

# Journal Club contents

- ◆ Article citation
- ◆ Background
- ◆ Methods
- ◆ Results
- ◆ Interpretation
- ◆ Critique

# Citation

◆ Authors

◆ Title

◆ Journal

◆ Year; Volume: pages

**Shults et al**  
**Effect of Coenzyme**  
**Q10 in Early**  
**Parkinson's**  
**Disease**  
**Arch Neurol**  
**2002; 59:1541**

# Journal Club contents

- ◆ Article citation

- ◆ **Background**

- ◆ Methods

- ◆ Results

- ◆ Interpretation

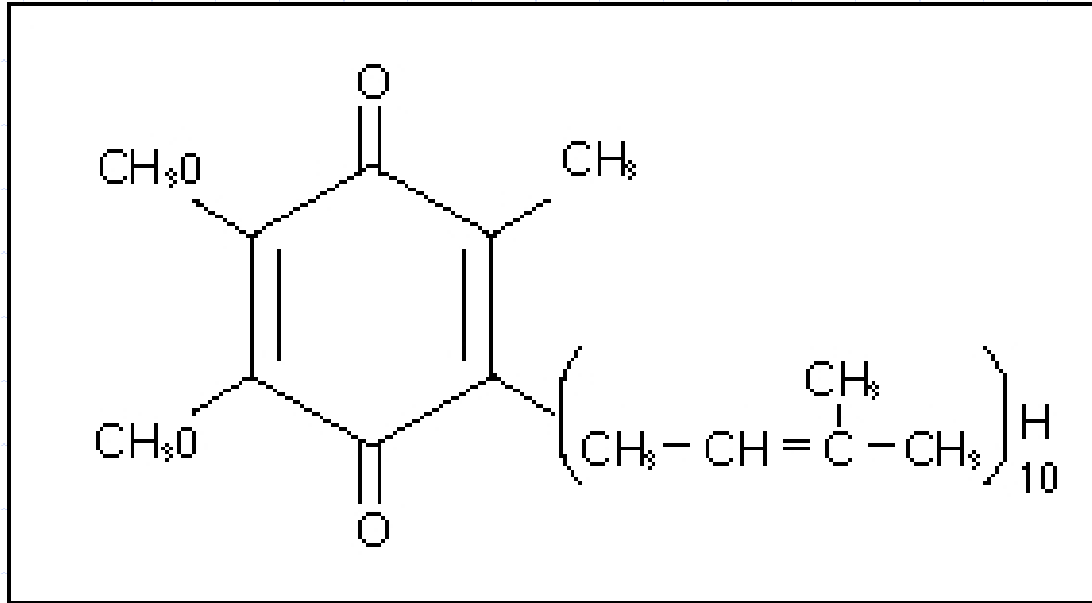
- ◆ Critique

- ◆ What is coenzyme Q10?

# What is Coenzyme Q<sub>10</sub>?

- ◆ Coenzyme Q<sub>10</sub> is essential to human life and is a crucial component in the primary energy production cycle. Research indicates that supplementation with this nutrient may support normal heart function, provide antioxidant protection and maintain the health of gums.\*

# What is Coenzyme Q<sub>10</sub>?



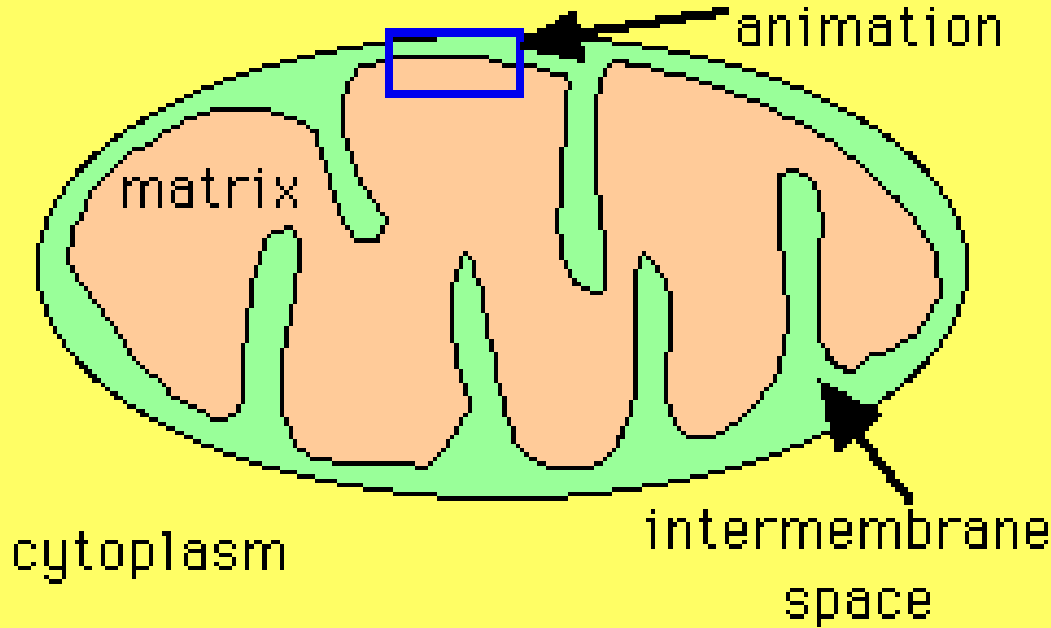
Coenzyme Q<sub>10</sub>. The 'Q' indicates that this molecule is a quinone, characterized by the ring structure at the left with 2 attached double-bonded oxygen molecules (O). The '10' refers to the ten repetitions of the side chain on the lower right of the molecule. It's also called ubiquinone.

# What is Coenzyme Q<sub>10</sub>?

- ◆ Antioxidant
- ◆ Vitamin
- ◆ Available in health food stores, not subject to FDA drug regulations
- ◆ Coenzyme – facilitates chemical reactions, especially in the mitochondria

# Mitochondrion

region in animation

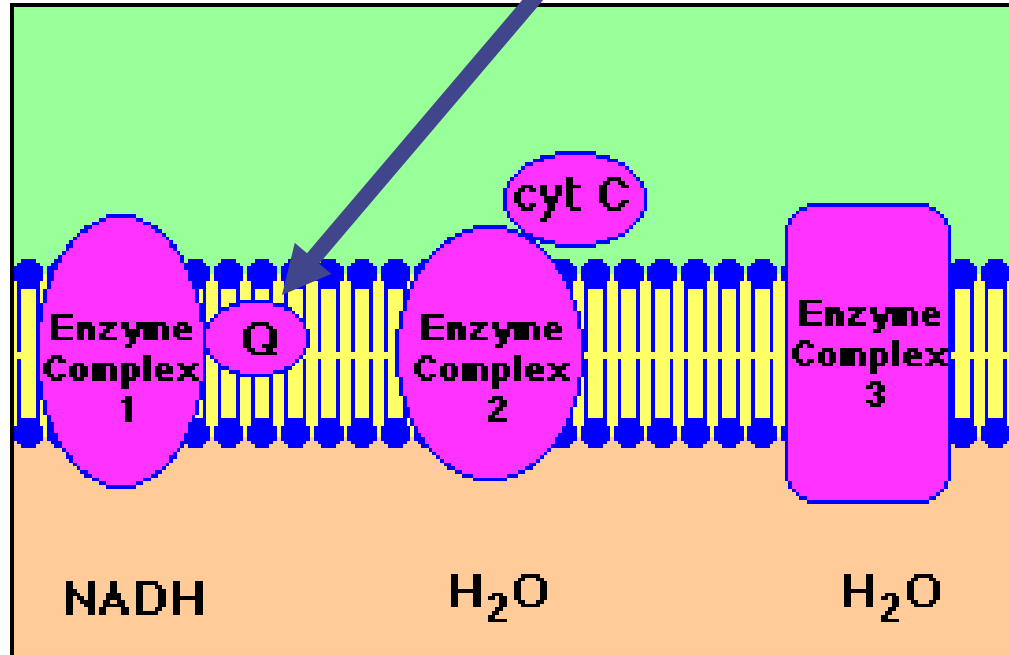


[www.sp.uconn.edu/~terry/images/anim/mitomaster1.gif](http://www.sp.uconn.edu/~terry/images/anim/mitomaster1.gif)

Copyright 1997.  
Thomas M. Terry

Coenzyme Q<sub>10</sub>

The electron transport chain includes enzyme complexes in the mitochondria.



# Journal Club contents

- ◆ Article citation
  - ◆ **Background**
  - ◆ Methods
  - ◆ Results
  - ◆ Interpretation
  - ◆ Critique
- ◆ What is coenzyme Q10?
  - ◆ Why was it chosen for trial in early Parkinson's disease?



# Why was it chosen for trial in early Parkinson's disease?

- ◆ MPTP toxicity involves mitochondria.
- ◆ Rotenone given to rats injures substantia nigra neurons.
- ◆ Some recessive gene mutations that cause Parkinson's seem to affect mitochondria.
- ◆ Patients with Parkinson's disease have decreased complex I activity in substantia nigra.
- ◆ Patients with mild untreated Parkinson's disease have low complex I and complex II activity in platelets.
- ◆ Patients with mild untreated Parkinson's disease with low Coenzyme Q<sub>10</sub> levels.

# Journal Club contents

- ◆ Article citation
- ◆ Background
- ◆ **Methods**
- ◆ Results
- ◆ Interpretation
- ◆ Critique

# Coenzyme Q<sub>10</sub> (ubiquinone)

- ◆ 4 groups of 20 patients with early Parkinson's disease
- ◆ Randomized
- ◆ Double-blind
- ◆ Outcome measure UPDRS
- ◆ Assessments at baseline, 1, 4, 8, 12, & 16 months
- ◆ 300 mg wafers
- ◆ Cost \$1.60/wafer
- ◆ Wafers also contain vitamin E

# Coenzyme Q<sub>10</sub> (ubiquinone)

- ◆ 4 groups of 20

- ◆ **Randomized**

- ◆ **Double-blind**

- ◆ **Outcome measure  
UPDRS**

- ◆ **Assessments at  
baseline, 1, 4, 8,  
12, & 16 months**

- ◆ 300 mg wafers

- ◆ Cost \$1.60/wafer

**Randomized --  
assigned among  
the treatment  
groups by chance**

# Randomized

- ◆ Are the patients in the study allocated among the treatment groups by chance?
  - **Statistics at Square One**
  - Ninth Edition
  - T D V Swinscow
  - Revised by M J Campbell, University of Southampton
  - **Copyright BMJ Publishing Group 1997**
  - <http://resources.bmj.com/bmj/readers/statistics-at-square-one/>

# Randomized

- ◆ Are the patients in the study allocated among the treatment groups by chance?
  - **Statistics at Square One**
  - Ninth Edition
  - T D V Swinscow
  - Revised by M J Campbell, University of Southampton
  - **Copyright BMJ Publishing Group 1997**
  - <http://resources.bmj.com/bmj/readers/statistics-at-square-one/>
- ◆ Are the patients in the study a random sample of the population under consideration?

# Randomized

- ◆ Are the patients in the study allocated among the treatment groups by chance?
  - **Statistics at Square One**
  - Ninth Edition
  - T D V Swinscow
  - Revised by M J Campbell, University of Southampton
  - **Copyright BMJ Publishing Group 1997**
  - <http://resources.bmj.com/bmj/readers/statistics-at-square-one/>
- ◆ Are the patients in the study a random sample of the population under consideration?
  - **Not often!!!**

# Randomized

- ◆ Are the patients in the study allocated among the treatment groups by chance?
  - **Statistics at Square One**
  - Ninth Edition
  - T D V Swinscow
  - Revised by M J Campbell, University of Southampton
  - **Copyright BMJ Publishing Group 1997**
  - <http://resources.bmj.com/bmj/readers/statistics-at-square-one/>
- ◆ Are the patients in the study a random sample of the population under consideration?
  - **Not often!!!** Usually patients are a **convenience** sample of those who come to clinic and are willing to participate.



# Clinical trials

- ◆ Phase I – dose finding
- ◆ Phase II – therapeutic value and adverse effects
- ◆ Phase III – randomized controlled double blind

# Coenzyme Q<sub>10</sub> (ubiquinone)

- ◆ 4 groups of 20
- ◆ Randomized
- ◆ Double-blind
- ◆ Outcome measure UPDRS
- ◆ Assessments at baseline, 1, 4, 8, 12, & 16 months
- ◆ 300 mg wafers
- ◆ Cost \$1.60/wafer
- ◆ **Phase II dose-ranging clinical trial**
  - Placebo
  - 300 mg/day
  - 600 mg/day
  - 1200 mg/day

# Unified Parkinson's Disease Rating Scale -- UPDRS

- ◆ Mentation, Behavior, and Mood – 4 items
- ◆ ADL – 13 items
- ◆ Motor – 14 items
- ◆ Complications of therapy – 11 items
- ◆ Each item rated 0 to 4
- ◆ Higher score = worse disease

# Unified Parkinson's Disease Rating Scale -- UPDRS

## ◆ Motor items

- Speech
- Facial expression
- Tremor at rest
- Action or postural tremor
- Rigidity
- Finger taps
- Hand movements
- Rapid alternating movements
- Foot agility
- Arising from chair
- Posture
- Gait
- Postural stability
- Body bradykinesia

# Unified Parkinson's Disease Rating Scale -- UPDRS

## ◆ ADL items

- Speech
- Salivation
- Swallowing
- Handwriting
- Use of eating utensils
- Dressing
- Hygiene
- Turning in bed
- Falling
- Freezing while walking
- Walking
- Tremor
- Sensory complaints

# Unified Parkinson's Disease Rating Scale -- UPDRS

## ◆ Motor items

- Tremor at rest
  - ◆ 0 – absent
  - ◆ 1 – slight, infrequent
  - ◆ 2 – Bothersome
  - ◆ 3 – Interferes with some activities
  - ◆ 4 – Interferes with many activities
- Arising from chair
  - ◆ 0 – Normal
  - ◆ 1 – Slow
  - ◆ 2 – Pushes self up
  - ◆ 3 – Tends to fall back or retry
  - ◆ 4 – Needs help

# Publication Types

- ◆ Case report
- ◆ Clinical trial
- ◆ Meta-Analysis
- ◆ Editorial
- ◆ Letter
- ◆ Review
- ◆ Randomized controlled trial
- ◆ Practice Guideline

# Publication Types

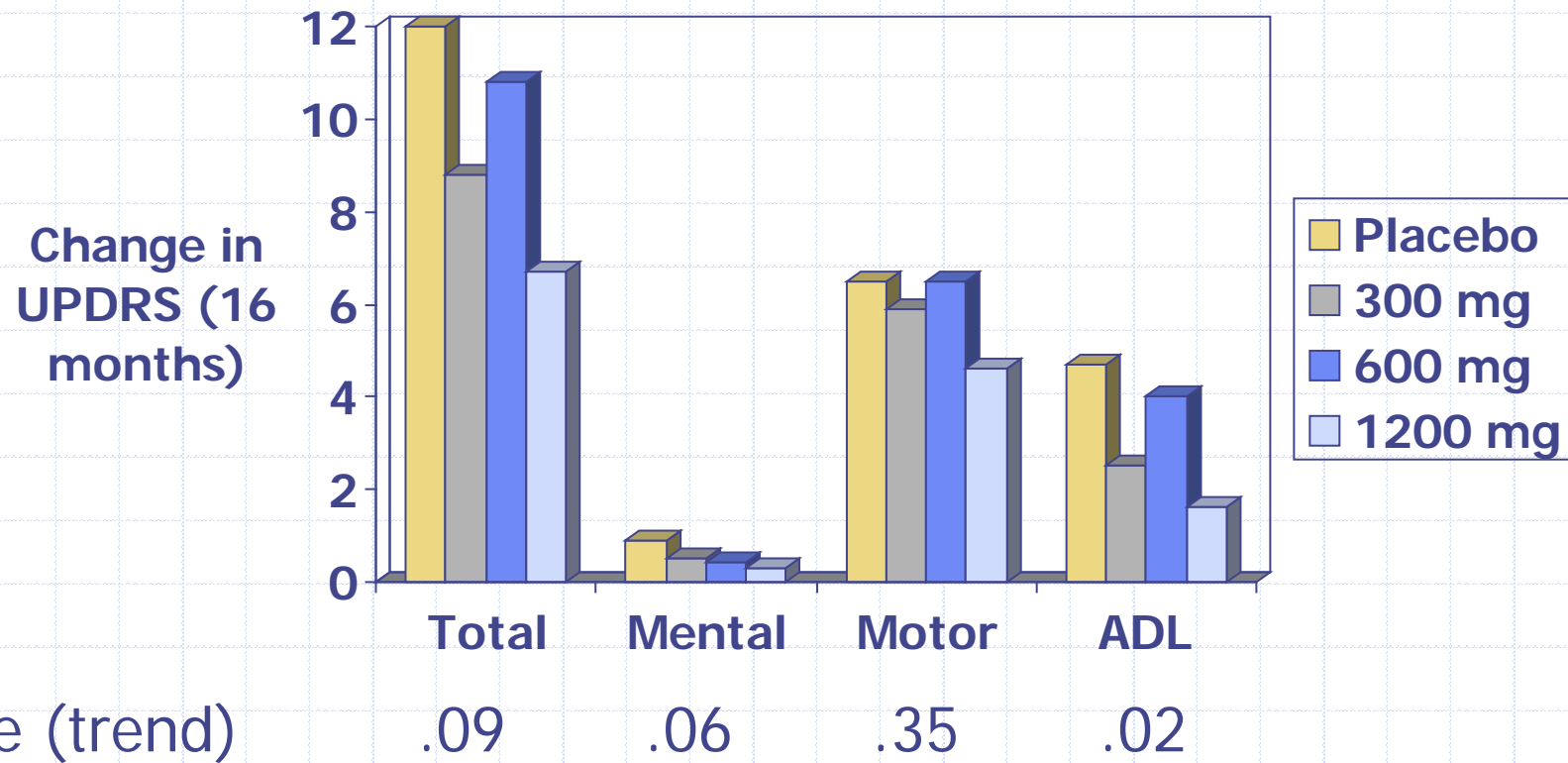
- ◆ Case report
- ◆ Clinical trial
- ◆ Meta-Analysis
- ◆ Editorial
- ◆ Letter
- ◆ Review
- ◆ **Randomized controlled trial**
- ◆ Practice Guideline



# Journal Club contents

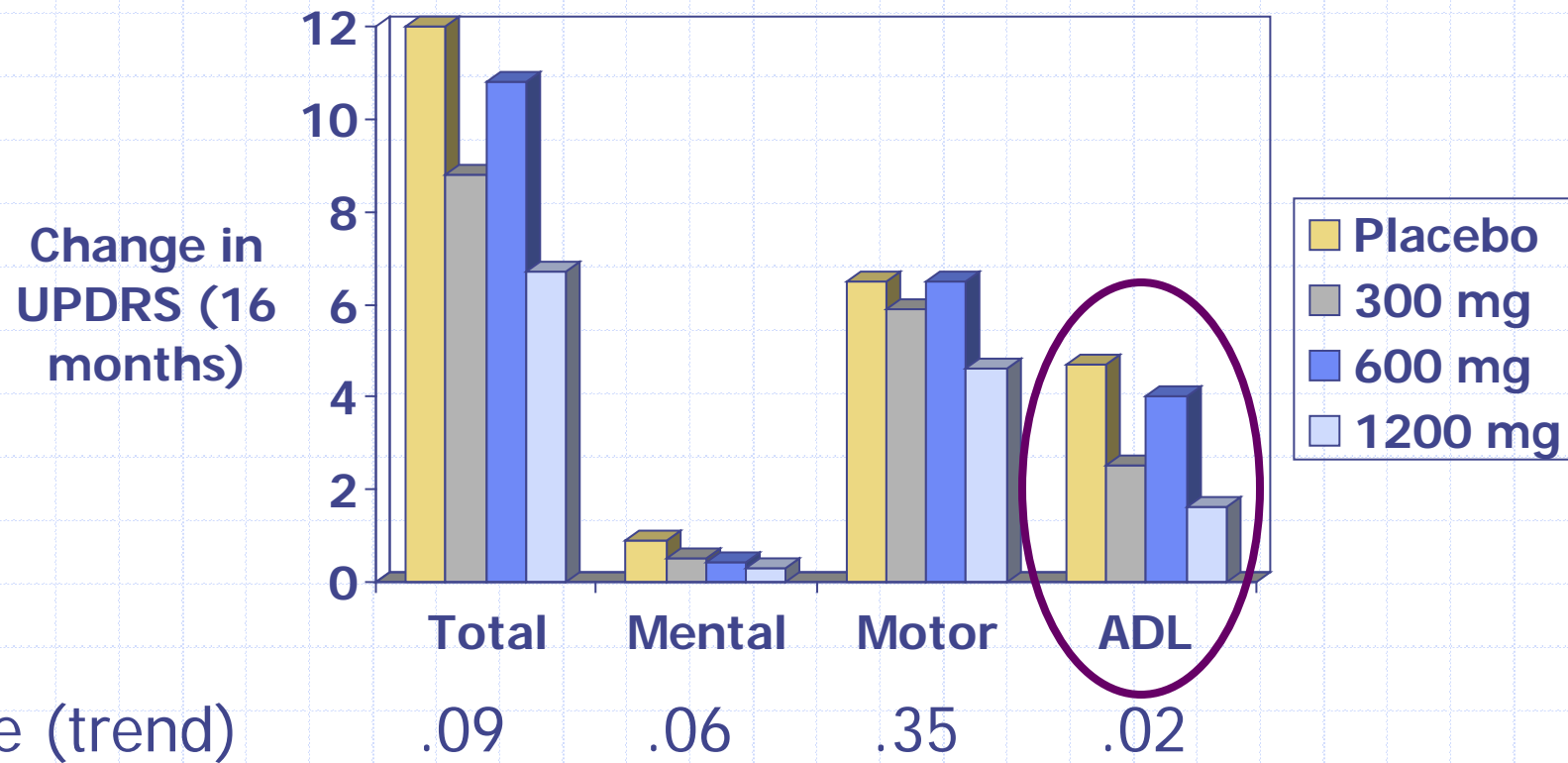
- ◆ Article citation
- ◆ Background
- ◆ Methods
- ◆ **Results**
- ◆ Interpretation
- ◆ Critique

# Effects of Coenzyme Q<sub>10</sub> in early Parkinson's disease

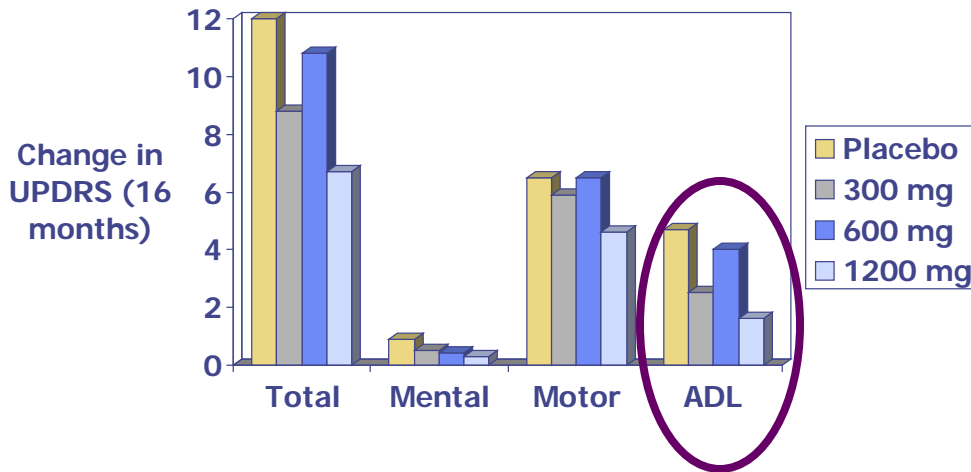


Arch Neurol 2002; 59:1541

# Effects of Coenzyme Q<sub>10</sub> in early Parkinson's disease



# Effects of Coenzyme Q<sub>10</sub> in early Parkinson's disease



- ◆ ADL items
- Speech
  - Salivation
  - Swallowing
  - Handwriting
  - Use of eating utensils
  - Dressing
  - Hygiene
  - Turning in bed
  - Falling
  - Freezing while walking
  - Walking
  - Tremor
  - Sensory complaints

# Journal Club contents

- ◆ Article citation
  - ◆ Background
  - ◆ Methods
  - ◆ Results
  - ◆ Interpretation
  - ◆ Critique
- ◆ Coenzyme Q<sub>10</sub> was safe & well-tolerated up to 1200 mg/day
  - ◆ Treated subjects had less disability and did best with highest dose
  - ◆ Coenzyme Q<sub>10</sub> seemed to slow progression

## Strengths

- Study groups very similar before treatment
- Conducted by well-established methodologic rules
- Considered gold standard for assessing efficacy
- Can be registered to prevent selective reporting

## Weaknesses

### Randomized, controlled trial

- Costly, cumbersome
- Involve limited number of participants
- Often underrepresent key patient groups
- Short duration
- Comparator (or placebo) often irrelevant
- May measure surrogate end points rather than clinical outcomes
- Protocol may not reflect typical care

Avorn **In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research**

N Engl J Med. 2007 Nov 29;357(22):2219-21



# Randomized Controlled Trials Strengths

- Study groups very similar before treatment
- Conducted by well-established methodologic rules
- Considered gold standard for assessing efficacy
- Can be registered to prevent selective reporting

Avorn **In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research**

N Engl J Med. 2007 Nov 29;357(22):2219-21



The NEW ENGLAND  
JOURNAL of MEDICINE

# Randomized Controlled Trials Strengths

Study groups very similar before treatment

Conducted by well-established methodologic rules

Considered gold standard for assessing efficacy

Can be registered to prevent selective reporting

Avorn **In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research**

N Engl J Med. 2007 Nov 29;357(22):2219-21



The NEW ENGLAND  
JOURNAL of MEDICINE



# Journal Club contents

- ◆ Article citation
- ◆ Background
- ◆ Methods
- ◆ Results
- ◆ Interpretation
- ◆ Critique

# Critique of Cotzias, NEJM, 1967 vs. Shults, Arch Neur. 2002

## Cotzias – L-DOPA

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years.
- ◆ Diagnostic criteria were unspecified; sample was biased.
- ◆ Outcome measures were poorly quantified.
- ◆ Controls were imperfect.

## Shults – CoQ<sub>10</sub>

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years

# Critique of Cotzias, NEJM, 1967 vs. Shults, Arch Neur. 2002

## Cotzias – L-DOPA

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years.
- ◆ Diagnostic criteria were unspecified; sample was biased.
- ◆ Outcome measures were poorly quantified.
- ◆ Controls were imperfect.

## Shults – CoQ<sub>10</sub>

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years

# Critique of Cotzias, NEJM, 1967 vs. Shults, Arch Neur. 2002

## Cotzias – L-DOPA

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years.
- ◆ Diagnostic criteria were unspecified; sample was biased.
- ◆ Outcome measures were poorly quantified.
- ◆ Controls were imperfect.

## Shults – CoQ<sub>10</sub>

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years
- ◆ Is high dose safe for everyone? Should the dose have been higher?

# Critique of Cotzias, NEJM, 1967 vs. Shults, Arch Neur. 2002

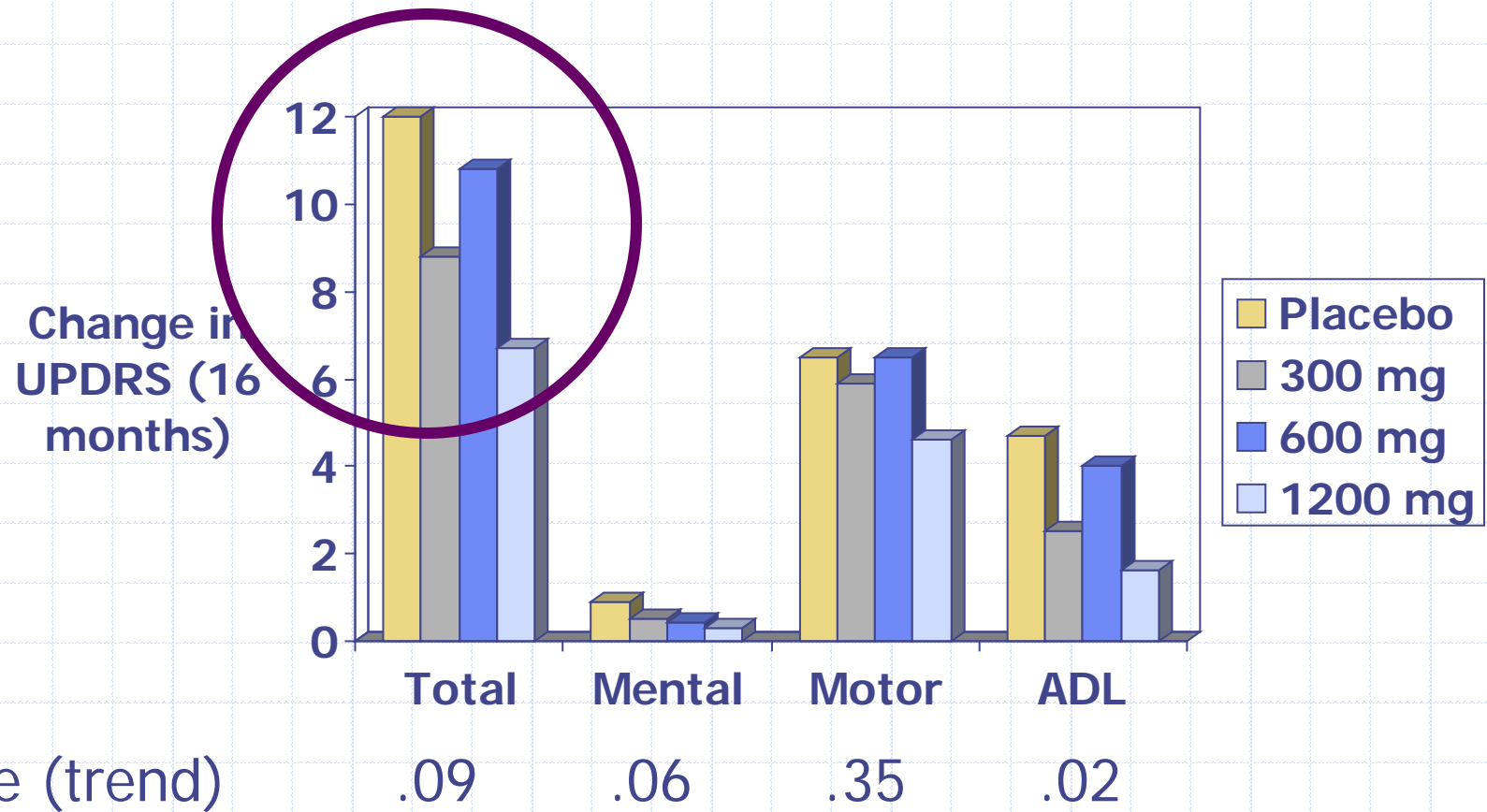
## Cotzias – L-DOPA

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years.
- ◆ Diagnostic criteria were unspecified; sample was biased.
- ◆ Outcome measures were poorly quantified.
- ◆ Controls were imperfect.

## Shults – CoQ<sub>10</sub>

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years
- ◆ Is high dose safe for everyone? Should the dose have been higher?
- ◆ Is outcome clinically significant?

# Does a 5 point difference in the UPDRS matter to a patient?



# Clinically Important Difference

## Summary of Distribution- and Anchor-Based Analyses of the CID on the UPDRS Total and Motor Scores

**Table 4. Summary of Distribution- and Anchor-Based Analyses of the CID on the UPDRS Total and Motor Scores**

	CID, UPDRS Motor Score			CID, UPDRS Total Score		
	Minimal	Moderate	Large	Minimal	Moderate	Large
Distribution-based analysis	2.7	6.7	10.7	4.1	10.3	16.4
Anchor-based analysis						
SF-12 PH	2.4	4.7	...	4.2	8.5	...
SF-12 MH	2.3	4.7	...	4.5	9.1	...
SE Scale	...	4.5	...	...	8.6	...
HY stages	...	...	10.8	...	...	17.8
Mean of all analyses	2.5	5.2	10.8	4.3	9.1	17.1

Abbreviations: CID, clinically important difference; ellipses, not applicable. For other abbreviations, see Table 1.

# Clinically Important Difference

CID, UPDRS Total Score		
Minimal	Moderate	Large
4.1	10.3	16.4
4.2	8.5	...
4.5	9.1	...
...	8.6	...
...	...	17.8
4.3	9.1	17.1

ions, see Table 1.



# Critique of Cotzias, NEJM, 1969 vs. Shults, Arch Neur. 2002

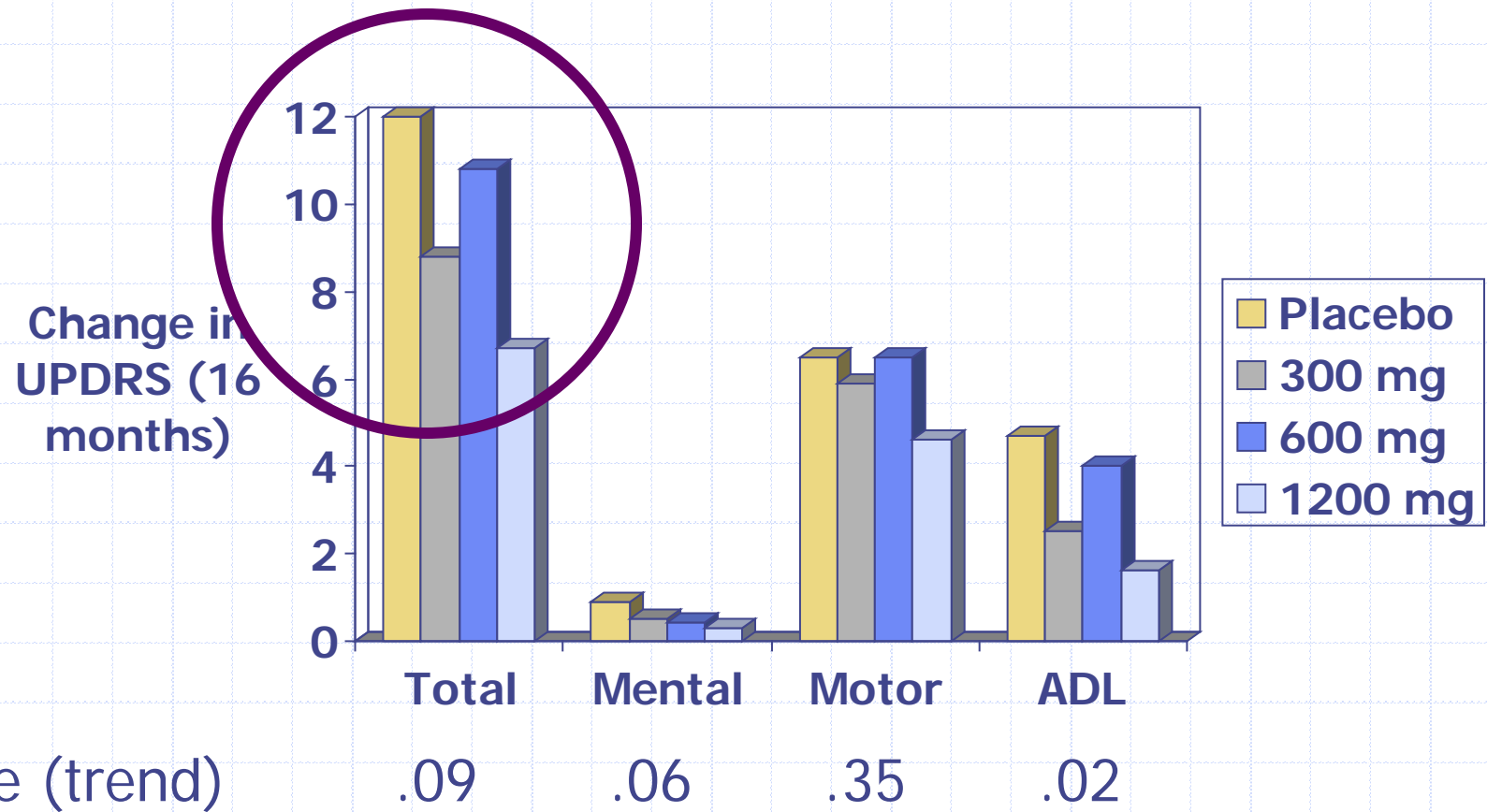
## Cotzias – L-DOPA

- ◆ Few patients were tested.
- ◆ Follow-up was limited
- ◆ Diagnostic criteria were unspecified; sample was biased.
- ◆ Outcome measures were poorly quantified.
- ◆ Controls were imperfect.

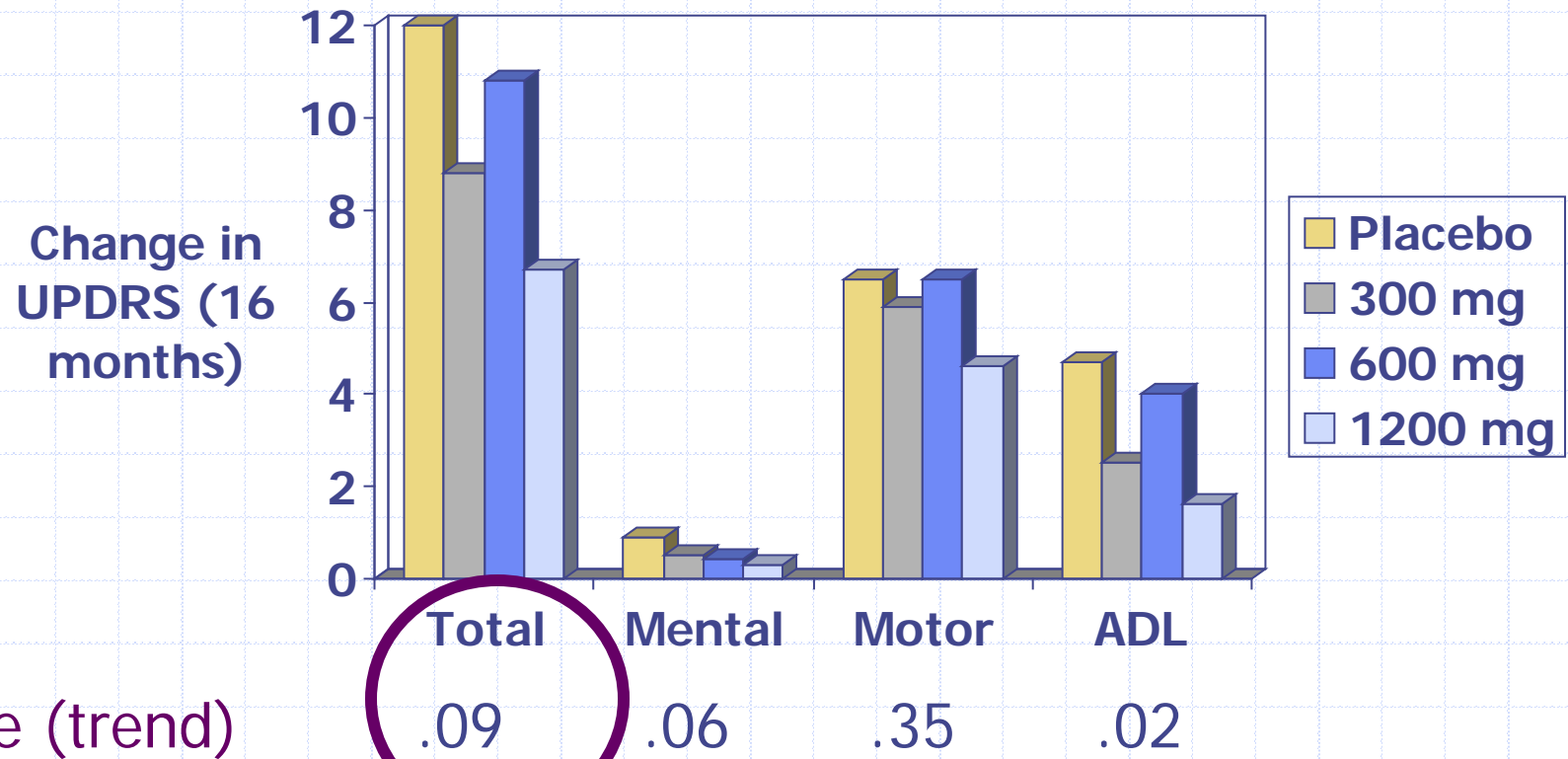
## Shults – CoQ<sub>10</sub>

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years
- ◆ Is high dose safe for everyone? Should the dose have been higher?
- ◆ Is outcome clinically significant?
- ◆ Statistically significant?

# Does a 5 point difference in the UPDRS matter to a patient?



# Does a 5 point difference in the UPDRS matter to a patient?



Arch Neurol 2002; 59:1541

# Diagnostic Accuracy

	Clinical Diagnosis	
	PD	Not PD
PD pathology	True Positive	False Negative
No PD pathology	False Positive	True Negative

# Truth of Hypothesis

	Study Results	
	True	False
Really true	True Positive	False Negative
Really false	False Positive $P = 0.09$	True Negative

P value = chance that a study favoring a hypothesis is a false positive

	Study Results	
	True	False
Really true	True Positive	False Negative
Really false	False Positive $P = 0.09$	True Negative

# Critique of Cotzias, NEJM, 1969 vs. Shults, Arch Neur. 2002

## Cotzias – L-DOPA

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years.
- ◆ Diagnostic criteria were unspecified; sample was biased.
- ◆ Outcome measures were poorly quantified.
- ◆ Controls were imperfect.

## Shults – CoQ<sub>10</sub>

- ◆ Few patients were tested.
- ◆ Follow-up was limited to 2 years
- ◆ Is high dose safe for everyone? Should the dose have been higher?
- ◆ Is outcome clinically significant?
- ◆ Statistically significant?
- ◆ Is result reproducible?

**A larger Phase III trial is needed!**

# Randomized Controlled Trials Weaknesses

- ◆ Limited # of patients
- ◆ Underrepresent key patient groups
- ◆ Short duration
- ◆ May use surrogate end points rather than clinical outcomes
- ◆ Protocol may not reflect typical care
- ◆ Costly, cumbersome

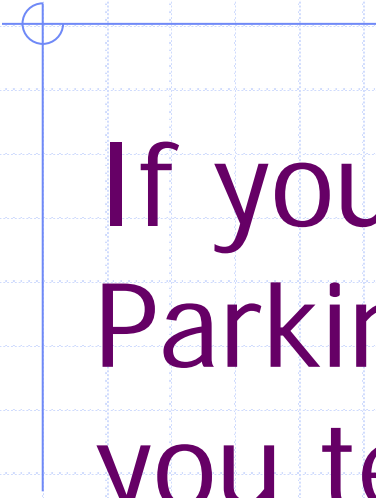
Avorn **In Defense of Pharmacoepidemiology —  
Embracing the Yin and Yang of Drug Research**

N Engl J Med. 2007 Nov 29;357(22):2219-21



The NEW ENGLAND  
JOURNAL of MEDICINE





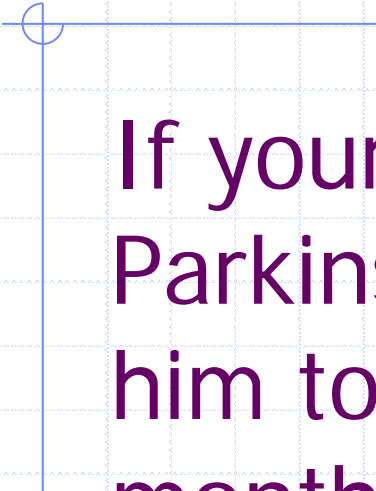
If your grandfather had early Parkinson's disease, would you tell him to take Coenzyme Q<sub>10</sub>?

# Publication Types

- ◆ Case report
- ◆ Clinical trial
- ◆ Meta-Analysis
- ◆ Editorial
- ◆ Letter
- ◆ Review
- ◆ **Systematic Review**
- ◆ Randomized controlled trial
- ◆ Practice Guideline

# The Cochrane Library

- ◆ Liu et al Coenzyme Q10 for Parkinson's Disease, Published Online 12/7/11
- ◆ 4 randomized controlled double blind studies
- ◆ 467 patients
- ◆ "Coenzyme Q10 therapy with 1200 mg/d for 16 months was well tolerated by patients with Parkinson's disease. The improvements in **ADL**, **UPDRS** and Schwab and England were positive, but it need to be further confirmed by larger sample. For total and other subscores of UPDRS, the effects of coenzyme Q10 seemed to be less clear."



If your grandfather had early Parkinson's disease, would you tell him to spend about \$100 each month on Coenzyme Q<sub>10</sub> based on a Phase II dose-ranging clinical trial of questionable statistical significance?

# Clinical trials

- ◆ Phase I – dose finding
- ◆ Phase II – therapeutic value and adverse effects
- ◆ Phase III – randomized controlled double blind

# A Randomized Clinical Trial of High-Dosage Coenzyme Q10 in Early Parkinson Disease: No Evidence of Benefit

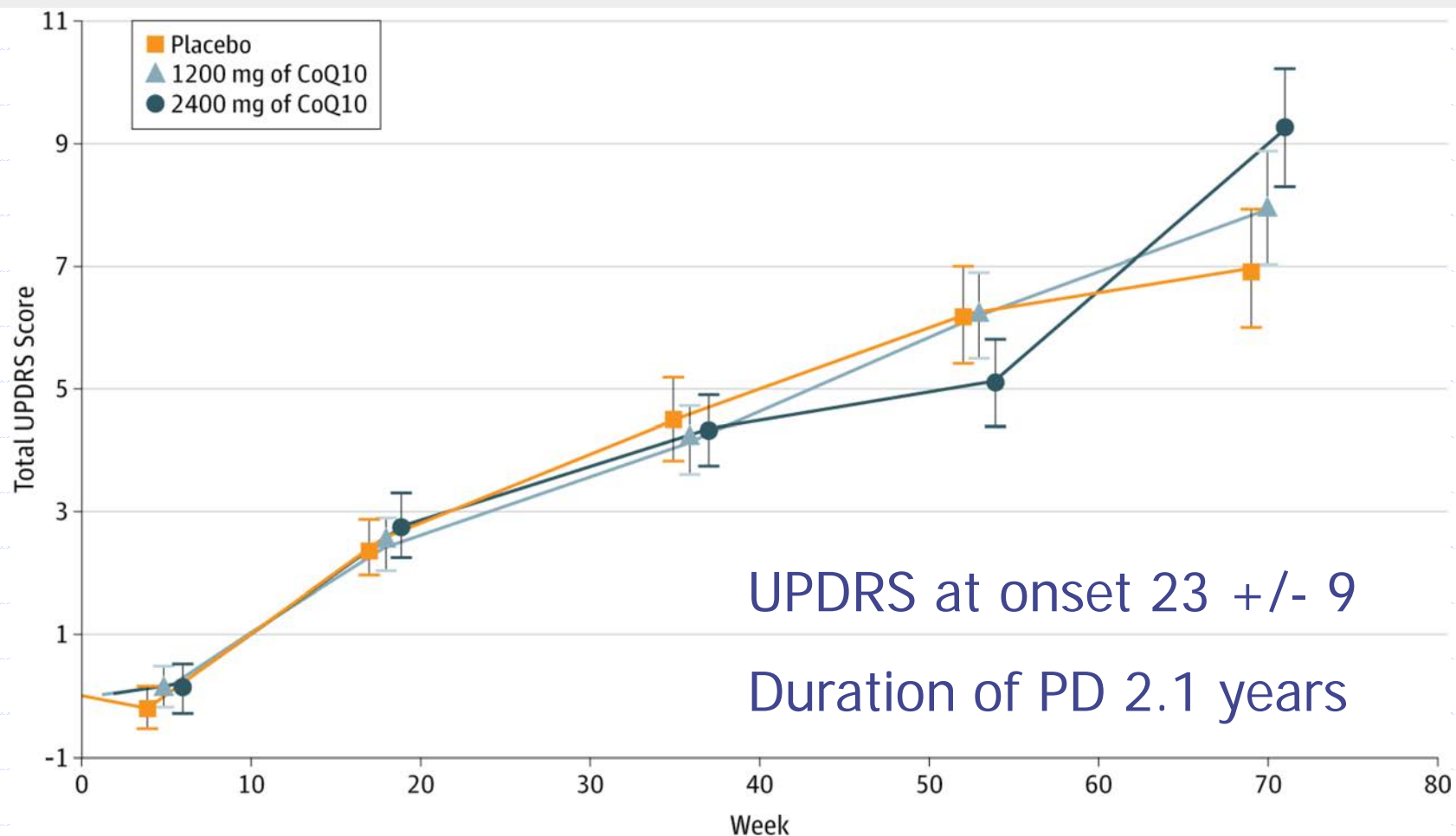
The Parkinson Study Group QE3 Investigators *JAMA Neurol.*

- ◆ 600 patients from 67 clinics
  - Placebo
  - Coenzyme Q10 – 1200 mg
  - Coenzyme Q10 – 2400 mg
  - All also received vitamin E, 1200 IU daily
- ◆ 18 month follow-up
- ◆ Terminated early May, 2011 due to lack of benefit
- ◆ No significant toxicity

**Published online  
March 24, 2014.**

# From: A Randomized Clinical Trial of High-Dosage Coenzyme Q10 in Early Parkinson Disease: No Evidence of Benefit

JAMA Neurol. 2014;():. doi:10.1001/jamaneurol.2014.131



UPDRS at onset 23 +/- 9

Duration of PD 2.1 years

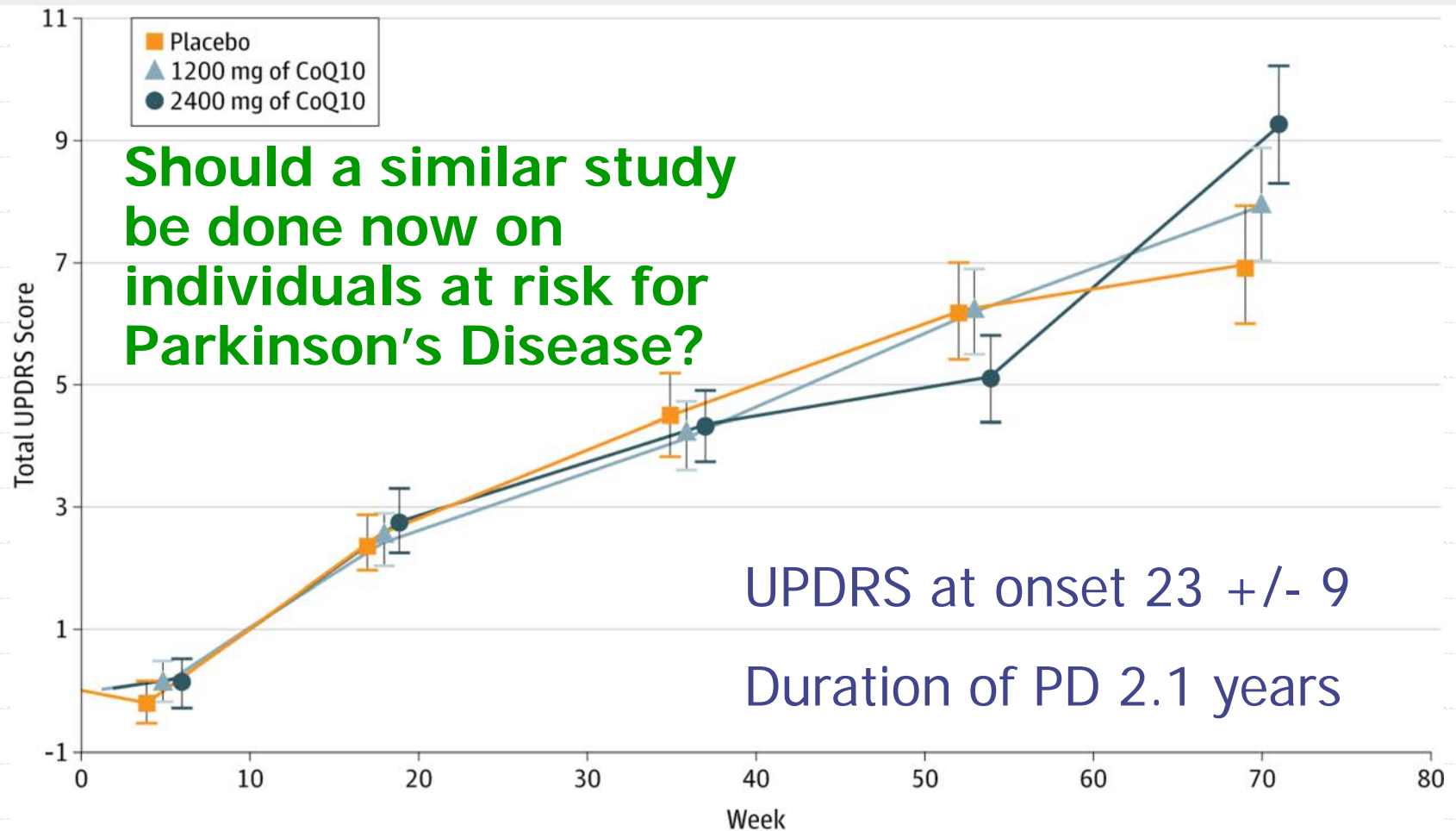
# The Cochrane Library

- ◆ Liu et al Coenzyme Q10 for Parkinson's Disease, Published Online 12/7/11
- ◆ 4 randomized controlled double blind studies
- ◆ 467 patients
- ◆ "Coenzyme Q10 therapy with 1200 mg/d for 16 months was well tolerated by patients with Parkinson's disease. The improvements in ADL UPDRS and Schwab and England were positive, but it need to be further confirmed by larger sample. For total and other subscores of UPDRS, the effects of coenzyme Q10 seemed to be less clear."
  - [Cochrane Database Syst Rev. 2012 May 16;5:CD008150. doi: 10.1002/14651858.CD008150.pub3.](#)
  - **WITHDRAWN**: Coenzyme Q10 for Parkinson's disease.
  - [Liu J](#), [Wang LN](#), [Zhan SY](#), [Xia Y](#).



From: A Randomized Clinical Trial of High-Dosage Coenzyme Q10 in Early Parkinson Disease: No Evidence of Benefit

JAMA Neurol. 2014;():. doi:10.1001/jamaneurol.2014.131



Prior to April 7, 2014

Read: Shults et al Effect of Coenzyme Q10 in Early Parkinson's Disease Arch Neurol 2002; 59:1541

Watch video: Science Talk 8 on Coenzyme Q10

Be ready to answer the following questions in class:

- ◆ What is coenzyme Q10?
- ◆ Why was it chosen for trial in early Parkinson's disease?
- ◆ What was the method of the drug trial?
- ◆ What were the results?
- ◆ Critique the methods as we did for the Cotzias paper.
- ◆ If your grandfather had early Parkinson's disease, would you tell him to take Coenzyme Q10? Why or why not?