

Common Adverse Drug Effects Seen by Primary Care Physicians

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Objectives

- At the end of this presentation you should be able to:
 - Recognize common adverse drug effects experienced by patients
 - Understand how common adverse drug effects present
 - Differentiate which medication may cause an adverse drug effect



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Patient Case

- 72 y/o female, with a PMH of hypertension, GERD, and urinary incontinence presents with visual disturbances, a dry mouth, and complaining of abdominal pain due to constipation.
- Current medications include: Valsartan (Diovan), Omeprazole (Prilosec), and Oxybutynin ER (Ditropan XL)
- Which of the patient's medication could be causing these adverse effects?



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Dizziness¹

- Dizziness and vertigo are among the most common disorders in medicine, affecting approximately 20-30% of people in the general population.
- Dizziness is a general term used to express subjective complaints of the patients related to changes in sensation, movement, perception, or consciousness.
- Vertigo is a subtype of dizziness, defined as an illusion of movement caused by asymmetric involvement of the vestibular system.
 - The incidence of vertigo increases with age and is about two to three times higher in women than in men



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Dizziness¹

- ❑ Analgesics
- ❑ Antibiotics:
 - ❑ Fluoroquinolones, Aminoglycosides, Macrolides
- ❑ Anti-convulsants:
 - ❑ Carbamazepine, lamotrigine, lacosamide, oxcarbazepine
- ❑ Anti-depressants:
 - ❑ Amitriptyline, doxepin, mirtazapine, paroxetine, sertraline, trazodone
- ❑ Anti-hypertensives:
 - ❑ ACE Inhibitors, ARBS, Calcium Channel Blockers
- ❑ Anti-inflammatory:
 - ❑ NSAIDs, salicylates



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Dizziness¹

- ❑ Antipsychotics:
 - ❑ 1st generation and Atypical
- ❑ Benzodiazepines
- ❑ Diuretics
 - ❑ Furosemide, HCTZ
- ❑ Muscle Relaxants
 - ❑ Skeletal, Central
- ❑ Sedative Hypnotics
- ❑ “Statins”
 - ❑ Atorvastatin, simvastatin



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Blurred Vision/Dry Mouth²

- Antiemetics/anti-vertigo
 - ▣ Dimenhydrinate, meclizine, promethazine, prochlorperazine
- Antiparkinson
 - ▣ Benzotropine, trihexyphenidyl
- Antispasmodics (GI)
 - ▣ Dicyclomine, hyoscyamine
- Antispasmodics (GU)
 - ▣ Flavoxate, oxybutynin
- Bronchodilators
 - ▣ Ipratropium, tiotropium (Spiriva)



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Blurred Vision/Dry Mouth²

- Antidiarrheals:
 - ▣ Diphenoxylate/Atropine, loperamide
- Antihistamines:
 - ▣ Chlorpheniramine, diphenhydramine
- Antidepressants:
 - ▣ Amitriptyline, clomipramine, doxepin, imipramine, nortriptyline
- Antipsychotics:
 - ▣ Chlorpromazine, clozapine, fluphenazine, thiothixene
- Skeletal Muscle Relaxants
 - ▣ Cyclobenzaprine, orphenadrine



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Cough³

- ACE Inhibitors
 - A dry, persistent cough is a well-described class effect of the angiotensin-converting enzyme (ACE) inhibitor medications.
 - The mechanism of ACE inhibitor-induced cough remains unresolved, but likely involves the protussive mediators bradykinin and substance P, agents that are degraded by ACE and therefore accumulate in the upper respiratory tract or lung when the enzyme is inhibited.



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Cough³

- The incidence of ACE inhibitor-induced cough has been reported to be in the range of 5 to 35% among patients treated with these agents.
- The onset of ACE inhibitor-induced cough ranges from within hours of the first dose to months after the initiation of therapy.
- Resolution typically occurs within 1 to 4 weeks after the cessation of therapy, but cough may linger for up to 3 months.
- The only uniformly effective treatment for ACE inhibitor-induced cough is the cessation of treatment with the offending agent.



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Cardiac: QT Prolongation^{4,5}

- Antiarrhythmic drugs
 - Class Ia (Quinidine, Procainamide, Disopromide)
 - Class III (Dofetilide, Ibutilide, Sotalol)
- Antibiotics
 - Quinolone (Levofloxacin, Moxifloxacin)
 - Macrolide (Erythromycin, Clarithromycin)
- Antipsychotic and antidepressant agents
 - Neuroleptic
 - Haloperidol, Droperidol, Thioridazine, Chlorpromazine
 - Atypical antipsychotics
 - Citalopram, Risperidone, Ziprasidone
 - Antidepressants
 - Amitriptyline, Desipramine, Doxepin, Fluoxetine, Imipramine



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Cardiac: QT Prolongation^{4,5}

- Antiemetics:
 - Ondansetron
- Antifungals
 - Fluconazole
- Antimalarials
- Antiprotozoal
- Methadone



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Cardiac: Orthostatic Hypotension⁶

- Orthostatic hypotension is defined by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology as a reduction of systolic blood pressure of at least 20 mmHg or a reduction of diastolic blood pressure of at least 10 mmHg within three minutes of standing.
 - For individuals who cannot stand, a drop in blood pressure within three minutes of tilting the head up to at least a 60° angle is indicative of orthostatic hypotension.
- Common symptoms of orthostatic hypotension include light-headedness, dizziness, weakness, fatigue, cognitive impairment, nausea, palpitations, and tremulousness



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Cardiac: Orthostatic Hypotension⁶

- The prevalence of orthostatic hypotension may increase with age, and studies report that as many as 13% to 30% of elderly people have orthostatic hypotension.
- It is estimated that about 50% of orthostatic hypotension cases involve causative medications



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Cardiac: Orthostatic Hypotension⁶

- Antihypertensives
 - Diuretics (thiazide, loop)
 - Clonidine
 - Methyldopa
 - ACE Inhibitors
 - Diltiazem
 - Nifedipine
- Vasodilators
 - Nitrates, Hydralazine
- Alpha-Blockers
 - Terazosin, doxazosin, prazosin



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Cardiac: Orthostatic Hypotension⁶

- Antidepressants
 - TCAs, SSRIs, MAOIs, Venlafaxine, Trazodone
- Atypical Antipsychotics
- Parkinson's Disease drugs
 - Levodopa, Bromocriptine, Selegiline
- Narcotics
- Barbiturates
- Insulin
- PDE-5 Inhibitors



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Cardiac: Hypertension/Tachycardia⁷

- **Bronchodilators:**
 - Albuterol
- **Corticosteroids**
 - Prednisone, prednisolone, hydrocortisone
- **CNS Stimulants**
 - Caffeine
- **Estrogens and progestin**
 - Oral contraceptives, ERT/HRT



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Cardiac: Hypertension/Tachycardia⁷

- **Immunosuppressants**
 - Cyclosporine, tacrolimus
- **NSAIDs and COX-2 inhibitors**
 - Ibuprofen, diclofenac, celecoxib
- **SNRIs**
 - Venlafaxine
- **Sympathomimetic Agents**
 - Amphetamines, ephedrine, pseudoephedrine



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Gastrointestinal: Nausea and Vomiting⁸

- Chemotherapy
 - ▣ The likelihood that nausea and vomiting will develop after chemotherapy treatment depends on several factors:
 - Age (younger is higher risk)
 - Sex (Female is higher risk)
 - Patient expectation (higher the expectation the greater the chance)
- Treatment related factors
 - ▣ Chemotherapy dose
 - ▣ Emetogenicity



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Gastrointestinal: Nausea and Vomiting⁹

- Dopaminergic agonists (Ropinirole, Pramipexole)
- Digoxin
- Erythromycin
- Nicotine
- NSAIDs
- Opiates
- Oral hypoglycemic
- Oral contraceptive
- SSRIs
- Vitamins and minerals



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Gastrointestinal: Constipation^{10,11}

- ❑ Opiates
- ❑ Drugs with Anticholinergic activity
- ❑ Diuretics
 - May lead to dehydration, causing constipation.
- ❑ Nondihydropyridine calcium channel blockers (verapamil, diltiazem)
- ❑ Vitamins and Minerals (iron, calcium, antacids)



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Gastrointestinal: Diarrhea¹²

- ❑ Diarrhea is a relatively frequent adverse event, accounting for about 7% of all drug adverse effects.
- ❑ More than 700 drugs have been implicated in causing diarrhea



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Gastrointestinal: Diarrhea¹³

- ❑ Antibiotics
- ❑ Chemotherapy
- ❑ H-2 Antagonists
- ❑ Laxatives
- ❑ Magnesium containing antacids
- ❑ Metformin
- ❑ NSAIDs
- ❑ Proton Pump Inhibitors (PPIs)



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Genitourinary: Urinary Retention¹⁴

- ❑ Data from observational studies suggest that up to 10% of episodes might be attributable to the use of concomitant medication.
- ❑ Drugs with Anticholinergic activity
- ❑ Alpha-adrenoceptor agonists
- ❑ Benzodiazepines
- ❑ Calcium channel blockers
- ❑ NSAIDs
- ❑ Opioids



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Genitourinary: Urinary Incontinence¹⁵

- Alpha-adrenergic Antagonists
- Antipsychotics
- Diuretics
- Sedative-hypnotics
- ACE inhibitors and ARBs
- Estrogens
- Hydroxychloroquine



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Genitourinary: Urinary Incontinence¹⁵

- Overflow Incontinence
 - Alpha-adrenergic Agonists
 - Antidepressants
 - Calcium channel blockers
 - NSAIDs



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Peripheral Edema¹⁶

- Dihydropyridine Calcium Channel Blockers
 - ▣ Nifedipine, felodipine, amlodipine
- Pioglitazone
- NSAIDs
- Estrogen and testosterone
- Pramipexole
- Gabapentin and Pregabalin
- Proton pump inhibitors (PPIs)



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Bleeding/Bruising¹⁷

- Anticoagulants
 - ▣ Argatroban, bivalirudin, heparin, warfarin
- Antiplatelets
 - ▣ Aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine
- NOACs
 - ▣ Apixaban, dabigatran, edoxaban, rivaroxaban
- NSAIDs
 - ▣ Low risk: celecoxib, etodolac, ibuprofen, meloxicam, nabumetone, salsalate
 - ▣ High risk: flurbiprofen, indomethacin, ketorolac, meclufenamate, naproxen, oxaprozin, piroxicam
- SNRIs
 - ▣ Desvenlafaxine, duloxetine, venlafaxine
- SSRIs
 - ▣ Citalopram, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline



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Skin Disorders¹⁸

- Drug-induced skin disorders are often classified as either acute or chronic.
- Acute diseases include:
 - erythematous eruptions; urticaria, angioedema, and anaphylaxis; fixed drug eruptions; hypersensitivity syndrome; Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); warfarin-induced skin necrosis; vasculitis; serum sickness–like reaction; acute generalized exanthematous pustulosis (AGEP); and photosensitivity.
- Chronic disorders include:
 - drug-induced lupus, drug-induced acne, and pigmentary changes



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Skin Disorders: Acute¹⁸

- Erythematous eruptions
 - Penicillins, cephalosporins, sulfonamides, anticonvulsants, allopurinol
- Urticaria, angioedema, and anaphylaxis
 - NSAIDs, antimicrobials, anticancer drugs, ACE inhibitors, corticosteroids
- Fixed-drug eruptions
 - Tetracyclines, barbiturates, sulfonamides, codeine, carbamazepine, acetaminophen, NSAIDs
- Drug hypersensitivity syndrome
 - Allopurinol, sulfonamides, anticonvulsants (barbiturates, phenytoin, carbamazepine, lamotrigine), dapsone, minocycline, gold salts
- Drug-induced vasculitis
 - Allopurinol, NSAIDs, cimetidine, penicillin, cephalosporins, fluoroquinolones, sulfonamides, hydantoin, propylthiouracil, minocycline, isotretinoin, methotrexate, colony-stimulating factors (drugs from almost every class have been implicated)



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Skin Disorders: Acute¹⁸

- Serum sickness–like reaction
 - Cefaclor, minocycline, penicillins, propranolol
- AGEP
 - Aminopenicillins, macrolides, quinolones, diltiazem, antimalarials
- Photosensitivity
 - Phototoxicity: quinolones, amiodarone, psoralens, methotrexate, voriconazole, furosemide, tetracyclines, sulfonamides, coal tar, NSAIDs, antineoplastic agents
 - Photoallergy: sulfonamides, sulfonylureas, thiazides, NSAIDs, chloroquine, carbamazepine, fluoroquinolones, phenothiazine, fibrates, statins, ACE inhibitors, calcium channel blockers, anticancer agents, topical treatments (antiseptics, sunscreen, cosmetics)
- SJS and TEN
 - Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, allopurinol, nevirapine
- Warfarin-induced skin necrosis: Warfarin



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Skin Disorders: Chronic¹⁸

- Drug-induced lupus
 - Procainamide and hydralazine (high risk); quinidine (moderate risk); isoniazid, methyldopa, minocycline, and chlorpromazine (low risk); TNF inhibitors (risk yet to be categorized)
- Drug-induced acne
 - Corticosteroids, androgenic hormones, some anticonvulsants, isoniazid, lithium, oral contraceptives, azathioprine, EGFR inhibitors, inhaled corticosteroids
- Pigmentary changes
 - Hyperpigmentation: minocycline, antimalarials, amiodarone, oral contraceptives, imipramine, anticancer drugs, NSAIDs
 - Hypopigmentation: topical tretinoin, corticosteroids
 - Depigmentation: monobenzyl ether of hydroquinone; contact with catechols, phenols, quinones



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Back to the patient case

- 72 y/o female, with a PMH of hypertension, GERD, and urinary incontinence presents with visual disturbances, a dry mouth, and complaining of abdominal pain due to constipation.
- Current medications include: Valsartan (Diovan), Omeprazole (Prilosec), and Oxybutynin ER (Ditropan XL)
- Which of the patient's medication could be causing these adverse effects?
 - Most likely the Ditropan XL due to anticholinergic activity



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Drugs with Anticholinergic activity¹⁹

- A 2015 study found that 77% of nursing home residents were administered at least one drug with Anticholinergic active each month.
- Prior studies have shown to be between 74% and 82%



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Drugs with Anticholinergic activity²

Mild	Moderate	Severe
Dryness of mouth (modest)	Moderately disturbing dry mouth/thirst Speech problems Reduced appetite	Difficulty chewing, swallowing, speaking Impaired perception of taste and texture of food Mucosal damage Dental decay, periodontal disease, denture mist Malnutrition Respiratory infection
Mild dilatation of pupils	Inability to accommodate Vision disturbances Dizziness	Increased risk of accidents and falls, leading to decreased function Exacerbation/precipitation of acute angle closure glaucoma
Urinary hesitancy	Oesophagitis Reduced gastric secretions, gastric emptying (atony) Reduced peristalsis, constipation	Faecal impaction (in patients with constipation) Altered absorption of concomitant medications Paralytic ileus, pseudo-obstruction
Decreased sweating	Increased heart rate	Urinary retention, urinary tract infection (in patients with urinary hesitancy) Conduction disturbances, supraventricular tachyarrhythmias Exacerbation of angina Congestive heart failure
Drowsiness Fatigue Mild amnesia Inability to concentrate	Excitement Restlessness Confusion Memory impairment	Thermoregulatory impairment leading to hyperthermia (heatstroke) Profound restlessness and disorientation, agitation Hallucinations, delirium Ataxia, muscle twitching, hyperreflexia, seizures Exacerbation of cognitive impairment (in patients with dementia)



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Drugs with Anticholinergic Activity

Anticholinergic side effects mnemonic

- ☐ Blind as a bat
- ☐ Dry as a bone
- ☐ Red as a beet
- ☐ Mad as a hatter
- ☐ Hot as a hare



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Questions



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