

PUTTING THE ACTION IN DRUG INTERACTION: DISEASE MODIFYING THERAPIES (DMTS) IN THE AGING ADULT

Jacquelyn Bainbridge, Pharm.D, FCCP
Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Clinical Pharmacy and Neurology

Objectives

- Identify medications typically taken by aging adults
- Review medications used for symptom management of MS
- Discuss common drug interactions with DMTs
- Classify major drug interactions with common medications for the aging adult, symptom management, and DMTs

Growth of Aging Adult Population

- Population >65 years old
 - ▣ 43.1 million in 2012
 - ▣ 35.5 million in 2002
 - Increase of 21%
 - ▣ Average life expectancy of an additional 19.2 years
 - ▣ Population projected to increase to 78.7 million in 2040
 - ▣ Average number of medications is at least 5
 - Prescription
 - Over the counter products (OTCs)
 - Herbals and supplements

US Department of Health and Human Services. (2013). Administration on Aging. A profile of older Americans: 2011. http://www.aaa.acl.gov/Aging_Statistics/Profile/2013/docs/2013_Profile.pdf

Common Health Conditions

- Arthritis
- Heart disease
- Diabetes
- Hypertension

US Department of Health and Human Services. (2013). Administration on Aging. A profile of older Americans: 2011. http://www.aaa.acl.gov/Aging_Statistics/Profile/2013/docs/2013_Profile.pdf

Common Medications in the Aging Adult

- Warfarin
- Aspirin
- Statins
- Benzodiazepines
- Antidepressants
- Antihypertensives
- Multivitamins
- Acetaminophen/ibuprofen

http://www.naturalnews.com/036482_prescription_drugs_side_effects_elderly.html

Beer's Criteria 2015

Medications to Avoid in the Aging Adult:

- First-generation antihistamines
- Antispasmodics
- Nitrofurantoin
- Alpha-1 blockers
- Alpha agonists (e.g., clonidine, guanabenz, methyldopa)
- Class Ia, Ic, and III antiarrhythmics
- Tertiary TCAs
- Antipsychotics
- Barbiturates
- Benzodiazepines
- Nonbenzodiazepine hypnotics (e.g., zolpidem)
- Metoclopramide
- Non-COX selective oral NSAIDs
- Skeletal muscle relaxants

APhA Beer's Criteria

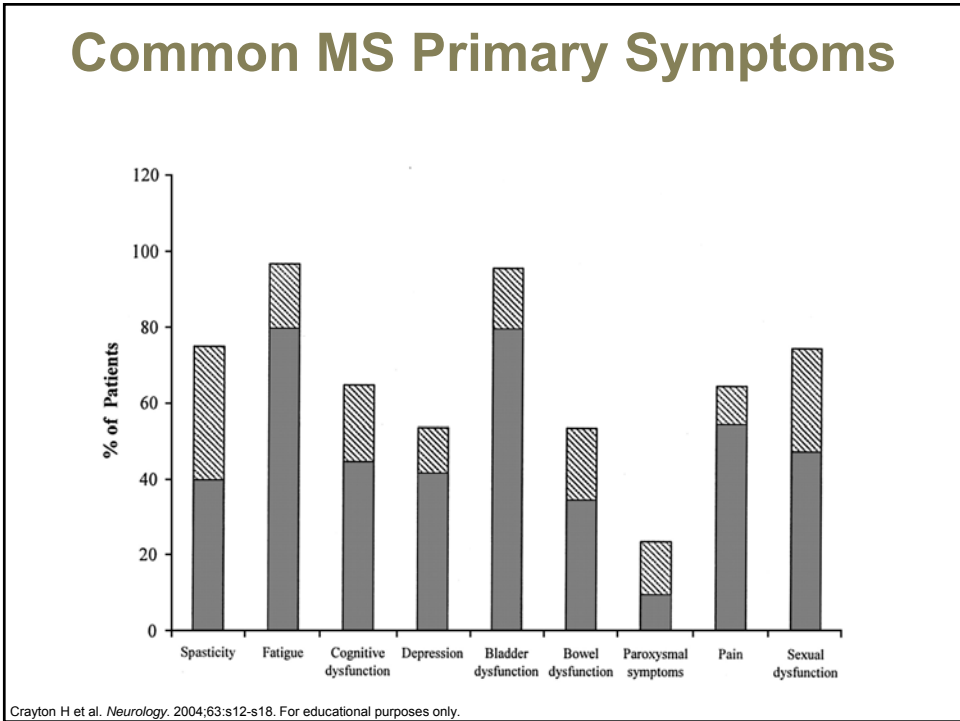
Summary of Age-Related Pharmacokinetic Changes

Absorption	↓ absorptive surface ↓ splanchnic blood flow ↓ GI motility & gastric emptying rate	↑ gastric pH
Distribution	↓ cardiac output & relative tissue perfusion ↓ hepatic/renal blood flow ↓ TBW & LBW ↓ albumin	↑ body fat
Metabolism	↓ liver mass ↓ hepatic blood flow ↓ enzyme activity	
Excretion	↓ renal blood flow ↓ GFR (CrCl) ↓ tubular secretion ↓ renal mass	

Drug Interactions

- Pharmacokinetic
 - ▣ What the body does to the drug
- Pharmacodynamic
 - ▣ What the drug does to the body
- Protein binding
 - ▣ Highly protein bound drugs
 - ▣ ~ >90%

MS Symptom Management



Common Symptomatic Problems

- Decreased cognition
- Depression
- Bladder dysfunction
- Neuropathic pain
- Spasticity
- Walking/mobility issues
- Fatigue
- Sexual dysfunction

Decreased Cognition

- Behavioral coping strategies: cognitive rehabilitation
- Cholinesterase inhibitor: donepezil, rivastigmine
- NMDA receptor antagonists: galantamine, memantine
- Stimulant or activating medications: amantadine, methylphenidate, dextroamphetamine, lisdexamfetamine, modafinil, fluoxetine, bupropion, dalfampridine
- Check for statins as they may cause decreased cognition

Neural Clin. 2011; 29: 449-463; National Multiple Sclerosis Society. www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/cognitive-function/index.aspx.
Multiple Sclerosis and Demyelinating Diseases. Lippincott, Williams, and Wilkins; 2006:227-255.

Depression

- Treat similar to major depressive disorder (SSRIs, SNRIs, bupropion, TCAs, mirtazapine, psychotherapy)
- Consider comorbidities when selecting agent:
 - Insomnia → Mirtazapine, TCAs
 - Neuropathy → Duloxetine, TCAs
 - Sexual dysfunction → Bupropion
 - Fatigue → SNRIs (venlafaxine, duloxetine, desvenlafaxine), fluoxetine, stimulants
 - Cognition/balance → Avoid TCAs
 - Incontinence → SNRIs, TCAs

Bladder Dysfunction

- Failure to store (hyperreflexive bladder, Overactive bladder)
 - Anticholinergic medications: oxybutynin, tolterodine
 - With or without low-dose imipramine (synergistic effect)
 - Remove cholinesterase inhibitor if incontinence started soon after its initiation
- Sphincter dyssynergia
 - Alpha-1 blockers: terazosin, tamsulosin
- Failure to empty
 - Cholinergic agents (bethanechol)
 - Crede maneuver, timed voids, catheterization
- Nocturia
 - Desmopressin acetate (DDAVP)

DIAPPERS: Transient Causes

- **D**elirium
- **I**nfection
- **A**trophic vaginitis/urethritis
- **P**sychiatric disorders
- **P**harmacologic treatments
- **E**xcessive urine output (DM, HF)
- **R**estricted mobility (PD, OA, RA, stroke, AD)
- **S**tool impaction

Marshall LL, Bailey W. Consult Pharm 2008;23:681-94

Drug Causes of UI

Table 94-1 Medications that Influence Lower Urinary Tract Function

Medication	Effect
Diuretics, acetylcholinesterase inhibitors	Polyuria, frequency, urgency
α -Receptor antagonists	Urethral relaxation and stress urinary incontinence in women
α -Receptor agonists	Urethral constriction and urinary retention in men
Calcium channel blockers	Urinary retention
Narcotic analgesics	Urinary retention from impaired contractility
Sedative hypnotics	Functional incontinence caused by delirium, immobility
Antipsychotic agents	Anticholinergic effects and urinary retention
Anticholinergics	Urinary retention
Antidepressants, tricyclic	Anticholinergic effects, α -antagonist effects
Alcohol	Polyuria, frequency, urgency, sedation, delirium
Angiotensin-converting enzyme inhibitors (ACEIs)	Cough as a result of ACEIs may aggravate stress urinary incontinence by increasing intraabdominal pressure

Pharmacotherapy 8e. Urinary Incontinence; Marshall LL, Bailey W. Consult Pharm 2008;23:681-94

Bladder Dysfunction

- Pelvic floor exercises
- Clean intermittent self-catherization
- Onobotulinum toxin A (Botox®)
- UTI prophylaxis is necessary in some cases
 - Agents include sulfamethoxazole/trimethoprim, cephalixin, and nitrofurantoin

Comparison of OAB Agents

Drug	Dry mouth %	Constipation %	Dizziness %	Vision changes %	Cash Price
Oxybutynin	88	32	38	22	\$4
Oxy ER/XL	68	9	11	3	\$40
Oxy TDS	10	5	4	2	\$400/ \$30-40
Oxy gel	8	1	3	?	\$240
Tolterodine IR, ER	50, 39	10, 10	4, 3	8, 6	\$80- 170/25 0
Fesoterodine	99	14	2	4	\$205
Trospium	33	11	?	3	\$70/14 5
Solifenacin	34	19	1	7	\$235
Darifenacin	59	28	0	4	\$225

Treatment of overactive bladder in women: AHRQ Publication No. 09-E017-10/12. www.goodrx.com

Roles of Muscarinic Receptor Subtypes in the CNS

Muscarinic Receptor Subtype	Phenotype	Summary of Effects on Cognitive Function
M₁	 Selective impairments of memory function – Working memory, consolidation 	Negative
M ₂	<ul style="list-style-type: none"> Learning and memory deficits; antagonists shown to enhance memory 	Negative Positive
M ₃	<ul style="list-style-type: none"> No major deficits in learning, memory, or cognitive function 	Neutral
M ₄	<ul style="list-style-type: none"> Antagonists shown to enhance ACh levels in striatum 	Neutral/+?
M ₅	<ul style="list-style-type: none"> No major deficits in learning, memory, or cognitive function 	Neutral

B3 Agonist for OAB


Myrbetriq[®]
 (mirabegron)
 extended-release tablets
 25 mg / 50 mg

- In June 2012, the beta-3 adrenergic agonist mirabegron was FDA-approved for the treatment of OAB
- B3 adrenergic activation relaxes the detrusor muscle during the storage phase to increase bladder capacity
 - Non-comparative data indicate slightly less efficacy than antimuscarinic agents, but much different adverse effect profile which may make the drug desirable
- Dose: 25-50 mg once daily
 - Max dose: 25 mg/d if CrCl 15-29 mL/min or moderate hepatic impairment
 - Not recommended in ESRD or severe hepatic impairment
 - Effective within 8 weeks

B3 Agonist for OAB

- Precautions:
 - B-1 adrenergic activity occurs at a dose of 200mg
- Drug interactions:
 - Moderate inhibitor of CYP2D6
 - Dose adjustment may be necessary for narrow therapeutic index drugs that rely on CYP2D6 (e.g. thioridazine, flecanide, propafenone, TCAs)
 - Digoxin: use the lowest initial dose of digoxin and monitor serum concentrations to obtain the desired effect
- Adverse effects: HTN (11%), UTI (4%), HA (3%), nasopharyngitis (4%)



"One of the nicest evenings I've ever spent at the Wilsons'... and then you had to go and do that on the rug!"

Sensory and Pain Symptoms

- Sensory symptoms
 - Trigeminal neuralgia (one of the more common symptoms)
 - Burning, itching, L'Hermitte's sign, face twitching
 - Carbamazepine 200 mg PO BID or TID
 - Alternatives: gabapentin, topiramate, tiagabine, TCAs
- Neuropathic pain (50%)
 - Difficult to treat
 - Carbamazepine, TCAs, gabapentin, pregabalin, duloxetine, topiramate, tiagabine, capsaicin cream, etc

Spasticity

- First line: Oral baclofen 5-25 mg po tid
- Second-line agents; frequently used in combination with oral baclofen
 - Tizanidine
 - Diazepam
 - Clonazepam
 - Dantrolene
 - Clonidine
 - Gabapentin
- Refractory spasticity
 - Botulinum toxin
 - Intrathecal baclofen

1. *Int MS J.* 2007;14:22-27; 2. *Multiple Sclerosis and Demyelinating Diseases.* Lippincott, Williams, and Wilkins; 2006:227-255; 3. *Neurology.* 2004;63(11 suppl 5): S12-18.

Walking/Mobility Issues

- Traditionally managed nonpharmacologically
 - ▣ Gait training, exercise, physical therapy, assistive devices
- Dalfampridine approved in 2011
 - ▣ Dosed 10mg BID
 - ▣ Only indicated for walking/mobility issues
 - ▣ Do not use in combination with 4-aminopyridine
 - ▣ Increased risk of seizures

Fatigue

- Modafinil
 - ▣ 100–400 mg once daily in the AM
- Armodafinil
 - ▣ 150-250 mg once daily in the AM
- 4-aminopyridine
 - ▣ 5–20 mg twice daily (AM and in the early afternoon)
- Selective serotonin reuptake inhibitors fluoxetine
 - ▣ Fluoxetine 10–40 mg once daily in the AM
- Amantadine
 - ▣ 100 mg twice daily (AM and in the early afternoon)

1. *Cleve Clin J Med.* 2006;73:177-186.
 2. *Multiple Sclerosis and Demyelinating Diseases.* Lippincott, Williams, and Wilkins; 2006:227-255. 3. *Int MS J.* 2007;14:22-27.

Sexual Dysfunction

- Male
 - Phosphodiesterase-5 inhibitors: sildenafil, tadalafil, vardenafil
 - Sublingual aporphorpine
 - Yohimbine
 - Alprostadil intracorporeal injection
 - Vacuum devices
- Female
 - PDE5 inhibitors may be option
 - Androgen hormone therapy: methyltestosterone
 - Topical estrogen cream
 - Vaginal lubrication jelly

Toosy A, Ciccarelli O, and Thompson A. Symptomatic treatment and management of multiple sclerosis. *Handbook of Clinical Neurology*. 2014;122:5-54.

Drug Interactions: Disease Modifying Therapies (DMTs)

FDA Approved DMTs

- Self-Injectable
 - Glatiramer
 - IFN β -1a IM
 - IFN β -1a SQ
 - Peg IFN β -1a SQ
 - IFN β -1b
- Oral
 - Dimethyl fumarate (BG12)
 - Fingolimod
 - Teriflunomide
- Infused
 - Alemtuzumab
 - Mitoxantrone
 - Natalizumab

IFN β Products

- Increased risk of infection with live vaccines
 - Measles, mumps, rubella
 - Yellow fever
 - Adenovirus
 - Herpes Zoster
 - FluMist (intranasal influenza)
 - Varicella
 - Smallpox
 - Typhoid

www.cdc.gov/vaccines

Glatiramer

- Interactions with other drugs have not been fully evaluated
- Results from existing clinical trials do not suggest any significant interactions with therapies commonly used in MS patients

Dimethyl fumarate (BG12)

- No potential drug interactions were identified in *in vitro* CYP inhibition and induction studies, or in P-glycoprotein studies

Tecfidera package insert

Fingolimod

- Concomitant use with class Ia or III antiarrhythmic drugs is contraindicated
 - Ia = quinidine, procainamide, disopyramide
 - III = amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, dronedarone
- Live virus vaccines
- Non-live vaccines may not be able to mount a response, vaccinate prior to starting.
- Check varicella zoster antibody titer prior to starting.
- Antineoplastic, immunosuppressive, or immunomodulating therapies
- Drugs that lower heart rate: beta blockers, diltiazem
- Ketoconazole: inhibits CYP 3A4 which increases fingolimod concentration by 70%
- Highly protein bound
- Substrate of: CYP2D6, CYP2E1, CYP3A4

CBC = complete blood count; LFTs = liver function tests; MOA = mechanism of action; PFTs = pulmonary function tests.
GILENYA Prescribing Information.

Teriflunomide Drug Interactions

- Induces CYP1A2
 - Major: clozapine, warfarin (decreased anticoagulant effectiveness – unknown mechanism of action + CYP1A2)
 - Moderate: olanzapine, tizanidine, fluvoxamine, haloperidol, imipramine, naproxen, duloxetine, cyclobenzaprine
- Inhibits CYP2C8
 - Pioglitazone (Moderate)
- Rosuvastatin with teriflunomide causes increased OAT substrate exposure
- Check TB-PPD prior to starting
- Highly protein bound

MicroMedex Solutions. Available at <http://micromedex.com>

Alemtuzumab

- No formal drug interaction studies have been performed
- An immune response may interfere with subsequent diagnostic serum tests that utilize antibodies

Campath package insert

Mitoxantrone

- CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited during *in vitro* studies
 - Mitoxantrone may be a weak inducer of CYP450 2E1
- Pharmacokinetic changes with concomitant medications have not been studied in humans
- Post-marketing reports have not revealed any significant drug interactions in patients

Novantrone package insert

Natalizumab

- Potential for increased risk of PML and other infections with concomitant immunosuppressants
 - 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, corticosteroids, or inhibitors of TNF- α

Tysabri package insert

Metabolism/Elimination of DMTs

Drug	Metabolism/Elimination
IFN β -1a	Inactivated in body fluids and tissue
IFN β -1b	Inactivated in body fluids and tissue
Glatiramer acetate	Hydrolyzed locally
Fingolimod	Hepatic via CYP4F2 Highly protein bound Substrate: CYP2D6, CYP2E1, CYP3A4 (all minor) Excreted: renal and fecal
Natalizumab	Broken down into peptides and AAs in body fluids
Dimethyl fumarate	Hydrolysis. No CYP involvement in metabolism Elimination: exhalation of CO ₂ (major) Renal and fecal (minor)
Teriflunomide	Hydrolysis to minor metabolites Highly protein bound Inhibits: BCRP (CYP2C8, OATP1B1 (influx) Induces: CYP1A2 Substrate: BCRP Eliminated: biliary and renal

70% of drugs are metabolized by CYP 3A4, 2D6, 2C, therefore if a drug is not a substrate/inducer/inhibitor of those CYPs or P-Glycoprotein, the drug-drug interactions will be minimal.
MicroMedex Solutions. Available at: <http://micromedex.com/>.

Drug Interactions

Major Carbamazepine Interactions

- Induces: CYP 3A4, 2B6, 2C9, 1A2, 2C19
 - Alters the metabolism of calcium channel blockers, atorvastatin, sulfamethoxazole/trimethoprim, bupropion, duloxetine, dantrolene, diazepam, losartan, modafinil, simvastatin, tamsulosin, tiagabine, tolterodine, venlafaxine

Major Warfarin Interactions

- **Enhance** the anticoagulant effect of warfarin: SSRI, SNRI, TCA, NSAIDs, methyltestosterone, ASA, sulfamethoxazole/trimethoprim

- **Decrease** the serum concentration of warfarin: carbamazepine, teriflunamide

- **Diminish** the anticoagulant effect of warfarin: multivitamins containing vitamin K

Lexicomp Drug Interactions

Major Interactions with DMTs, Symptom Control, and Common Drugs

- Concomitant CNS depressant use may advance the effects and cause clinically relevant depressed CNS function
 - Muscle relaxants, BZDs, carbamazepine, clonidine, gabapentin, pregabalin, dantrolene, SSRIs, SNRIs, TCA, mirtazapine, bupropion, tiagabine, topiramate, opioids, alcohol

- Increased serotonergic effect with concomitant use of TCAs, SSRIs, SNRIs, mirtazapine, bupropion, amphetamines, CNS depressants

Lexicomp Drug Interactions

Major Interactions with DMTs, Symptom Control, and Common Drugs

- Amphetamines may diminish antihypertensive effect

- QTc prolongation
 - Citalopram, sulfamethoxazole/trimethoprim, galantamine, mirtrazapine, paroxetine, TCA, tizanidine, tolterodine, venlafaxine, vardenafil, fluoxetine, amantadine, fingolimod, methadone

Lexicomp Drug Interactions

Major Interactions with DMTs, Symptom Control, and Common Drugs

- Drugs that decrease heart rate may enhance the effect of other medications that cause bradycardia
 - Clonidine, rivastigmine, tizanidine, galantamine, fingolimod, donepezil, beta blockers, non-dihydropyridines calcium channel blockers (diltiazem)

- PDE-5 inhibitors may enhance the hypotensive effect of alpha-1 blockers
 - Terazosin, tadalafil, vardenafil, sildenafil, tamsulosin

Lexicomp Drug Interactions

Summary

- The aging population is the fastest growing segment of our population
- The aging population is on a least 5 medications
- Important to ask about OTC agents and supplements
- Drug interactions are common and can be serious and averted

QUESTIONS?