characteristics

- Mean age: 45 years (SD = 10.1)
- 52% female
- 48% married/living with partner
- 86% Caucasian
- Type of MS
  - relapsing-remitting = 50.0%
  - secondary progressive = 16.7%
  - primary progressive = 19.0%
  - progressive relapsing = 11.9%

# ≥ 50% Reduction in Ham-D

Group	Intent-to-Treat	p-value	Completers	p-value
Paroxetine	57.1%	0.354	78.6%	0.073
Control	40.9%		42.1%	

# Persistent MDE on SCID at 12 weeks

Group	Intent-to Treat	p-value	Completers	p-value
Paroxetine	35.0%	1.00	13.3%	0.43
Control	30.0%		26.3%	

# Side Effects

Side Effect	Paroxetine	Control
Nausea*	57.1%	5.0%
Headache*	47.6%	10.0%
Dry mouth	47.6%	35.0%

\*  $p < .001$

# Conclusions from RCT

- Under ITT, paroxetine was not more efficacious than placebo in treating MDD
  - among completers, a greater proportion (78.6%) of the treatment group improved
  - response rates to paroxetine are at least as high as in samples of psychiatric patients and those with chronic medical conditions
  - study under-powered to detect a difference in response when response in control group is so high

# Placebo Response Rates

Study	Treatment Response Rate	Placebo Response Rate
Ehde	57%	40%
Mohr et al. (MS & MDD)	CBT: 50% sertraline: 24% group: 14%	-----
Walsh et al. (review of 75 MDD trials)	Mean: 50% (range = 32-70%)	Mean: 30% (range = 13-52%)

# Are Antidepressants Effective among persons with MS ?

## ■ No

- Nearly a third of those screened for study were excluded due to antidepressant use-yet remained depressed
- 35% of participants who received paroxetine remained depressed after 12 weeks of treatment

## ■ Yes

- antidepressant medications are effective, but major depressive episode in MS has higher probability of resolving spontaneously
- there are subgroups whose depression is particularly responsive to pharmacotherapy
- other medications may be more effective than SSRIs