Clinical Trials in Multiple Sclerosis: Why Do We Need Them?

Ellen M. Mowry, M.D., M.C.R.

Johns Hopkins University

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Objectives

- **To review the history of medication development for MS**
- **To review some other interventions that have been popular for people with MS**
- **To describe what's needed to convince the FDA (or your doctor) that a particular medication or intervention works**
- **To briefly review logistics of a clinical trial**

Quest for Approved MS Therapies: Through The Years

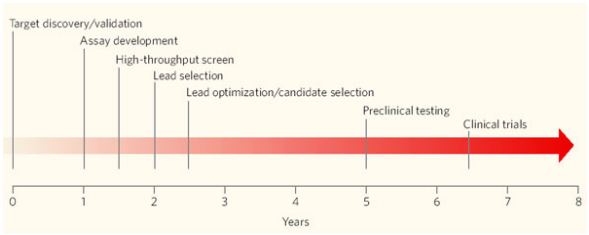
- **1868: Charcot publishes first report of someone with MS**
- **1935: Mouse model of MS (EAE) is created**
- **1969: ACTH (steroids) begun to be used for MS**
- **1981: first brain MRI done for MS**

Timeline: FDA-Approved MS Medications

Medication	First mentioned in literature	Approved by FDA
Interferon beta	1981	1993 (Betaseron) 1996 (Avonex) 2002 (Rebif)
Glatiramer acetate (Copaxone)	1977	1996
Natalizumab (Tysabri)	1999	2004 (2006)
Fingolimod (Gilenya)	2002	2010
Teriflunomide (Aubagio)	2004	2012
Dimethyfumarate (Tecfidera)	2005	2013
Mitoxantrone (Novantrone)	1992	2000

Why Does it Take SO Long To Get an FDA- Approved Drug?

- **Timeline of drug development**

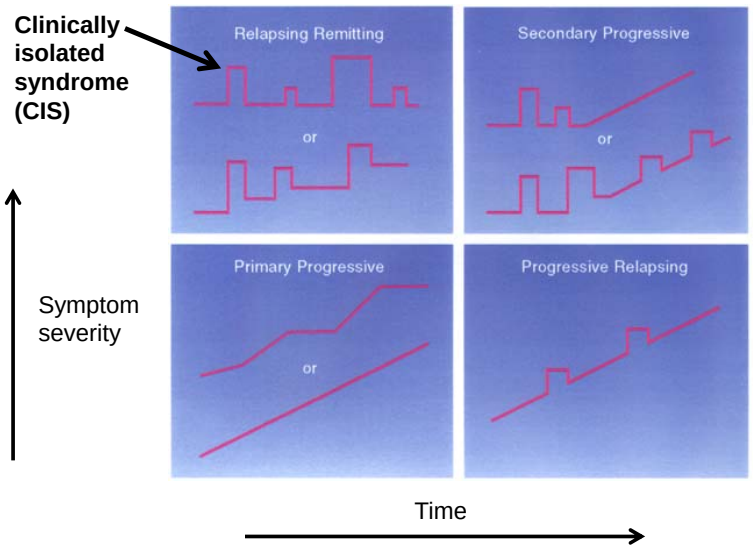


5,000 to 10,000 new compounds→250 promising enough to test on animals→10 suitable for testing in humans→ 2-3 pass initial safety screen

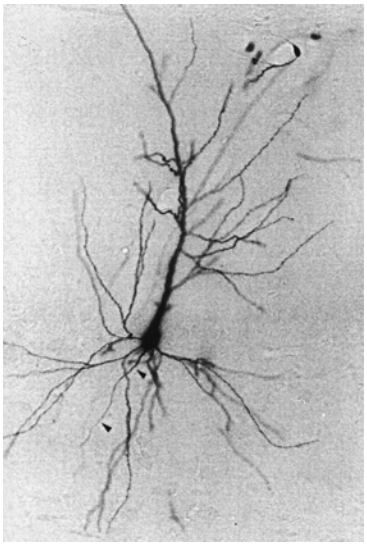
- **Different types of MS**

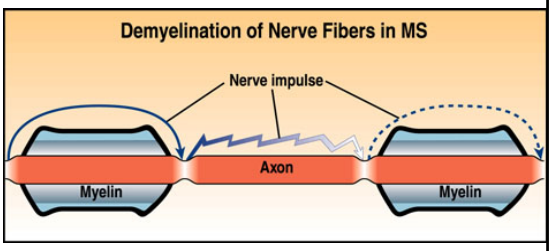
(why no progressive MS medications?)

Subtypes of MS



What Causes Relapses Vs. Progression?





Lifestyle Modifications in MS

- **Should I take acai berry?**
- **Should I just take vitamin D?**
- **Should I be on a special diet?**

"My Doctor Doesn't Believe in Natural Therapies"

Other Interventions (not FDA-regulated medications)

Intervention	First mentioned in literature	Year proved or debunked
Bee stings	1967	2005 (debunked)
Swank diet	1952	
CCSVI	2009	2010+ (debunked)
Fatty acids	1950s	
Vitamin D	1986	(2014/15?)

Who Cares?

- **Why do we need to prove that an intervention is helpful?**

  →Especially for diets, dietary supplements?

  "It's a vitamin…. I guess it can't hurt!"

My Two Cents

- **Whether or not the FDA regulates an intervention, doctors should still require good evidence that it will be helpful/safe before recommending**
- **If you are trying an intervention, you are using it as a drug/medication**
  - **→what if it's harmful?**
  - **→what if it doesn't hurt or help MS but consumes a lot of money or time?**

Levels of Evidence

I. One patient's experience (anecdote)

↓

II. Experience of a handful of patients (handful of anecdotes)

↓

III. Link between something that measures a person's status (ex. vitamin D levels) and some disease outcome (ex. attacks)

↓

IV. Link between an intervention (ex. giving vitamin D supplements to a group of people with MS) and a disease outcome (ex. fewer attacks)

↓

V. Evidence in a randomized controlled clinical trial that the intervention (ex. high-dose vitamin D supplements versus placebo) causes a disease outcome (ex. fewer attacks)

Level I. One patient's experience
Level II. Experience of a handful of patients

- "My mother has MS, and she swears that eating 3 eggs every day has made the disease better."
- "Everyone on an internet blog is saying that the gluten-free diet will help my MS."

Big Picture Problems: Level I/II Evidence

- Everyone's MS is different, and each person may have other diseases too.
  → EVEN IF some intervention/medication helps one person/group of people, it may not help most people
  → How do you measure intangible benefits in a small number of people?
- When we have an illness and try an intervention, we WANT to believe that something we take or do will make it better ("placebo effect")

Level III. Link between something that measures a person's exposure to something and an MS outcome

- **Level IIIa) People who are more disabled from their MS have lower levels of vitamin D**
- **Level IIIb) In people with MS, those who have lower levels of vitamin D had more attacks and more new white spots develop on MRI over the <u>prior</u> 2 years**
- **Level IIIc) In people with MS, those who have lower levels of vitamin D had more attacks and more new white spots develop on MRI over the <u>next</u> 2 years**

Big Picture Problem: Level III Evidence

<u>Vitamin D Levels: *Effect on* MS, or *Affected by* MS?</u>

<u>We think:</u>

Low vitamin D → MS risk
→ ↑attacks, MRI changes, disability

<u>What if:</u>

More severe MS → less time in sun → low vitamin D

OR

People with lower levels of MS also have lower levels of …. (sodium, zinc, chocolate intake)

AND

Chocolate intake → improved MS

Prior supplement experience

Some that appeared to be beneficial in observational studies had no effects/were harmful in clinical trials setting

→Folic acid: lower risk of colon cancer in observational studies

-increased risk of advanced colorectal adenoma in clinical trial

→Beta-carotene: protective against heart disease in observational setting

-increased lung cancer risk, increased deaths from heart disease in clinical trial

Level IV: Link between an intervention and a disease outcome

- **In a group of 100 people with MS, giving high-dose vitamin D supplements for two years was associated with fewer attacks and fewer white spots on brain MRI over the same time period compared to the two previous years**

- **Compared to 50 people with MS who didn't eat 6 cups of kale a day, 50 people with MS who did do so reported walking longer distances**

Level IV: Big Picture Problems

- **"Regression to the mean"**
  - **→ Doctors might have suggested vitamin D supplements to those people who were having more attacks… but the attacks were destined to cool off anyways**
- **Bias**
  - **→ people who choose to eat kale may have other reasons that they walk longer (ex. they also began yoga)**
  - **→ "unblinded;" people who ate kale believed it would help when they started**

Level V: Randomized Controlled Clinical Trials

- **Patients are RANDOMLY assigned to intervention group or control group**
- **Ideally, neither patients nor doctors know which group they're in until after the study is over (double-blind)**
- **Evaluate if those in intervention group do better than those in control group**

Some Minuses of Clinical Trials

- **Expensive**
- **Start-up, recruitment, completion, analysis can take a long time (especially for progressive MS)**
- **Results may not be applicable to a given patient**
  →safety; MS subtype; other background features

How Do Medications Make Their Way to Clinical Trials?

An example…

<u>Discovery phase</u>:

→ Mice with severe EAE (mouse model of MS) have higher levels of chemical X in their blood

→ infusing chemical X into mice with EAE makes the disease worse; blocking chemical X makes it better

→ MS patients with higher levels of chemical X have more severe disease

→ Pharmaceutical company manufactures chemical X blocker, tries to figure out in mouse studies what doses are safe

Phases of Clinical Trials

- **Phase I: chemical X blocker given to a small group of healthy human volunteers and assessed for safety, tolerable doses**
- **Phase II: chemical X blocker tested in a small group of people with MS and evaluated for safety and preliminary outcomes (new white spots on MRI); typically randomized**
- **Phase III: large randomized study of chemical X blocker versus placebo (or another medication) in people with MS, evaluating for very clear benefit as well as associated risks**
- **Phase IV: after chemical X blocker is approved by the FDA, patients are observed for bad outcomes associated with use of medication**

What Happens During a Clinical Trial?

- **Patients with MS are "screened" for eligibility**
- **Those enrolled are randomized to one of (usually 2 or 3) "arms"**
- **Participants observed for changes in MS, MRI changes, and safety items**

  →involves visits to study sites (more than usual)

Ongoing Clinical Trials at Johns Hopkins

- **Examples to illustrate the phase of clinical trials and discuss rationale for eligibility criteria**

Randomized Trial of Vitamin D in MS

<u>High- versus low-dose vitamin D as add-on to glatiramer acetate (2 years)</u>

→ all people given glatiramer acetate (Copaxone); randomized to high-dose versus low-dose vitamin D

Eligibility:

- **Relapsing-remitting MS**
- **Relapses +/- MRI changes in past 2 years**
- **No trouble with walking**
- **Aged 18-50**
- **Limited exposure to MS medications (including NOT on glatiramer acetate (Copaxone) for more than 3 months in the past**
- **No more than average of 1,000 IU/vitamin D per day in past 3 months (can do a washout)**
- **Can't have certain other health conditions/be taking certain other medications**

Vitamin D Trial

- **What phase?**
- **Why are recent relapses or MRI changes required?**
- **Why are the following people excluded?**
  - **Age >50**
  - **Trouble walking**

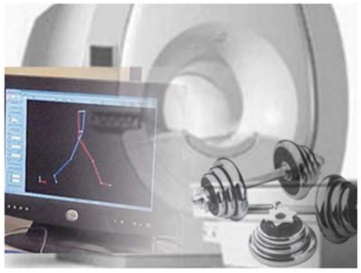
Pharmacokinetics of Vitamin D

Three month study of high-dose vitamin D supplementation in people with and without MS; goal is to evaluate if people with MS need same dose as those without MS

- **Relapsing-remitting MS with few ongoing MS symptoms**
- **White females, aged 18-60**
- **Taking only glatiramer acetate (Copaxone), interferon (Rebif, Betaseron, Avonex), or natalizumab (Tysabri)**
- **Otherwise fairly healthy**

WHY THESE CRITERIA?

Kennedy Krieger Institute Exercise Study (MS and controls)



The study is investigating the effects of strengthening exercise and whether MRI measures are predictive of training results. The study takes place over a six-month time frame, with three testing sessions at the Kennedy Krieger Institute Motion Analysis Lab in Baltimore, and 36 exercise training sessions. The first testing session will be used to individualize an exercise program that will be done in a small group setting in the early morning.

What types of criteria might this study have?

Exercise Study

- **What types of criteria might this study have?**

→people with multiple sclerosis and healthy controls

→ages 21-75

Long-acting Baclofen Study

- **This study is evaluating an extended-release baclofen pill that is dosed once per day instead of the standard 3 times per day.**
- **Why the following criteria?**
  - **18 years of age or older**
  - **Have spasticity due to MS**
  - **Are on a stable daily dose of Baclofen, ranging from 30 to 60 mg/day**

Bottom Line: Clinical Trials

- **Whether studying a "natural" therapy or intervention, or a medication developed by a pharmaceutical company…. we have the same pledge to our patients:**

First do no harm.

- **Often, this means a clinical trial may ultimately be needed to ensure a given intervention works.**

What Can You Do to Help?

- Consider participating in studies (consult with your doctor)
- Spread the word about studies to friends with MS
- Participate in MS Walks, bike rides, and other fundraisers for research
- Keep inspiring those of us doing research with your passion and determination!

Studies at Johns Hopkins

You can find out what studies are going on at:

http://www.hopkinsmedicine.org/neurology_neurosurgery/specialty_areas/multiple_sclerosis/research/

vitamindtrialms@jhmi.edu

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