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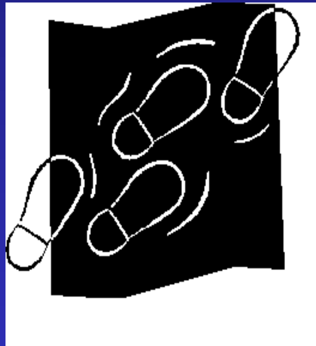
How Other Medical Problems Affect People with Parkinson's Disease



Stephen Grill, MD, PHD

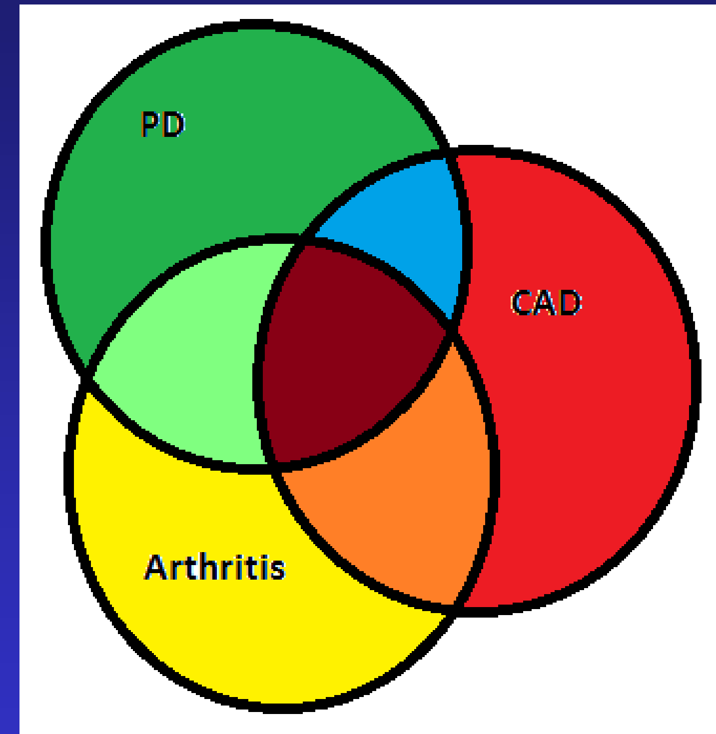
March 25, 2017

Parkinson's and Movement Disorders Center of Maryland

PARKINSON FOUNDATION
OF THE NATIONAL CAPITAL AREA
A COMMUNITY OF EDUCATION AND SUPPORT

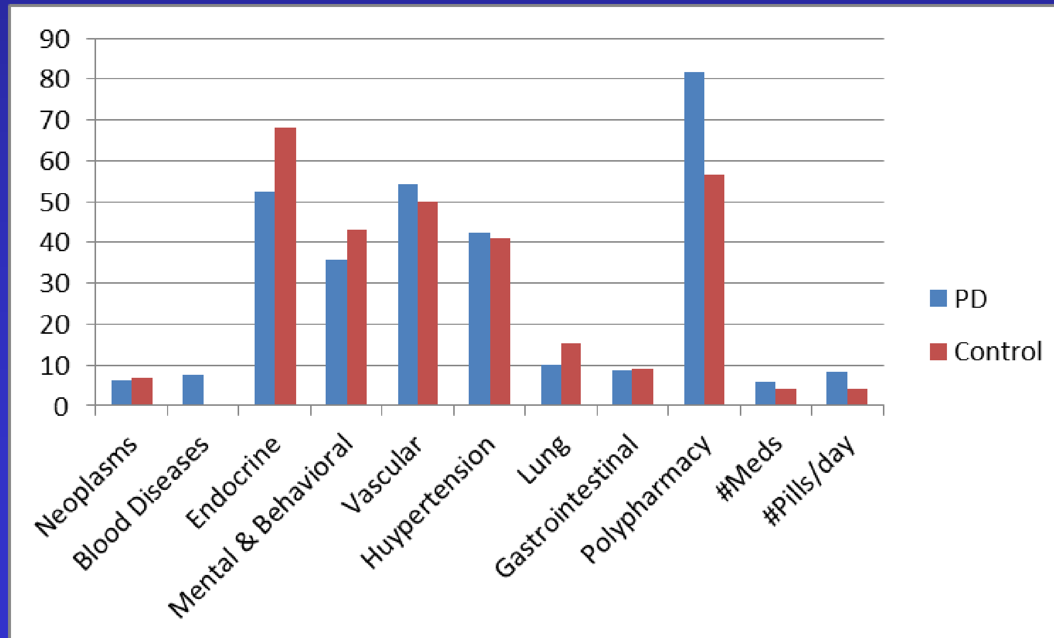
Almost No-one Has Just PD

- Increased Comorbidities
  - Osteoporosis
  - Melanoma
  - Sleep Apnea
  - ?Neuropathy, Diabetes
- Shared Symptomatology
  - Fatigue
  - Discoordination
  - Gait impairment/Imbalance
- Medication Interactions
  - Dopamine blockers
  - MAO inhibitors
- Importance of Communication



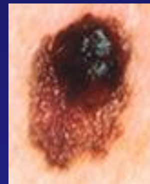
Non-Motor Symptoms vs Increased Comorbid Conditions

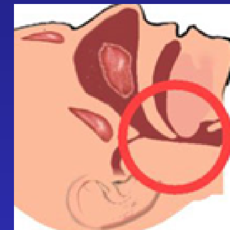
- People with PD have non-motor symptoms of their disease: pain, anxiety, depression, fatigue, dementia, psychosis, GI symptoms, urinary symptoms, sleep disorders
- Polypharmacy and comorbidity are common in PD
- Quality of life is dependent on all comorbidities
- Comorbidity is a predictor of death



Garcia et al 2017

Increased Comorbidities





- Skin CA (melanoma)
- Osteoporosis
- Sleep Apnea
- Small fiber neuropathy
- Diabetes
- Psoriasis (Ungprasert et al 2016)
- Inflammatory Bowel Disease (Lin et al 2016)

Cancer co-occurrence patterns in Parkinson's disease and multiple sclerosis—Do they mirror immune system imbalances?☆

Vladeta Ajdacic-Gross[a,b,*], Stephanie Rodgers[a,b], Aleksandra Aleksandrowicz[b], Margot Mutsch[a], Nina Steinemann[a], Viktor von Wyl[a], Roland von Känel[c], Matthias Bopp[a]

- Based on Swiss mortality data from 1969-2007
- Reduced risk of lung and liver cancer
- Increased risk of skin cancer (melanoma), breast CA and prostate CA

Parkinson's disease and risk of prostate cancer: A Danish population-based case-control study, 1995–2010

Christina G. Jespersen[a,b,*], Mette Nørgaard[c], Michael Borre[a]

- Risk of prostate CA in PD is REDUCED by 27%
- Risk reduction increased with increasing duration of PD

Cancer incidence among Parkinson's disease patients in a 10-yrs time-window around disease onset: A large-scale cohort study

Chava Peretz[a], Ron Gurel[a], Violet Rozani[a], Tanya Gurevich[b], Baruch El-Ad[c], Judith Tsamir[c], Nir Giladi[d,e,*]

- 7125 newly diagnosed with PD
- No difference in the risk of any cancer

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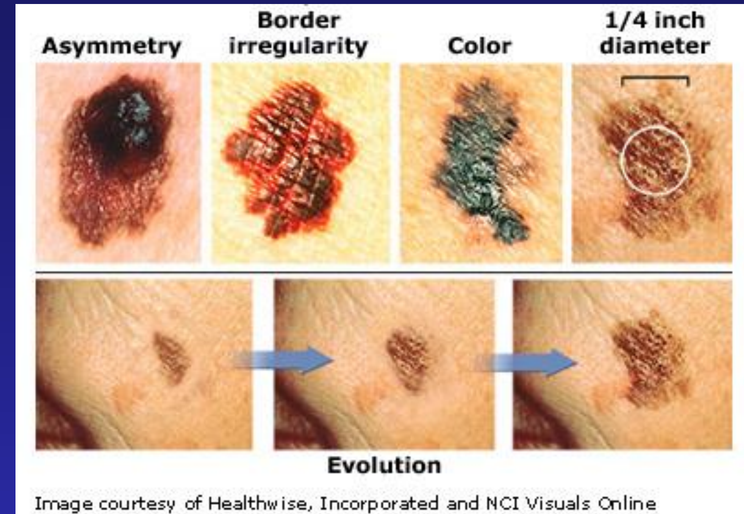
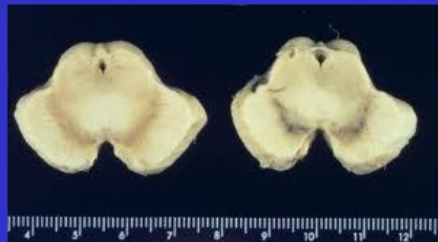
Melanoma

- Cutaneous malignant melanoma (CMM) rates are 1.5-3.5 that of controls
- This contrasts with evidence for lower CA rates in PD (except for perhaps Prostate and Breast CA)
- α-synuclein present in CMM
- People with PD should have regular skin examinations by a dermatologist





(Inzelberg et al 2016)

Osteoporosis

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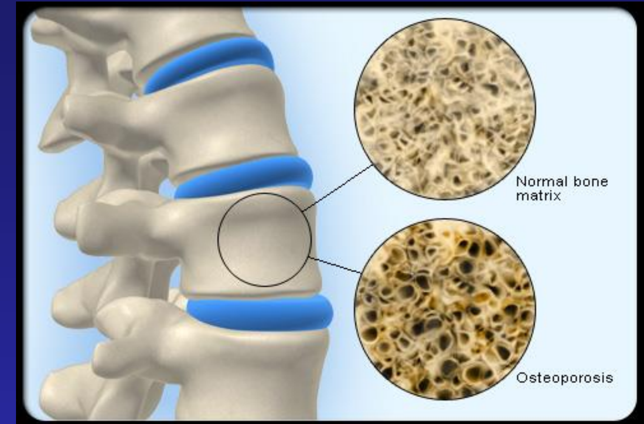
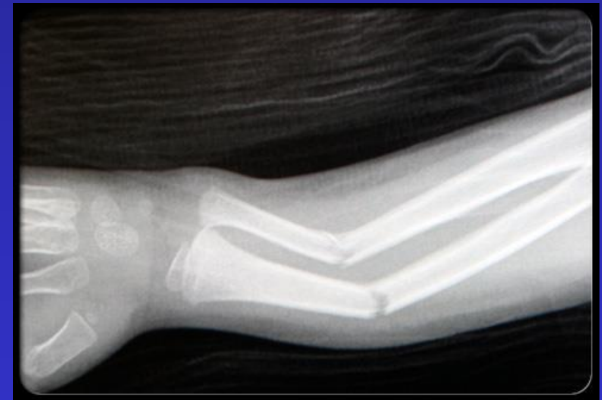
- Low bone mass and loss of bone tissue
- Leads to weak/fragile bones
- Risk is doubled in women (to 51%) and quadrupled in men (to 29%) with PD*
- Increased risk in PD may be related to reduced mobility in advancing disease
- Be checked

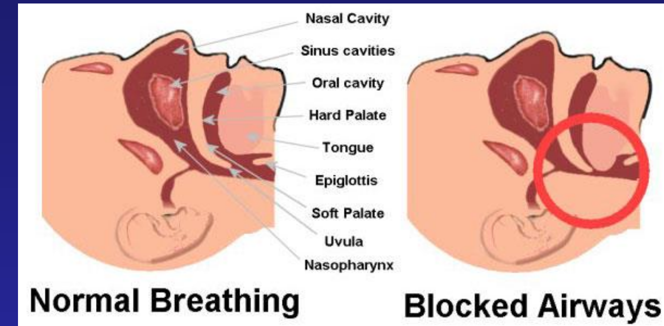




*Alhalabi 2006

Obstructive Sleep Apnea

- Sleep disorder with repeated upper airway collapse
- Results in apnea/hypopnea and hypoxemia (low O_2 in blood)
- Incidence: 20% general population
- Associated with metabolic, endocrine and cardiovascular disease



- Snoring increased in PD (71.8%); most snoring patients (60%) have sleep apnea
- Many studies indicate higher incidence in PD (Arnulf 2002, Maria 2003, Chotinaiwattarajul 2011)
- Associated with excessive daytime sleepiness
- Low oxygen is bad for the brain

Polyneuropathy in levodopa-treated Parkinson's patients

Karol Szadejko [a,*], Krzysztof Dziewiatowski [a], Krzysztof Szabat [a], Piotr Robowski [b], Michał Schinwelski [b], Emilia Sitek [b,c], Jarosław Sławek [b,c]

- 64 people with PD vs 59 control subjects
- 43.1% of PD had neuropathy vs 13.7 controls
- "Small fiber" neuropathy: symmetrical, distal sensory (vs motor) resembling diabetic neuropathy
- **Patients with neuropathy were older** (72.5 +/- 8.6) than those without neuropathy (63.4 +/- 8)
- **Patients with neuropathy had more advanced disease** and had more frequent gait impairment

- Neuropathy can affect gait and balance

2016

Increased risk of Parkinson disease with diabetes mellitus in a population-based study

Yu-Wan Yang, MD[a,b], Teng-Fu Hsieh, MD[c,d], Chia-Ing Li, PhD[e,f], Chiu-Shong Liu, MD[e,f,g], Wen-Yuan Lin, MD, PhD[e,g], Jen-Huai Chiang, MPH[h,i], Tsai-Chung Li, PhD[j,k,*], Cheng-Chieh Lin, MD, PhD[e,f,g,*]

- 36294 newly diagnosed with diabetes compared with 108,882 people without DM or PD
- Followed for about 7 ½ years

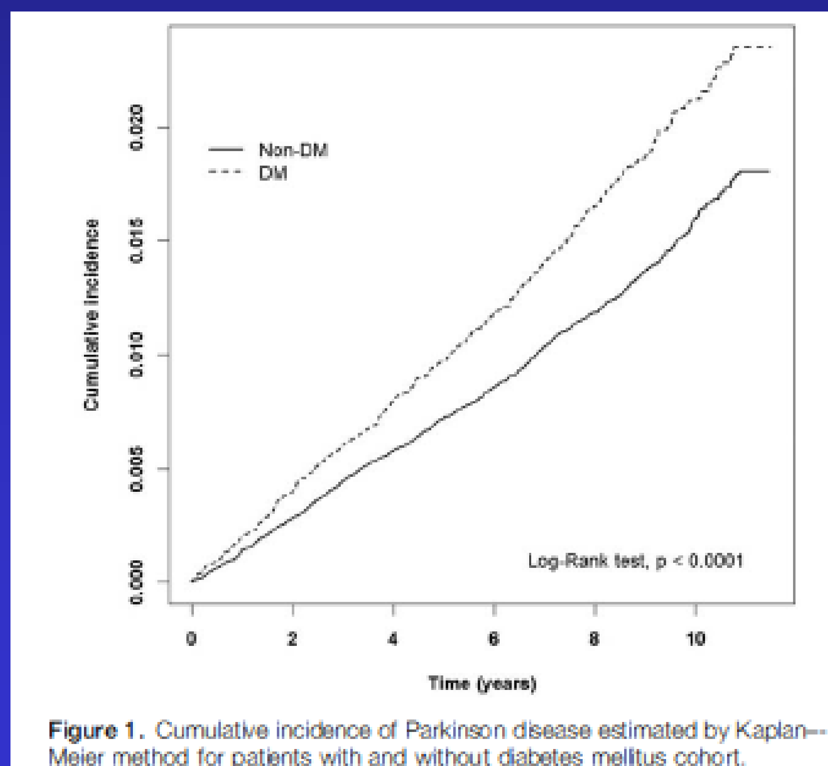


Figure 1. Cumulative incidence of Parkinson disease estimated by Kaplan–Meier method for patients with and without diabetes mellitus cohort.

2017

Coronary Artery Disease and Cerebrovascular Disease & PD

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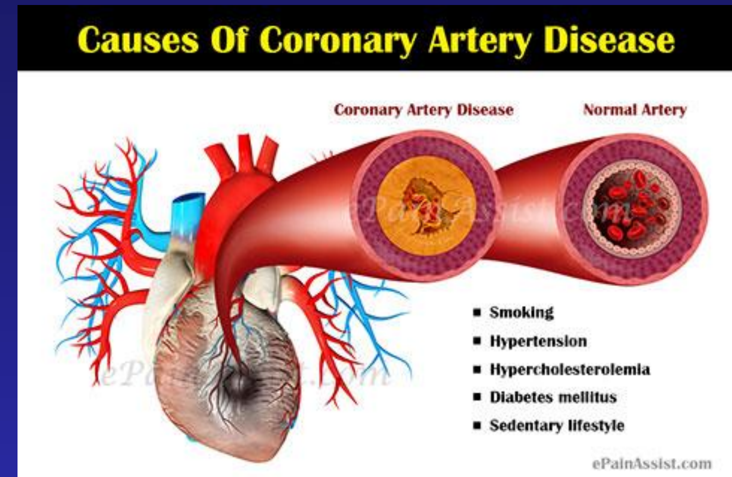
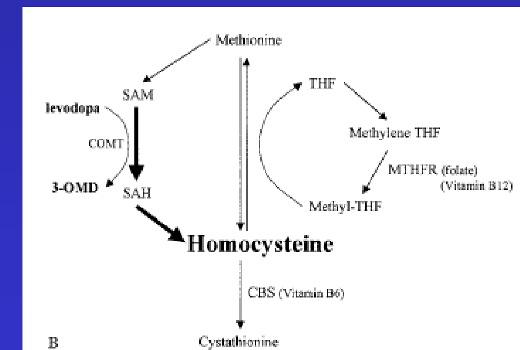
- Levodopa therapy raises homocysteine levels; increased homocysteine is a risk factor for stroke and coronary artery disease. However, risk of CAD same as controls
- Lower risk of stroke in persons with PD likely related to lower rate of smoking



Summary of comorbid conditions in Parkinson's disease and controls

Condition	Controls	Parkinson's disease
Hypertension	163/486 (33.5)	100/322 (31.1)
Orthostatic hypotension	9/108 (8.3)	23/145 (15.9)
CAD	106/488 (21.7)	77/384 (20.1)
Diabetes mellitus	59/486 (12.1)	44/340 (12.9)
Nonsmokers	224/410 (54.6)	210/320 (65.6)
Ex-smokers	112/410 (27.3)	90/320 (28.1)
Current smokers	74/410 (18.0)	20/320 (6.3)
Symptomatic CVD	39/489 (8.0)	29/482 (6.0)
Stroke	31/489 (6.4)	16/482 (3.3)
TIA	8/489 (1.7)	13/482 (2.7)
Asymptomatic stroke (n)	3	7



Nataraj and Rajput, 2005

Shared Symptomatology

- Sleepiness/Fatigue (under/over-medicated vs sleep disorder)
  - Sleep problems
  - Medication side effects
  - Hypotension
  - Cardiac disease
- Shortness of breath (wearing off vs pulmonary disease)
- Palpitations (wearing off vs cardiac disease)
- Gait Impairment/Imbalance (PD vs neuropathy vs arthritis)
- Discoordination (PD vs arthritis)

Specific Diseases

- Coronary Artery Disease
- Hypertension
- Arthritis
- Prostatic hypertrophy (enlarged prostate)
- Neuropathy

Coronary Artery Disease

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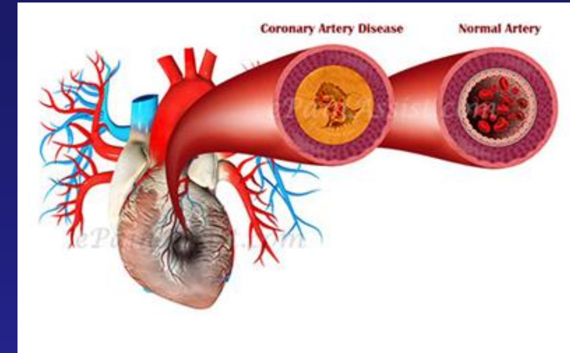
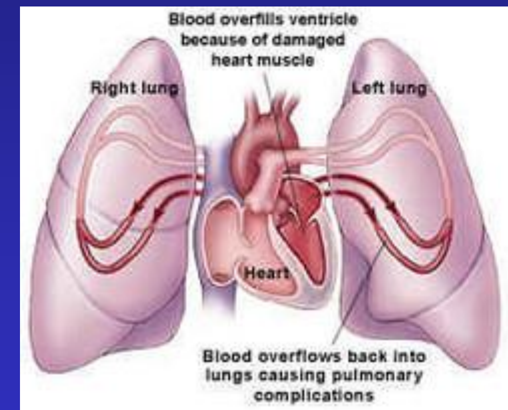
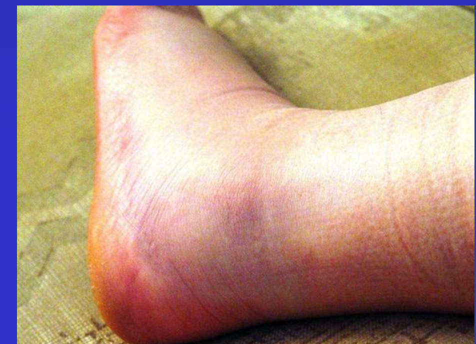
- Disease of the heart where arteries supplying the heart become hardened and narrowed due to plaque
- May cause chest pain or a heart attack.
- Symptoms include
  - Chest pain
  - Shortness of breath
  - Palpitations: irregular or fast heart rate
  - Weakness/fatigue
  - Heart failure with fluid in the lungs
  - Leg edema (swelling)







Coronary Artery Disease: Symptom Overlap

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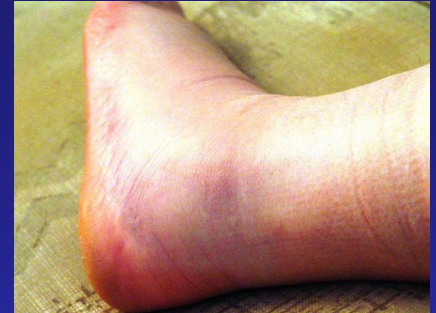
- Reduced exercise tolerance
- Fatigue
- Gait impairment
  - Leg edema may add 10 pounds to each foot; like wearing ankle weights
  - Treat with diuretics, elevate legs when sitting, compression stockings
- Shortness of breath
  - May be a “wearing-off” phenomenon
- Palpitations
  - Rarely may be a “wearing-off” phenomenon



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Coronary Artery Disease: Lifestyle

- Healthy diet low in cholesterol
- Regular exercise
- Maintain ideal body weight (BMI 20-25)
- Quit smoking
- Manage blood pressure

Coronary Artery Disease: Medication Issues

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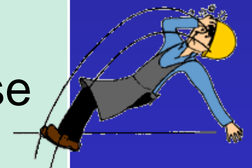
Medication	Use in CAD	Effect in PD
Beta Blockers	Decrease work of heart, benefit after heart attack	Lowers blood pressure, reduces exercise tolerance
Blood thinners (ASA, warfarin, thrombin inhibitors)	Reduces tendency of blood to form clots	Increases risk of bleeding
Diuretics	Treats fluid in lungs and leg edema	Lowers blood pressure, may cause dehydration
Angiotension-Converting Enzyme Inhibitors	Decreases BP and may prevent progression of CAD	Lowers blood pressure
Cholesterol-lowering medications	Lowers cholesterol which would deposit in arteries	May cause muscle pain/soreness and confusion



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Hypertension

- People with PD often develop low blood pressure and “orthostatic hypotension”
- Orthostatic hypotension: a drop in blood pressure when standing; may cause fainting
- As PD advances, people with hypertension usually need less or no medications for blood pressure
- Important to monitor BP
- Facilitate communication with internists and cardiologists

Arthritis

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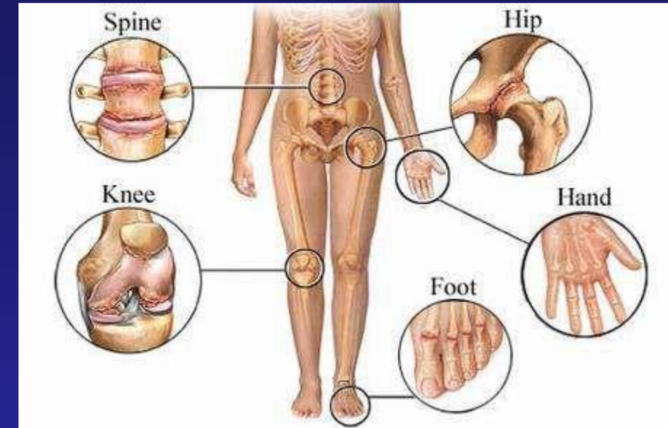
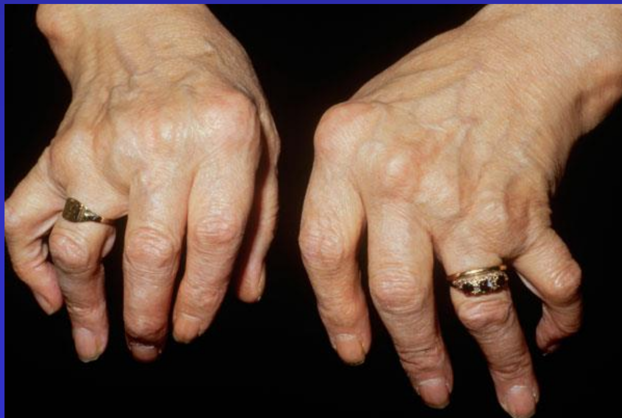
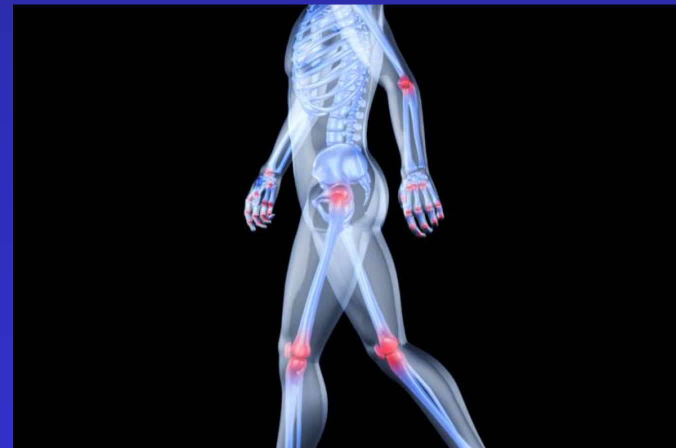


- **Arthritis – Painful inflammation and stiffness of the joints**

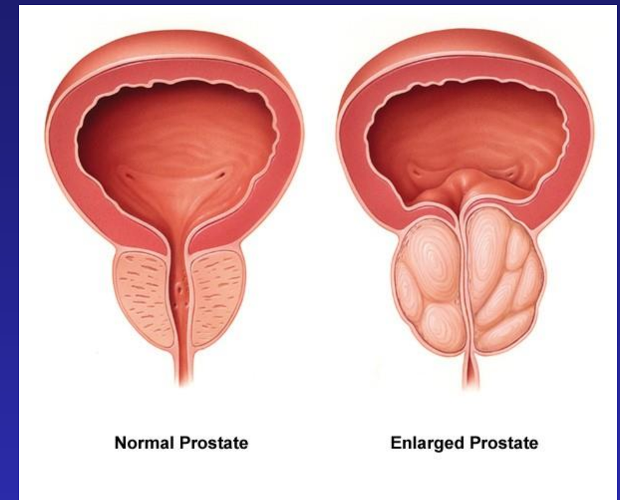
- **Impaired hand/finger dexterity**
- **Painful gait**

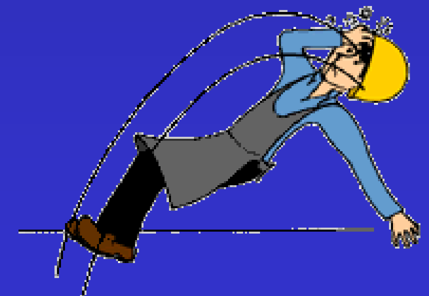




Prostatic Hypertrophy

- Prostate gland in men is underneath bladder
- When it enlarges it can block urinary flow
- Symptoms include frequent urination (> 8x/day), excessive urination at night, sense of incomplete emptying, urgency, leaking, weak urinary stream, increased risk of urinary infections
- People with PD have bladder spasms (contractions of the detrusor muscle) which can cause incontinence as well
- Men with PD and prostatic hypertrophy (and women with incontinence) often purposefully dehydrate themselves to avoid incontinence. This can lead to low blood pressure and fainting.





Peripheral Neuropathy

- Balance is dependent on sensory information from the vestibular system, vision and sensory structures in the skin and muscle
- People with PD have difficulty adapting to these deficits (Jeka et al 2016)
- Neuropathy can cause a loss of sensation in the feet; this leads to imbalance.
- People with sensory neuropathy walk with a widened stance and stagger.
- Combined with gait impairment due to PD, the balance is much worse
- Rely on physical therapy and assistive devices

Agents Used in the Treatment of Parkinson's Disease

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- **Levodopa Preparations**
  - Carbidopa/levodopa
  - Rytary®
  - Duopa®

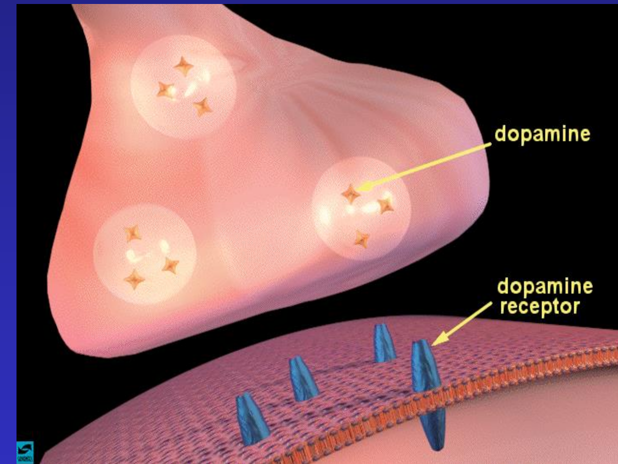
- **Helper Medications**
  - Dopa decarboxylase inhibitors
    - Carbidopa
    - Benserazide
  - COMT inhibitors
    - Entacapone
    - Tolcapone
  - MAOb inhibitors
    - Selegiline
    - Rasagaline*

- **Dopamine Agonists**
  - Ropinirole
  - Pramipexole
  - Rotigotine
  - Apomorphine

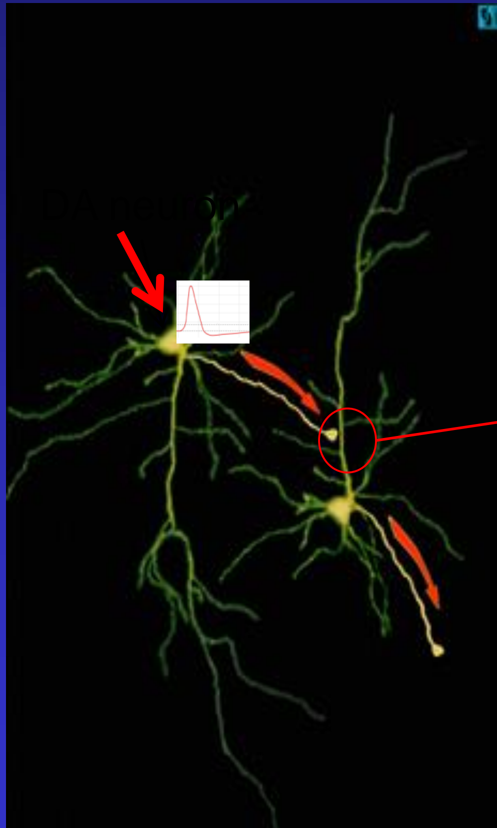
- **Anticholinergics**
  - Trihexyphenidyl
  - Benztropine
- **NMDA receptor antagonists**
  - Amantadine

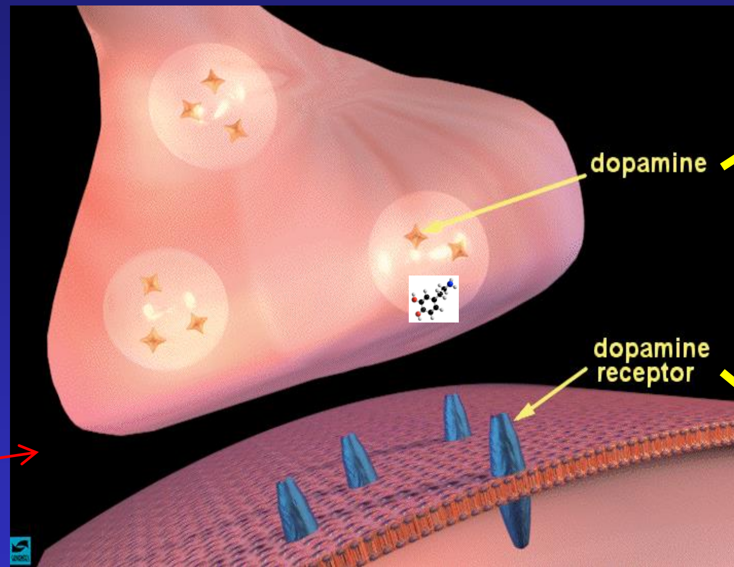
Medication Interactions

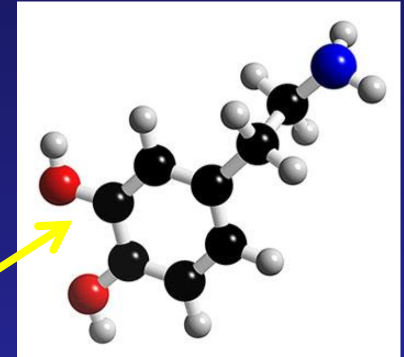
- Dopamine blocking agents induce PD symptoms
  - Antipsychotic medications (except pimavanserin (Nuplazid®))
  - Anti-emetic medications: metoclopramide (Reglan®), Prochorperazine (Compazine®)
- MAO inhibitors – Potentially Serious Interactions
  - MAOb inhibitors
    - Selegiline, rasagaline
  - MAOa inhibitors
    - Contra-indicated with MAOb inhibitors and also should not be used with carbidopa/levodopa as there is risk of hypertensive episode

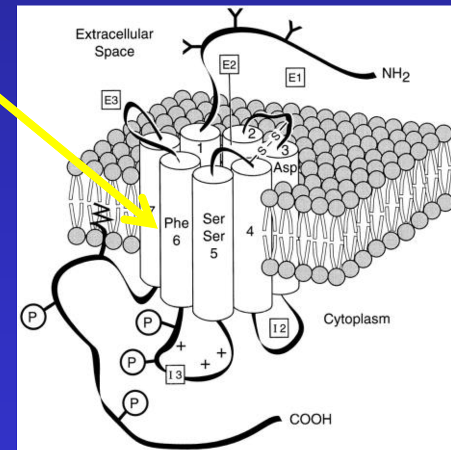


Dopamine: A Neurotransmitter









Neurotransmitter: A chemical which transmits a signal from one neuron to another.

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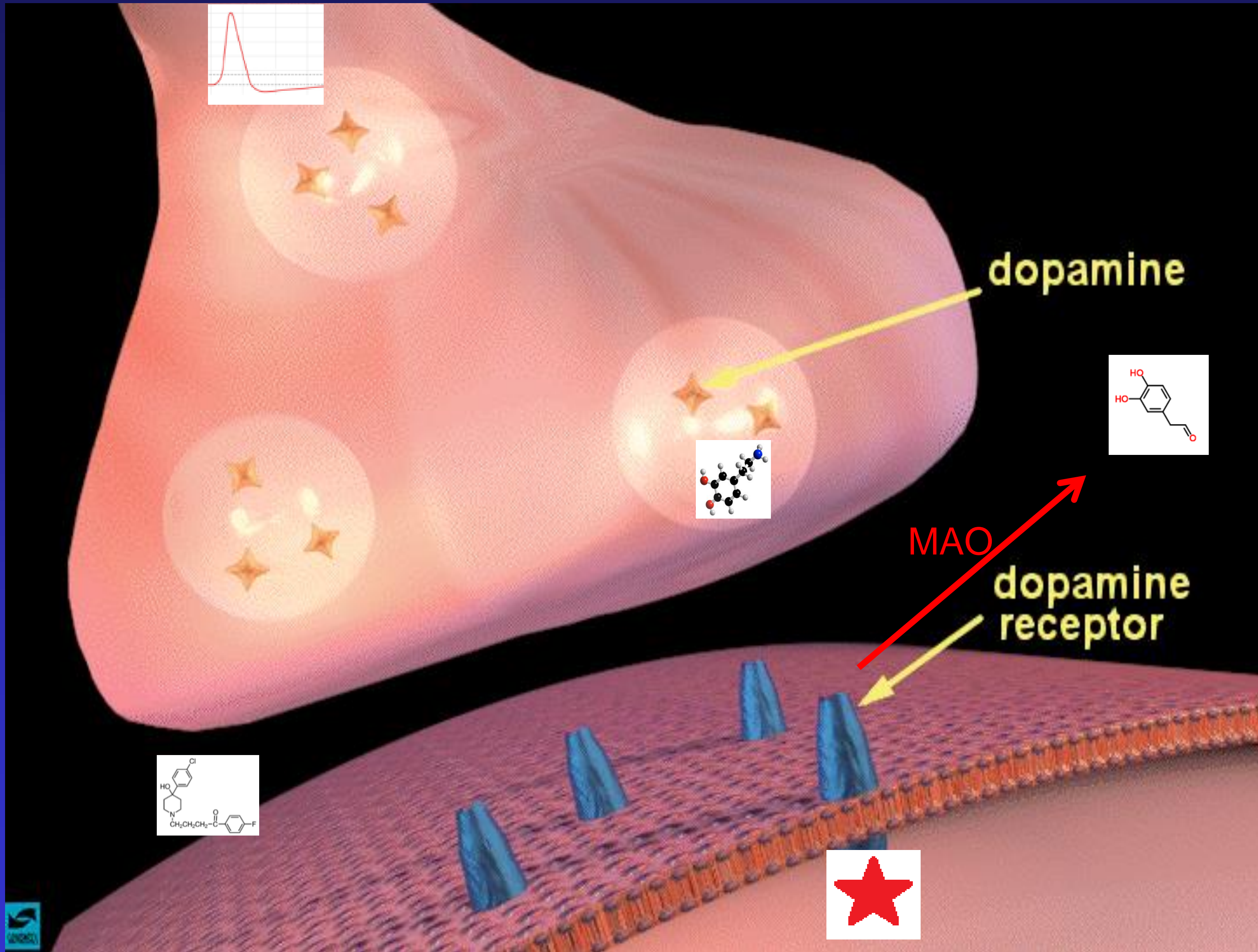
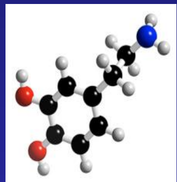
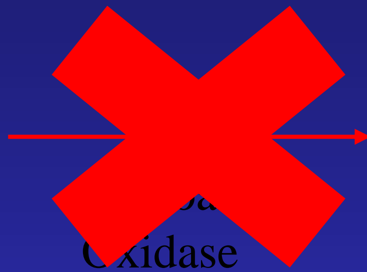
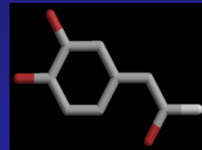


MAOb Inhibitors Make Dopamine Last Longer by Blocking an Enzyme Which Breaks it Down



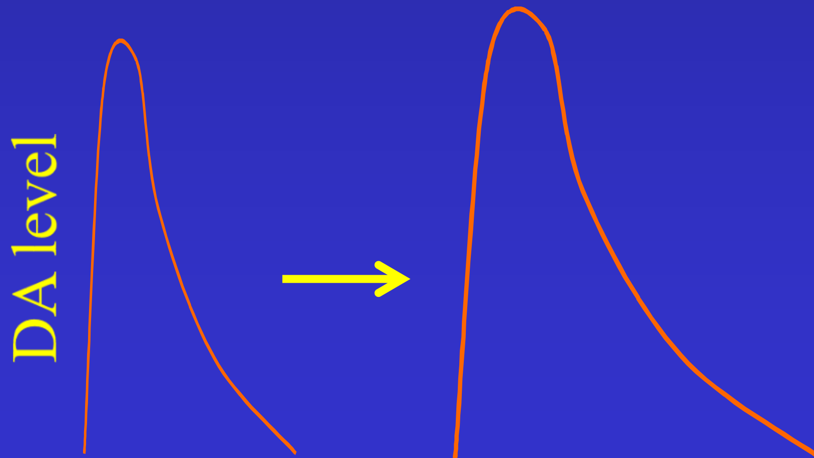
DOPAMINE





Dihydroxy-
phenylacet-
aldehyde

MAOb inhibitors block monoamine oxidase



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MAOb Inhibitors: Medication Interactions

- Serotonin Syndrome: neuromuscular hyper-excitability, confusion, fever; may be life-threatening. Due to excess serotonin in the brain.
- Use of MAO inhibitors and antidepressant medications can cause “Serotonin Syndrome” but risk with MAOb inhibitors (rasagiline, selegiline) is very low and no reports of it
- Serotonin syndrome occurs as an interaction of MAOb inhibitors with opioid analgesics such as **dextropropoxyphene** avoid)
- Recommend to stop M case opiates are used
- Use with sympathomi result in severe hypert
- Reports of psychosis
- Avoid muscle relaxant
- Don’t use other MAO inhibitors (including St. John’s wort)
- Ok to eat cheese (reasonable amounts)

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product; with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.

day while using this product.
Allergy alert: acetaminophen may cause severe skin reactions. Symptoms may include: skin reddening; blisters; rash. If a skin reaction occurs, stop use and seek medical help right away.
Sore throat warning: If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly.
Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product; with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.
Ask a doctor before use if you have: liver disease; heart disease; high blood pressure; thyroid disease; diabetes; trouble urinating due to an enlarged prostate gland; cough that occurs with too much phlegm (mucus); a breathing problem or chronic cough that lasts or as occurs with smoking, asthma, chronic bronchitis, or emphysema.
Ask a doctor or pharmacist before use if you are: taking the blood thinning drug warfarin; taking any other oral nasal decongestant or stimulant; taking any other pain reliever/fever reducer.

SEVERE
Multi-Symptom
Cough Cold + Flu
CF MAX
ACETAMINOPHEN (Pain Reliever/Fever Reducer)
DEXTROMETHORPHAN HBr (Cough Suppressant)
GUAIFENESIN (Expectorant)
PHENYLEPHRINE HCl (Nasal Decongestant)
4 FL OZ (118 ml)

cup with product. ml = milliliter. This adult product is not intended for children under 12 years of age. Adults and children 12 years and over: every 4 hours; Children under 12 years: do not use.
Other information: each 20 ml contains: sodium 14 mg. Store at 20-25°C (68-77°F).
Inactive ingredients: anhydrous citric acid, edetate disodium, FD&C red no. 40, glycerin, menthol, natural & artificial flavors, polyethylene glycol, propyl gallate, propylene glycol, purified water, sodium benzoate, sodium citrate, sorbitol solution, sucralose, triacetin, xanthan gum
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Ensure Integrated Care: A Team Approach

Reasons an Integrated Approach is Needed

- Broad range of motor and non-motor symptoms
- Symptoms and rate of progression vary among individuals
- Progressive diseases require continuous adaptations to new problems
- Most people have more than one disease

Issues in Facilitating Integrated Approach

- Which disciplines should be involved?
- How team members collaborate/communicate
- Specialists should operate in parallel rather than in isolation

Potential Team Members

- Physicians – Internists, other specialists, psychiatrists
- Allied Healthcare – Physical therapists, occupational therapists, speech therapists, psychologists, dieticians, social workers
- Patients, family members, caregivers, friends
- Others – Exercise trainers, home safety contractors

Van der Marck 2014

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Team Approaches Being Studied

- **Multidisciplinary Care – each discipline responsible for a specific need**
- **Interdisciplinary care – team members work collaboratively with face-to-face meetings and make group decisions**
- **Integrative care – synergistically charged plan of care with consensus building**

Ain’t gonna happen!

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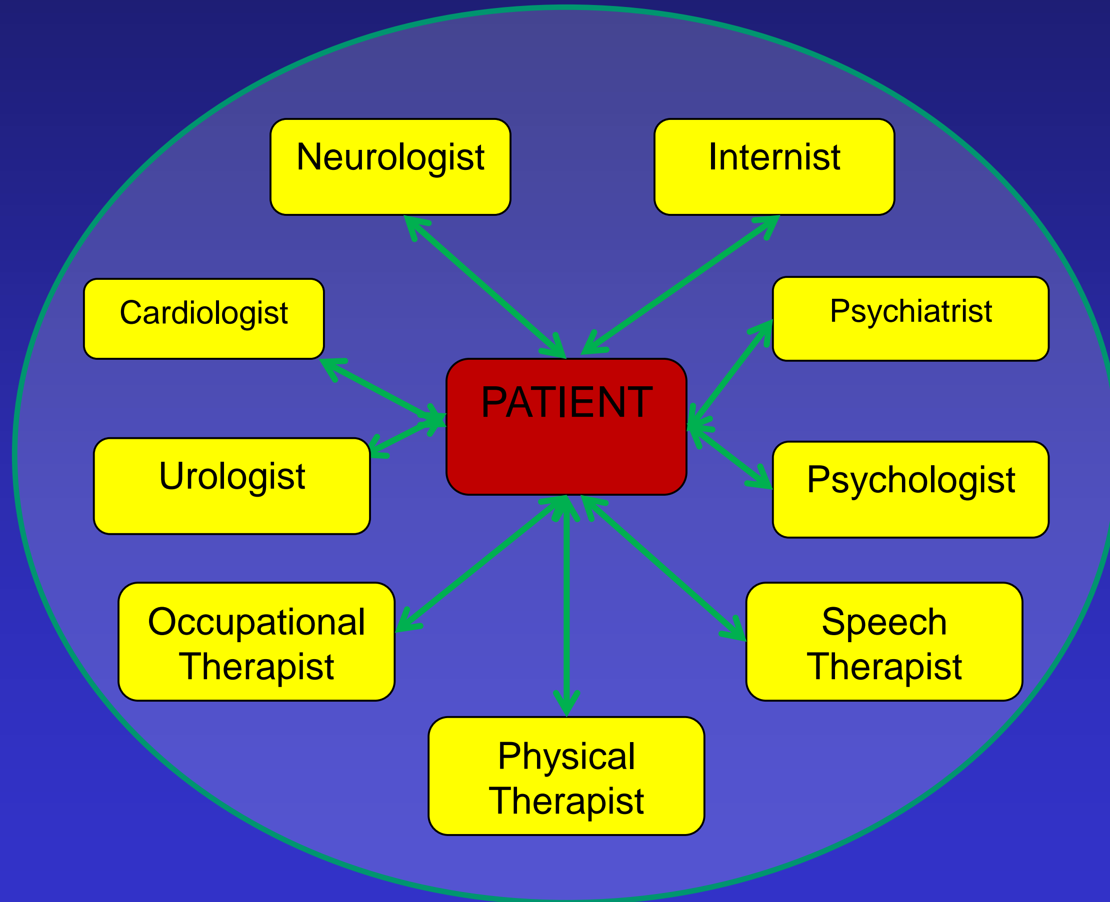
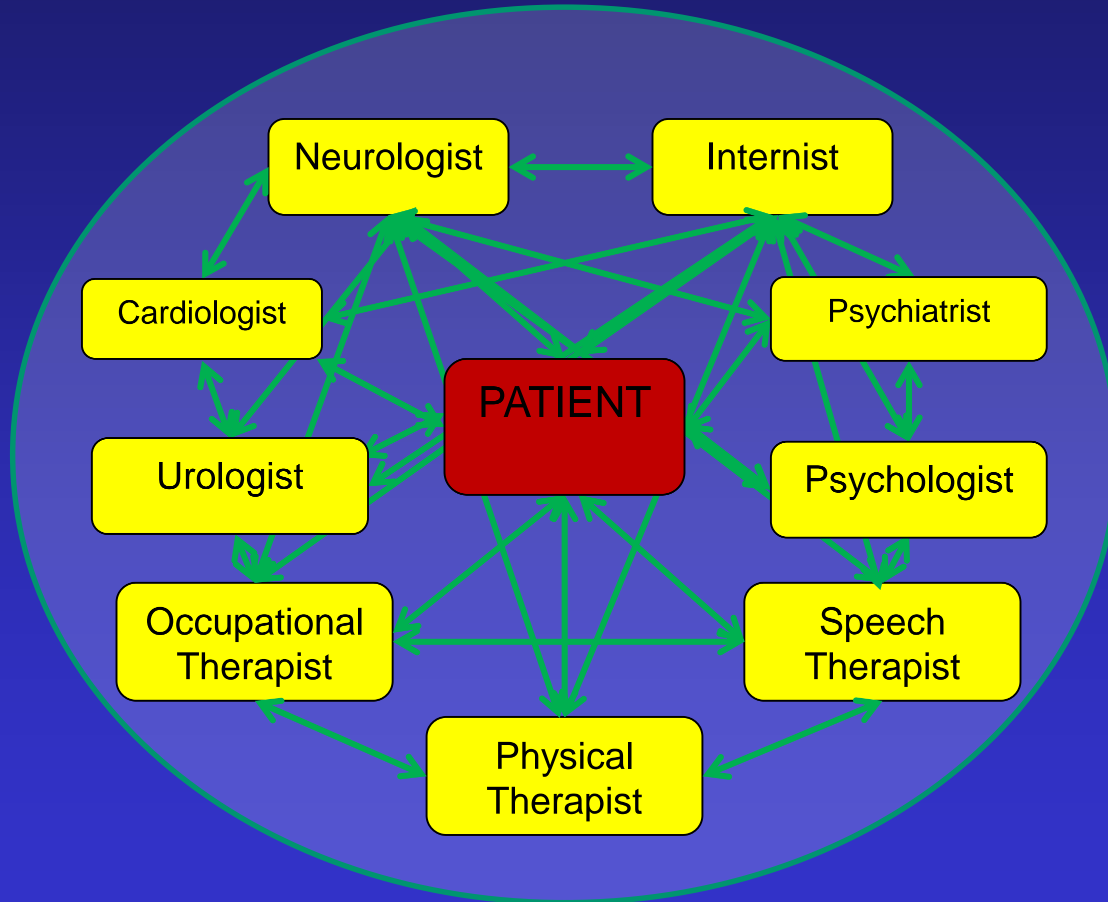
Multi-Disciplinary Care



RQPCTRS01
NEW2/6/02

Inter-Disciplinary Care



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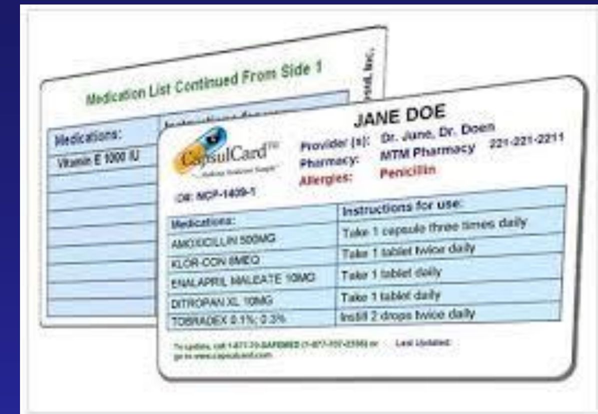
What can you do?



- Bring a medication list to each visit of all of your physicians
- Bring a contact list of all of your physicians
- Remind physicians and therapists to send notes to each other
- When hospitalized, arrange to have hospital records sent to your physicians
- Bring a list of discussion topics to your visits