Update on the Treatment of PSP, CBD and MSA

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Director of Research and Clinical Affairs
CurePSP
Disclosures

• ALL drugs discussed will be off-label
• Institutional investigator for contracts with:
  – Bristol Myers Squibb
  – Allon
• Consulting
  – Bristol Myers Squibb
  – Sanofi
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  – PSP Research Fund of Rutgers
  – Rainwater Charitable Foundation
  – CBD Solutions, Inc. (via CurePSP)
• Research Center of Excellence grant:
  – American Parkinson’s Disease Association
• Volunteer work for CurePSP
  – Director of Research and Clinical Affairs
  – Member, Board of Directors
  – Chair, Grant Review Committee
Levodopa


- Review of (mostly) uncontrolled open trials
- Benefited 82 of 199 patients (42%)
  - Mostly for only a year or two
  - Improved:
    - Rigidity
    - Gait
  - Unimproved:
    - Ocular motor dysfunction
    - Dysarthria
    - Dysphagia
Levodopa: Retrospective, uncontrolled data on response of patients with PSP
Nieforth and Golbe, *Clin Neuropharm* 1993

<table>
<thead>
<tr>
<th>Levodopa/carbidopa</th>
<th>Benefit</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>31%</td>
</tr>
</tbody>
</table>

- Results similar to Litvan et al.
- Mean maximum daily dosage = 1,015 mg (range 100 – 3,000)
Not studied adequately in PSP/CBD/MSA:

- Levodopa duration of benefit
- Maximum target dosage for levodopa
Dopamine Agonists

- **Bromocriptine**
  - Improvement in 13 of 51 (25%) [Litvan and Chase review].

- **Pergolide**
  - Double-blind trial in 3 patients [Jankovic]
    - Global motor improvement by 21% in 2 patients.
    - But the benefit lasted only 6 months.
  - Retrospective review: [Kompoliti]
    - 1 of 6 patients improved modestly
    - Orthostatic hypotension in 3 of 6 patients

- **Pramipexole:**
  - A double-blind trial of pramipexole in 6 patients for 2 months gave no benefit. [Weiner]
  - A larger, multi-center, unpublished study using up to 6 mg per day gave the same result.

- **There is no evidence that any patient who does not respond to levodopa would respond to an agonist.**
## Amantadine
Retrospective, uncontrolled data on response of patients with PSP
2. Golbe, subsequent unpublished data

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Benefit</th>
<th></th>
<th></th>
<th>Adverse effects</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Marked</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>39%</td>
<td>0</td>
<td>0</td>
<td>15%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>9%</td>
<td>31%</td>
<td>7%</td>
<td>2%</td>
<td>56%</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>43%</td>
<td></td>
<td></td>
<td></td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

- This evidence supports trying amantadine in every patient with PSP without severe dementia.
- The benefits are mostly in gait and attention.
Amitriptyline 50 mg HS in 4 patients
  - Double-blind, crossover trial

Improvement relative to placebo
  - “Definite” in 2
  - “Probable” in 1

There was no placebo benefit relative to baseline.

One patient suffered worsening of postural instability on amitriptyline.
  - A major problem with amitriptyline in PSP in practice.
  - I no longer use amitriptyline in PSP for that reason.
Amitriptyline in PSP
Nieforth and Golbe, *Clin Neuropharm* 1993

<table>
<thead>
<tr>
<th>Amitriptyline</th>
<th>Benefit</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mild</td>
</tr>
<tr>
<td>28 (pub)</td>
<td>28</td>
<td>18%</td>
</tr>
<tr>
<td>50 (unpub)</td>
<td>50</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Anecdotally, amitriptyline can aggravate postural instability in PSP and should be avoided in these patients.
- I no longer use amitriptyline in PSP.
SSRIs, SNRIs

• Commonly used for the depression of PSP and CBD
  – No controlled trials
  – Anecdotal support sparse
• Pseudobulbar affect and other disinhibited behavior
  – Major problem in PSP (“rocket sign”)
  – No data
  – Dextromethorphan/quinidine not tested in PSP and no anecdotal data.
Baclofen and Benzodiazepines

- Baclofen or other muscle relaxants
  - No formal data
  - Worth trying in
    - CBD with dystonia painful spasms
    - PSP with dystonia
  - Titrated gradually from 5 mg per day to at least 60 mg per day
    - Major adverse effects
      - Weakness
      - Sedation
- Benzodiazepine and other bedtime sedatives are used for the sleep disturbances that are common in PSP.
Cholinesterase Inhibitors and Memantine

• Cholinesterase inhibitors
  – Donepezil
    • No benefit in PSP. [Fabbrini; Litvan]
  – Rivastigmine
    • Moderate benefit in PSP [Liepelt]
    • Inhibits both acetylcholinesterase and butyrylcholinesterase
  – Start with rivastigmine

• Memantine (glutamate antagonist)
  – Anecdotal, unpublished data
    • Frequently causes nausea, dizziness and somnolence
    • No benefit for dementia of PSP
# Recent Controlled Drug Trials in PSP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Trial ended</th>
<th>N</th>
<th>Phase</th>
<th>Drug on market?</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davunetide</td>
<td>Neurotrophic factor fragment</td>
<td>2012</td>
<td>300</td>
<td>3</td>
<td>No</td>
<td>No benefit</td>
<td>Boxer et al *Lancet Neurol 2014</td>
</tr>
<tr>
<td>Tidegusib</td>
<td>GSK-3β inhibitor</td>
<td>2012</td>
<td>300</td>
<td>3</td>
<td>No</td>
<td>No benefit*</td>
<td>Tolosa et al *Mov Dis 2014</td>
</tr>
<tr>
<td>Lithium</td>
<td>GSK-3β inhibitor</td>
<td>2010</td>
<td>45</td>
<td>2</td>
<td>Yes (mood disorders)</td>
<td>Terminated; not tolerated</td>
<td>In preparation (Galpern et al)</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Multiple possible</td>
<td>2009</td>
<td>398</td>
<td>3</td>
<td>Yes (ALS)</td>
<td>No benefit</td>
<td>Bensimon et al *Brain 2009</td>
</tr>
<tr>
<td>Coenzyme Q-10</td>
<td>Mitochondrial nutrient</td>
<td>2008</td>
<td>21</td>
<td>2</td>
<td>Yes</td>
<td>Modest benefit</td>
<td>Stamelou et al *Mov Dis 2008</td>
</tr>
</tbody>
</table>
A phase 2 trial of the GSK-3 inhibitor tideglusib in PSP (Tolosa et al Mov Dis 2014)

Tideglusib reduces progression of brain atrophy in PSP in a randomized trial (Höglinger et al Mov Dis 2014)

No slowing of progression of PSPRS or any other clinical measure, but progression of atrophy on MRI was significantly (p < .05) slower in the tideglusib group than in the placebo group for the:

<table>
<thead>
<tr>
<th>Location</th>
<th>Tideglusib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAIN</td>
<td>−1.3% ± 1.4% vs. −3.1% ± 2.3%</td>
<td></td>
</tr>
<tr>
<td>CEREBRUM</td>
<td>−1.3% ± 1.5% vs. −3.2% ± 2.1%</td>
<td></td>
</tr>
<tr>
<td>PARIETAL LOBE</td>
<td>−1.6% ± 1.9% vs. −4.1% ± 3.0%</td>
<td></td>
</tr>
<tr>
<td>OCCIPITAL LOBE</td>
<td>−0.3% ± 1.8% vs. −2.7% ± 3.2%</td>
<td></td>
</tr>
</tbody>
</table>

Evidence of neuroprotection by reduction of tau phosphorylation in PSP shown by MRI volumetry
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>End date</th>
<th>N</th>
<th>Comment</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcranial magnetic stimulation</td>
<td>Neuroplasticity</td>
<td>2014</td>
<td>10</td>
<td>Result not announced</td>
<td>Allan Wu (UCLA)</td>
</tr>
<tr>
<td>TPI-287</td>
<td>Microtubule stabilizer (a taxane)</td>
<td>2016</td>
<td>66</td>
<td>Recruiting at UCSF and UAB</td>
<td>Adam Boxer (UCSF)</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Kinase inhibitor (reduces tau hyperphosphorylation)</td>
<td>2016</td>
<td>10</td>
<td>Futility trial; drug on market as NSAID</td>
<td>Adam Boxer (UCSF)</td>
</tr>
<tr>
<td>BMS-986168</td>
<td>Antibody against tau</td>
<td>2018</td>
<td>48</td>
<td>Investigator meeting in June 2015</td>
<td>?</td>
</tr>
</tbody>
</table>
Coenzyme Q-10

Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial.


Neurology & Clinical Trials Center, University Marburg

Brain Imaging Center, University of Frankfurt
Changes after 6 weeks treatment Q10 vs. Placebo


Difference = 1.6 points (~4% of BL)  p = .008

Difference = 0.8 points (~6% of BL)  p = .04
$^{1}$H-MRS

- total creatine
- lactate
- N-acetylaspartate

$^{31}$P-MRS

- ATP, ADP
- inorganic phosphate
- phosphocreatine

Changes after 6 weeks treatment
Q10 vs. Placebo

pCRE / tCRE

ATP / ADP

* P < 0.02

* P < 0.01
## Effect of CoQ-10 and placebo on PSPRS

Apetauerova D, et al. Presented at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, June 8-12, 2014

<table>
<thead>
<tr>
<th></th>
<th>CoQ-10</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSPRS</td>
<td>sd</td>
<td>N</td>
<td>PSPRS</td>
<td>sd</td>
</tr>
<tr>
<td>Baseline</td>
<td>37.6</td>
<td>11.9</td>
<td>31</td>
<td>39.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Change at 3 months</td>
<td>-0.6</td>
<td>8.2</td>
<td>27</td>
<td>1.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Change at 6 months</td>
<td>2.8</td>
<td>7.1</td>
<td>24</td>
<td>5.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Change at 9 months</td>
<td>3.2</td>
<td>7.8</td>
<td>22</td>
<td>7.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td><strong>5.9</strong></td>
<td>10.0</td>
<td>20</td>
<td><strong>11.8</strong></td>
<td>8.6</td>
</tr>
</tbody>
</table>
Symptomatic treatment of MSA

• Rigidity/slowness
  – Carbidopa/levodopa and other Parkinson’s medications
    • Can aggravate low blood pressure!

• Cerebellar ataxia
  – Physical therapy
  – Balance re-training (tai chi, etc)
  – Gait aids
  – Wrist weights for tremor
Symptomatic treatment of MSA

- Bladder problems
  - Peripherally-acting anticholinergics
    - Oxybutinin, Detrol, Vesicare, others
    - Can cause dry mouth, dry eyes, constipation
  - Alpha-adrenergic blockers
    - Flomax and others
    - Can aggravate low blood pressure
  - In extreme cases, urostomy
  - Consult a neuro-urologist
    - BPH surgery often helps PD but not MSA (Sakakibara R, Panicker J, Finazzi-Agro E. et al 2014)
- Constipation
- Docusate, fiber, hydration
- Laxatives as needed; try to minimize
Symptomatic Treatment of MSA

• Low blood pressure
  – Non-drug measures
    • Salt and fluid repletion
    • Pressure stockings
    • Elevate head of bed 6 inches
    • Full glass of water when feeling lightheaded
  – Drugs
    • Fludrocortisone (Florinef)
    • Midodrine (ProAmatine)
    • Pyridostigmine (Mestinon)
    • Droxidopa (Northera)
    • Many others with less consistent benefit
Symptomatic Treatment of MSA

• Depression
  – Cognitive-behavioral therapy
  – Other psychotherapy
  – Standard antidepressants

• Dementia
  – Anticholinesterases
    • Donepezil (Aricept)
    • Rivastigmine (Exelon)
    • Galantamine (Razadyne)
    • All can aggravate the bladder problem of MSA
Symptomatic Treatment of MSA

• Sleep disorder
  – Insomnia
    • Sleep hygiene
    • Exercise
    • Standard sleeping pills
  – REM behavioral disorder
    • Clonazepam
  – Obstructive sleep apnea
    • Continuous positive airway pressure (CPAP) machine
    • May require tracheotomy
Symptomatic Treatment of MSA

• Dystonia
  – Bracing
  – Botulinum toxin (Botox)

• Myoclonus
  – Clonazepam
  – Levetiracetam (Keppra)

• Erectile dysfunction
  – Sildenafil (Viagra) and other phosphodiesterase inhibitors
    • Can aggravate low blood pressure
  – Penile injections of alprostadil (Caverject)
  – Prostheses
  – Consult a neuro-urologist
Symptomatic Treatment of MSA

• Restless legs syndrome
  – Carbidopa/levodopa (Sinemet)
  – Dopamine receptor agonists (Mirapex, Requip)
  – Clonazepam

• Hallucinations
  – Quetiapine (Seroquel)
  – Clozapine (Clozaril)

• Daytime sleepiness
  – Measures for night-time insomnia
  – Modafinil (Provigil), armodafinil (Nuvigil)
<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Phase</th>
<th>Drug on Market?</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>100</td>
<td>3</td>
<td>Yes (TB)</td>
<td>No benefit</td>
<td>Low et al. <em>Lancet Neurol</em> 2014</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>174</td>
<td>2</td>
<td>Yes (PD)</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>20</td>
<td>2</td>
<td>Yes (mood disorders)</td>
<td>Terminated (not tolerated)</td>
<td>Sacca et al. <em>J. Neurol</em> 2013</td>
</tr>
<tr>
<td>Intravenous immuno-globulin</td>
<td>9</td>
<td>1</td>
<td>Yes (auto-immune dis.)</td>
<td>Slight benefit, well tolerated</td>
<td>Novak et al. <em>BMC Neurology</em> 2012</td>
</tr>
<tr>
<td>Riluzole</td>
<td>398</td>
<td>3</td>
<td>Yes (ALS)</td>
<td>No benefit</td>
<td>Bensimon et al <em>Brain</em> 2009</td>
</tr>
</tbody>
</table>
Current experimental treatment for MSA (1 of 2)

<table>
<thead>
<tr>
<th>N</th>
<th>Phase</th>
<th>Drug on Market?</th>
<th>Result</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>No</td>
<td>Not yet enrolling</td>
<td>Low et al (Mayo Clinic)</td>
</tr>
</tbody>
</table>

**STEM CELLS**

- **Autologous mesenchymal stem cells (IA& IV)**
- **Autologous mesenchymal stem cells (intrathecal)**

**ANTIBODIES**

- **Anti-α-synuclein Ab (PD01A, PD03A) (SQ injection)**
### Classes of current and recent experimental neuroprotective treatment in MSA (2 of 2)

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibit handling of α-synuclein by oligos</strong></td>
<td>sertraline, paroxetine, lithium</td>
</tr>
<tr>
<td><strong>Inhibit α-synuclein aggregation</strong></td>
<td>rifampicin, lithium, NSAIDs</td>
</tr>
<tr>
<td><strong>Enhance growth factor activity</strong></td>
<td>intranasal insulin</td>
</tr>
<tr>
<td><strong>Neuroprotective (various other mechanisms)</strong></td>
<td>riluzole, rasagiline, fluoxetine, mesenchymal stem cells</td>
</tr>
<tr>
<td><strong>Inhibit inflammation and microglial activation</strong></td>
<td>minocycline, IViG, AZD3241</td>
</tr>
</tbody>
</table>
Palliative Management

• Dysphagia
  – Swallowing evaluation including modified barium swallow at first sign/symptom of dysphagia
  – Consider PEG insertion for
    • Weight loss
    • Prolonged feeding time
    • First episode of aspiration pneumonia
    • Small amount of aspiration with each meal
  – Be realistic and frank with patient and family about issues of quality vs quantity of life.

• Gait/limb
  – Be alert to “rocket sign.”
  – Passive ROM exercises by family
  – Formal PT for advice/training in walking aid use
• **Downgaze palsy**
  – Prisms are rarely successful for gaze palsy.
  – A single lens prism may help the dysconjugate gaze with diplopia.
  – Patient can learn to direct the gaze down to the plate
    • Learn to follow a target such as the caregiver’s finger.
    • Raising the plate on a platform is also helpful.
  – The patient’s environment must be cleared of low-lying obstacles or loose rugs.

• **Eyelid movement problems**
  – Low blink rate with reactive conjunctivitis
  – Frequent use of methylcellulose or polyvinyl alcohol drops by day
  – Petrolatum-based lubricating ointment at night.
  – Blepharospasm
  – Botulinum toxin injections into the orbicularis oculi is highly efficacious. It has been reported to last for up to 50 weeks. [Muller et al. J Neurol 2000]
• Other focal dystonia
  – Retrocollis and rotational torticollis of PSP and CBD
    • Respond to botulinum toxin injections,
    • Use low dosages to minimize diffusion of the drug into the pharyngeal muscles, exacerbating the dysphagia.
  – Limb dystonia of CBD
    • Levetiracetam (Keppra)
    • May respond to botulinum, but control of dystonic pain is the principal beneficiary. (Vanek and Jankovic, Mov Disord 2001)
    • Despite relief of pain and dystonia, apraxia may still disable the limb.
    • A pain management specialist referral for:
      – regional blocks
      – intravenous lidocaine (reported to help pain of retrocollis)
    • Referral to a neurological rehabilitation specialist, at least for a one-time opinion.
Surgical Approaches

• Not useful:
  – DBS of
    • STN
    • GPI
  – Pallidotomy
  – Adrenal implant

• Investigational:
  – DBS of pedunculopontine nucleus
  – Direct cortical electrical stimulation
Pedunculopontine nucleus DBS in PSP

  • Three patients died of unrelated causes after PPN DBS. Benefit was moderate. No adverse effects. Electrodes were in PPN at autopsy.

  • “The observed response (slight changes on non-motor and motor domains, negligible on FOG) and the cognitive profile were unimpressive. “

• No published reports since 2009.
• Not being pursued to my knowledge.
RESOURCES

Lay organizations devoted to support, information and research in PSP and CBD

• North America: CurePSP

• Formerly:
  – The Society for Progressive Supranuclear Palsy
  – The Foundation for PSP | CBD and Related Brain Diseases
  – www.psp.org
  – 1-800-457-4777

• Europe:
  – PSP Association www.pspassociation.org.uk
  – PSP France www.pspfrance.org
  – Others starting