PSP Treatment: Symptomatic Approach

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Know Your Enemy?

• Diffuse neuronal loss & neurotransmitter involvement
• Basic pathophysiology of PSP still not known
• Animal models do not fully recapitulate disease features
• Difficulty identifying tractable targets
Symptomatic Treatment Aims

• Improve mobility/bradykinesia/reduce falls
  – dopaminergic drugs
• Improve memory/behaviour?
  – cholinergic drugs
• Other symptoms
  – dysphagia & dysarthria
  – mood
  – gritty/dry eyes
A Few Home Truths

• No drug therapy has major symptomatic benefit in PSP
  – treatment is anecdotal & idiosyncratic

• Very few high quality studies have been performed
  – majority case studies & small series

• “Simple” neurotransmitter replacement strategies ineffective to date
## Trial Considerations in PSP

<table>
<thead>
<tr>
<th>Observation</th>
<th>Qualification</th>
<th>Implication for Trial</th>
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<tbody>
<tr>
<td>Uncommon disorder</td>
<td>Prevalence 5 per 100,000</td>
<td>Large geographical area or multicentre study required</td>
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<td>Delayed diagnosis &amp; misdiagnosis common</td>
<td>May be up to 50% disease duration</td>
<td>Early disease modification may be difficult</td>
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<td>Emerging animal models</td>
<td>FTDP-17 &amp; related transgenics</td>
<td>Ability to assess drugs at mechanistic level</td>
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<td>Lack of biomarker</td>
<td>Imaging? Blood / CSF marker?</td>
<td>Dependence upon clinical observations / new validation required</td>
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<tr>
<td>Short disease course</td>
<td>Median disease duration 6-7 years</td>
<td>May use functional / death as robust end-points</td>
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# PSP: Overview of RCTs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dopaminergic</th>
<th>Cholinergic</th>
<th>Serotonergic</th>
<th>Adrenergic</th>
<th>Glutamatergic</th>
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<tbody>
<tr>
<td>Trial</td>
<td>Bromocriptine</td>
<td>Donepezil</td>
<td>Physostigmine</td>
<td>RS-86</td>
<td>Desipramine</td>
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<td>pergolide</td>
<td>Physostigmine</td>
<td>Physostigmine</td>
<td>Scopolamine</td>
<td>Efavoxan</td>
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<td>(Williams et al., 1979)</td>
<td>(Litvan et al., 2001)</td>
<td>(Litvan et al., 1994)</td>
<td>(Foster et al., 1989)</td>
<td>(Newman 1985)</td>
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<td>(Jankovic 1983)</td>
<td>(Litvan et al., 1994)</td>
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<td>(Basso et al. 1998)</td>
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<td>(Litvan et al., 1994)</td>
<td>(Geoffman et al., 1990; Keenan et al., 1990; Frattali et al., 1999)</td>
<td>(Newman 1985)</td>
<td>(Chiari et al., 1991)</td>
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<td>(Daniele et al., 1999)</td>
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</table>

| | No of patients | Motor function | Oculomotor function | Cognition/behavior | Bulbar symptoms |
| | 6 3 19 6 9 8 10 9 4 4 14 9 10 | 3 2 0 0 0 0 0 0 3 2 0 0 4 2 0 0 0 2 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 |

van Balken & Litvan 2008
Dopaminergic Drugs I

• Review of L-dopa based on 56 reports (n=548)
  – small open-label trials, retrospective series / case reports

• Mild to moderate benefit reported in ~ 35% (rigidity & gait)
  – effects ill-sustained
  – side effects
    • nausea, low blood pressure, confusion
    • hallucinations, jaw spasm, dyskinesias (uncommon)

Van Balken & Litvan 2008
Dopaminergic Drugs II

• Oral dopamine agonists
  – bromocriptine, lisuride, pramipexole
  – range of receptor affinity profiles
  – small studies
  – negative results & visual hallucinations common

• Apomorphine
  – 5/6 failed to respond to s/c injection

Burn & Warren 2005; Van Balken & Litvan 2008
Cholinergic Treatments

ACh: Acetylcholine
AChE: Acetylcholinesterase

Scopolamine blockade of cholinergic system worsens gait & cognition in PSP

Cholinesterase inhibitors improve symptoms in AD & PDD
Cholinergic Drugs

• Cholinesterase inhibitors
  – early physostigmine trials inconclusive
    • some benefits on cognition noted
    • CSF studies suggested poor CNS penetration
  – 2 donepezil trials (6 & 19 patients, latter in cross-over RCT design)
    • no overall benefit
    • some motor symptoms worse

• Muscarinic receptor agonists
  – RS-86 (M1/M2 receptor agonist) no benefit
    • M1 predicted to have positive effects & M2 negative effects
    • more selective receptor strategies helpful?

Foster 1989; Fabbrini 2001; Litvan 2001
Serotonergic Therapies

• Amitriptiline (25-75mg)
  – response rate of 42% in aggregate of 60 patients
• Nortriptyline & imipramine
  – less evidence & anecdotally less benefit
• Fluoxetine
  – inconsistent benefits (impulsivity?)
• Methysergide
  – initial reports of benefit in 9/12 not replicated
Other Drugs

- **Amantadine**
  - “minor benefit” in ~ 20%

- **Noradrenergic agents**
  - idazoxan ($\alpha_2$ antagonist: minor benefit in mobility, balance & dexterity)$^1$
  - efaroxan ($\alpha_2$ antagonist: no benefit)$^2$
  - L-DOPS

- **Zolpidem$^3,4$**
  - $\alpha_1$GABA$_A$ agonist may produce minor improvements
  - not confirmed in clinical practice

- **Gabapentin$^5$**
  - reduced anti-saccadic error rate but no UPDRS III benefit

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Botulinum Toxin

- Dystonia
  - present in ~33% PSP
  - variable benefit
- Blepharospasm & eyelid apraxia
  - success rate up to 95%
  - pretarsal site preferred?
- Drooling
  - care not to increase dysphagia
- Freezing of gait (?)

Van Balken & Litvan; Barsottini 2010
Electroconvulsive Therapy

• ECT
  – n=5 patients (9 treatments)
  – transient AEs included
    • confusion (all)
    • worsening of speech & swallowing
  – “dramatic response” (from completely wheelchair-bound state to independent ambulation) in 1, mildly improved (2), & unchanged (2)

• rTMS
  – some improvement in dysarthria after 2 weeks of cerebellar intermittent theta burst stimulation

Barclay 1996; Brusa 2014
Deep Brain Stimulation

• DBS-STN or GPi not indicated
  – case reports failed to improve
• DBS-PPN evaluated in small series
  – 2 cases (died 3 & 6 months post-surgery)
  – “slight” & “transient” improvements noted in gait, mood & eye movements

Okun 2005; Hazrati 2012
Further Management I

- Depression / apathy
  - tricyclic vs. SSRI vs. SNRI
- Impulsivity
  - SSRI (valproate?)
- Constipation
  - push fluids / high fibre diet / aperients
- Eating & swallowing
  - OT devices
  - SLT advice
  - PEG
Further Management II

• Vision
  – dry / sore eyes: eye sprays or eye drops
  – inability to look down: prism glasses
  – photophobia: wrap-around dark glasses
  – eyelid apraxia / blepharospasm: botox

• PSP Association / Support Groups
  – Specialist Care Advisers
  – carer support
Personal Practice

Accurate diagnosis

Motor = L-dopa

Amantadine

Amitriptyline

NMS, esp. mood

Venlafaxine
**Conclusion**

- *What has been achieved in symptomatic management of PSP over 50 years?*
- Drug treatments of limited benefit for most symptoms
- Multi-disciplinary input vital as aids may be of considerable help
- Emphasis switched to disease-modification for paradigm-shift