Update on the Treatment of PSP, CBD and MSA

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Disclosures

- ALL drugs discussed will be off-label
- Institutional investigator for contracts with:
  - Bristol Myers Squibb
  - Allon
- Consulting
  - Bristol Myers Squibb
  - Sanofi
- Investigator-initiated grant support :
  - 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

Litvan I, Chase TN. Traditional and experimental therapeutic approaches. In: Litvan I, Agid T, eds. *Progressive Supranuclear Palsy: Clinical and Research Approaches.* Oxford, Oxford University Press, 1993, p 254.

- 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

		Benefit			Adverse effects		
	N	Mild	Moder-ate	Marked	Mild	Moder-ate	Marked
Levo-dopa/ carbi-dopa	82	31%	7%	0	17%	6%	0

- 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  - A larger, multi-center, unpublished study using up to 6 mg per day gave the same result.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

1. Nieforth and Golbe, *Clin Neuropharm* 1993
2. Golbe, subsequent unpublished data
3. Rajput AH, et al. *Park Rel Dis* 1997

		Benefit			Adverse effects		
Source	N	Mild	Mod-erate	Marked	Mild	Mod-erate	Marked
1	13	39%	0	0	15%	8%	0
2	55	9%	31%	7%	2%	56%	2%
3	14	43%			29%		

- This evidence supports trying amantadine in every patient with PSP without severe dementia.
- The benefits are mostly in gait and attention.

Amitriptyine in PSP

Newman GC. *Neurology* 1985

- 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.

Amitriptyine in PSP

Nieforth and Golbe, *Clin Neuropharm* 1993

		Benefit			Adverse effects		
	N	Mild	Mod-erate	Marked	Mild	Mod-erate	Marked
Amitrip-tyline	28 (pub)	18%	14%	0	32%	14%	4%
	50 (unpub)	10%	26%	2%	2%	68%	4%

- Anecdotally, amitriptyline can aggravate postural instability in PSP and should be avoid in those 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

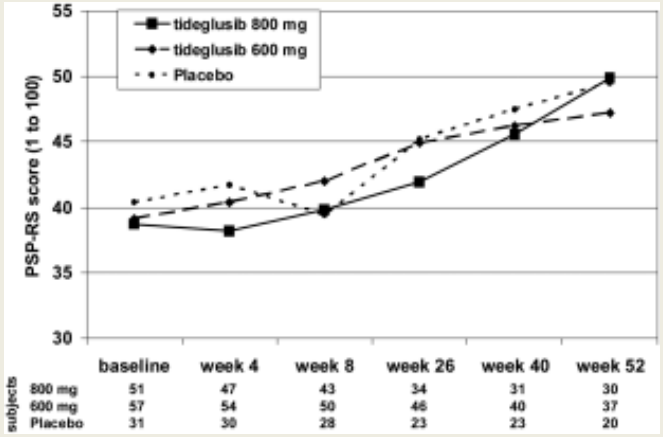
Recent Controlled Drug Trials in PSP

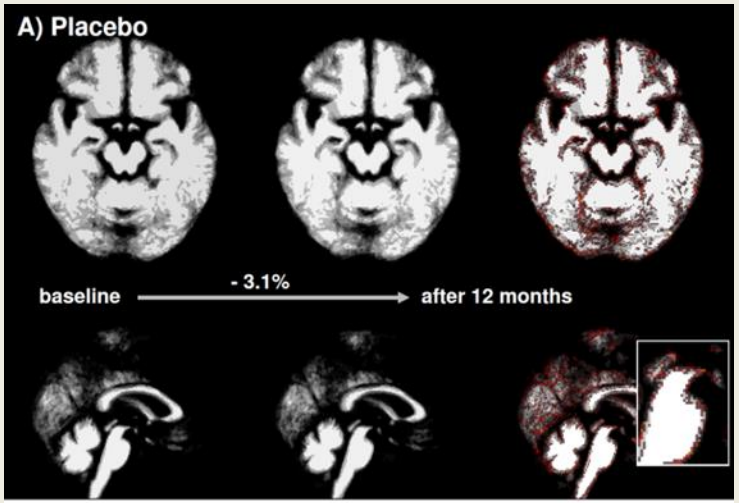
Drug	Mechanism	Trial ended	N	Phase	Drug on market ?	Result	Reference
Davunetide	Neuro-trophic factor fragment	2012	300	3	No	No benefit	Boxer et al *Lancet Neurol* 2014
Tideglusib	GSK-3β inhibitor	2012	300	3	No	No benefit*	Tolosa et al *Mov Dis* 2014
Lithium	GSK-3β inhibitor	2010	45	2	Yes (mood dis-orders)	Terminated; not tolerated	In preparation (Galpern et al)
Riluzole	Multiple possible	2009	398	3	Yes (ALS)	No benefit	Bensimon et al *Brain* 2009
Coenzyme Q-10	Mitochon-drial nutrient	2008	21	2	Yes	Modest benefit	Stamelou et al *Mov Dis* 2008

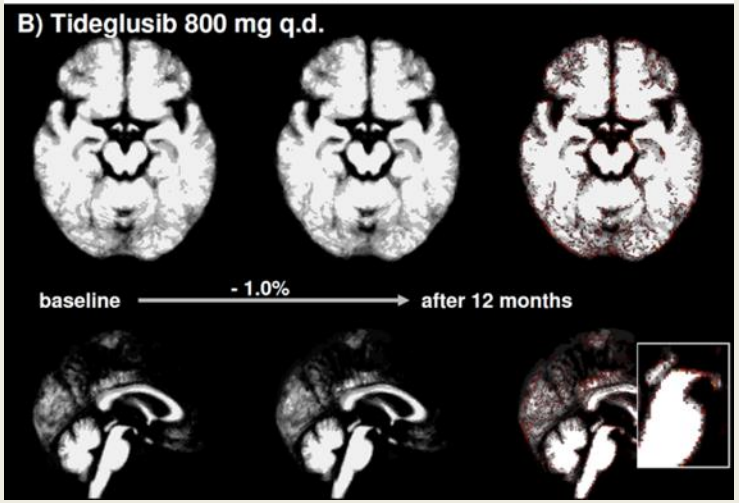
A phase 2 trial of the GSK-3 inhibitor tideglusib in PSP (Tolosa et al *Mov Dis* 2014)

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

Evidence of neuroprotection by reduction of tau phosphorylation in PSP shown by MRI volumetry







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:

	TIDEGLUSIB		PLACEBO
BRAIN	−1.3% ± 1.4%	vs.	−3.1% ± 2.3%
CEREBRUM	−1.3% ± 1.5%	vs.	−3.2% ± 2.1%
PARIETAL LOBE	−1.6% ± 1.9%	vs.	−4.1% ± 3.0%
OCCIPITAL LOBE	−0.3% ± 1.8%	vs.	−2.7% ± 3.2%

Current and Pending Controlled Treatment Trials in PSP

Drug	Mechanism	End date	N	Comment	PI
Transcranial magnetic stimulation	Neuroplasticity	2014	10	Result not announced	Allan Wu (UCLA)
TPI-287	Microtubule stabilizer (a taxane)	2016	66	Recruiting at UCSF and UAB	Adam Boxer (UCSF)
Salsalate	Kinase inhibitor (reduces tau hyperphos-phorylation)	2016	10	Futility trial; drug on market as NSAID	Adam Boxer (UCSF)
BMS-986168	Antibody against tau	2018	48	Investigator meeting in June 2015	?

Coenzyme Q-10

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

M Stamelou, et al. *Mov Disord* 2008

Neurology & Clinical Trials Center, University Marburg

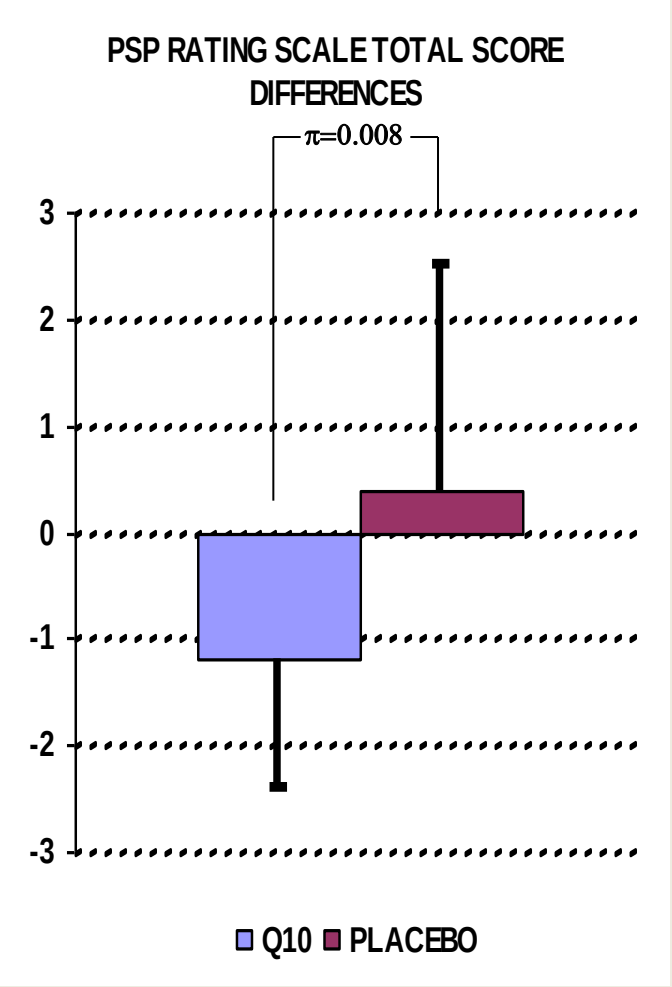
Brain Imaging Center, University of Frankfurt

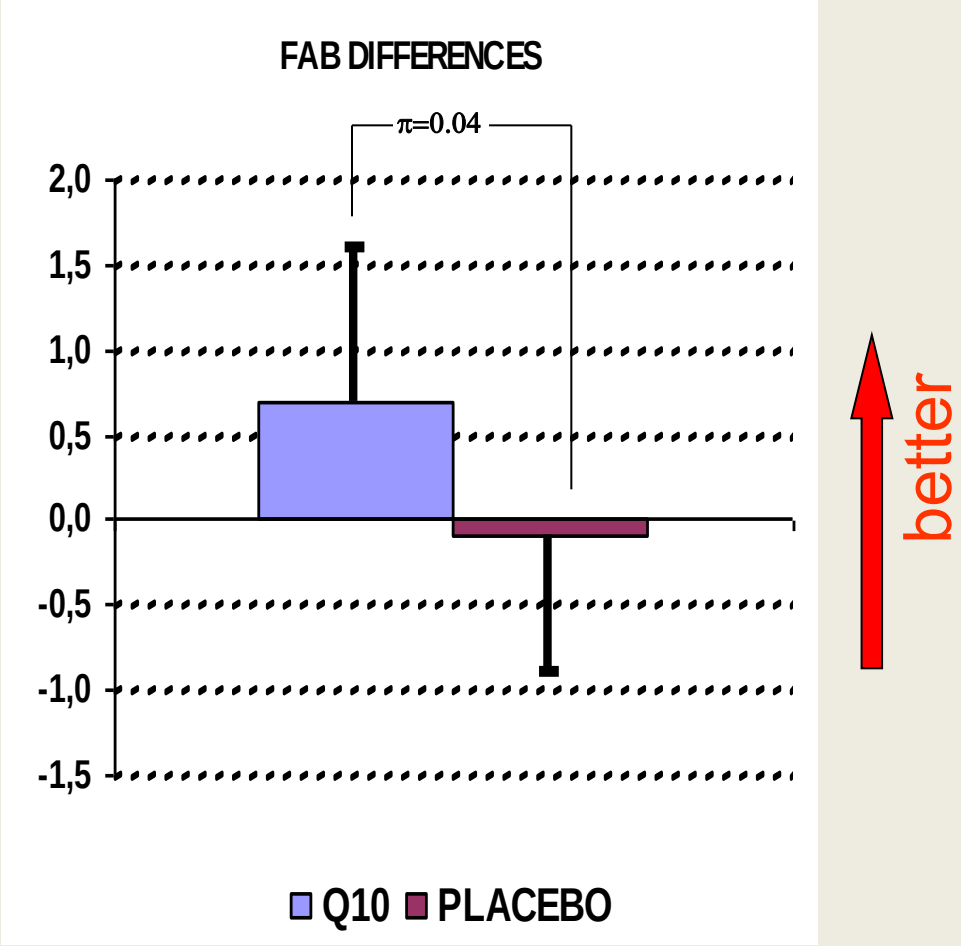
Changes after 6 weeks treatment Q10 vs. Placebo

Stamelou, et al. *Mov Disord* 2008

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

Difference = 0.8 points (~6% of BL)
p = .04



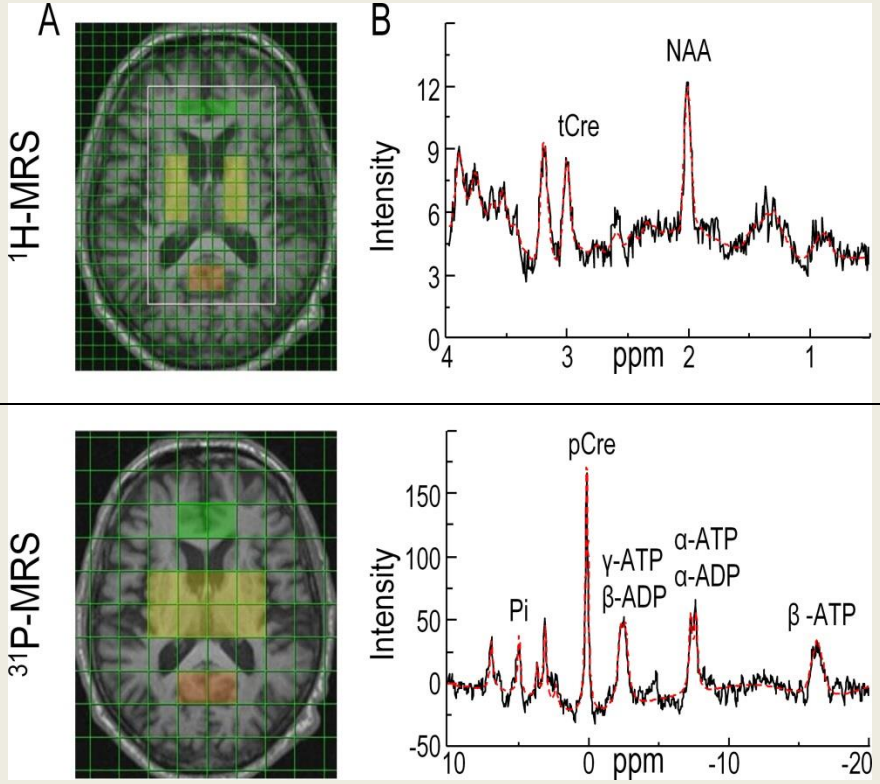


^{1}H-MRS

total creatine
lactate
N-acetylaspartate

^{31}P-MRS

ATP, ADP
inorganic phosphate
phosphocreatine

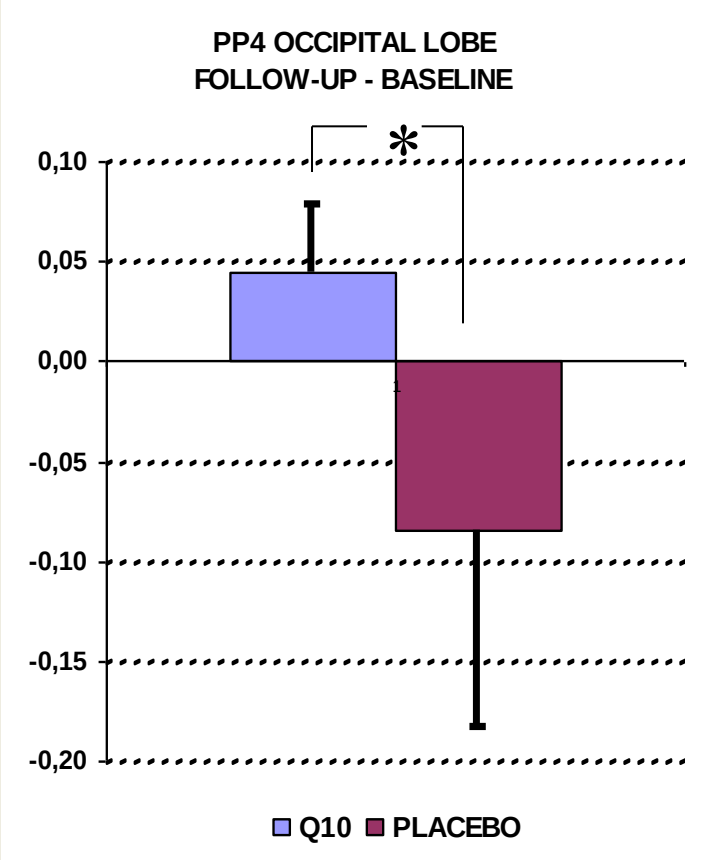


M Stamelou, et al. *Mov Disord* 2008

Changes after 6 weeks treatment

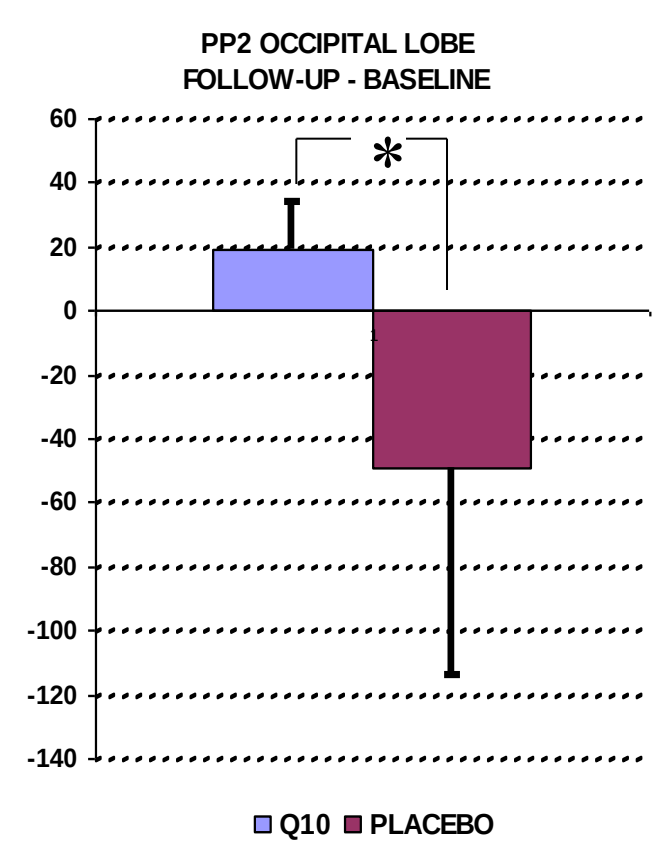
Q10 vs. Placebo

pCRE / tCRE



* P < 0.02

ATP / ADP



* 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

	CoQ-10			Placebo			p
	PSPRS	sd	N	PSPRS	sd	N	
Baseline	37.6	11.9	31	39.6	14.1	30	0.55
Change at 3 months	-0.6	8.2	27	1.1	5.9	26	0.39
Change at 6 months	2.8	7.1	24	5.0	5.9	21	0.27
Change at 9 months	3.2	7.8	22	7.3	7.6	20	0.09
Change at 12 months	**5.9**	10.0	20	**11.8**	8.6	16	0.07

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)

Recent Experimental Treatment for MSA

	N	Phase	Drug on Market?	Result	Reference
Rifampicin	100	3	Yes (TB)	No benefit	Low et al. *Lancet Neurol* 2014
Rasagiline	174	2	Yes (PD)	?	__
Lithium	20	2	Yes (mood disorders)	Terminated (not tolerated)	Sacca et al. *J. Neurol* 2013
Intravenous immuno-globulin	9	1	Yes (auto-immune dis.)	Slight benefit, well tolerated	Novak et al. *BMC Neurology* 2012
Riluzole	398	3	Yes (ALS)	No benefit	Bensimon et al *Brain* 2009

Current experimental treatment for MSA (1 of 2)

	N	Phase	Drug on Market?	Result	Reference
STEM CELLS					
Autologous mesenchymal stem cells (IA& IV)	33	2	No	Slight benefit, well tolerated	Lee et al. *Ann. Neurol.* 2012
Autologous mesenchymal stem cells (intrathecal)	24	1	No	Not yet enrolling	Low et al (Mayo Clinic)
ANTIBODIES					
Anti-α-synuclein Ab (PD01A, PD03A) (SQ injection)	30	1	No	Enrolling	Affiris AG

Classes of current and recent experimental neuroprotective treatment in MSA (2 of 2)

- Inhibit handling of α-synuclein by oligos
  - sertraline
  - paroxetine
  - lithium
- Inhibit α-synuclein aggregation
  - rifampicin
  - lithium
  - NSAIDs
- Enhance growth factor activity
  - intranasal insulin
- Neuroprotective (various other mechanisms)
  - riluzole
  - rasagiline
  - fluoxetine
  - mesenchymal stem cells
- Inhibit inflammation and microglial activation
  - minocycline
  - IViG
  - AZD3241

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

- Hazrati, L.N., et al., Clinicopathological study in progressive supranuclear palsy with pedunculopontine stimulation. Mov Disord, 2012. 27: 1304-7.
  - Three patients died of unrelated causes after PPN DBS. Benefit was moderate. No adverse effects. Electrodes were in PPN at autopsy.
- Brusa, L., et al., Implantation of the nucleus tegmenti pedunculopontini in a PSP-P patient: safe procedure, modest benefits. Mov Disord, 2009. 24: 2020-2.
  - “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