

# Pharmacology in MS

## Advanced Practice Management



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# Objectives

- Discuss basic principles of pharmacology, pharmacokinetics and pharmacodynamics.
- Describe the pharmacotherapeutics of drugs used in MS
- Identify the role of advanced practice nurse in MS pharmacological management.

# Advanced Practice Pharmacology Background

- Pharmacology: study of a drug's effects within a living system
- Each drug is identified by 3 names: chemical, generic, trade or marketing name
  - N-4-(hydroxyphenyl) acetamide; acetaminophen; Tylenol**
  - sodium hypochlorite; bleach; Clorox**
  - 4-(diethylamino)-2-butynyl ester hydrochloride; oxybutynin chloride; Ditropan**
- Drugs are derived from: plants, humans, animals, minerals, and chemical substances
- Drugs are classified by clinical indication or body system

# APN Role

## Safe drug administration

**Nurses are professionally, legally, morally, and personally responsible for every dose of medication they prescribe or administer**

Know the usual dose

Know usual route of administration

Know significant side effects

Know major drug interactions

Know major contraindication

Use the nursing process

# Pregnancy Safety

- Teratogenicity: ability to produce an abnormality in the fetus (thalidomide)
- Mutagenicity: ability to produce a genetic mutation (diethylstilbestrol, methotrexate)

# Pregnancy Safety Categories

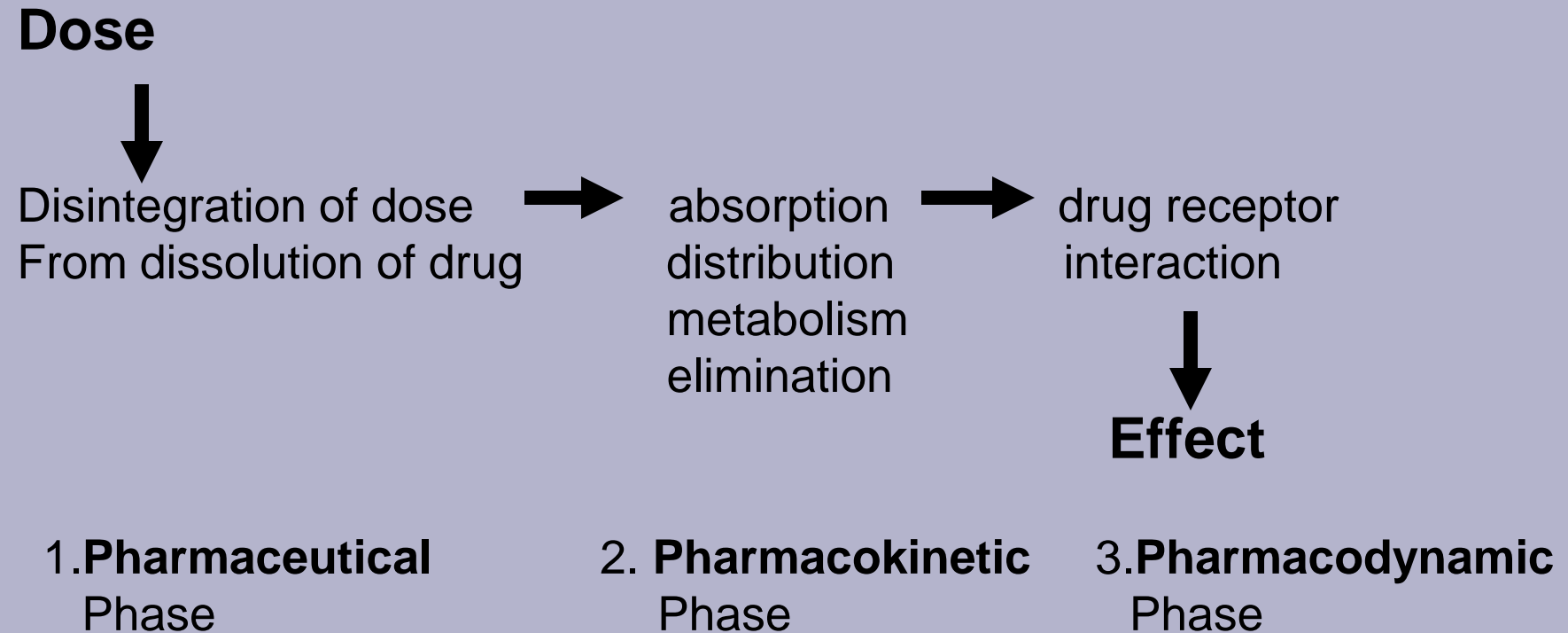
- **A:** studies indicate no risk to the fetus  
(levothyroxan; low dose vitamins, insulin)
- **B:** studies indicate no risk to animal fetus; information in humans is not available  
(naproxen; acetaminophen; glatiramer acetate; macrolides; B lactams)
- **C:** adverse effects reported in animal fetus; information in humans not available  
(Inf-B; methylprednisolone; topiramate; fluoroquinolones)
- **D:** evidence of human fetal risk, but potential benefits may be acceptable despite risks  
(mitoxantrone; cladribine; cyclophosphamide; all ACE in 2<sup>nd</sup> and 3<sup>rd</sup> trimester; ARBs; lithium; streptomycin; tetracyclines; carbamazepine, valproic acid)
- **X:** fetal abnormalities reported and positive evidence of fetal risk in humans is available from animal and human studies  
(methotrexate; misoprostol; quinine)

# History: A summary of major drug discoveries

Opium tincture, coca, and ipecac	17 <sup>th</sup> century
Digitalis	1785
Smallpox vaccine	1796
Morphine	1815
Quinine, atropine, codeine	19 <sup>th</sup> century
Ether and chloroform	1840's
Insulin	1922
Phenytoin	1940's
Cortisone	Mid-1940's
Polio vaccines	1955 and 1961
Carbamazepine	1960
Oral contraceptives	Late 1950's
Antivirals	Mid-1970's
immunomodulators	1990's

# Phases Affecting Drug Activity

## Mechanisms of Drug Action





# Pharmacokinetics

1. Absorption : route, dose, dosage form, and bioavailability
  - cell membrane, blood flow, nature of the drug
2. Distribution via circulation
  - plasma protein binding: expressed as a degree, very high to very low with. **Binding site competition:** consequences for toxicity and drug interaction
  - tissue binding: fat (cumulative effect), bone
  - barriers (skin, placenta, BBB)

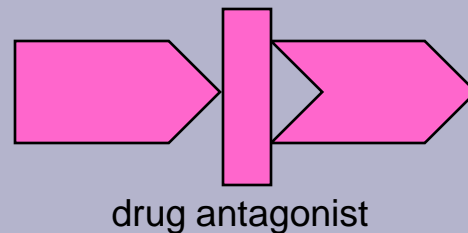
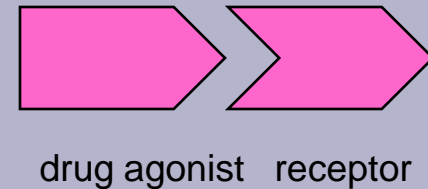
# Pharmacokinetics

1. Metabolism or biotransformation, primarily liver to increase water solubility
  - Delayed metabolism (excessive or prolonged response)
  - Stimulated metabolism (tolerance)
  - Hepatic first-pass-give > dose or parenterally
  - Biological half-life
2. Elimination: kidneys, lungs, intestines, sweat, salivary and mammary glands
  - Lipid soluble drugs are not excreted
  - Altering urine pH can encourage elimination

# Pharmacodynamics

- Drug action produce effect by:
  - drug **receptor interaction** (example: opioids)

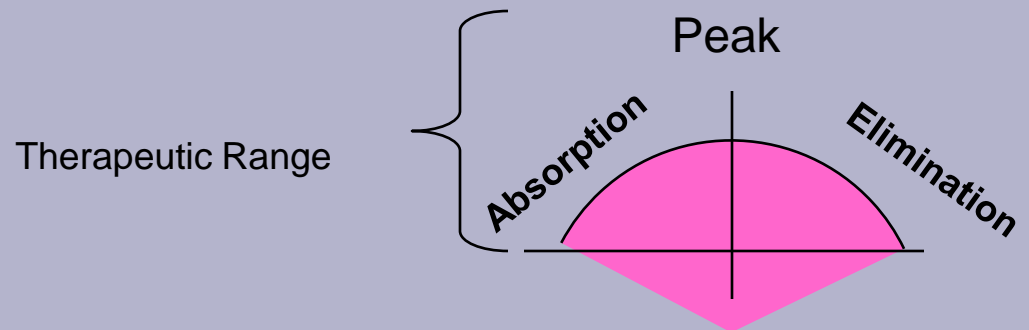
- Affinity: “lock and key”
- Agonist (morphine)
- Antagonist (naloxone)



- drug **enzyme interaction** (example: neostigmine)
- **nonspecific** drug interaction (example: general anesthetic; cathartics; ointments; detergents)

# Drug Response

- An enhanced or diminished effect of one drug when used with another
  - **Summation:**  $1+1=2$  (codeine + ASA)
  - **Synergism:**  $1+1=3$  (bupropion + fluoxetine)  
(propranolol + lisinopril)
  - **Potentiation:**  $0+1=2$  (caffeine + ibuprofen)  
(diazepam + codeine)
- Plasma level and therapeutic index
- Biologic  $\frac{1}{2}$  life



# Adverse Effects

*Any response to a drug which is unfavorable, and unintended, occurring at doses used for prophylaxis, diagnosis or therapy, or for the modification of physiological function*

- **Mechanism:** iatrogenic response, immune (allergic) response or local irritation
- **Causality**
- **Severity:** mild, moderate, severe

**APN role:** promote health, prevent illness, restore health, alleviate suffering with respect for individual's rights and dignity

**APN role:** educate re: side effects, management strategies, and when to report persistent or adverse effects; **understand risk/benefit**

# APN Role

## Take a Medication History

1. Name, dose, route, schedule
2. OTC and CAM use
3. Age, gender, race, height, weight
4. Medical condition for which drug is prescribed
5. Manual dexterity, mobility, literacy, sight and hearing
6. Adherence ???
7. Hx of allergies (food & drug), adverse drug effects
8. Psychosocial Hx.: tobacco, caffeine, alcohol, recreational drugs, sexual orientation and no. of partners, childbearing potential, & financial/educational status
9. Exposure to environmental & occupational substances

# Drugs Causing LFT Abnormalities

- Almost any drug but digitalis and prednisone
- Most common offenders: antibiotics (quinolones, nitrofurantoin, penicillins, azoles)
- Anti-epileptics
- NSAIDS
- Acetaminophen

# Abnormal LFT

- Repeat to confirm
- Order CPK enzyme test
- Assess alcohol history
- Assume medication-induced causes
- Normal AST <40

AST/ALT that is > 10x-15x nml in necrosis

AST/ALT usually <300 in alcoholic damage



# Liver Function Tests: Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Lactic Dehydrogenase, Albumin, Ammonia, Bilirubin, Prothrombin, Gamma-glutamyl Transferase

## Alanine Aminotransferase (AST, SGPT)

**Normal range:** men 10-40U/L; women 7-35U/L

**Significance:** Marker of hepatic injury; found primarily in liver; more specific indicator of liver damage than AST

**Factors that increase:** acute MI, pancreatitis, acute renal infarct, CHF, mono, liver dz., heparin, skeletal muscle dz.

**Factors that decrease:** not clinically significant

## Alkaline Phosphatase

**Normal range:** 25-100 U/L

**Significance:** Reflects bile formation and flow, non-specific measure of liver or bone disease

**Factors that increase:** Alcoholism, CHF, CMV, Fanconi's syndrome, healing, Hodgkin's, mono, liver dz, lung ca, Paget's dz, rickets, pregnancy, pulmonary and MI, sarcoid, sepsis, sickle cell, ulcerative colitis

**Factors that decrease:** anemia, celiac dz, hypothyroidism, malnutrition, sarcoma, vit D intoxication, zinc depletion

## Aspartate Aminotransferase (AST, SGOT)

**Normal range:** men 14-20 U/L; women 10-36U/L

**Significance:** non-specific marker of hepatic injury found in brain, cardiac, skeletal, kidney, liver.

**Factors that increase:** Acute MI, acute renal infarct, acute pulmonary infarct, anemia, mono. Liver dz (hepatitis, alcoholism, drug toxicity), malignancies, skeletal muscle dz, tissue necrosis, 3<sup>rd</sup> degree burns, trauma, tylenol, ASA, heparin, INH, oral contraceptives

**Factors that decrease:** chronic dialysis, B6 deficiency

## Lactic Dehydrogenase (LDH)

**Normal range:** 118-273 IU/L men; 125-220 IU/L female

**Significance:** non-specific isoenzyme found in most tissue. Incr. indicated tissue damage.

**Factors that increase:** alcoholism, anemia, burns, cancer, CVA, CHF, DT's, hepatitis, mono, muscular dystrophy, myxedema, pain, pulmonary embolism, sickle cell, trauma, codeine, lithium, lorazepam

**Factors that decrease:** irradiation tx., oxalates, favorable response to cancer tx.

# Cytochrome P450

## Recognizing Interactions

- Major enzyme system for metabolizing a drug by using iron to oxidize
- Occurs mostly in liver or gut wall during absorption
- **Inducers** can decrease the therapeutic levels of substrates e.g., modafinil and CYP3A inducer carbamazepine
- **Inhibitors** can increase or potentiate a drug effect e.g, modafinil and CYP3A inhibitors, ketoconazole
- CYP classified in isoforms that are genetically derived: CYP3A (50%), CYP2D6 (30%), CYP1A2, 2C9/10, 2C19, 2E1 (10%)

<http://medicine.iupui.edu/flockhart/table.htm>

# Common CP3A Use in MS

## Substrates

alprazolam  
amitriptyline  
dexamethasone  
buspirone  
cannabinoids  
caffeine  
carbamazepine  
cyclophosphamide  
dexamethasone  
diazepam  
progesterone  
17  $\beta$  estradiol  
oxybutinin  
tolterodine  
trazadone  
sildenafil, tadalafil, verdenafil  
methylprednisilone  
clarithromycin  
Statins

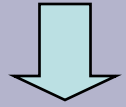
## Inhibitors

cimetidine  
ciprofloxacin  
clarithromycin  
cyclosporine  
danazol  
ethynyl estradiol  
fluconazole  
grapefruit



## Inducers

carbamazepine  
  
garlic supplements  
glucocorticosteroids  
modafinil  
oxcarbazepine  
phenobarbitol  
phenytoin  
St. John's Wort



Increase the potential  
for toxicity from substrate

decrease therapeutic  
level of substrate

# Pharmacogenomics

- Personalized drug therapy based on genes- AmpliChip- ID slow and fast metabolizers so dosages can be adjusted
- May explain some “idiosyncratic” reactions
- Can learn a lot by a good family drug history
- 7-15% caucasians (4-18% Middle Eastern Jews) poorly metabolize **CYP2D6** –either rapid or slow (antidepressants, beta blockers, antiarrhythmics, antipsychotics, narcotics, dextromethorphan)
- 25% of Asians slowly metabolize **CYP2C19** (clomipramine, diazepam, imipramine, omeprazole, propranolol)

# APN Role

- Learn about the specific drugs that are most likely to elicit a varied response in people from different ethnic groups, as well as potential for adverse effects.
- Conduct a cultural assessment on each patient
- Ask specific questions about adverse effects and side effects associated with drug history
- Monitor, document, identify slow and fast metabolizers and adjust dosages per individual patient
- Keep cultural context in mind when planning education for families and patients
- Check your cultural competence and measure attitudes at <http://implicit.harvard.edu/implicit/demo/index.jsp>

# Glucocorticoids

**Indication:** acute exacerbation (no evidence for long term benefit); speeds recovery; use in functional deficits of visual, motor, cerebellar system

**Mechanism of action:** decrease CNS inflammation; close BBB

**Side effects:** hypertension; diabetes; cataracts; ulcers; mood changes high & low and mania; difficulty sleeping; fluid retention; restlessness; joint pain (hip); stomach ulcers, weight gain, acne, osteoporosis (thinning of the bones).

Pregnancy Cat. C; secreted in breast milk

# Pharmaceutical Management of MS Acute Exacerbations

## Glucocorticoids

naturally occurring hormones

- IM **adrenocorticotrophic hormone** (ACTH®)  
80-100 U/d for 2-3wks

administered as synthetic prep

- IV **methylprednisolone** (Solu-medrol®)  
1G QD 3-5 days
- IV **dexamethasone** (Decadron®) 160-  
180mg/d 3-5d (contains sulfites)
- PO **prednisone**, taper: 60mg QD, 7 d; 60mg  
qod, 8d; 40mg qod, 8d; 20mg qod, 8d

# Immunosuppressive Agents/ Antineoplastic Agents

azathioprine (Immuran®) PO 2.5-3.0mg/kg/d

cyclophosphamide (Cytoxan®) IV, adjust dose to  
leukocyte count,  $1\text{g}/\text{m}^2$

methotrexate (Folex®) PO 7.5mg/wk

mitoxantrone (Novantrone®) IV  $12\text{mg}/\text{m}^2$  q 3mos for  
up to 2yrs; lifetime dose  $140\text{mg}/\text{m}^2$

**Indication:** progressing MS

**Mechanism of action:** interfere with cell  
reproduction; suppress T & B cell production

Pregnancy Category D & X



**azathioprine** (Immunan®) PO 2.5-3.0mg/kg/d

**Side effects:** anorexia, nausea, vomiting, leukopenia

**Interactions:** 1) steroid conserving effect, allopurinol, live vaccines

**cyclophosphamide** (Cytosan®) IV, adjust dose to leukocyte count,  
1g/m<sup>2</sup>

**Side effects:** bone marrow suppression; hemorrhagic cystitis

**Interactions:** cocaine toxicity, probenecid

**methotrexate** (Folex®) PO 7.5mg/wk

**Side effects:** bone marrow suppression, diarrhea, stomatitis

**Interactions:** alcohol or hepatotoxic drugs, acyclovir injection, NSAIDS,  
probenecid or salicylates, live vaccine

**mitoxantrone** (Novantrone®) IV 12mg/m<sup>2</sup> q 3mos for up to 2yrs

**Side effects:** cardiotoxicity, severe myelosuppression

**Interactions:** live vaccine, probenecid & sulfapyrazone, antithyroid agents,  
ganciclovir, AZT, azathioprine,

# Drugs Affecting Fatigue

## CNS Stimulants

- modafinil (Provigil®) PO 200mg/d
- pemoline (Cylert®) PO 37.75mg/d titrated by 18.75 to 112.5mg/d
- methylphenidate (Ritalin®) PO 5-20mg/bid or tid
- dextroamphetamine (Dexadrine®) PO 5-60mg/tid
- Caffeine PO 100-200mg q4h max 1000mg/d; metabolizes to theophylline (60-180mg in a 5oz cup; Starbuck's tall drip 12oz=240mg; solo espresso=89mg)

**Indications:** narcolepsy and fatigue in MS

**Mechanism of Action:** stimulate cerebral cortex; antagonizes adenosine receptors; block reuptake of dopamine

**Pregnancy Category C & B (pemoline)**

**May produce psychological and physical dependence/tolerance**

- **methylphenidate**

**Side effects:** heart arrhythmia, HTN, loss of appetite, nervousness, trouble sleeping; decreases convulsive threshold

**Interactions:** other CNS stimulants, MAO's, pimozide (Tourette's), antidepressants, guanethidine, cold & sinus & allergy meds, caffeine, appetite suppressant, bupropion, clonidine, asthma meds, cocaine

- **dextroamphetamine**

**Side effects:** irritability, restlessness, trouble sleeping, dry mouth, fast, pounding or irregular heartbeat

**Interactions:** tricyclic antidepressants, beta blockers, CNS stimulants, amantadine, digitalis, MAO inhibitors, thyroid hormones, meperidine, cold, sinus & allergy meds, caffeine, asthma meds, cocaine

- **caffeine**

**Side effects:** heart arrhythmias, incr. nervousness, GI irritation, withdrawal = irritability, headache, incr wkness

**Interactions:** CNS stimulants, MAO inhibitors

- **modafinil**

**Side effects:** dizziness, unclear thinking, blurred vision, **anxiety, insomnia, nausea, headache, nervousness**

**Interactions:** Same as for other CNS stimulants PLUS cyclosporine, diazepam, phenytoin, propranolol, theophylline, warfarin, tricyclic antidepressants, steroid contraceptives

- **pemoline** (beneficial effect at 3-4 wks)

**Side effects:** Most common: anorexia, insomnia, weight loss; Less common: dizziness, daytime sedation, irritability, depression, nausea, rash abdominal pain. Rare: jaundice

**Interactions:** no significant drug interactions but r/o liver dz.; caffeine

Chewable form of pemoline **MUST** be chewed before swallowing

Associated with life threatening hepatic failure

Two FDA black box warnings (1996/1999)

LFT's at baseline and q 2wks throughout therapy.

Written informed consent required

# Drugs Affecting Fatigue

- **amantadine** (antiviral;dopamine agonist) 100mg tid PO

**Action:** releases dopamine

**Side effects:** livedo reticularis, edema, anxiety, sleepiness, hallucinations

- **4-aminopyridine and 2,3-aminopyridine**  
30-40mg/d PO

**Action:** K<sup>+</sup> channel blocker-not FDA approved

**Side Effects:** seizures, confusion, nausea, hepatitis, dizziness, paresthesias, insomnia

- **SSRI antidepressants** (negligible effect in clinical trials)

**Action:** increase serotonin

**Side effects:** agitation, insomnia, sexual dysfunction (anorgasmia), weight gain, dizziness, headache, nausea, loose stools, sleepiness, initial anorexia, tremor, weight loss then weight gain, nervousness

# Drugs Affecting Depression

- **Selective serotonin reuptake Inhibitors**

- fluoxetine (Prozac®, Sarafem®) PO 20-80mg/10-20mg
- paroxetine (Paxil® and CR) PO 20-50mg/25-62.5
- sertraline (Zoloft ®) PO 100-200mg
- citalopram (Celexa ®) PO 20-60mg
- escitalopam (Lexapro ®) PO 10-20mg
- fluvoxamine (Luvox ®) 100-300mg

**Indications:** mild to moderate depression, OCD, panic disorder, PMS, PTSD, anxiety, bulimia, pain, enuresis, stress incontinence, fatigue

**Mechanism of action:** Neurotransmitter effect, cell membrane stability

**Side Effects:** nausea, insomnia, nervousness, headache

**Pregnancy Category:** **B** (bupropion, fluoxetine, sertraline); **C** (all others); **D** lithium

- **Norepinephrine and Serotonin Reuptake Inhibitors**

- venlafaxine (Effexor ®, XR) PO 50-375mg; 75-225mg
- duloxetine (Cymbalta ®) PO 40-60mg

**Side Effects: same as SSRI, wt. loss, raises diastolic, > somnolence**

- **Tricyclics**

- amitriptyline (Elevil ®) PO 100-300mg
- desipramine (Norpramin ®) PO 100-300mg
- imipramine (Tofranil ®) PO 100-300
- nortriptyline (Pamelor ®) PO 50-150
- doxepin (Sinequan ®, Adapin ®) PO 100-300mg

**Side effects:** Anticholinergic, sedation, insomnia, agitation, orthostatic hypotension, cardiac arrhythmia with TCA, GI distress, weight gain, sexual dysfunction

**All the above: caution in hepatic impairment**

- **Dopaminergic reuptake blocking agents (also serotonin & 5HT)**

- bupropion (Wellbutrin ® and XL) PO 75-100mg / 150-300mg XL

**Side effects:** agitation, rarely seizures, low incidence of sexual dysfunction or orthostatic hypotension, little sedation, anticholinergic

**Contraindications:** (antipsychotics and MAOI's)

thioridazine (Mellaril ®) and pimozide (orap ®)

duloxetine contraindicated in uncontrolled narrow angle glaucoma

bupropion contraindicated in seizure risk

TCA's and antithyroid drugs

**Potentially fatal interactions:** antiarrhythmics (c TCA) and MAOI's

**CTP2D6 inhibition:** *Potent:* fluoxetine, paroxetine;

*Moderate:* bupropion, citalopram, escitalopram, sertraline;

*Little or none:* venlafaxine, duloxetine, TCA's except desipramine may inhibit

flvoxamine potent inhibitor CYP 1A3, CYP 2C19, CYP3A4



## **Mood stabilizing drugs**

lithium carbonate (Eskalith®, Lithobid JDS®)

**Interactions:** diuretics, NSAIDS, ACE, ARBS, haloperidol, carbamazepine, calcium channel blocks, azoles, fluoxetine, antithyroid drugs

**Action:** corrects overactive catecholamine state by inhibit of synapse release

**Side effects:** hand tremor, thirst, incr urination, diarrhea, nausea, weight gain

**Toxic:** blurred vision, confusion, dizziness  
divalproex sodium (Depakote®)  
carbamazepine (Tegretol®)

# Pseudobulbar Affect

- TCA's
- SSRI's
- dextromethorphan and quinidine (AVP-923)
- **Indications:** uninhibited brain stem response to emotional stimuli secondary to disruption of cortico-ponto-cerebellar pathways; pain
- **Action:** quinidine inhibits the metabolism of dextromethorphan allowing more to roam in CNS and acting on NMDA receptors to decrease glutaminergic signaling
- Side effects: headache, dizziness, spasticity
- May increase serotonin

# Drugs Affecting the Urinary Tract

## Urinary antimicrobials

- **Sulfonamide:** sulfamethoxazole and trimethoprim, DS (Septra ®, Bactrim ®) Side effects: anorexia, diarrhea, nausea, vomiting, rash, pruritus, headaches, dizziness
- **Cephaloporphins:** cefixime (Suprex®), cefpodoxime (Vantin®) 3<sup>rd</sup> generation safest in pregnancy for UTI
- **Quinolones:** ciprofloxacin, XR (Cipro ®), levofloxacin (Leviquin®), ofloxacin (Floxin®), trovafloxacin (Trovan®), norfloxacin (Noroxin®), Gatifloxacin (Tequin®), gemifloxacin (Factive®), moxifloxacin (Avelox®)

**Side effects:** dizzy, drowsy, photosensitivity, rash, GI upset, headache, diarrhea, pruritis, candidiasis

# Drugs Affecting Urinary Tract

## Urinary antiseptics

- methenamine (Hiprex ®, Mandelamine®)-must have an acidic urine (pH<5.5)
- Do not use c drugs that alkalize urine e.g., antacids-serious interaction with certain sulfonamides (sulfamethizole, Thiosulfil Forte®)
- nitrofurantoin (Macrobid ® or Macrochantin ®)-take c food
- Side effects: drowsiness, nausea, vomiting, rash, headache, pruritus, “brownish” urine

## Urinary analgesics

Phenazopyridine (Pyridium®)

Analgesic and anesthetic effect on urinary mucosa

Used for pain and burning on urination

Side effects: GI distress, red urine may stain clothing

# Drugs Affecting Bladder

**Indications:** neurogenic bladder; urgency, frequency, incontinence; detruser muscle hyperreflexia

**Action:** anti-muscarinic/anticholinergic (block muscarinic effects of acetylcholine) receptor specific; antispasmodic

**Side effects:** dry skin, eyes & mucous membranes; constipation or diarrhea; nausea; tachycardia; blurred vision; somnolence; headache  
**Caution:** narrow angle glaucoma

- oxybutynin (Ditropan, XL®) PO 5mg qid/5-30mg QD
- oxybutynin patch (Oxytrol®) 3.9mg/d twice wkly (low incidence SE)
- tolterodine (Detrol®, LA) PO 1-2mg bid; 2-4mg QD (LA best SE profile)
- darifenacin (Enablex®) PO 7.5-15mg QD
- solifenacin (Vesicare®) PO 5-10mg QD
- trospium (Sanctura®) PO 20mg bid-not metabolized; take on empty stomach; best SE profile

Preganancy Category B (oxybutynin®); C all others

## **Anticholinergic/antispasmodics continued:**

- hycoscyamine Sulfate (Levsin<sup>®</sup>, Levsinex/timed release<sup>®</sup>)  
PO 0.125-0.25mg qid ac/0.375-0.75mg bid
- propantheline bromide (Pro-Banthine<sup>®</sup>) PO 15mg tid
- baclofen (Lioresol<sup>®</sup>) PO 5-80mg

## **Antidepressant TCA:** (for anticholinergic effects)

- imipramine (Tofranil<sup>®</sup>) PO 25-125mg HS

**Pregnancy Category: C**

## **Indication:** Nocturia

- desmopressin (DDAVP<sup>®</sup>/vasopressin<sup>®</sup>) PO 0.1-0.2mg;  
nasal spray 10micrograms/0.1ml/rhinal tube spray to 40ug

**Pregnancy Category B**

**Side effects:** rhinitis, nasal congestion, abdominal cramps,  
hyponatremia

# Urinary Hesitancy and Retention

– bethanecol (Urecholine®) PO 10-50mg qid

**Action:** cholinergic, stimulates parasympathetic, muscarinic with selective action on detrusor and bowel smooth muscle. “SLUD”

**Side effects:** bradycardia, hypotension, sweating, salivation, vomiting, diarrhea, intestinal cramps

– tamsulosin (Flomax®) PO 0.4-0.8mg 1/2h after meal

– terazosin (Hytrin®) PO 1-5mg HS

**Action:** alpha adenergetic blockers: decr peripheral vascular resistance; bladder wall receptors

**Side effects:** hypotension, syncope, dizziness, somnolence, shortness of breath, stuffy nose, peripheral edema; **caution** with other alpha blocks, cimetidine, warfarin, other antihypertensives

**Pregnancy Category C** all but tamsulosin: B

# Drugs Affecting Bowel

## **Fecal urgency or incontinence**

- imipramine (Tofranil®)
- propantheline (Pro-Banthine®)
- antidiarrheals (bulk forming; opioids, anticholinergics; antimicrobials)

## **Agents for constipation**

1. Diet & lifestyle: fluids, fruit & vegetables, exercise
2. Emollients: docusate (colace®)
3. Fiber and bulk producing agents: psyllium hydrophillic mucilloid (Metamucil®, Konsyl®); methylcellulose (Citrucel®)
4. Intestinal lubricants: mineral oil (decr vit K to fetus)
5. Hyperosmotic agents: MOM; Glycerin suppository; lactulose (Miralax®, Kristalose®); polyethylene glycol (Glycolax®, GoLytely®, Colyte®, NuLytley®)-caution in diabetes
6. Saline laxatives: sodium biphosphate (Fleet enema®)
7. Stimulants: peri-colace Bisacodyl®; senokot; castor oil; cascara (Sagrada®); tegaserod (Zelnorm®)5HT receptor antagonist- PO 2-6mg bid (diarrhea, abd. cramps)

**Pregnancy: unlabeled or B/C**



# Drugs Affecting Bowel

- **Side effects:** flatulence, cramping, belching, gas; excessive doses may cause diarrhea and nausea
- Decrease the effect of: antibiotics especially tetracycline, anticoagulants, digitalis, fat soluble vitamins, oral contraceptives and salicylates
- Do not dose stimulant laxatives with antacids or dairy

# Drugs Affecting Sexuality

**Indication: erectile dysfunction**

**Action:** PDE-5 inhibitors increase concentration of NO allowing cGMP which mediates erectile response and enhanced blood flow to penis and clitoris-onset: 30min

- sildenafil citrate (Viagra®) PO 25-100mg (18h ½ life)
- tadalafil (Cialis®) PO 5-20mg
- vardenafil (Levitra®) PO 2.5-20mg

**Side effects:** sudden vision loss; hypotension, headache, facial flushing, GI, dyspepsia, nasal congestion, blue-green visual aura (sildenafil), tachycardia, priapism (erections > 4h risk damage)

**Contraindication:** nitrates, concomitant alpha blocker, ETOH

**Caution:** cardiovascular dz; recent MI, bleeding disorder, hepatic impairment

**Potent CYP3A inhibitors:** azoles, grapefruit juice, erythromycin, protease inhibitors

**Pregnancy Category B**

# Intracavernosal injection and intraurethral insertion

**Action:** vasodilator; relaxation of smooth muscle to allow for engorgement and trapping

- alprostadil, prostaglandin E, (Prostin VR®, Caverject®)  
IC 5-40/80ug reconstitute
- alprostadil (Muse®) pellet, IU 250-1000ug
- papaverine (Pavabid®) IC 30-60/80mg
- phentolamine/regitine 0.5-1mg-used in combination with the above
- **Side effects:** priapism, injection site bleeding, dizziness, fibrosis, burning, difficulty ejaculating, tingling of glans, aching during injection

**Contraindications:** sickle cell, Peyronie's dz.

**Caution:** anticoagulants

Autoinjector available; apply pressure 3-5min to injection site

**Pregnancy Category C: MUSE®**

**Indication:** Nonconventional ED and libido enhancement

- *yohimbine* PO 5.4mg tid: vasodilator/aphrodisiac;

**Side effects:** anxiety, nervousness, hypertension, headache, tremor, flushing, dizziness, GI, tachycardia

**Contraindication:** psychiatric pts, renal & hepatic dz., ulcer

**Interaction:** TCA, SSRI, tyramines, CNS stimulants, caffeine

- *apomorphine (Uprima®)*: dopamine agonist, central mediation, incr NO; morphine derivative

2-4mg sublingual, allow to dissolve, do not repeat for 8hs

**Side effects:** nausea, hypotension, syncope, flushing, dizziness, yawning, sweating, somnolence

- *L-Arginine (VasoRect®, AginMax®)*: amino acid dietary supplement, incr. NO; PO 5G/d (given tid)

**Side effects:** mild hypotention; no systemic effects

Avoid alcohol; caution in cardiac disease

# Drugs Affecting Spasticity

## Muscle Relaxants

- baclofen (Lioresal®): 20-80mg/d up to 240mg/d PO
- baclofen pump 25-750ug/d intrathecally

**Action:** GABA analog, down regulates Ca<sup>+</sup> influx; decreases muscle response to tonic stretch & decreases clonus & spasms

**Side effects:** drowsiness, nausea, ataxia, dizziness, confusion; possible hepatic dysfunction; avoid alcohol and CNS depressants

- tizanidine (Zanaflex®): 4-32mg divided doses PO; slow titration

**Action:** alpha 2-adrenergic agonist with decr. excitatory transmitter release

**Side effects:** somnolence, dry mouth, bradycardia, hypotension, **hepatotoxicity**; avoid alcohol, CNS depressants, diazepam, alpha 2 agonists, potentiated by OC & anti-HTN

- dantrolene sodium (Dantrium®): 25-100mg bid PO

**Action:** decreases Ca<sup>+</sup> flux, uncoupling depolarization

**Side effects:** significant weakness and drowsiness; hepatotoxicity (monitor LFT); estrogen incr. risk of **hepatotoxicity**; avoid verapamil, CNS depressants

# Agents of Spasticity

- diazepam (Valium®): 2-10mg qid PO

**Action:** inhibits glutamate and aspartate, therefore inhibits spinal motoneuron activity

**Side effects:** drowsiness, weakness, CNS depression, ataxia, memory impairment; avoid ETOH, CNS depressants, incr. cimetidine, potentiates sertraline

- clonazepam (Klonopin®) 0.5mg tid PO

**Action:** Same as above

**Side effects:** same as above with hypersalivation, GI upset, liver disorders

Antagonize CYP450 inducers e.g. phenytoin, carbamazepine, phenobarbital; caution c azoles & antifungals

# Agents of Spasticity

- clonidine (Catapres®) 0.1mg tid PO & transdermal

Action: central alpha 2 adrenergic block

Side effects: dry mouth, drowsiness, dizziness, weakness, constipation, rash, impotence, orthostatic hypotension; antagonized by TCA, potentiates CNS depressants

- gabapentin (Neurontin®) 100-900mg tid
- botulinum toxin A (Botox®)(BTX®) 400U IM

**Action:** inhibit release of acetylcholine at neuromuscular junction- reduces spasticity and preserves function via targeted muscle grps. >effect at 3-4wks; lasts 3months

**Side effects:** pain on injection, fever

# Drugs for Nociceptive Pain

- salicylate (Aspirin®) PO 1600mg bid max
- acetaminophen (Tylenol®) PO up to 2- 4g/d (toxic at 5-8g/d)
- NSAIDs: indomethacin (Indocin®), ibuprofen (Motrin®, Nuprin, Advil®), naproxen (Aleve®, Naprosyn®), diclofenac (Voltaren®), sulindac (Clinoril®), oiroxicam (Feldene®), ketoprofen (Oruvail®), nabumetone (Relafen®) peripheral prostaglandin antagonism

**Action:** inhibit production of prostaglandin which protect the lining of the stomach, ensure adequate renal function, maintain balance in CNS so NSAIDs can cause GI irritation and bleeding, renal insufficiency, edema, hypertension, and CNS imbalance

**Side effects:** GI bleed, peptic ulcer, nephritis, peripheral edema, headache, dizziness, constipation, rash, fluid retention

**Contraindicated:** renal dz, bleeding disorders, hypersensitivity (allergy to ASA, nasal polyps, asthma)



# Selective NSAIDs

- misoprostol (Cytotec®) is a synthetic prostaglandin to protect GI (SE: diarrhea) PO bid
  - diclofenac + misoprostol (Arthrotec®)  
H2 blockers and proton pump inhibitors
  - COX 2 inhibitor selective agents: celecoxib (Celebrex®), rofecoxib (Vioxx®)\*, valdecoxib (Bextra®)\*
    - **Side effects:** CVD, edema, GI, incr LFT
    - **Caution:** CYP2C9/2D6; HTN, DM, PVD, smoking, hyperlipidemia, CVD
    - **Contraindicated:** stroke, ischemic heart dz., CABG
- Pregnancy Category:** B (acetaminophen, ketoprofen, naproxen, flurbiprofen, diclofenac, diflunisal; C (the rest); D (salicylates); X misoprostol

- **FDA removed from market**
- <http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090b1.htm>

# Drugs For Neuropathic Pain

## Topical agents

## Oral agents

### Membrane stabilizing:

- Antiepileptics
- Antiarrhythmic
- Corticosteroids

### Dorsal horn inhibition:

- Antidepressants
- Gaba agonists-Baclofen
- Antiepileptics

### NMDA antagonists:

- Ketamine
- Dextromethorphan
- Methadone

## Opioids

## Intrathecal agents

# Topical Agents

- capsaicin (Zostrix®): 0.075% 4X/d  
SE: burning, sneezing, coughing

## **Transdermals:**

- fentanyl (Duragesic®), buprenorphine
- lidocaine/prilocaine (EMLA®)
- lidocaine patch 5%
- aspirin cream
- clonidine gel (0.05% qid)

# TCA's and SNRI

- Mainstay treatment of painful neuropathies
- Act to inhibit reuptake of serotonin and norepinephrine

imipramine (Tofranil®) PO 200mg QD max,

amitriptyline (Elevil®), PO 150mg QD max

nortriptyline (Pamelor®) PO 150mg QD max

desipramine (Norpramin®) PO to 200mg QD max

SE: sedation, hypotension, seizures,  
dry mouth, weight gain

duloxetine (Cymbalta®) PO 120mg max

venlafaxine (Effexor®) PO 375mg QD max dose

SE: nausea, dizziness, sedation, constipation, dry  
mouth

# Antiepileptics (AED's)

- Trousseau coined “neuralgic epilepsy” in 1853
- phenytoin used to tx. pain in early 40's
- carbamazepine used for pain in 1960

**Action:** block sodium channels and nerve membrane stabilizing agents

**Side effects:** sedation, nausea, vertigo, dizziness, rash, fatigue, diplopia, liver toxicity, interfere c cognitive fx (side effects minimized with long acting formulas)

# Antiepileptic Drugs

- carbamazepine (Tegretol®, XR)-assoc c neural tube defects **Preg Cat: D**
- phenytoin (Dilantin®)-hirsutism, gingival hyperplasia, constipation
- valproic Acid (Depakene®) **Preg Cat.: D** tremor; wt. gain
- clonazepam (Klonopin®) **Preg Cat: D** anticholinergic

Newer antiepileptic drugs are better tolerated, have fewer drug interactions and less affect on cognitive function

- gabapentin (Neurontin®) 900 titrated to 3600mg tid **1/1000 suicide**
- tiagabine (Gabitril®) up to 56mg/d in 2-4 divided doses
- lamotrigine (Lamictal®)-rash in 10%-hypersensitivity rx
- topiramate (Topamax®) wt. loss; incr. fluids
- oxcarbazepine (Carbatrol, Trileptal®), XR) **Preg Cat: D**
- pregabalin (Lyrica®) 100mg tid (2-10X more potent than neurontin)
- felbamate (Felbatol®), aplastic anemia, acute hepatic failure, cardiotoxic
- levetiracetam (Keppra®)
- zonisamide and vigabatrin less cognitive impact, hypersensitivity

# Antiarrhythmics for Nociceptive Pain

- Mexilitine (Mexitil®)  
sodium channel modulator

SE: palpitations, chest pain, tremor, GI, dizziness double vision, nervousness

- Lidocaine

Sodium  
channel  
modulators:

CBZ,  
OXC,PHT,  
Mexiletine,  
Lidocaine,  
Lamotrigine

Inhibit  
reuptake of  
NE, 5Ht:

Imiprimine,  
Desiprimine,  
Amitriptyline,  
Nortriptyline,  
Tramadol

Calcium  
channel  
modulators:

Gabapentine  
Topiramate  
Pregabalin



# Non-Narcotic and Narcotic Opioids

- **Cannabis:** dronabinol (Marinol®) PO 10mg; Sativex® (mouth spray)
  - Dizziness, tiredness, weakness
- **tramadol** (Ultram®) Tramadol/acetaminophen (Ultracet®)  
weak agonist at opioid receptors; inhibits NE & 5HT reuptake with 30% of activity of morphine-no withdrawal effects
  - SE: lowers seizure threshold; tiredness, dizziness, constipation, sedation, headache- habit forming

## Opioid Agonists:

**Pregnancy Category C:** morphine (Avinza®, Kadian®, MS Contin®, MSIR®), codeine, fentanyl (Duragesic®) hydrocodone, hydromorphone (Dilaudid®, Palladone®)

**Pregnancy Category B:** meperidine (Demerol®), methadone (Dolophine®), levorphanol, oxycodone, oxymorphone, propoxyphene (Darvon®)

- methadone is a NMDA receptor agonist
- Intrathecal pump (baclofen with morphine)

## Combination Opioids

- propoxyphene/acetaminophen (Balacet®, Darvocet®)
- propoxyphene/ASA/caffeine (Darvon Compound®)
- oxycodone/ibuprofen (Combunox®)
- oxycodone/acetaminophen (Percoset®, Tylox®)
- oxycodone/ASA (Percodan®)
- codeine/acetaminophen (Tylenol#3,#4®)
- dihydrocodeine/ASA/caffeine (Synalgos-DC®)
- dihydrocodeine/acetaminophen/caffeine (Panlor-DC, SS®)
- hydrocodone/ibuprofen (Vicoprofen®)
- hydrocodone/acetaminophen (Lortab®, Vicodon®, Maxidone®, Norco®, Zydone®)

**Side Effects:** vertigo, faintness, constipation, nausea, vomiting, flatulence, sedation, urinary retention, dizziness, diaphoresis

# Dietary Supplements

## Vitamins

- **Vitamins:** organic compounds that help maintain normal metabolic function, growth and tissue repair.
- A balanced diet is best but supplemental therapy is essential during periods of **nutritional challenge** (rapid growth, pregnancy, lactation, illness)
- Vit K formed by bacteria in gut
- Vit D produced by exposure to sunlight
- Fat-soluble: A, D, E, K
- Water-soluble: B complex group and C
- Antioxidant vitamins A, C, E may have effect in MS

**Pregnancy Category:** **A** (thiamine B1, folic acid B9, pyridoxine B6); **C** (vit. D, cyanocobalamin B12, ascorbic acid C); **X** (vit. A)

Unclassified: niacin B3, riboflavin B2, vit. K, vit. E

- **Vitamin A/ Beta-Carotene:** antioxidant, immunological effects (more studies needed in MS)
  - **Contraindications:** liver dz, osteoporosis, angioplasty, male smokers, asbestos workers; lg doses (10,000IU) toxic
  - **Interactions:** minocycline, HMG-CoA reductase inhibitors and OC
- **Vitamin D:** hormone and vitamin-important in bone loss; mildly immunosuppressive; >1000mmg/d=liver injury
  - **Contraindications:** hypercalcemia, sarcoidosis, hypoparathyroidism, renal dz
  - **Interactions:** cardiac glycosides
- **Vitamin E** anti-oxidant, suggested as MS tx.-no adverse effect from one small study-suggest dietary sources; With PUFA diets use E to replace losses
  - **Contraindications:** angioplasty, retinitis pigmentosa, K deficiency
  - **Interactions:** anticoagulants and antiplatelets
- **Vitamin K** no known relevance to MS
  - **Interactions:** coumadin

- **B1/Thiamine:** possible to tx. fatigue in MS-
- **B2/Riboflavin:** may be effective for migraine; no application for MS
- **B3/Niacin:** used as antilipidemic; no application in MS
- **B6/Pyridoxine:** deficiencies and excess may cause polyneuropathy; no application in MS and may decrease effectiveness of DMA-nerve injury at >50mg/d
- **B9/Folic Acid:** may be decreased in serum of MS pts. May decr. toxicity of methotrexate
  - **Contraindications:** may mask Vit B12 deficiency; possible worsening of seizure disorder and schizophrenia
  - **Interactions:** decreases serum levels of phenytoin, mysoline, and phenobarbital
  - Supplements have twice the bioavailability of diet

- **B12/Cyanocobalamin:** no evidence for use in MS unless deficient
  - **Contraindications:** Leper's hereditary optic neuropathy
  - **Interaction:** folic acid may mask deficiency
- **C/Ascorbic Acid:** possible UTI prophylaxis and decrease duration of common cold (viral infections precipitate exacerbation); acidify urine; antioxidant good and bad-best to obtain antioxidant compounds through diet
  - >1000mg/d may produce diarrhea and kidney stones
  - **Contraindications:** angioplasty; Hx. kidney stones
  - **Interaction:** anticoagulants

# Minerals

- **Calcium:** nerve conduction, muscle contraction, blood clotting, treat osteoporosis; mild immunosuppressive -further clinical trials needed; Dose 1000-1600mg divided doses
  - As citrate(Citracal, Solgar): on empty stomach
  - As carbonate (TUMS, Caltrate): need acid to absorb, take c food;
  - lactate
  - gluconate
  - **Contraindications:** hypothyroidism, hyperphosphatemia, renal insufficiency, sarcoidosis; risk kidney stones
  - **Interactions:** thiazide diuretics
  - **absorption:** biphosphonates, fluoroquinolones, levothyroxine, tetracycline, iron, zinc, magnesium, tannins, laxatives, fiber, phytates and oxaltic acid bind calcium in foods e.g., spinach, cocoa, kale, soybeans

- **Iron:** needed for tissue respiration; most common nutritional deficiency; absorption increased if taken with Vitamin C; coffee, tea, milk, eggs, whole grain breads and cereals, calcium decrease absorption; ferrous forms absorbed better than ferric forms.
- **Magnesium:** (constipation, migraine, tetanus associated spasms) decreases MS spasticity in one case study
- **Zinc:** stimulates immune function and may increase severity of dz.; Zinc gluconate lozenges decrease the severity of the common cold; involved in metabolism of PUFAs; avoid or limit in MS to low doses (10-15mg)
  - **Contraindications:** HIV, hemochromatosis
  - **Interactions:** diuretics, tetracycline, fluoroquinolones
- **Selenium:** antioxidant effect; may prevent certain forms of cancer-suggest small doses 50mcg or <



# Dietary Supplements

## Polyunsaturated Fatty Acids (PUFA)

- **PUFA:** omega-3 (alpha linoleic acid, ALA & eicosapentaenoic acid, EPA) and omega-6 (linoleic acid, LA & gamma-linoleic acid, GLA):
- Immunomodulatory effect; mortality effect
- LA found in sunflower oil, soybean oil, corn oil, walnut oil, wheat germ oil, grape seed oil, & safflower oil
  - PO17-23g
  - **Contraindications:** allergy to daisy plant family
- GLA found in primrose oil, blackcurrent seed oil, borage seed oil, & spirulina
  - PO 340-360mg/d
  - **Contraindications:** incr risk of seizures, prolongs bleeding time
  - **Interactions:** phenothiazines and other epileptogenic medications, anticonvulsants, anticoagulants and antiplatelets
  - Take vitamin E to prevent Vit. E deficiency

- ALA found in flaxseed oil, canola oil, walnut oil
  - PO 800-1800mg/d; IV 100-1200mg/d
  - **Contraindications:** diabetes, bleeding disorders
  - **Interactions:** oral hypoglycemics, insulin, anticoagulants
- EPA & DHA found in fish oils, (salmon, Atlantic herring and mackerel, bluefin tuna, sardines & cod liver)
  - Dose < 3g combined EPA & DHA/d
  - Vitamin E supplementation necessary
  - Diet concerns with mercury contaminants
  - **Contraindications:** bleeding disorders, diabetes, aspirin sensitivity, bipolar, depression
  - **Interactions:** anticoagulants, oral hypoglycemic and insulin, antihypertensives

**Pregnancy category: not enough information**

# Dietary Supplements

- Herbal used in MS
  - cranberry tablets: UTI prophylaxis
  - psyllium: constipation
  - Valerian: insomnia
  - St. John's Wort: mild depression; two large clinical trial showed no effect for moderate and severe depression
    - **Interactions:** indinavir, cyclosporine; may interfere with the effectiveness of OC, medications for heart dz, seizures and cancer

- **Herbals that may worsen MS**
  - Alfalfa, astragalus, echinacea, garlic, Asian ginseng: immune-stimulating
  - Fatigue is worsened by: chamomile, Asian & Siberian ginseng, barberry
  - Steroid side effects worsened by: aloe, bayberry, Asian ginseng, licorice
  - Hormones melatonin and DHEA activate the immune system
- **Herbs recommended with serious side effects (no proven worth)**
  - yohimbe, chaparral, comfrey, lobelia

# **Case study: Maggie, 36yo c 5y HX of RRMS treated for UTI and exacerbation**

## **Current Medications:**

- INFB1a (132ug/wk)
- carbamazepine 600mg
- modafinil 400mg
- amitriptyline HS 75mg
- baclofen 60mg
- tolterodine 4mg
- sertraline 150mg
- depo-provera 150mg q 3mos
- ciprofloxacin 500mg for 3 d
- St. John's Wort 900mg,
- Vit A 5000IU, Vit C 1500mg, Vit D 800mg, Omega-3 3G,
- Senokot 17.2mg,
- methyprednisilone 1G over 5d

- **Recent labs:** AST 180U/L; ALT 175 U/L; LDH 900 U/L; leukocytes 7.4, Hgb 12.0, Hct 40; leukocyte count 9.9; U/A: leukocytes:  $10^{10}$ ; SG: 1.028; bacteria: escherichia coli, and candida albicans
- Maggie continues to c/o of lower extremity pain described as continuous “pins and needles”, VAS=4; urinary urgency, frequency, incontinence controlled; Ashworth scale=3; reports mild depression; constipation, MFIS=20, dizziness, rash on upper chest and face

Evaluate risk

What is your assessment?

How would you manage?

# How would you treat?

- The disease
  - MS
- The symptoms
  - Bladder
  - Fatigue
  - Depression
  - Spasticity
  - Pain
- Advice on supplements
- Advice on birth control

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