

DISCLOSURES

- No financial disclosures
- Off-label (non-FDA approved) use of medications will be discussed





MANAGING PSYCHIATRIC SYMPTOMS IN NEUROLOGIC DISEASE

Evaluation

- Common neuropsychiatric conditions
- Alpha-synucleinopathies:
- Diffuse Lewy Body Dementia (DLB)
- Parkinson's disease (PD)
- Huntington's disease (HD)
- Multiple sclerosis (MS)

Considerations for care of patients with neuropsychiatric symptoms



BEDSIDE TESTING

Mini Mental Status Exam (MMSE)

- Proprietary
- Can complete under 10 min
- Score <24/30 suggests impairment
- Sensitivity of 87%, specificity of 82% in hospital-based sample
- Not sensitive for mild dementia
- Changes of 2 points or less not considered significant
- Weaker screen for visuospatial/constructional skills



Montreal Cognitive Assessment Both (MoCA)

- At mocatest.org (free!)
- Around 10 min to administer
- 3 versions as well as a blind version
- Threshold of scores <26: sensitivity 94%, specificity 60%
- Lower cut-offs in veterans seeking care at a VA



- Screening for baseline cognition cannot occur if patient is currently delirious
- Requires effort, ability to write
- Need to know educational background, including learning disabilities, total education
- Deficits in patients with high educational attainment may not be obvious on exams
- Sensory impairments can falsely lower score (but are important to function)
- Should be followed over time
- Repeat any dramatically changed results

Davis DH et al Cochrane Review 2015 Creaven ST et al Cochrane Review 2016 Mocatest.org





ALPHA-SYNUCLEINOPATHIES

Lewy Bodies: Intraneuronal inclusion bodies containing alpha-synuclein

- Distribution varies in the different diseases:
 - Parkinson's disease: substantia nigra, the basal nucleus of Meynert, locus ceruleus. Later in the cortex
- Lewy body dementia: anterior frontal and temporal lobes, the cingulate gyrus, and the insula; also substantia nigra and locus ceruleus, nucleus basalis of Meynert, and brainstem nuclei

REM Sleep Behavior disorder

- Failure of paralysis during REM sleep leading to complex motor behaviors
- Found in > Half of all PD and Lewy body dementia cases
- Possible predictor for developing an alpha-synucleinopathy (Jung et al 2017)
- Patients with REM sleep behavior disorder and MCI (vs MCI alone) more nonamnestic features (89%) such as executive function deficits and depression (Szeto et al 2017)
- Typical treatment for REM sleep behavior disorder is clonazepam
 Use benzos in the elderly should be weighed against risks
- Can also consider melatonin or pramipexole









LEWY BODY DEMENTIA, DSM 5 CRITERIA

Criteria met for major or mild neurocognitive disorder

Insidious onset and gradual progression

•For probable major or mild neurocognitive disorder with Lewy bodies: two core features, or one suggestive feature with one or more core features. For possible major or mild neurocognitive disorder with Lewy bodies: only one core feature, or one or more suggestive features:

- Core diagnostic features:
- Fluctuating cognition with pronounced variations in attention and alertness (looks like delirium)
- Recurrent visual hallucinations (VH) that are well-formed and detailed
- Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline
- Suggestive diagnostic features:
 - Meets criteria for REM sleep behavior disorder
- Severe neuroleptic sensitivity
- The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder

DIFFUSE LEWY BODY DEMENTIA (DLB)

- Considered second most common type of dementia (10-20%)
 Some patients show mixed features of AD and DLB or DLB and PD with mixed neuropathology
- Cognitive impairment PRECEDES parkinsonism (in contrast to PD)
- Death up to 10-15 years after onset (typically faster than AD)
- Pathology (gold standard for diagnosis):
- Lewy bodies in cortical neuroses diffusely (anterior frontal and temporal lobe, the cingulate gyrus, and the insula; also substantia nigra and locus ceruleus, nucleus basalis of Meynert, and brainstem nuclei)
- Loss of dopamine transporter (DaT) seen at autopsy in striatum
- Clinical diagnosis (no blood test, imaging that is definitive)
 DaTSCAN (single photon emission CT scan) may facilitate dx
- Alpha-synuclein is found in peripheral nerve fibers in DLB patients but not control dementia pts (Donadio et al 2017) → possible test







(A) MRI: relative preservation of medial temporal lobe volume in DLB, similar to control, whereas atrophy is obvious in AD.



DIFFERENTIATING DLB FROM AD DLB AD More vivid hallucinations, apathy, and dysphoria Less hallucinations Greater impairment of attention, executive and More recent memory impairment visuospatial functions Alzheimer's disease Dementia with Lewy bodies 5000 Parkinsonism more common Periods of stupor not related to delirium 4000 8 Relative preservation of memory function al (in 3000 Difference is attenuated with age

- Faster progression of illness
- Higher cost of care per month of survival

Bowman et al 2017 Mueller et al 2017 Bronnick 2016 Oliveira et al 2015 Nagahama et al 2017



PHARMACOLOGIC TREATMENT OF DLB: ANTICHOLINESTERASE INHIBITORS

- There is loss of cholinergic transmission in DLB
- Lewy bodies found in the nucleus basalis and pontine nuclei
- Treatment with anticholinesterase inhibitors can reduce VH
- Resolution of VH correlated with reduction of PET activity in medial occipital cortex with donepezil treatment (Satoh 2010)
- Anticholinesterase inhibitors do not seem to worsen motor symptoms in RCT (Mori et al 2015)



Honore' Daumier: Caricature, number 15 in the series L'Imagination, depicting visual hallucinations. National Library of Medicine, Bethesda, MD





RIV	ASTIGM	INE	V	S	D	ON	EPEZ	IL FO	R DLB	
MMSE	Study or Subgroup	Experir Gro Mean S	nental up D Total	Contro Mean	ol Grouj SD To	b tal Weight	Mean Difference ^a (95% CI)	Mean Di (95)	ifference ^a % Cl)	Meta-analysis of donepezil
Donepezil	DLB, donepezil likeda et al. (20) Mori et al. (15) Subtotal (95% CI) Heterogeneity: $tau^2=0.00$; $\chi^2=$ Test for overall effect: Z=4.10,	2.2 2 2 3 0.70, df=1, p <0.0001	.9 49 .3 36 85 =0.40; I ² =	0.6 -0.4 0%	3 4	14 14.5% 31 11.6% 75 26.2%	1.60 (0.40, 2.80) 2.40 (0.96, 3.84) 193 (1.01, 2.85)		 ◆	and rivastigmine for DLB favors donepezil for MMSE but not necessarily for symptoms measured in the
Rivastigmine	DLB, rivastigmine McKeith et al. (21) Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z=1.59,	0.67 4.2 p=0.11	26 59 - 59	0.57 4	.26	51 10.7% 51 10.7%	1.24 (-0.28, 2.76) 1.24 (-0.28, 2.76)	:	•	neuropsychiatric inventory
	Total (95% CI) Heterogeneity: tau ² =0.27; χ^2 = Test for overall effect: Z=4.10, Test for subgroup differences:	12.20, df=7, p<0.0001 y ² =3.19, df	692 p=0.09; l ² =3. p=0.36	=43% : I ² =5.99	5:	10 100.0%	1.26 (0.66, 1.86)	-4 -2 Favors control	0 2 4 Favors experime	nntal
Neuropsychiatric	, .	~						condition	condition	
inventory	1	Experiment	al Group	Cont	rol Gro	qr	Mean Differen	ce* Mea	in Difference*	
	Study or Subgroup	Mean SI) Total	Mean	SD	Total Weig	ht (95% CI)		(95% CI)	
Donepezil	DLB, donepezil likeda et al. (20) Mori et al. (15) Subtotal (95% CI) Heterogeneity: tau ² =35.15; x ² = Test for overall effect: Z=0.65,	-5.5 1. -8 12. 5.90, df=1, j p=0.52	4 49 8 35 84 0=0.02; I ²	-6.4 0.3	1.5 17.5	44 31.1 32 5.1 76 36.2	% 0.90 (0.31, 1.49 % -8.30 (-15.70, - % -2.93 (-11.82, 5.	0.90)	2	
Rivastigmine	DLB, rivastigmine McKeith et al. (21) Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z=1.37, p	-5 16	2 47 47	-1.2	10.7	53 8.4 53 8.4	 -3.80 (-9.25, 1.6 -3.80 (-9.25, 1.6 -1.36 (-3.20, 0) 	5)		
Stinton et al 2015	Heterogeneity: tau ² =2.72; χ^{2} =2 Test for overall effect: Z=1.46, Test for subgroup differences:	23.86, df=5, p=0.14 χ ² =1.38, df=	p=0.0002	l ² =79%		474 100	- <u></u>	-20 -10 Favors experimental condition	0 10 Favors o cond	

PHARMACOLOGIC TREATMENT OF DLB

- Anticholinesterase inhibitors, first line
- Antipsychotics can be used but there may be sensitivity in terms of dosing, side effects (worsening confusion, movement symptoms)
- Olanzapine: post-hoc trial of AD patients that including DLB patients showed improvement in psychotic sx (Cummings 2002); however, side effects in 1/3. No RCT data
- Quetiapine: does not worsen motor symptoms but has inconsistent data to support improvement in psychotic symptoms
- Risperidone: worsened cognition (MMSE change -2.3) Culo et al 2010
- Antidepressants have not been studied systematically.
- Citalopram is not efficacious or well-tolerated, 70% discontinuing for adverse effects (Culo et al 2010)
- Memantine: weak data, with low numbers, mixed with PDD patients
- May improve survival (Subendorff et al 2014)
- ADR of hallucinations

Medications in pipeline: intepirdine a selective 5HT6 receptor antagonist that enhances ACh





PARKINSON'S DISEASE (PD)

- Chronic progressive neurodegenerative disorder characterized by:
- Tremor
- Bradykinesia
- Rigidity
- Postural instability
- Affects 1%, M>F

 Loss of pigmented dopaminergic neurons in the substantia nigra that project to the striatum

- Lewy bodies found in substantia nigra, the basal nucleus of Meynert, locus ceruleus, cerebral cortex, sympathetic ganglia, the dorsal vagal nucleus, myenteric plexus, cardiac sympathetic plexus
- "Parkinsonism" (features of PD) may be caused by medications, trauma, or stroke with different prognoses and response to treatment

Normal brain

Parkinson's disease



NON-MOTOR SYMPTOMS OF PD

- Increasing recognition of symptoms not improved with DA replacement
- Alterations of other pathways: 5HT, NE, ACh
- Non-motor symptoms (psychosis and dementia) predict mortality
- Non-motor symptoms predict nursing home placement
- Non-motor symptoms are more common in patients who were older at age of disease onset



Forsaa et al 2010 Zhou et al 2013

https://i.ytimg.com/vi/OdhhsPplbOY/maxresdefault.jpg

- Mood symptoms (depression)
- Dementia
- Psychosis
- Sleep changes
- Dopaminergic therapy complications
- Psychotic symptoms
- Impulse control disorders
- Autonomic dysfunction
- ■Pain
- Gastrointestinal changes (constipation)
- Impaired olfaction



DEPRESSION DUE TO PARKINSON'S DISEASE

- Up to 50% of patients with PD have depressive symptoms
- Depression is associated with worsened functional impairment and reduced quality of life
- Depression is associated with a more rapid cognitive decline in PD
- Features of the disease (masked face/blunted affect), avolition/apathy, poor concentration, insomnia may be part of the degenerative process
- Worsening debility, self-consciousness about tremor, and increasing dependency can contribute to poor mood



DEPRESSION DUE TO PARKINSON'S DISEASE (SAD-PD)

- Multi-center RCT of antidepressants for depression in PD; N=115 randomized to paroxetine, venlafaxine or placebo
- Primary outcome was change in HAM-D
 Paroxetine 10-40mg
 - Improved insomnia
- ■Venlafaxine XR 37.5mg 225mg
 - More likely to increase BP
- Movement symptoms were relatively mild
- Higher pre-treatment depression and lower anxiety scores predicted greater improvement (Moonen et al 2014)
- Affective, then somatic, followed by cognitive improvements (Broen et al 2016)



DEPRESSION DUE TO PARKINSON'S DISEASE

- Sertraline and amitriptyline were beneficial in open label trials (Antonini 2006; Marino et al 2008)
- Nortriptyline (25-75mg) was more efficacious than paroxetine CR (12.5-37.5mg) in 8 wk RCT (N=52) using HAM-D (Menza et al 2009)
- 6/11 patients in paroxetine group dropped out due to side effects vs 4/12 in nortriptyline group
- MAO inhibition with antidepressant may enhance reponse: ADAGIO study, N= 192 patients on an antidepressant (citalopram 20mg, amitriptyline 50mg, trazodone 100mg, sertraline 100mg, paroxetine 30mg, escitalopram 10mg) with added rasagiline 1-2mg (MAO-B inhibitor) vs. placebo (Smith et al, 2014)
- ■72 week, double-blind to rasagiline status
- No restriction of tyramine in diet
- No events of serotonin syndrome or tyramine hypertensive crisis
- Rasagiline group had less decline in mood as compared to placebo group

ECT can be effective in treating mood symptoms in PD and can improve motor symptoms (Anderson et al 1987)

PARKINSON'S DISEASE DEMENTIA, DSM 5 CRITERIA

- Criteria met for major or mild neurocognitive disorder
- Disturbance occurs in the setting of established Parkinson's disease
- Insidious onset and gradual progression of impairment
- Neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder
- Major or mild neurocognitive disorder probably due to Parkinson's disease should be diagnosed if 1 and 2 are both met. Major or mild neurocognitive disorder possibly due to Parkinson's disease should be diagnosed if 1 or 2 is met:
- 1. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).
- 2. Parkinson's disease clearly precedes the onset of the neurocognitive disorder

PARKINSON'S DEMENTIA (PDD)

- Subcortical dementia with slower processing, difficulties with construction, and memory concerns
- Dementia is typically a late feature of PD and up to 80% of patients will have it at 20 years
- As compared to age-matched controls, 4-6x greater risk of dementia in PD (Aarsland et al 2001)
- In contrast to Lewy Body Dementia, the movement disorder precedes the change in cognition
- Dementia in PD is associated with increased apathy, delusions, hallucinations as compared to PD patients without dementia (Leroi et al 2012)
- Rivastigmine is FDA approved for mild to moderate PD dementia

EFFICACY OF RIVASTIGMINE AND DONEPEZIL FOR PDD



EFFICACY OF RIVASTIGMINE AND DONEPEZIL FOR PDD (MMSE)

	Exp	Experimental Group			Control Group			Moon Difference	Mann Difference)		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	(95% CI)	(95% CI)		
PDD, donepezil											
Aarsland et al. (16)	22.8	3.7	12	21	5	12	2.7%	1.80 (-1.72, 5.32)			
Dubois et al. (17)	1.72	2.96	173	0.06	2.96	170	25.3%	1.66 (1.03, 2.29)			
Leroi et al. (18)	-0.67	1.67	9	0.12	1.67	7	9.6%	-0.79 (-2.44, 0.86)			
Ravina et al. (19)	22.5	6.9	19	24.4	9.4	19	1.3%	-1.90 (-7.14, 3.34)			
Subtotal (95% CI)			213			208	38.8%	0.57 (-1.21, 2.34)			
Heterogeneity: tau ² =1.83; χ^2 =8 Test for overall effect: Z=0.63,	8.94, df= p=0.53	=3, p=	0.03; I ²	=66%							
PDD, rivastigmine											
Emre et al. (22)	0.8	3.8	335	-0.2	3.5	166	24.3	1.00 (0.33, 1.67)			
Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z=2.92,	p=0.00	3	335			166	24.3	1.00 (0.33, 1.67)	*		
Total (95% CI) Heterogeneity: tau ² =0.27; χ^2 =: Test for overall effect: Z=4.10, Test for subgroup differences:	12.20, df p<0.000 χ ² =3.19	f=7, p= 01 , df=3	692 =0.09; I , p=0.3	² =43% 6; I ² =5.	9%	510	100.0%	1.26 (0.66, 1.86)	Favors control condition condition		
									Stinton et al 201		

Seppi et al 2011 Stinton et al 2015 Wang et al 2015

EFFICACY OF MEMANTINE IN PDD

	Experir Gro	mental oup	Control	Group		Disk Datio		Disk Datio		
Study or Subgroup	Events	Total	Events	Total	Weight	(95% CI)		(95% CI)		
PDD										
Emre et al. (27)	31	60	28	56	47.8%	1.03 (0.72, 1.48)				
Leroi et al. (28)	6	10	6	14	8.2%	1.40 (0.64, 3.08)				
Subtotal (95% CI)		70		70	56.0%	1.09 (0.78, 1.51)				
Total events	37		34							
Heterogeneity: x ² =0.47, df=1, p=0.4	9; I ² =0%									
Test for overall effect: Z=0.50, p=0.6	51									
Test for overall effect: Z=1.68, p=0.0	19								+	-
Test for subgroup differences: $\chi^2=1.0$	54, df=2,	p=0.44	; I ² =0%			0	.2 0.5	i	ż	5
							Favors control	Favo	rs experimental	
							condition		condition	

Studies complicated by not separating PDD from DLB patients

- Data for memantine are weak in 2 meta-analyses and show no difference in cognition
- Movement Disorder Society recommends rivastigmine, and considers both donepezil and memantine with "insufficient evidence; acceptable risk"

 Consensus definition: psychotic symptoms >1 month, not due to another cause, with subtypes: Presence or absence of dementia Presence of insight Concurrent use of dopaminergic medications 	
 PDP typically arises later in the disease (~10 years after initial diagnosis) Initially, insight is retained, with symptoms progressing and insight lost 	
 Risk factors for PDP: Exposure to dopaminergic medications Advancing age Increasing impairment in executive dysfunction/dementia PD severity Comorbid psychiatric symptoms (depression, anxiety) Fatigue 	
 sleep disorders Visual impairment Polypharmacy 	

PARKINSON'S DISEASE PSYCHOSIS (PDP)

- Psychotic symptoms can include:
- Hallucinations, Illusions
- Paranoia
- Delusions: typically younger age of onset than hallucinations
- Minor hallucinations: "false sense of presence"
- Psychotic symptoms are associated with:
- Poorer quality of life
- Caregiver distress
- Worse outcomes:
- Nursing home placement
- Mortality
- Prevalence varies in the literature, but may be as high as 60%

	Primary psychotic disorder	PDP				
Hallucinations	Most often auditory, occasionally somatic; persecutory in nature	Primarily visual with persistent images superimposed on a normal environment, false sense of presence and illusions also common				
	Typically no insight	Insight generally retained early				
Delusions	Paranoid, bizarre (being followed, mistreated, poisoned, mind-reading, ideas of reference, thought broadcasting, thought insertion, thought withdrawal), religious, grandiose (special powers)	Paranoid in nature typically related to jealousy, infidelity, abandonment, parasitosis				
Mania	Can be present	Typically not present				
		Jakel & Stacy 2012				

ETIOLOGY OF PDP

- Psychotic symptoms in untreated PD is thought to be low, but is unknown
- Little data on natural course of untreated PD, as rarely see untreated advanced disease
- Historical accounts of hallucinations in late-stage PD, especially with dementia and depression

Majority PDP symptoms likely related to dopaminergic agents Increased risk with dementia, # of medications, pergolide treatment

Odds of Psychosis

Dopamine agonists	Odds ratio (confidence interval)	Odds ratio adjusted for age sex, dementia
Pergolide	2.22 (1.01-4.87)	2.01 (1.22-5.45)
Ropinerole	1.18 (0.60-2.32)	1.05 (0.55-2.11)
Pramipexole	0.52 (0.22-1.24)	0.94 (0.33-1.66)
Cabergoline	0.32 (0.16-0.63)	0.65 (0.39-1.09)
Levodopa	0.14 (0.07–0.26)	0.11 (0.06–0.19)
Ecker et al 2009		

cker et al 2009

DIAGNOSIS AND MANAGEMENT OF PDP

- Clinical history of psychotic symptoms
- Examination of patient
- Collateral histories from family and caregivers
- Rule-out other causes, such as delirium, Lewy body dementia, AD
- Treatment aims to reduce psychosis without worsening the movement symptoms
- Reduce doses of dopaminergic agents as able
- Reduce polypharmacy with adjuvants especially anticholinergics
- If reduction in medication does not work, can consider addition of another medication, typically an atypical antipsychotic
- Low dose clozapine (50mg): effective in an RCT (Pollock 2004) without worsening of motor symptoms
- Quetiapine also does not worsen movements in studies, but RCTs have failed to show benefits
- Other antipsychotics worsen movement symptoms
- Rivastigmine has data for improving hallucinations, but other AChE inhibitors do not
- Consider that ECT can improve psychotic symptoms in PD and improve movements (Usui et al 2011; Ueda et al 2010)

ANTIPSYCHOTICS IN PDP

 TABLE 3. Changes in Scores for Primary Outcome Measures

 from Base Line to Follow-up.*

PRIMARY OUTCOME MEASURE	PLACEBO GROUP (N=27)	CLOZAPINE GROUP (N=27)	P VALUE
	change	in score	
Measures of parkinsonism†			
UPDRS, total score	-3.8 ± 1.5	-6.4 ± 2.9	0.36
UPDRS, motor score	-1.8 ± 1.2	-3.6 ± 1.9	0.34
UPDRS, tremor score	-0.2 ± 0.4	-1.5 ± 0.5	0.02
Psychiatric measures			
BPRS score	-2.6 ± 1.3	-9.3 ± 1.5	0.002
BPRS-M score	-2.5 ± 1.2	-8.6 ± 1.3	0.003
CGIS score	-0.5 ± 0.2	-1.6 ± 0.3	< 0.001
SAPS score	-3.8 ± 1.9	-11.8 ± 2.0	0.01
MMSE score	-0.1 ± 0.4	0.0 ± 0.5	0.90

*This analysis was based on the actual treatment each patient received. UPDRS denotes Unified Parkinson's Disease Rating Scale, BPRS Brief Psychiatric Rating Scale, BPRS-M the modified BPRS, CGIS Clinical Global Impression Scale, SAPS Scale for the Assessment of Positive Symptoms, and MMSE Mini-Mental State Examination. Plus-minus values are means ±SE, and negative values indicate improvement.

[†]The scores for these items are based on 25 patients in each group. Parkinson's study group 1999

- Conventionally, psychosis in PDP has been treated with atypical antipsychotics that block dopamine
- Goal is symptom reduction without worsened movements
- Data for clozapine has been replicated; considered an acceptable choice for PDP with required lab monitoring
- Quetiapine has had at least 7 trials (3 blinded)
- Reduction in BPRS in the unblinded trials
- Ineffective in blinded trials
- Quetiapine compared to clozapine (rater-blinded) and they were not found to differ (no placebo group; Eng et al 2010)
- Evidence for quetiapine is weak but it is frequently chosen due to ease of use as compared to clozapine







Study day

Cummings et al 2014 Lance

PIMAVANSERIN SIDE EFFECT PROFILE

• Treatment-emergent adverse events group in all participants who received ≥ 1 dose of study drug (occurring in $\geq 5\%$ in either treatment)

	Placebo (n=94)	Pimavanserin 40 mg (n=104)
Nausea	6 (6%)	6 (6%)
Peripheral edema	3 (3%)	7 (7%)
Urinary tract infection	11 (12%)	14 (13%)
Fall	8 (9%)	11 (11%)
Confusional state	3 (3%)	6 (6%)
Headache	5 (5%)	1 (1%)
Hallucination (including visual)	4 (4%)	7 (7%)

QTc interval change 13.5 msec at a 2x therapeutic dose

- Concentration-dependent QTc interval prolongation in the therapeutic range
- Mean increases in QTc interval of ~5-8 msec at 34mg
- Still has the same black-box warning for antipsychotics in dementia
- Causes phospholipidosis (lungs, kidneys, muscle, retina) in animal studies at supratherapeutic concentrations

SLEEP PROBLEMS IN PD

•Occur in 60-98% of patients with PD

- Disturbances include:
- Sleep fragmentation, insomnia
- Daytime somnolence
- Sleep-disordered breathing
- Restless legs/periodic limb movements
- Nightmares
- REM sleep behavior disorder
- Minimal studies to examine treatment specific to PD patients
- Doxepin or CBTi + bright light therapy more effective than placebo in small study of 18 patients (Rios Romenets et al 2013)
- Eszoplicone improved multiple awakenings, not total sleep time, in RCT of N=30 (Menzo et al 2010)

Recommend directing treatment based on underlying symptom given lack of data



MEDICATION-INDUCED SYMPTOMS: IMPULSE CONTROL DISORDERS



- ICARUS trial examined outpatients on DA replacement therapy for 2 years, incidence of impulse control disorders: 26.5-29.3%
- Most common: compulsive eating, followed by punding, compulsive sexual behavior, gambling and buying disorder
- Punding: stereotyped, repetitive, stereotype movements including manipulations of objects, excessive grooming, hoarding, fidgeting with clothing
- Risk factors: male, younger, earlier age at onset, longer disease duration, more severe non-motor symptoms, depressive symptoms, sleep impairment and poorer PD-related quality of life
- PD motor severity and cognitive function did not predict impulse control disorders
- First line treatment is reduction of dopaminergic agent
 No evidence with naltrexone, amantadine



Antonini et al 2017



HD SYMPTOMATOLOGY

 Motor symptoms: chorea, dystonia, gait disturbances, eye movements; late parkinsonism

Neuropsychiatric symptoms:

- Mood symptoms: depression, manic-like symptoms (irritability)
- Obsessions and compulsions
- Anxiety
- Hypersexuality
- Psychotic symptoms: paranoia, delusions
- Disinhibition
- Apathy
- Cognitive symptoms:
- Poor judgment
- Poor memory
- Decreased insight
- Inflexible thought
- Decreased concentration

Symptoms may be subtle and predate the chorea



Suchowersky 2017

HD: NEUROPSYCHIATRIC SYMPTOMS

- Up to 73% will be diagnosed with a psychiatric disorder, at any time during the disease course
- Mood symptoms: depression, manic-like symptoms (irritability with dishinhibition) 33-76%
- Obsessions and compulsions 10-76%
- Psychosis 3-11%
- Anxiety
- Hypersexuality
- Disinhibition
- Apathy

Risk of suicide is higher than population rate, and extends to non-affected family members (as high has 20%)

Psychotic symptoms treated with antipsychotics may have beneficial effects on the motor disorder

Trials without effect: Lamotrigine, Lithium

No quality trials of sufficient size or duration to make conclusions regarding antidepressants

No Trials: depakote

HD: COGNITIVE SYMPTOMS

- Cognitive symptoms (subcortical dementia: executive function, multi-tasking, decision-making)
- Poor judgment
- Poor memory
- Decreased insight
- Inflexible thought
- Decreased concentration
- Rivastigmine for 6 months did not show improvements in cognition as based on neuropsych testing in early HD (N=18; Sesok et al 2014).
- No effect with memantine and donepezil, citalopram (for cognition), L-acetyl carnitine, riluzole, amantadine, atomoxetine
- Modafinil: improved attention but not cognition or mood with worsened working memory and visual recognition (Blackwell et al 2008)

Mestre & Frrerira 2012

APPROACH TO MANAGEMENT OF HD SYMPTOMS Ihere are no disease-modifying treatments → symptomatic treatment There is minimal data high quality to support specific medications for neuropsychiatric and cognitive symptoms: Motor symptoms: antidopaminergic agents (tetrabenazine approved) Mood symptoms: antidepressants (avoid bupropion), mood stabilizers Psychotic symptoms: antipsychotics (D2 blockade may improve chorea) No effects with: Coenzyme Q10: for total functional capacity. No difference (McGarry et all 2016) Sativex (nabiximols), equimolecular combination of delta-9 THC and cannabidiol: no effect on motor, behavioral, and cognitive domains (Moreno et al 2016). Ethyl-eicosapentaenoic acid (EPA) treatment (Ferreira et al 2015) Recommend multi-modal care (neurology, psychiatry, PT/OT, speech, SW)

UNIQUE CHALLENGES TO HD

- •Knowing about the disease (i.e. having a positive HD gene testing) prior to overt onset of symptoms is itself a serious psychological burden
- Impact of being raised by, living with and/or caring for ill family member also with the disease can impact stress
- •Familial financial toxicity of an autosomal dominant illness that strikes during working years

Impact on family planning, child rearing

Stigmatization as a carrier





MULTIPLE SCLEROSIS (MS)

- Demyelinating disease of the CNS that can affect any region
 Cognitive impairment (40-60%) and depression are common complaints
- Cognitive impairment is generally mild and in mild dementia range in 20%
 Found in all subtypes and worsens with time
- Not all cognitive domains are affected evenly
- Typically memory and executive function
- Rarer: semantic language, attention
- Correlation with MRI findings is robust; however, only 1/3 to 1/2 of variance is explained by MRI
- Impacts ability to maintain employment, ADLs, IADLs, benefit from physical rehab
- Evaluation of cognition is challenging
 Patient report may not correlate with severity and may reflect depression
- Neuropsych testing may be needed to assess for subtle deficits
- Treatments aimed at:
- Disease modification
- Symptomatic management

Amato et al 2012

DISEASE MODIFYING TREATMENTS FOR COGNITION IN MS

Potential to reverse the processes that lead to cognitive dysfunction

- Approved agents reduce nervous system damage on MRI, reduce atrophy
- •Treatments aimed at improving the underlying neuroimmunological processes such as interferon beta-1b and beta-1a are associated with modest cognitive improvements
- •Limited data due to methodology (typically a secondary endpoint, studies underpowered to detect effect)
- Patients will typically be on these medications prior to coming to psychiatry for further assistance with cognition



SYMPTOMATIC TREATMENTS FOR COGNITION IN MS

Reference	Drug	Number treated	Design	Duration	Primary outcome	Result	Anialo el al 2
Smits et al. [80]	4 aminopyridine	20	DB, PC, RCT, CO	4 weeks	Cognitive function	-	
Bever et al. [74]	3,4 diaminopyridine	28	DB, PC, RCT, CO	$2 \times 30 \text{ days}$	Leg strength	-	
Rossini et al. [76]	4 aminopyridine	49	DB, PC, RCT, CO	6 months	Fatigue (NP Tests secondary)	-	
Geisler et al. [61]	Amantadine or pemoline	16	DB, PC, RCT	6 weeks	Multiple NPTests	-	
Wilken et al [72]	Modafinil	23	Randomized, evaluator blind	4 months	Multiple NP Tests	+	
Lange et al. [69]	Modafinil	8	DB, PC, RCT	8 weeks	D2 Alertness Test	+	
Stankoff et al. [71]	Modafinil	59	DB, PC, RCT	5 weeks	MFIS cognitive dimension Trail making A & B	-	
Möller et al. [68]	Modafinil	62	DB, PC, RCT	8 weeks	Symbol Digit Modalities Test Paced Auditory Serial Addition Test	-	
Harel et al. [64]	Methylphenidate	14	DB, PC, RCT	Single dose	Paced Auditory Serial Addition Test	+	
Benedict et al. [65]	1-amphetamine	19	Counterbalanced, within-subject	4× single doses	Multiple NP Tests	+	
Morrow et al. [66]	1-amphetamine	108	DB, PC, RCT	4 weeks	Symbol Digit Modalities Test	-	
Sumowki et al. [67] (re-analysis of 66)	1-amphetamine	108	DB, PC, RCT	4 weeks	California Verbal Learning Test 2; Brief Visuospatial Memory Test Revised	+	
Krupp et al. [77]	Donepezil	35	DB, PC, RCT	24 weeks	Selective Reminding Test; Self Report	+	
Krupp et al. [78]	Donepezil	61	DB, PC, RCT	24 weeks	Selective Reminding Test; Self Report	-	
Shaygan nejad et al. [79]	Rivastigmine	30	DB, PC, RCT	12 weeks	Wechsler Memory Scale	-	Intel
Lovera et al. [81]	Memantine	58	DB, PC, RCT	16 weeks	Paced Auditory Serial Addition Test and Selective Reminding Test	-	

He et al 2011 Li et al 2015

COGNITION IN MS: COCHRANE REVIEW

- 4 RCTs with all subtypes of MS and at least mild memory complaints
- Examined: donepezil, ginko biloba, memantine and rivastigmine vs placebo
- No serious adverse events
- Nausea, diarrhea, somnolence, constipation
- Low quality data, poorly matched variables, small samples
- Conclusion: No evidence to support pharmacologic intervention to target cognition with existing data

DEPRESSION IN MS

- Etiology unclear:
- May be due to demyelinating lesions
- Some disease modifying treatments could promote depression
- There has been concern that interferon-beta-1b and glatiramer worsened depression, but data don't support this (Schippling et al 2016)
- Therapeutic trials have limited data, small numbers, many patients lost to follow-up
- Cochrane review for antidepressants showed only quality studies of paroxetine and desipramine for 12 weeks compared to placebo with a *trend* toward efficacy
- Recommend treating depression as per general guidelines



MANAGING CONDITIONS WITH LIMITED DATA

- Many disease conditions affect multiple neurotransmitter systems and our understanding is evolving
- Patients may present with features of multiple types of dementia, let this guide medication choices
- Consider that some symptoms may be related to the specific neurologic rather than a separate DSM 5 diagnoses
- Despite limited evidence base, we still have patients with specific concerns
- Some conditions have no FDA-approved medications
- At this point, treating specific symptoms with knowledge of disease and comorbidities is warranted
 Monitor side effects, including the specific impact on the motor aspects of the disease
- Attention to interactions with the medications used to target motor symptoms



Keenmon & Sulzer 2013

HOW TO APPROACH NEUROPSYCHIATRIC SYMPTOMS

Counsel patients and families before neuropsychiatric symptoms occur, if possible; risk of delirium

- Identify target symptoms; follow with a rating scale like the NPI, CGI, BPRS
- When symptoms arise, full medical, neurologic, environmental assessment
- Select intervention with least risk and monitor results
- Environmental modification
- Redirection
- Caregiver education
- If this fails, consider pharmacologic management with least risky medication
- If this fails, consider atypical antipsychotic, after thorough discussion with patient and caregiver re: risks and black box warning
- Medication monitoring for effect
- Symptom monitoring
- Reassess and stop medication if clear benefit is not seen

PHARMACOLOGY IN THE ELDERLY

- "Everything" increases falls risk
- Start low and go slow
- Think about renal and liver function
- Get an ECG and follow QTc and pulse (particularly with antipsychotics and ACHe inhibitors)
- Think about polypharmacy and medication burden
- If possible, avoid benzos, anticholinergics, and excessive pain medications
- Medications may not be tolerated as well
- TCAs may have more side effects (worsening glaucoma, sedation, cognition, delirium)



ATTENTION TO SAFETY

- Medications (other chemicals) stored properly
- Administered by family/caregiver
- Driving:
- DMV notification for need for reassessment
- Also consider riding lawnmowers, ATVs, motorcycles, motorbikes
- Firearms
- Locked, unloaded
- Knives, other weapons, tools
- Loose rugs, stairs, bathroom safety
- Supervision, chimes, home alarms



"Any tool is a *weapon* if you hold it right." ~ Ani Difranco



CAREGIVER BURNOUT

Impact of burden of previously shared responsibilities (housework, cooking, bills, taxes, etc)

- Additional burdens of caring for individual
- Physical care (ADLs such as bathing, feeding, dressing, toileting)
- Care of agitated patient
- Loneliness of losing aspects of the relationship to the disease
- Lack of a break or assistance
- Caregiver factors
- Physical and cognitive impairments
- Lack of understanding of pathology
- "Bad" behaviors can appear volitional
- Repetitive conversations can by annoying and frustrating
- Expectations for improvement or difficulty accepting that symptoms will likely worsen
- Relationship factors
- Old relationship dynamics often persist



https://cdn.inquisitr.com/wpcontent/uploads/2016/08/rome -elderly-couple.jpg

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