Rivastigmine debate: Patch vs Pill

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Objectives

- Review the diagnostic criteria for dementia and apply it to a case patient.
- Review the evidence for transdermal versus oral cholinesterase inhibitors in the treatment of Alzheimer's Disease and determine the best treatment option for a case patient.

Mr. D

- ID: 92 yo retired engineer transferred from SPH to 7N in July for recurrent falls, vomiting, loss of appetite, weight loss, depression and cognitive impairment.
- Allergies: none
- SH: non-smoker, non-drinker, lives alone, uses walker
- Discharge plans: assisted living vs long term care
- PMHx: AF, hyperlipidemia, T2DM, BPH
- Meds PTA:
  - ASA 81 mg daily
  - Atorvastatin 10 mg qhs
  - Tamsulosin 0.4 mg qhs
  - Metformin 1000 mg BID
  - Glyburide 1.25 mg qam

Review of Systems

System	Findings	Med changes
CNS	CT→ Subdural hematomas OT assessment: -MMSE 26/30, MOCA 27/30 - impaired → recall, executive function & planning -Independent with ADLs -Requires prompting for meals/ ward activities	ASA 81 mg D/C due to ⇧ bleeding risk
Psych	SPH → trialed multiple antidepressants Mood improving, appetite & energy ↑	Methylphenidate 10 mg qam & noon

Review of Systems

System	Findings	Med changes
EENT	Hearing aid left ear, Right ear deaf	
Resp	No issues	
Cardio	AF → currently NSR HR 75, BP 110/72 Lipids - LDL 1.61, TC/HDL: 2.9, HDL 1.25	Atorvastatin D/C
GI/Liver	Appetite → improving, no vomiting, has meals delivered from Dine In Victoria Wt: 60 kg, Ht: 188 cm, BMI 17 Gained 2 kg over last 2 weeks Alb 26, PreAlb 113, LFTs: WNL	

Review of Systems

System	Findings	Med changes
Renal/GU	Scr 64, eGFR 96	Tamsulosin continued
MSK	Recurrent falls Osteoarthritis – no issues with pain	
Endo	HA1C 7% OT QID: 5.7→ 11.5 → 6.1 → 14.1	D/C MTF & glyburide Novorapid SS Lantus 14 units qhs
Heme	Hgb 108, Hct 0.3, MCV 98 Iron 11, TSAT 23%, TIBC 48 Serum B12 469	
Fluids/lytes	All WNL	

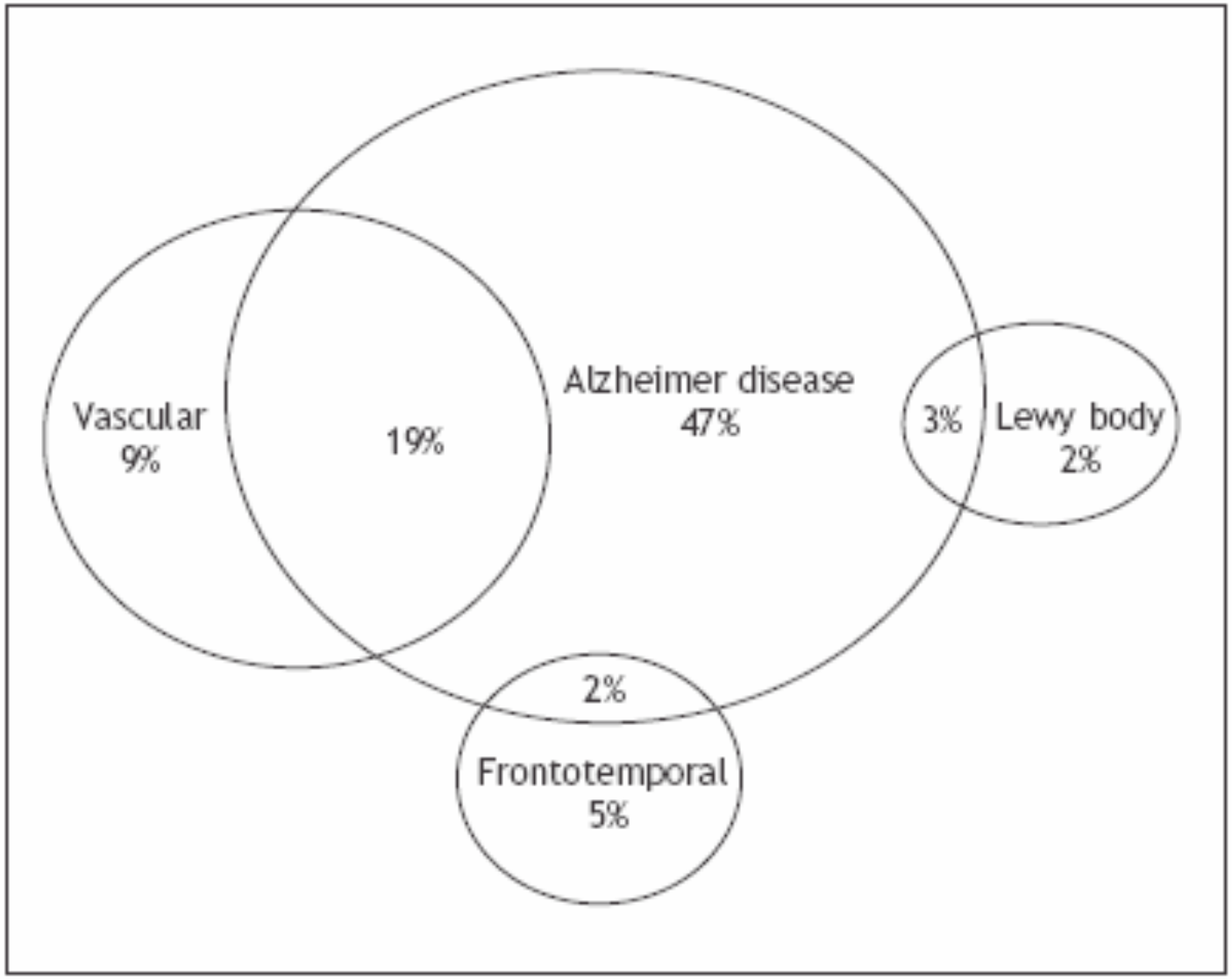
DRPs

- Mr D is at increased risk of a CVA due to lack of statin and anti-platelet/anti-coagulant therapy.
- Mr D is at increased risk of non-compliance with his insulin regimen at discharge due to cognitive impairment and complexity of dosing.
- Mr D has cognitive impairment/ dementia and would benefit from a cognitive enhancer.
- Mr D is at increased risk of fractures due fall history/risk, poor mobility and lack of vitamin D and calcium.
- Mr D is at increased risk of malnutrition due to poor diet and would benefit from a multivitamin.
- Mr D is at increased risk of anemia due to poor diet.

Dementia

- "Clinical syndrome of cognitive function and decline"
- Personality and/or behavior changes
- DSM IV Criteria:
  - Impairment in memory AND at least one of the following:
  1) Aphasia (language disturbance)
  2) Apraxia (impaired ability to carry out motor activities despite intact motor function)
  3) Agnosia (failure to recognize or identify objects despite intact sensory function)
  4) Impaired executive functioning (planning, organizing etc)
  - Impaired social/professional life compared to previous level of functioning
  - Decline does not occur only during delirium
  - Not explained by other medical conditions

Types of Dementia



Types of Dementia

Alzheimer's Disease (> 50%)

- Diagnosis of exclusion
- Gradual onset with progressive worsening of memory and cognitive function
- Mild-moderate (MMSE 10-26) vs Severe (MMSE < 10)

Vascular Dementia (~ 10%)

- Abrupt onset with stepwise decline
- Associated with cerebrovascular disease (temporal relationship)
- Radiologic evidence (infarcts in white matter)
- Gait disturbances, urinary incontinence/urgency, personality or mood changes

Back to Mr. D

- Diagnosis → mild-moderate Alzheimer's Disease or mixed vascular/Alzheimer's dementia
- Treatment
  - 1st line: Cholinesterase inhibitors
  - 2nd line: Memantine
  - Control vascular risk factors
    - Blood pressure
    - Blood glucose
    - Lipids

Cholinesterase inhibitors (ChEIs)

Drug	Dose	Comments
Donepezil 5, 10 mg tabs	5 mg daily X 4 weeks ⇧ to 10 mg daily if needed	CYP 3A4 & 2D6 substrate Long t ½ (72 hrs)
Galantamine 8, 16, 24 mg ER caps	8 mg daily X 1-2 weeks ⇧to 16 mg daily May ⇧ to 32 mg daily if needed.	CYP 3A4 & 2D6 substrate
Rivastigmine 1.5, 3,4,5,6 mg caps 2 mg/mL solution 4.6 mg & 9.8 mg per day patch	Caps: 1.5 – 3 mg BID X 2-4 weeks Titrate to 6 mg/ day May ⇧ to 12 mg/ day if needed Patch: 4.6 mg patch daily X 4 weeks May ⇧ to 9.8 mg patch if needed	Non-CYP metabolism

No evidence that one agent is better for mild-moderate AD

Adverse Effects of ChEIs

- GI (less common with rivastigmine patch?)
  - Nausea/vomiting/diarrhea (~ 10%)
  - Abdominal cramps
  - Anorexia/ Weight loss
- Cardiovascular: bradycardia, postural hypotension
- Respiratory: exacerbation of COPD
- GU: urinary incontinence
- CNS: insomnia, nightmares, dizziness

Considerations for Mr D

- Adverse effects
  - **History of vomiting & anorexia**
- Potential drug interactions
  - None noted with current medications
- Other medical conditions
  - No COPD, renal failure, UI, or bradycardia

Consider rivastigmine patch over oral ChEIs?

Rivastigmine Patch

- Proposed benefits
  - Minimizes drug level fluctuations
  - Avoids GI tract
  - Independent of food intake
  - Avoids first pass effect
  - Fewer side effects
  - Visual reminder that medication is taken
  - Avoids accidental overdose
  - Improves treatment compliance
  - Option for patients with swallowing difficulties

Evidence – Winblad et al.

P	Age 50-80 years with moderate AD, MMSE 10-20, n = 1195 Exclusion: advanced/ severe disease, investigational, psychotropic drugs, dopaminergic drugs or cholinesterase inhibitors 4 weeks prior to randomization
I	Rivastigmine 10 cm^2 patch (9.5 mg/24 hrs) daily (n = 293) Rivastigmine 20 cm^2 patch (17.4 mg/24 hrs) daily (n= 303) Rivastigmine capsules 1.5-6 mg PO BID (n=297)
C	Placebo patch daily and/or one placebo capsule BID (n= 302)
O	1°: ADAS-Cog scores (change from baseline) 2°: MMSE (change from baseline), Adverse effects
S	Multicentre, randomized, double blind, double dummy, active controlled over 24 weeks

Evidence – Winblad et al.

Results (LOCF ITT)			
Outcome	Mean baseline (SD)	Mean changes at week 24 (SD)	P value*
1 ° ADAS-Cog			
Patch 10 cm^2 Patch 20 cm^2 Capsules Placebo	27.0 (10.3) 27.4 (9.7) 27.9 (9.4) 28.6 (9.9)	-0.6 (6.4) -1.6 (6.5) -0.6 (6.2) 1.0 (6.8)	0.005 <0.001 0.003
2° MMSE			
Patch 10 cm^2 Patch 20 cm^2 Capsules Placebo	16.7 (3.0) 16.6 (2.9) 16.4 (3.0) 16.4 (3.0)	1.1 (3.3) 0.9 (3.4) 0.8 (3.2) 0 (3.5)	0.002 <0.001 0.002

* vs placebo

Evidence – Winblad et al.

Results		
Outcome	% of patients	P value
4 point decrease ADAS-Cog (MCID)		
Patch 10 cm^2 Patch 20 cm^2 Capsules Placebo	27.4% 32.8% 28.5% 19.9%	< 0.05 vs placebo

Evidence – Winblad et al.

Safety (ITT)			
Adverse event	10 cm^2patch	Capsules	OR (95% CI)
Withdrawal due to any AE	22/293	24/297	0.92 (0.51, 1.59)
≥ 1 event nausea	21/291	68/294	0.26 (0.14, 0.43)
≥ 1 event of vomiting	18/291	50/294	0.32 (0.18, 0.57)
≥ 1 event of diarrhea	18/291	16/294	1.15 (0.57, 2.29)
≥ 1 event of weight loss	8/291	16/294	0.49 (0.32, 1.72)
≥ 1 event of ↓ appetite	2/291	12/294	0.16 (0.04, 0.73)
≥ 1 event of dizziness	7/291	22/294	0.30 (0.13, 0.72)
≥ 1 event of headache	10/291	18/294	0.55 (0.25, 1.2)
≥ 1 event of asthenia	5/291	17/294	0.28 (0.10, 0.78)

Evidence – Winblad et al.

- **Conclusion**
  - Rivastigmine 10 cm^2 patch non-inferior to rivastigmine capsules 3-12 mg per day.
  - Statistically significant difference in adverse effects between 10 cm^2 patch and capsules
    - Less nausea, vomiting, appetite decrease, dizziness and asthenia (≥ 1 event)
    - No difference in withdrawal rates due to AEs

Evidence – Winblad et al.

- **Limitations**
  - Sponsored by Novartis (involved in data collection and analysis)
  - Same trial published in two different journals
  - Disadvantages of patch not addressed
    - More difficult to titrate dose
    - Adherence of formulation in cognitively impaired patients unknown

Back to Mr. D

- Recommendation
  - Rivastigmine patch likely better tolerated due to Mr. D's history of vomiting, anorexia and fall risk.
  - Suggest rivastigmine 5 cm^2 patch daily X 4 weeks
  - Increase to 10 cm^2 patch if tolerated

Back to Mr D.

- Recommendation
  - Recheck lipid profile, LFTs & CK
    - Restart atorvastatin 10 mg qhs if warranted.
  - Monitor blood pressure
  - Monitor A1C and fasting blood glucose.
    - Switch back to oral hypoglycemics once patient's appetite/diet more stable
  - Stroke prophylaxis
    - ASA 81 mg ✖ (bleeding risk)

Goals of therapy

- Maintain independence for ADLs
- Improve initiation → less prompting for ward activities/meals
- Slow progression of cognitive decline
- Minimize medication adverse effects

Monitoring

Efficacy	How Often?
ADLs – maintain at current level Behavior – prompting for ward activities/meals Cognition – memory/ recall, executive function May take 3-12 weeks for noticeable improvement	Weekly progress in hospital Reassess in 3 months if no benefit

Toxicity	How Often?
Weight	**Weekly in hospital**
GI: Nausea, vomiting, diarrhea, appetite	**Daily while in hospital**
Skin: application site reaction Ensure same site not used within 2 weeks	Daily while in hospital
Cardio: heart rate	Daily while in hospital
CNS: insomnia, nightmares, dizziness	Daily while in hospital
GU: incontinence	Daily while in hospital

Monitoring

Vascular risk factors		
	Target	How often?
Blood pressure	< 130/ 80 mm Hg	Daily while in hospital
Blood glucose	HA1C ≤ 7% Fasting BG 4-7mmol/L	Every 6 months OT QID until insulin discontinued
Lipids	LDL < 2 mmol/L TC/HDL < 4	Re-check in hospital If statin started: -Every 6-8 weeks until at target then q4-6 months

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Questions?