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# Research recommendations from the NICE Parkinson's disease guideline

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# Research recommendations from the NICE Parkinson's disease guideline

1. Development of neuroprotective (disease-modifying) therapies for Parkinson's disease
2. Which people with PD and dementia benefit from cholinesterase inhibitor drugs and / or memantine and is the use of these agents cost-effective?
3. Is treating mild to moderate depression in Parkinson's disease with an antidepressant cost effective?
4. Is occupational therapy in Parkinson's disease cost effective?
5. Is physiotherapy in Parkinson's disease cost effective?
6. Is NHS speech and language therapy in Parkinson's disease cost effective?
7. Development of diagnostic investigations for Parkinson's disease and biomarkers to measure its progression

# Research recommendations from the NICE Parkinson's disease guideline

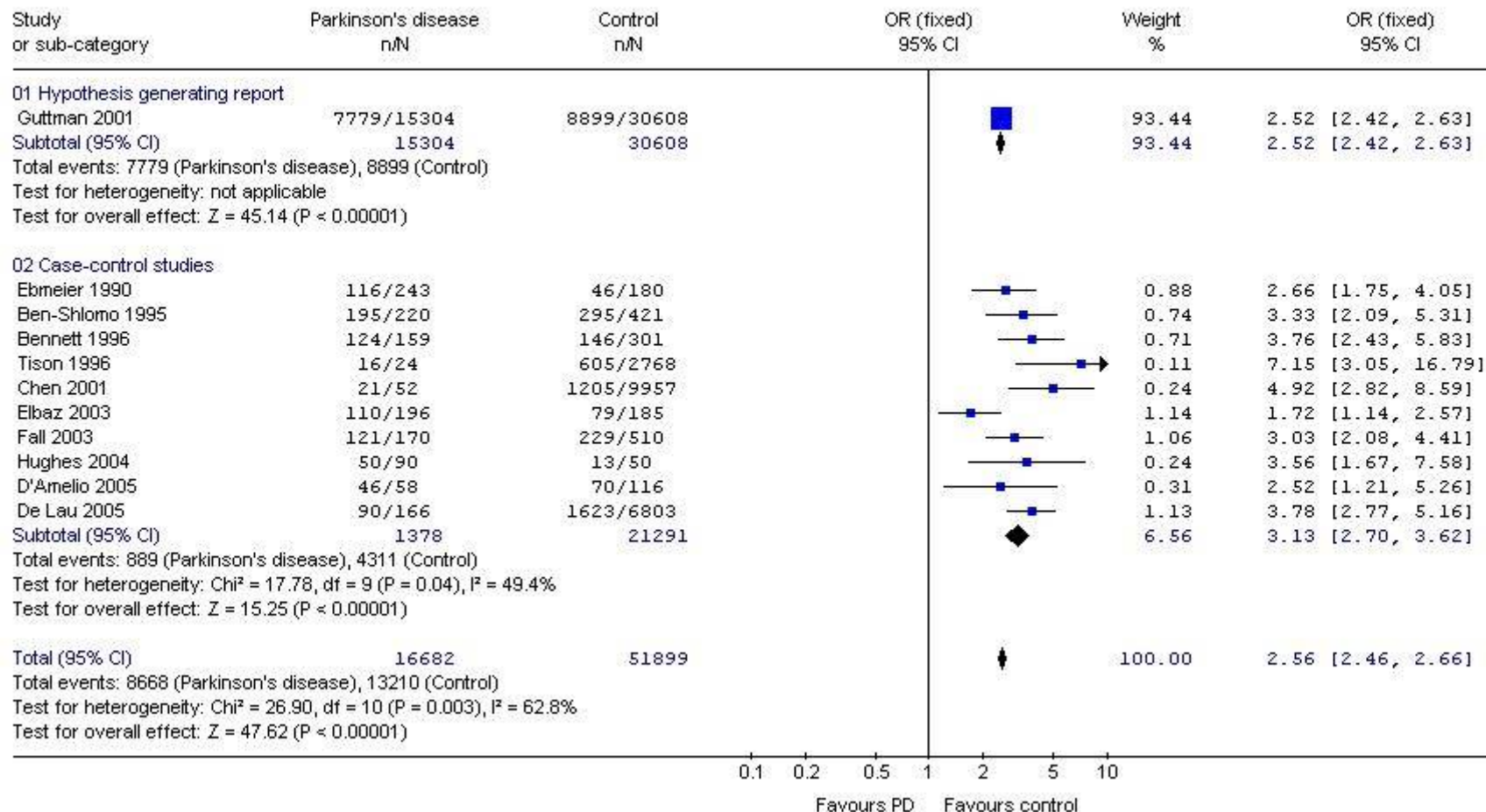
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# 1 Development of neuroprotective (disease-modifying) therapies for Parkinson's disease

Population	People with early Parkinson's disease – some trials with patients on no medication; other trials may randomise patients stabilised on symptomatic medication. Any gender, age, ethnic group. Trials performed in secondary care.
Intervention	Systematic reviews in North America have identified 12 agents that require study. The UK could contribute to the raft of ongoing studies which are funded by the NIH and the Michael J Fox Foundation. Support should also be given to innovative surgical approaches to neuroprotection.
Comparison	Each putative neuroprotectant versus placebo in double-blind parallel design or delayed start design trial.
Outcome	Total UPDRS change

# Meta-analysis of mortality in case-control studies

Review: Mortality in Parkinson's disease  
 Comparison: 01 Mortality  
 Outcome: 01 Mortality



# Neuroprotection trials

- Use a surrogate or biomarker to measure disease progression
  - Rating scales – non-symptomatic therapy design; withdrawal studies; delayed-start design; futility studies
  - Time to endpoint trials
  - Imaging
  - Mortality
  - Quality of life

# Outcome measures

## *Rating scales*

- Non-symptomatic therapy design – if **sure** the drug in question does not have a symptomatic effect
- Withdrawal studies – if possible or known symptomatic effect
- Delayed-start design– if possible or known symptomatic effect
  
- Futility studies

# Unified Parkinson's Disease Rating Scale (UPDRS)

## ■ Part 1 Mentation

– 4 items; worst score 16; early disease ~ 0

## ■ Part 2 Activities of daily living

– 13 items; worst score 52; early disease ~ 8

## ■ Part 3 Motor

– 14 (27) items; worst score 108; early disease ~ 20

## ■ Part 4 Motor complications

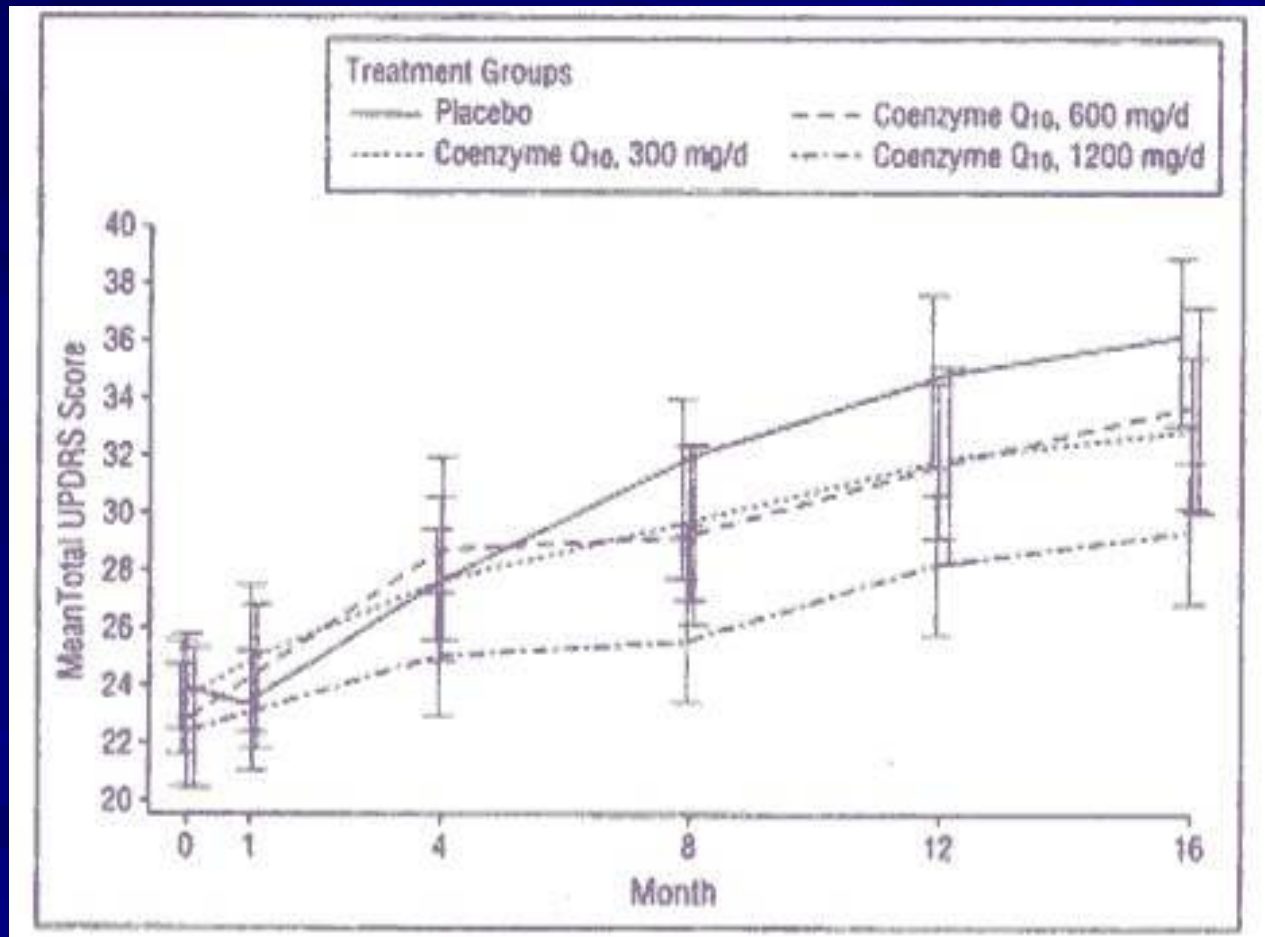
– 11 items; worst score 23; early disease ~ 0

## ■ Total score

– 42 items; worst score 199; early disease ~ 28

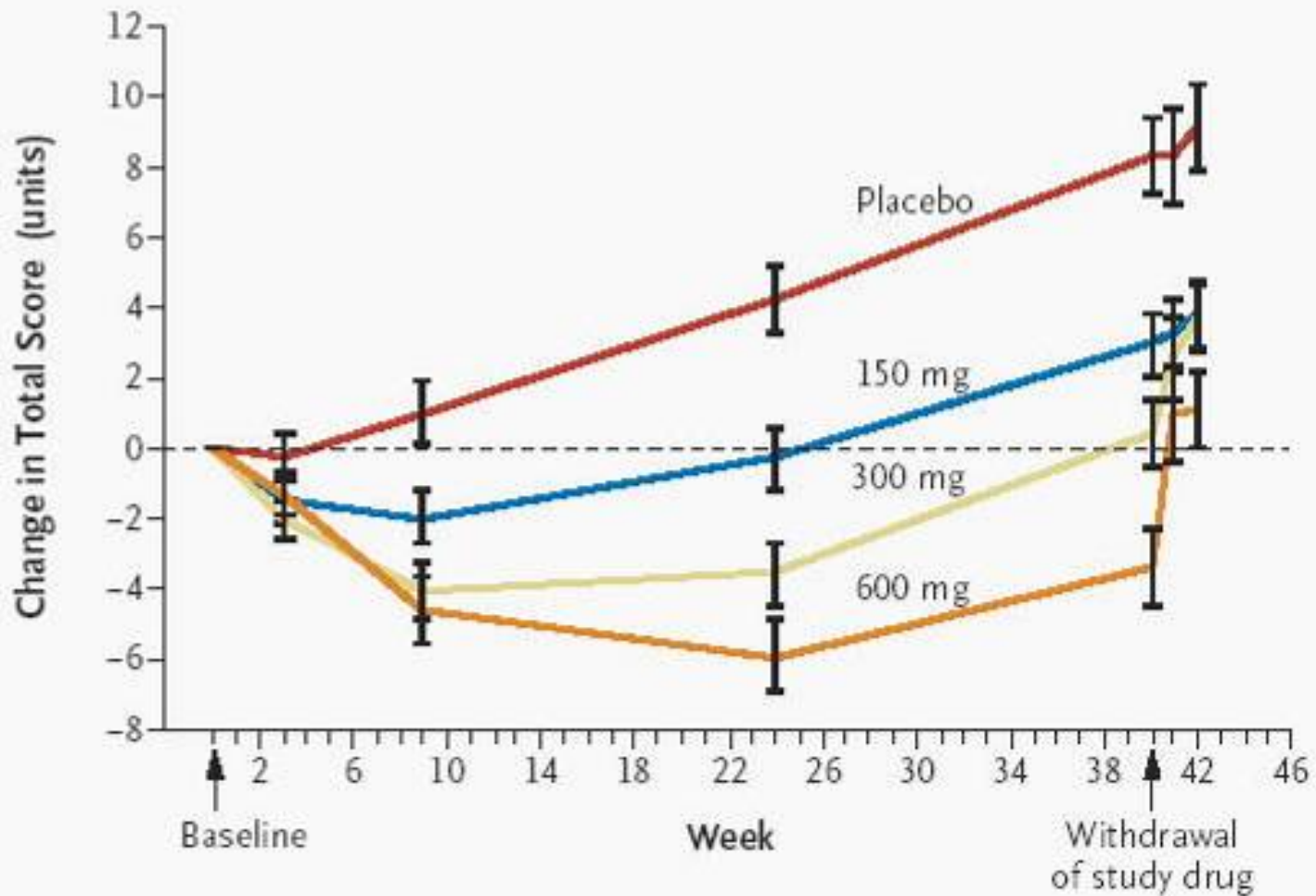
# Non-symptomatic therapy design

## Coenzyme Q<sub>10</sub>

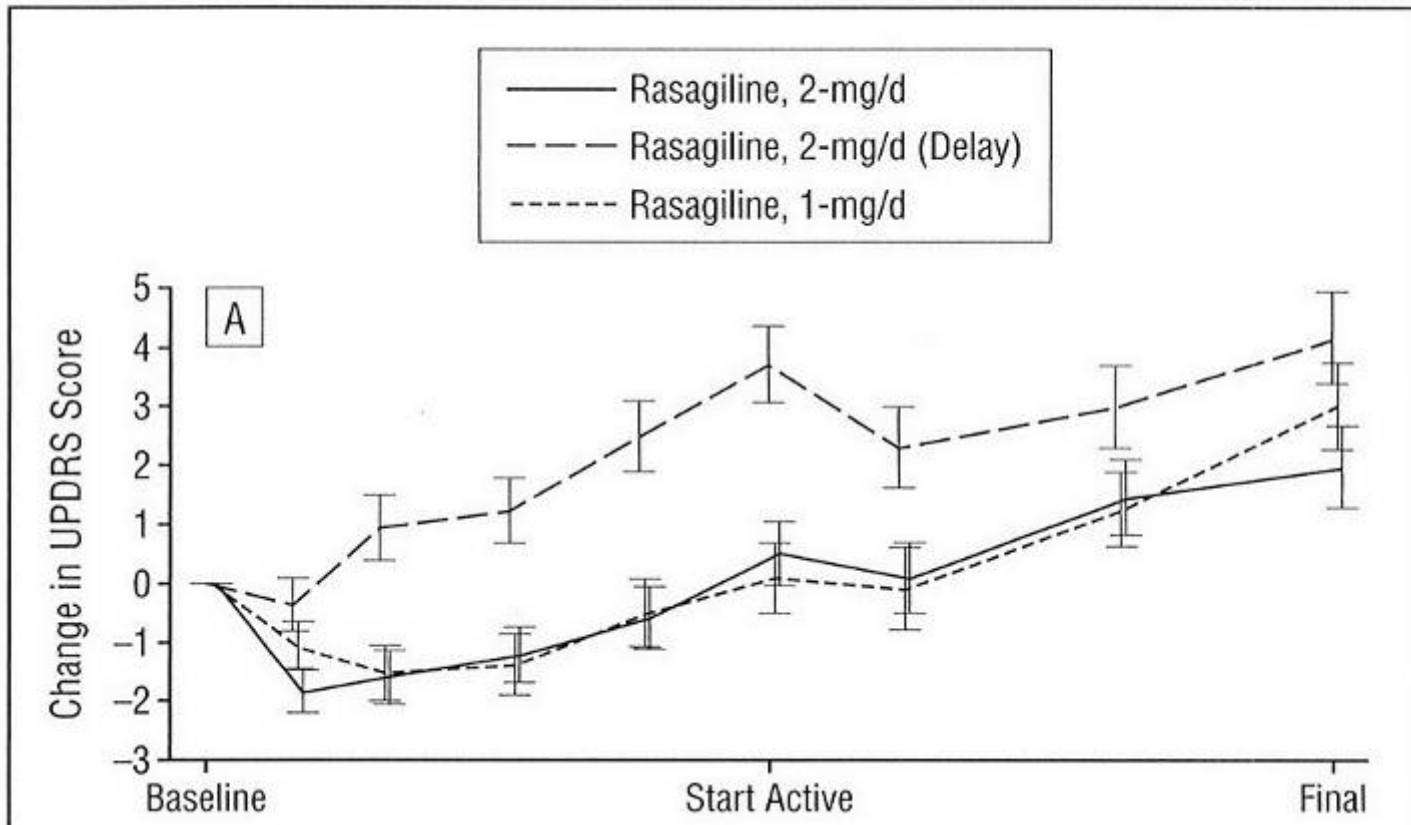


# Withdrawal studies

## *ELLDOPA trial*

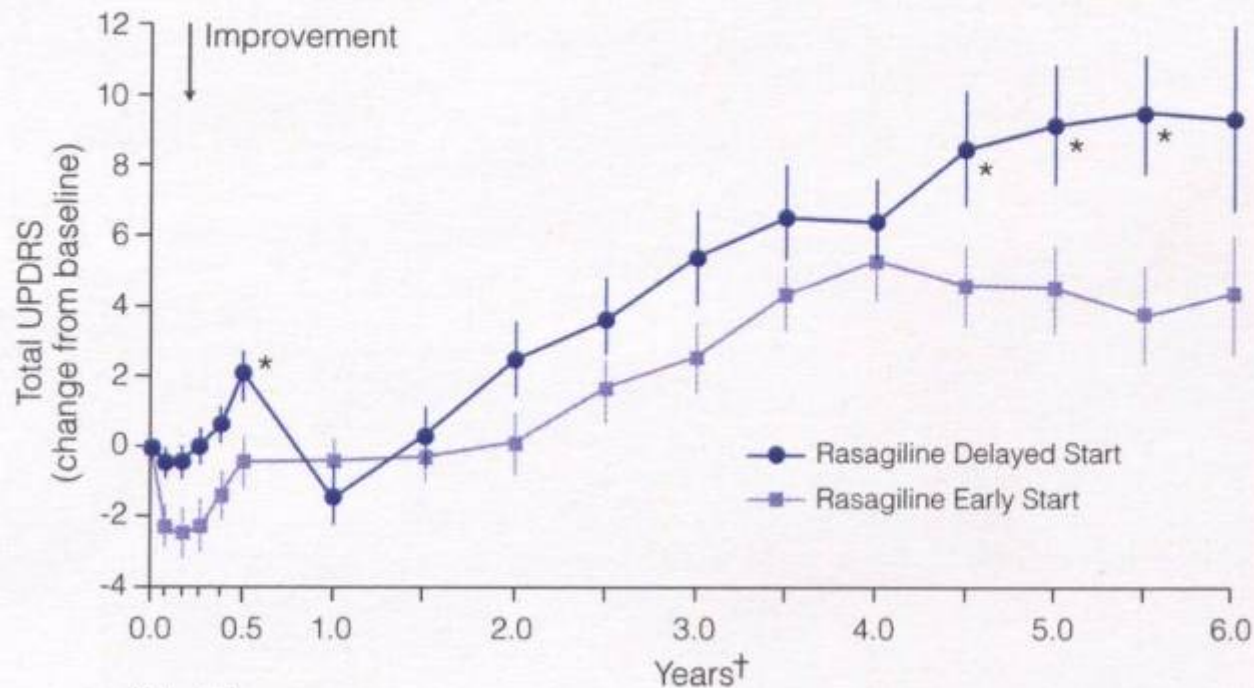


# Delayed-start design *Rasagiline Trial (TEMPO)*



# Delayed-start design *Rasagiline Trial (TEMPO)*

Figure 2. Change from TEMPO baseline in total UPDRS, by early vs delayed rasagiline treatment.



\* $P < .05$ .

† $N = 177$  for all time points except for 5.5 y ( $N = 153$ ) and 6.0 y ( $N = 101$ ).

# Futility studies

- Systematic programme of neuroprotection trials in North America (NET-PD)
- Funded by NINDS
- Screening potential agents in small 'futility studies'
- Looking for 30% reduction in total UPDRS score decline in treatment group compared with historical control data
- Successful agents will go through to larger definitive studies

## National Institute for Neurological Disorders and Stroke (NINDS) short list of 12 candidate drugs for neuroprotection trials

Caffeine
Co-enzyme Q10
Creatine
GM-1 ganglioside
GPI-1485
Minocycline
Nicotine
Oestrogen
Monoamine oxidase inhibitors (rasagiline and selegiline)
Dopamine agonists (ropinirole and pramipexole)

# Futility studies

- First futility study (Neurology 2006;66:664)
- Minocycline and creatine
- Significant ( $p < 0.1$ ) delay in decline in total UPDRS by more than 30%
- However, a small placebo comparator group showed a similar effect raising doubts about the use of historical controls

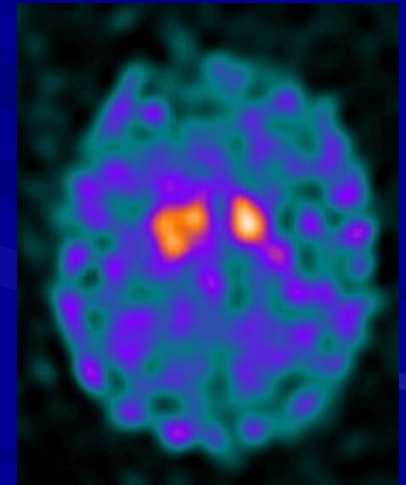
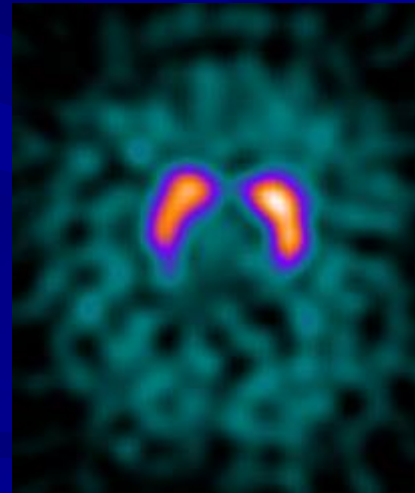
# Time to endpoint trials

- Look for significant difference in treated group in time to onset of suitable biomarker
- Previously used and potential new markers:
  - Time to need symptomatic therapy (e.g. DATATOP – selegiline v placebo – time to need levodopa)
  - Time to onset of motor complications - ?just delaying need for levodopa (confounding variables)
  - Time to onset of falls – never used
  - Time to onset of dementia – never used

# Outcome measures

## *Imaging*

- Positron emission tomography
- Single photon emission tomography



# Outcome measures

## *Imaging*

- Pramipexole v levodopa trial
  - $\beta$ -CIT SPECT
  - Loss of uptake from baseline = 16.0% v 25.5% at 46 months,  $p=0.01$
  - *JAMA 2002;287:1653-1661*
- Ropinirole v levodopa trial
  - Fluorodopa PET
  - Loss of uptake from baseline = 13% v 20% at 2 years,  $p=0.022$
  - *Ann Neurol 2003;54:93-101*

*Lancet 2002;360:1767-9*

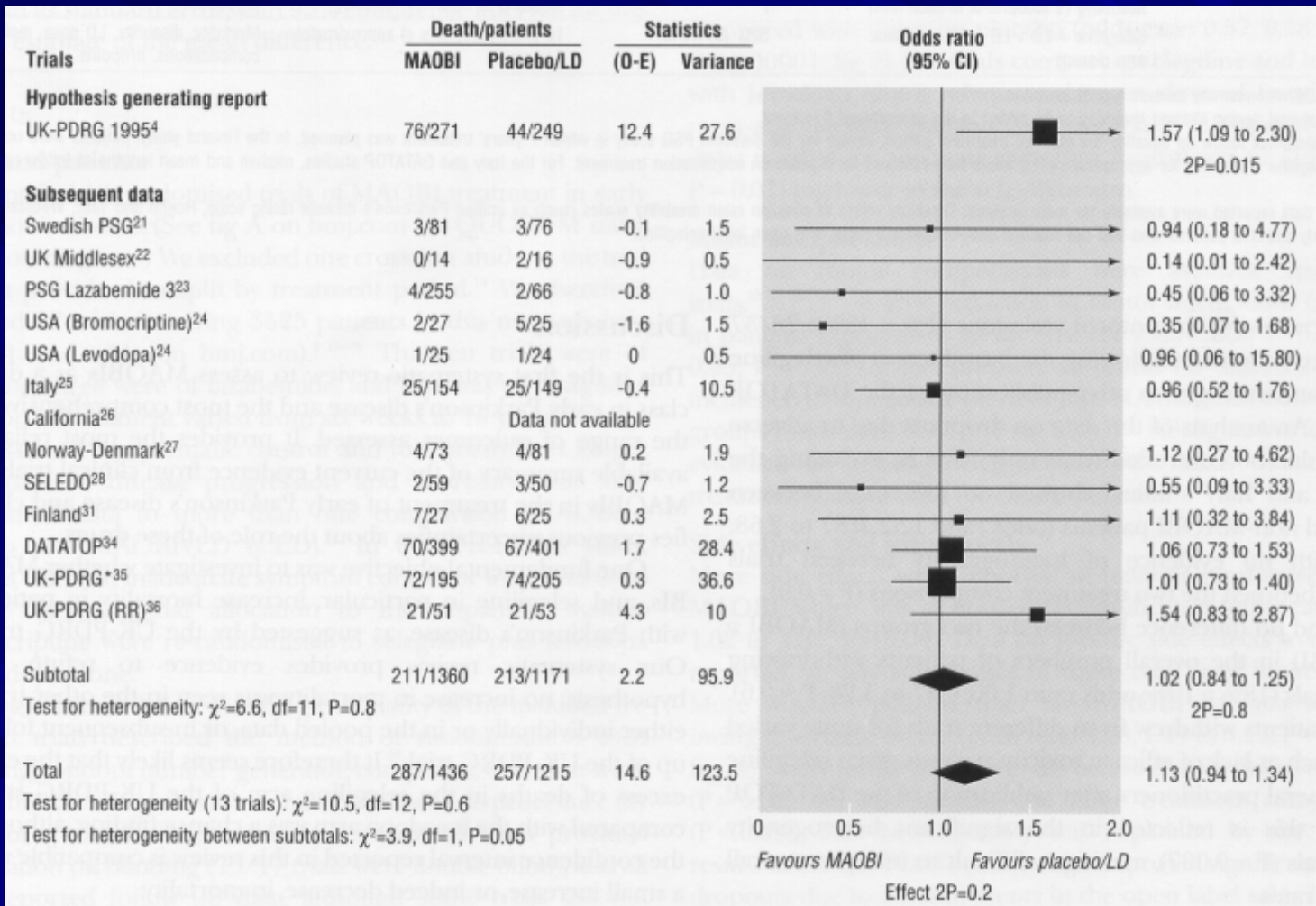
# Outcome measures

## *Mortality*

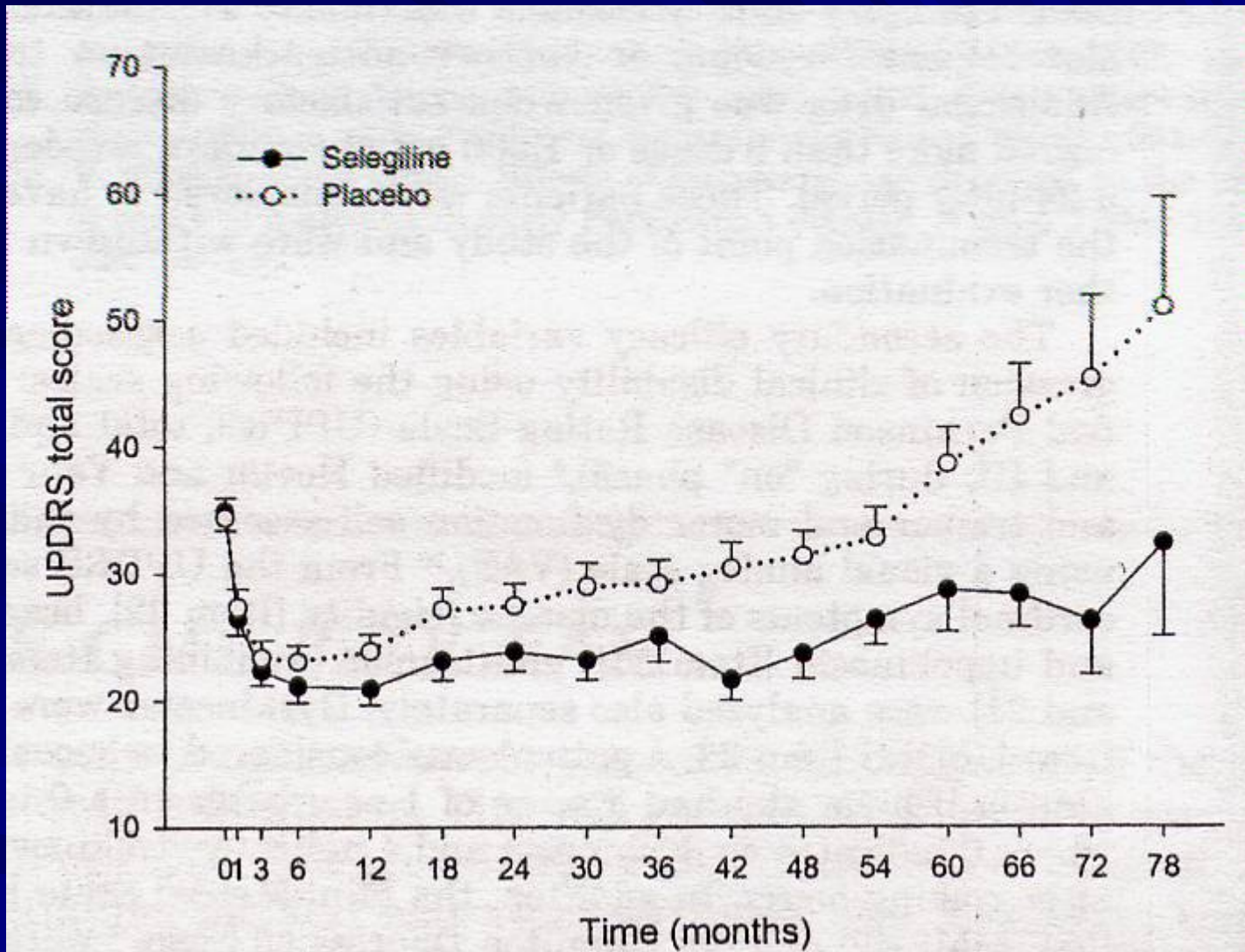
- Compare mortality in treated group with that in untreated group over a long period (case-control study)

# Mortality

## Selegiline trials



# Swedish selegiline trial



# Outcome measures

## *Quality of life*

- Disease-specific rating scales
  - PDQ39
- Generic rating scales
  - Short Form 36
  - EuroQol EQ5D
- If neuroprotective agent has a meaningful clinical effect, it should be measurable in terms of patient-rated quality of life measures
- No trials have used these designs so far

# Problems with neuroprotection trial designs

Outcome measures	Benefits	Problems
Clinical rating scales	Standard method used for many years	Open to symptomatic effects of therapy unless evaluated after drug withdrawal
SPECT and PET imaging	Intuitively a good biomarker for the disease May improve diagnostic accuracy at start of trials May be more sensitive than clinical outcomes	People who have PD clinically but have normal baseline scan People with PD with abnormal baseline radionuclide studies may have PSP/MSA Lack of clinical correlation of neuroprotection in imaging studies to date Poor sensitivity to change and reproducibility of radionuclide studies Differential regulation of ligand pharmacokinetics by medication
Time to endpoint (e.g. delaying motor complications)	Has direct relevance to people with PD	More likely to be a pharmacokinetic or dynamic effect than neuroprotection
Mortality	Has direct relevance to people with PD	Open to symptomatic effects of therapy Studies need to be large or long term to have adequate power
Quality of life	Patient-rated so more meaningful to them	Open to symptomatic effects of therapy Likely to have low sensitivity unless agent has large treatment effect

## 2 Which people with PD and dementia benefit from cholinesterase inhibitor drugs and / or memantine and is the use of these agents cost-effective?

Population	<p>Patients with Parkinson's disease of more than two years' duration (to exclude DLB patients) and dementia defined according to DSM-IV Criteria or new MDS Task Force criteria for PD Dementia (due mid 2006).</p> <p>Patients stratified according to pattern &amp; severity of cognitive impairment and neuropsychiatric burden (e.g. visual hallucinations)</p> <p>Concomitant use of stable atypical anti-psychotic regimen will be permitted.</p> <p>Any sex, age, ethnic group.</p> <p>Trials performed in secondary care</p>
Intervention	Donepezil / rivastigmine / galantamine / memantine
Comparison	Cholinesterase inhibitor / memantine versus placebo in RCT design
Outcome	<p>Change in cognition according to validated scales (e.g. ADAS-cog, new MDS Task Force instrument for PDD – due mid 2006)</p> <p>Neuropsychiatric Inventory</p> <p>Care-giver stress scales</p> <p>Health economics using disease-specific models</p>

# 3 Is treating mild to moderate depression in Parkinson's disease with an antidepressant cost effective?

Population	People with any stage of Parkinson's disease with mild to moderate depression according to a depression rating scale. Patients with severe depression will be excluded as treatment is mandatory. Any sex, age, ethnic group. Trials performed in secondary care.
Intervention	Any SSRI class of antidepressant.
Comparison	SSRI antidepressant versus no treatment in a pragmatic open label design.
Outcomes	Quality of life rated by disease specific (PDQ39) and generic (SF36; EuroQol) measures. Health economics. Depression scores on accepted depression rating scale.

# 4 Is occupational therapy in Parkinson's disease cost effective?

Population	People with any stage of Parkinson's disease. Any sex, age, ethnic group. Trials based in secondary care with primary care support.
Intervention	Best practice NHS occupational therapy.
Comparison	Pragmatic parallel design trial comparing no treatment with occupational therapy.
Outcome	Quality of life rated by disease specific (PDQ39) and generic (SF36; EuroQol) measures. Health economics. Secondary outcomes to include disease-specific and therapy-specific measures.

# 5 Is physiotherapy in Parkinson's disease cost effective?

Population	People with any stage of Parkinson's disease. Any sex, age, ethnic group. Trials based in secondary care with primary care support.
Intervention	Best practice NHS physiotherapy.
Comparison	Pragmatic parallel design trial comparing no treatment with physiotherapy.
Outcome	Quality of life rated by disease specific (PDQ39) and generic (SF36; EuroQol) measures. Health economics. Disease-specific and therapy-specific outcomes including: gait, balance, posture, transfers and reaching and grasping.

# 6 Is NHS speech and language therapy in Parkinson's disease cost effective?

Population	People with any stage of Parkinson's disease who have developed speech problems as defined by the observing clinician. Any sex, age, ethnic group. Trials based in secondary care with primary care support.
Intervention	Best practice NHS speech and language therapy.
Comparison	Pragmatic trial comparing NHS speech and language therapy with no treatment.
Outcome	Quality of life rated by disease specific (PDQ39) and generic (SF36; EuroQol) measures. Health economics. Measures of intelligibility. Secondary outcomes to include disease-specific and therapy-specific measures.

# 7 Development of diagnostic investigations for Parkinson's disease and biomarkers to measure its progression

Population	People with suspected Parkinson's disease. Any sex, age, ethnic group. Trials performed in secondary care.
Interventions	(1) Development of existing and novel diagnostic tests to differentiate PD from (a) non-parkinsonism (i.e. normality and essential tremor) and (b) other parkinsonian disorders (i.e. PSP, MSA, CBD). (2) Development of biomarkers to follow the progression of PD, mainly to be used in neuroprotection trials.
Comparison	Diagnostic accuracy of test versus UK Brain Bank Diagnostic Criteria for PD or $^{123}\text{I}$ -FP-CIT SPECT.
Outcome	Well designed diagnostic studies using receiver-operator characteristic curves, where appropriate, to establish standard diagnostic clinimetrics of investigations (e.g. sensitivity and specificity).

# NICE research recommendations trials suitable for PD MED trial collaborators

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