Mental health disorders in Parkinson's disease

Graham Lennox
Great Western Hospital, Swindon

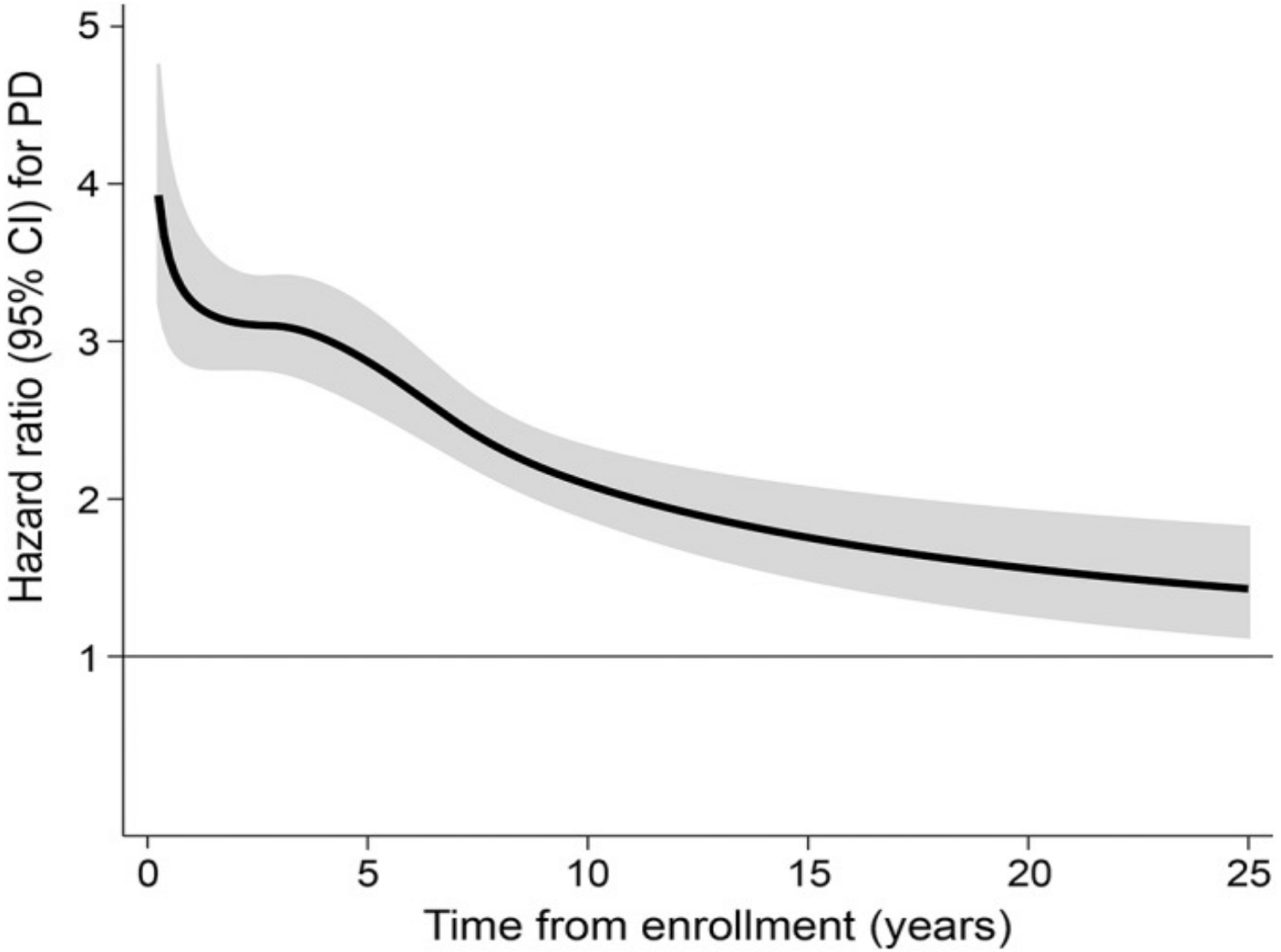
Birmingham Movement Disorders Course 2016

The problems

Early	• Anxiety • Depression • Apathy
Middle	• Psychosis • Impulsive behaviours • DAWS
Late	• Mild cognitive impairment • Dementia

Anxiety and depression

- Very common in PD
- May precede the motor symptoms by several years
- First depressive illness in midlife increases odds ratio for PD by 3 fold



Gustaffson et al, 2015

Screening for anxiety and depression

- Ask and look

Screening for anxiety and depression

- Ask and look
- “Do you feel cheerful and relaxed?”

Screening for anxiety and depression

- Ask and look
- “Do you feel cheerful and relaxed?”
- Pay attention to reaction of spouse

Screening for anxiety and depression

- With anxiety, ask about specific situations and times when anxiety occurs

- With depression, ask about mood and anhedonia

Treatment of anxiety and depression

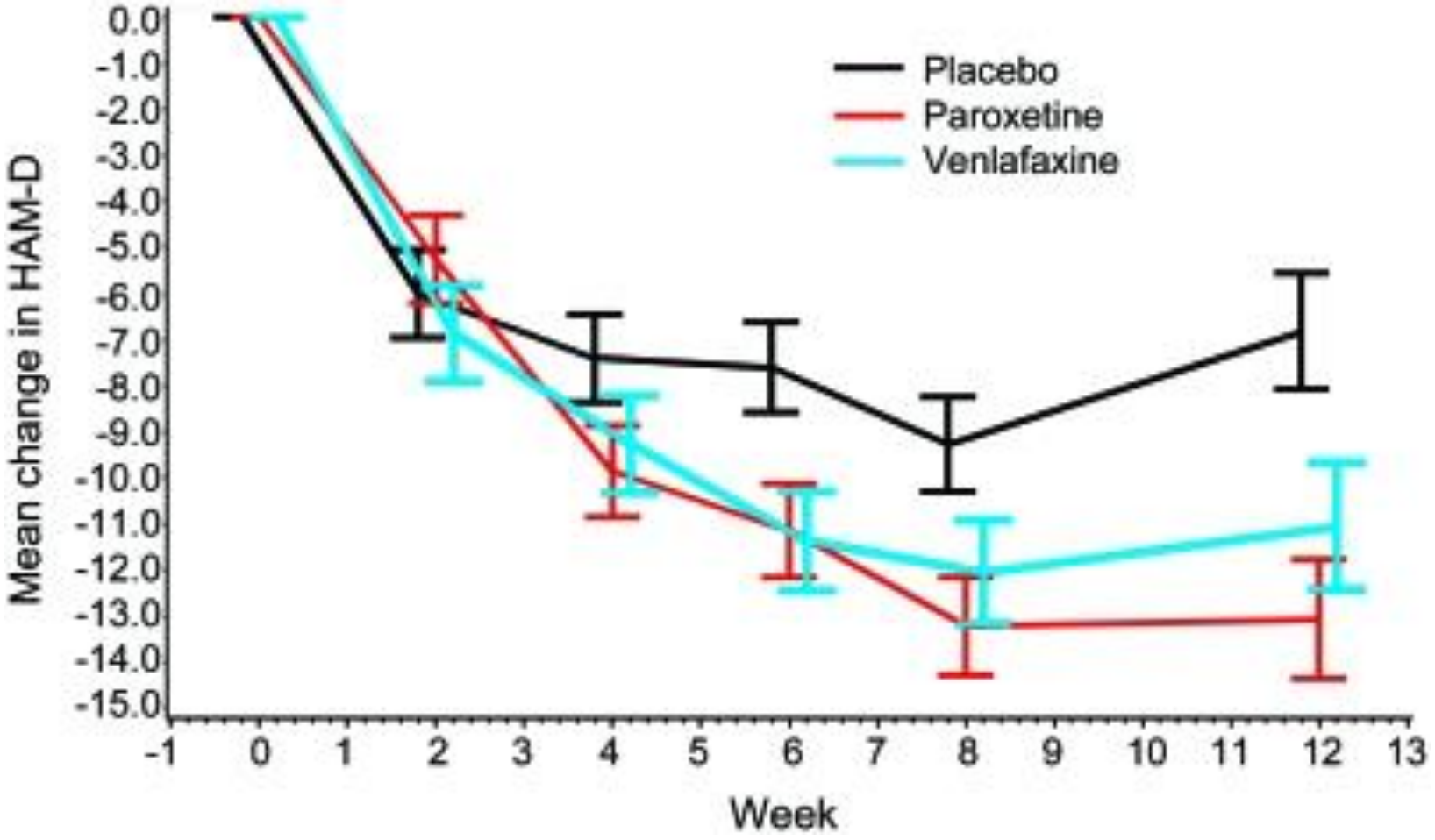
- Many studies showing benefit of antidepressants and CBT for depression

- Fewer studies in anxiety, some evidence for antidepressants and CBT, probably not pregabalin

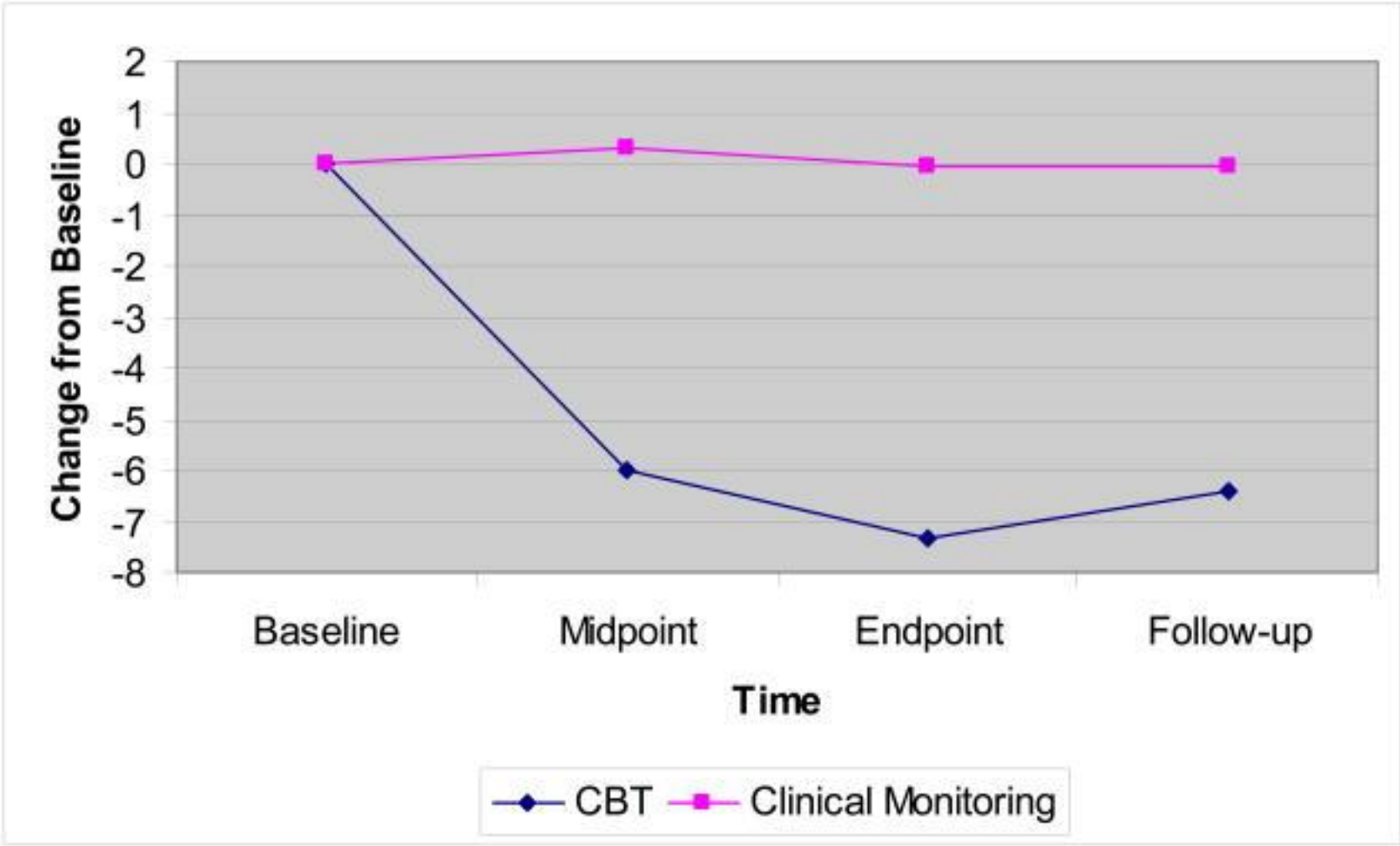
Depression treatment trials

Study	Number	Duration	Results
Devos, 2008	48	4	Desimipramine > placebo Citalopram = placebo
Menza, 2009	52	8	Nortriptyline > placebo Paroxetine = placebo
Richard, 2012	115	12	Paroxetine > placebo Venlafaxine > placebo
Dobkin, 2011	80	10	CBT > monitoring

SAD - PD


Placebo
Paroxetine
Venlafaxine
Mean change in HAM-D
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-8.0
-9.0
-10.0
-11.0
-12.0
-13.0
-14.0
-15.0
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Week

CBT for depression in PD



Apathy

- Again may be prodromal
- Often associated with depression or dementia, but may occur without either (perhaps 20% of patients)
- Associated with impairments in frontal-executive function
- Perhaps reflects reduced frontal dopamine
- Hard to treat

Apathy

- Regular routine of activities
- Cheerful spouse
- One small RCT suggests rivastigmine is helpful
- Brief/small studies suggesting potential role for dopaminergic treatments, noradrenergic antidepressants and amantadine
- May be made worse by STN DBS

Two main problems with too much dopamine

- Psychosis

- Impulse control disorders
- Dopamine agonist withdrawal syndrome (DAWS)

Psychosis

- Mack et al, 2011
  - N = 250 PD community clinics
  - 26% any psychotic symptom
  - ½ mild, associated with depression
  - ½ significant delusions or hallucinations

Visual hallucinations

Hallucinations

- Can happen to any patient with excessive treatment

Hallucinations

- Can happen to any patient with excessive treatment
- Much more likely in older/cognitively-impaired

Hallucinations

- Can happen to any patient with excessive treatment
- Much more likely in older/cognitively-impaired
- More likely with depression, visual impairment or intercurrent illness

Hallucinations

- Can happen to any patient with excessive treatment
- Much more likely in older/cognitively-impaired
- More likely with depression, visual impairment or intercurrent illness
- May be associated illusions of presence, auditory or sensory hallucinations, delusions

Hallucinations

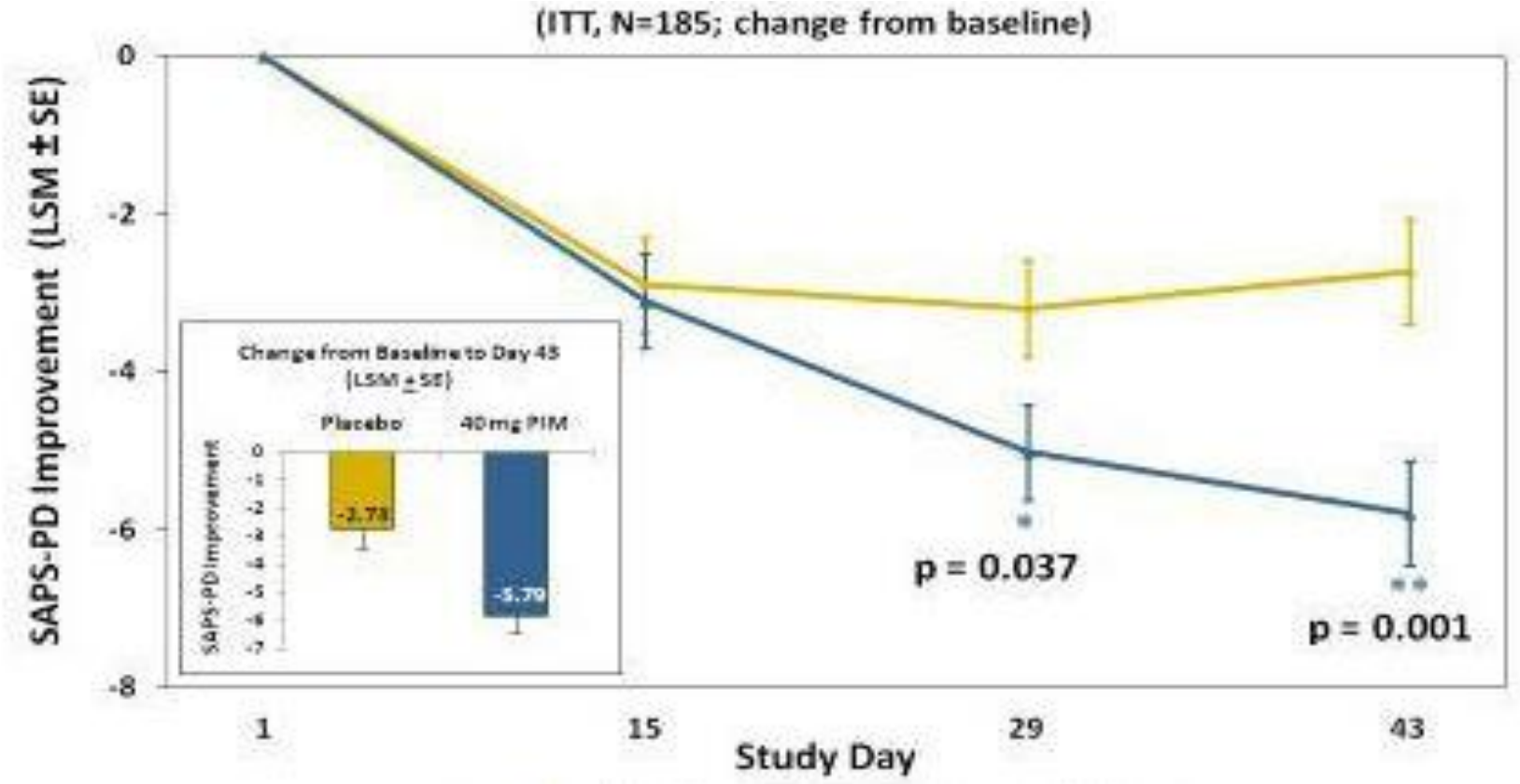
- Reduce latest PD drug if possible
- Treat associated problems
- Cholinesterase inhibitors
- Quetiapine (25 - 200 mg at night)
- Clozapine (through registered pharmacy)

Hallucinations

- Reduce latest PD drug if possible
- Treat associated problems
- Cholinesterase inhibitors
- Quetiapine (25 - 200 mg at night)
- Clozapine (through registered pharmacy)

- 5HT drugs?

Pimavanserin ($5HT_{2A}$ inverse agonist)



Cummings et al, Lancet 2013

Impulse control behaviours

- All characterised by an urge, which is hard to control, to perform repeatedly an action which is usually at best transiently pleasurable and which has risky or adverse consequences

Impulse control behaviours

Impulse control behaviours

- Different high-risk group

- Young at onset of PD
- Male > female*
- On dopamine agonists*
- History of alcohol or drug misuse (or FH)
- Other impulsive behaviours
- Depression

Prevalence

- Dopamine dysregulation 3% in specialist clinics
- Gambling 2-8% (14% of those on agonists)
- Hypersexuality 3-4%
- Binge eating 4%
- Excessive spending 5-6%
- Punding (widely defined) 14%

Prevalence

- Any ICB about 20%

ICB: prevention

- Warn patients, especially high-risk groups

ICB: prevention

- Warn patients, especially high-risk groups
- Ask about alcohol, gambling, hobbies

ICB: prevention

- Warn patients, especially high-risk groups
- Ask about alcohol, gambling, hobbies
- Ask about anxiety and depression

ICB: prevention

- Warn patients, especially high-risk groups
- Ask about alcohol, gambling, hobbies
- Ask about anxiety and depression

- Try to negotiate lower treatment goals in high-risk individuals

ICB: screening

- Routinely ask and record
- Especially in patients with perfect motor control (or dyskinesia), and in patients with erratic attendance, and in patients with depression

ICB: management

- Reduce PD medication where possible
  - especially dopamine agonists, with compensatory levodopa if necessary

ICB: management

- Reduce PD medication where possible
- Practical measures
  - Handing over control of medication, credit cards, computer; blocking software; support groups

ICB: management

- Reduce PD medication where possible
- Practical measures
- Antipsychotics do not seem to work

ICB: management

- Reduce PD medication where possible
- Practical measures
- Antipsychotics do not seem to work
- STN DBS
  - Several small series now, showing benefit for gambling and over-medicating
  - One report of failure due to compulsive fiddling with wires

- Often more than one eg punding and dysregulation

- Excessive ventral striatal dopamine release in response to visual cues
- Excessive ventral striatal activity in response to visual cues, gambling tasks etc

- ‘Buzz’ from placing the bet, regardless of outcome
- Imbalance between effort/risk and reward

Dopamine agonist withdrawal syndrome (DAWS)

- Described in patients coming off agonists rapidly for ICD
- Anxiety, depression, sweating, cravings
- Not clear if it is a distinct entity

Mild cognitive symptoms

- Mild frontal-executive dysfunction
  - Dopaminergic
  - Not necessarily progressing to dementia

Mild cognitive symptoms

- Mild frontal-executive dysfunction
  - Dopaminergic
  - Not necessarily progressing to dementia
- Memory/language/visuospatial impairment
- Drowsiness and visual hallucinations
  - Usually progress to dementia

Cambridge studies

- Incident cohort
- 17% dementia after 5 years

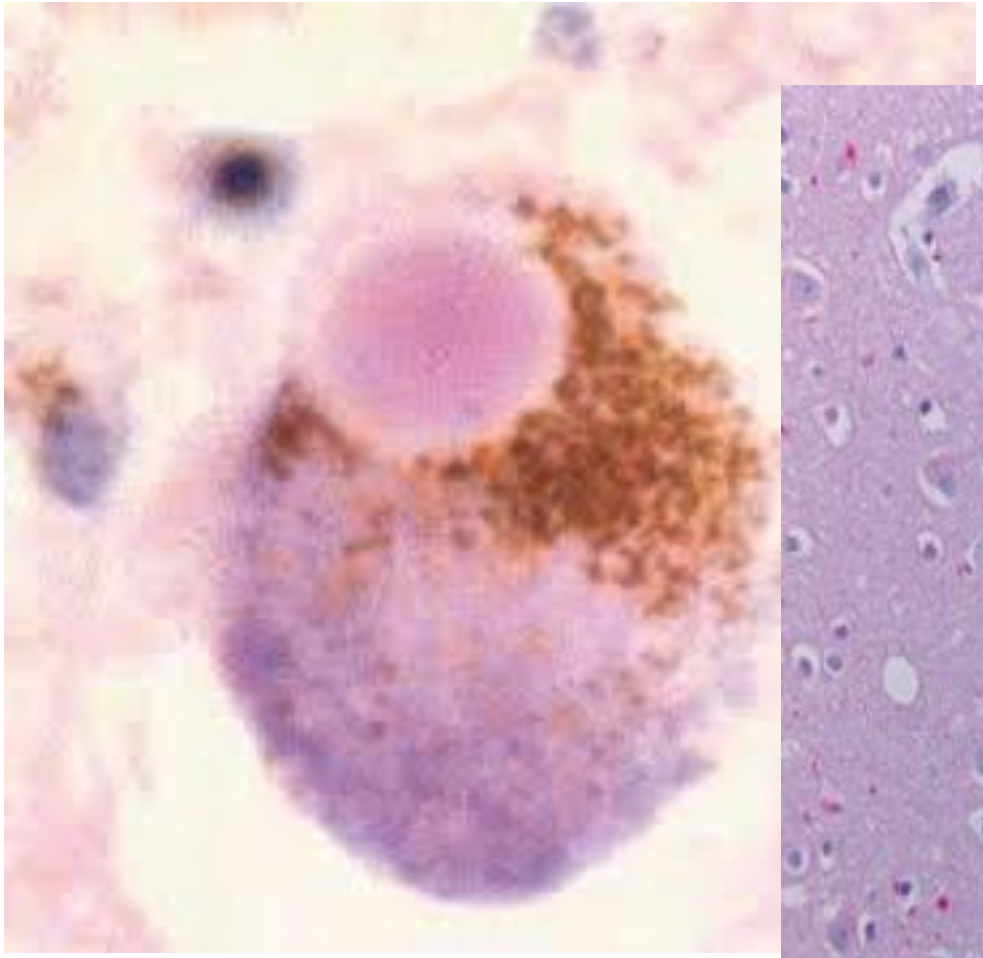
- Baseline risk factors:
  - Age 72 years +
  - Reduced semantic fluency
  - Imperfect pentagons
  - Tau H1/H1 haplotype

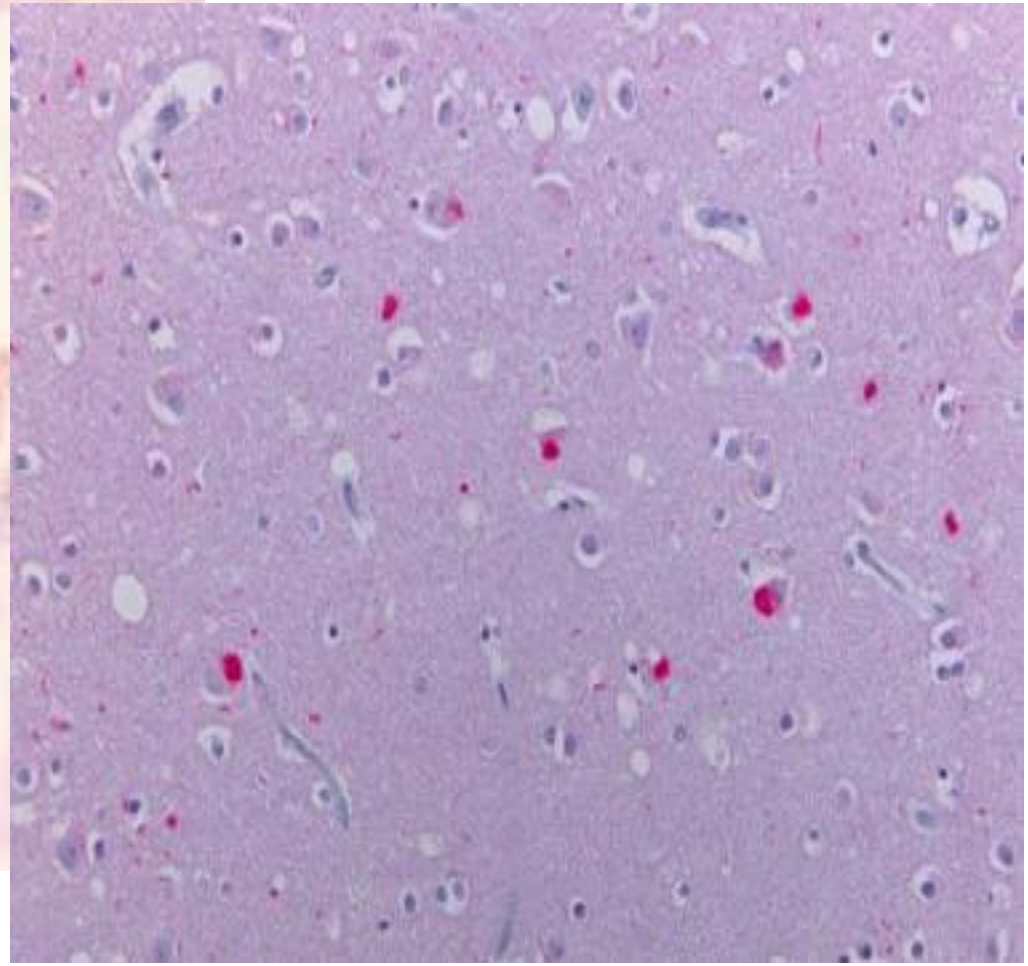
Dementia

- Main unsolved problem in PD
- Primary target for neuroprotection

- Prevalence after 10 years 65-80%

Pathology





Risk factors for dementia in PD

- PD
- Age > 75 years
- Postural instability-gait disorder phenotype > mixed phenotype >> tremor phenotype
- Depression
- REM sleep behaviour disorder
- Other risk factors for dementia

- Tau polymorphisms

The start of dementia in PD

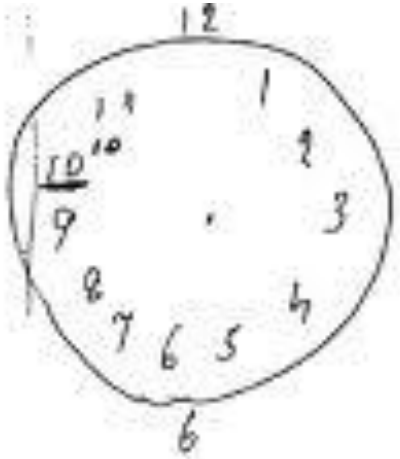
- Cognitive symptoms
- Drowsiness
- Visual hallucinations
- Episodes of delirium

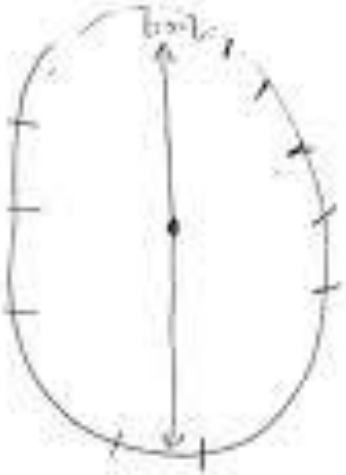
Cognitive symptoms

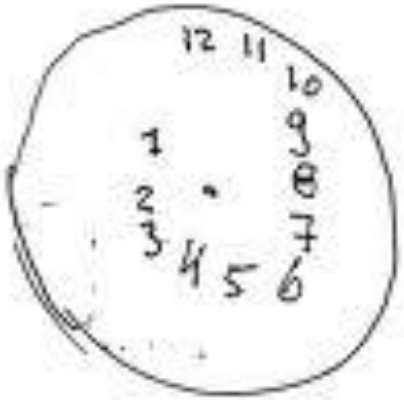
- Inattention
- Memory
- Language
- Visuospatial

- More frontal than Alzheimer’s
- More visuospatial than Alzheimer’s


11 12 1
10 2
9 3
8 7 6 5 4


12
1
11
10
2
9
3
8
7
6
5
4
6




12 11 10
1
9
8
2
7
3
6
4 5

Cognitive fluctuations

- Hour by hour
- Day by day
- Episodes of confusion

- Attention
- Drowsiness
- Staring into space

Investigation

- Acute confusion:
  - Rule out infection and metabolic upset
- CT head
  - Cerebrovascular disease
  - Subdural haematoma

Treatment

- Cholinesterase inhibitors
  - Good for hallucinations
  - Quite good for fluctuations
  - Sometimes help baseline cognition

- Agitation, anorexia and diarrhoea
- Rivastigmine/galantamine > donepezil
- Rolinski et al, Cochrane review 2012

Treatment

- Cholinesterase inhibitors
- Higher-than-licensed doses of cholinesterase inhibitors?
- Memantine

Other approaches

- Improve vision and lighting
- Withdraw aggravating PD drugs
- Atypical neuroleptics
- Consider depression
- Improve sleep

Prognosis

- Gradual decline
- Benefit of drug treatment wanes

- Very high carer burden
- Marked reduction in life expectancy

Prevention

- Exercise
- Social engagement
- Control vascular risk factors

THE ALEHOUSE SERMON.

See Page 10.

THE

VILLAGER's
FRIEND AND PHYSICIAN;

OR,

A FAMILIAR ADDRESS

ON THE

PRESERVATION OF HEALTH,

AND THE

REMOVAL OF DISEASE, ON ITS FIRST APPEARANCE;

Supposed to be delivered by a Village Apothecary:

WITH FURTHER OBSERVATIONS ON

THE TREATMENT OF CHILDREN, ON SOBRIETY, INDUSTRY, &c.

Intended for the Promotion of Domestic Happiness.

By JAMES PARKINSON.

SECOND EDITION.

——— Be timely wise:
With *HEALTH* all taste of Heaven's Gifts.
GAY.

LONDON:

PRINTED BY C. WHITTINGHAM,
[illegible],

AND SOLD BY H. D. SYMONDS, PATERNOSTER ROW.

1804.

[Price One Shilling.]

Prevention

- Exercise
- Social engagement
- Control vascular risk factors

- Cognitive training?
- Neuroprotection?

Exenatide

- Glucagon-like peptide-1 (GLP1) agonist

Exenatide

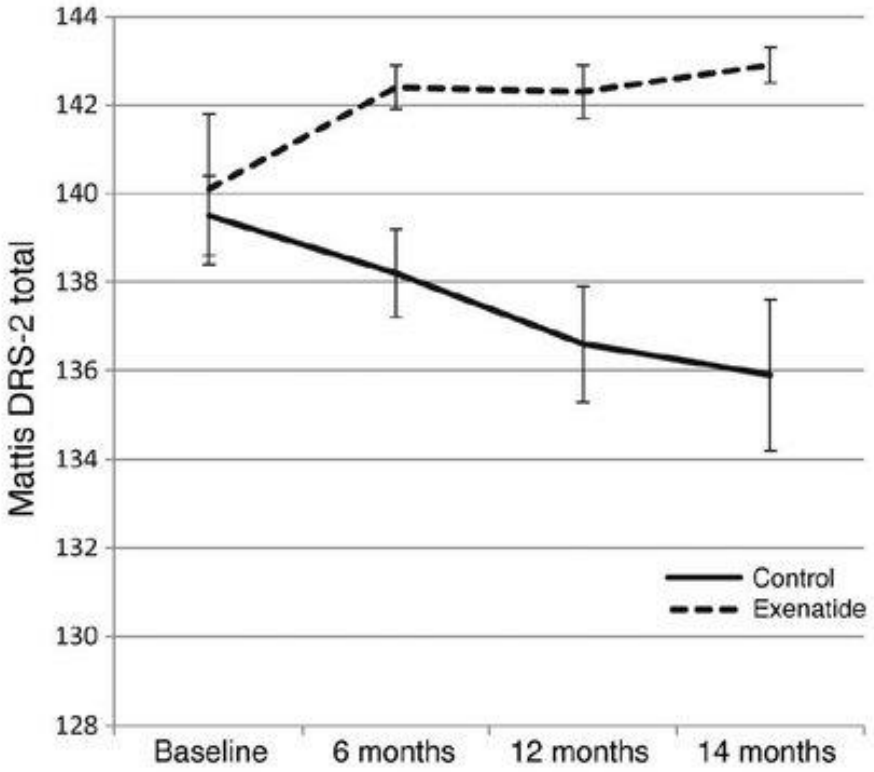


Figure 3
Change from baseline in the Mattis DRS-2 score by study visit. Data represent mean ± SEM.

Summary

- Think of Parkinson's disease as a psychiatric disease with some motor features
- Look out for anxiety, depression, apathy and impulse control disorders
- The big challenge is dementia