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Clinical Connection: Pharmacologic Agents and the Integument

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Sonya Dick, PT, DPT
Certified Wound Specialist by the American Board of Wound
Management
Fellow of the American College of Clinical Wound Specialists

Assistant Professor/Associate Director of Clinical Education
Western Kentucky University Doctor of Physical Therapy Program

Introduction and Course Objectives

- › Identify at least three common pharmacologic agents developed over last 5-7 years which may impact the integument and wound healing.
- › List at least three classes of pharmacologic agents that effect wound healing and overall physiology of the integument in patients.
- › Differentiate between at least two signs and at least two symptoms of disease process and possible adverse drug reactions (ADRs).
- › Outline at least three strategies for management of a patient with polypharmacy and potential integumentary disorder.
- › Understand why physical therapists need education and training in pharmacologic agents and how those agents impact the care of our patients

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Why do Physical Therapists study Pharmacology?

- › Understand your patient's response to a drug
- › Determine the ideal treatment schedule/timing
- › Recognize drug-therapy interactions when they occur
- › Recognize an ADR immediately and take appropriate action
- › Differentiate between ADR or actual disease process

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Naming & Classification Systems of Pharmacologic Agents

- › Body system treated (cardiovascular)
- › **Therapeutic effect (antihypertensive)** 46 classes
- › Pharmacologic action "MOA" (arterial vasodilator)
- › Molecular categories (beta-blocker)
- › Chemical or Source compound ("Atropine" from *Atropa*)
- › Chemical vs generic vs trade names: Can be confusing, Healthcare Professionals (HCPs) should use **Generic** drug names; Pharma companies will always market trendy trade names.

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Pharmacodynamics, Pharmacokinetics & ADRs

- › Dynamics are “how” a drug is delivered or acts at cellular or molecular level
- › Mechanism of action (MOA)
- › Agonists & Antagonists
- › Dose Response Curves
- › Therapeutic Index
- › Kinetics are “how” drugs are absorbed, metabolized, distributed and eliminated “AMDE” in the body
- › Delivery routes & barriers
- › Metabolic phases I & II
- › Age, genetics, disease and exercise effects on kinetics

ADRs : Unintended or unwanted effect of a drug that may occur even at acceptable levels (WHO definition)

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Adverse Drug Reaction vs Event

- › ADR must establish causal relationship
- › ADE no need to establish causal relationship
- › Patients **most likely** to experience an ADR:
 - Women
 - Elderly (> 60 y/o)
 - Polypharmacy patient
 - Infants-children (1-4 y/o)
- › Classification of ADRs
 - Mild: Opioids cause constipation
 - Moderate: NSAIDs cause HTN so another treatment required
 - Severe: ACE inhibitors cause Angioedema must DC drug
 - Lethal: Anticoagulants cause hemorrhage/CVA and results in patient death (15,107 in 2005 of 89,842 total ADRs)

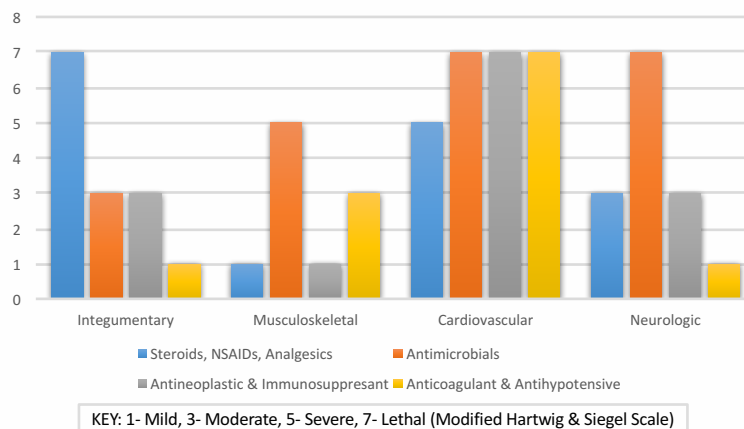
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› **Definition of *polypharmacy***

- › : the practice of administering many different medicines especially concurrently for the treatment of a single disease; ***also*** : the concurrent use of multiple medications by a patient to treat usually coexisting conditions and which may result in adverse drug interactions
- › "Polypharmacy." *Merriam-Webster.com*. Merriam-Webster, n.d. Web. 2 Feb. 2017.

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Drug Classes and Body Systems Interactions/ADR



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Drug Class: Side effect on Integument or Tissue repair

Therapeutic Drug Class	Negative effect	Positive effect
Steroids & NSAIDs	X	X
Antimicrobial & Antibiotics	X	X
Antineoplastics & Immunosuppressive	X	X
Anticoagulants & antihypertensives	X	X
Antihypertensives	X	X
Analgesics/Opioids	X	X

- There are approximately 46 Therapeutic Classes of drugs per Davis's Guide
- There are hundreds of Pharmacologic Classes of drugs assigned by the mechanism of action (MOA)
- Immunosuppressive(-) vs. Immunomodulatory(+ or -)

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Drugs Commonly used to promote healing....

- › “Trental” or pentoxifylline: Hemorrheologic or anticoagulant used for intermittent claudication and PVD symptoms, decreases fibrinogen & inhibits platelet aggregation.
- › “Regranex” or becaplermin: Platelet derived growth factor (PDGF) used for diabetic foot ulcers. > 3 tubes increased cancer rate.
- › “Doxy” or doxycycline: Antibiotic/tetracycline used orally at sub-antimicrobial doses for VLU's (inhibit MMP-9).
- › “Epogen” or epoetin alfa: Erythropoietin, hormonal, anti-anemic for increasing RBC production used topically in burns, pressure injuries, DFU's and other chronic wounds.

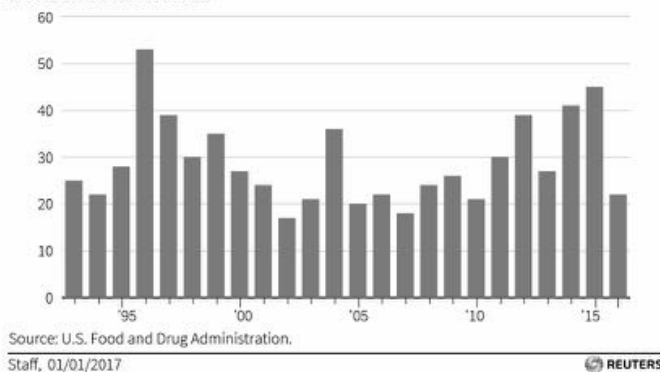
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Average cost: \$802M (2001) to \$1B USD (2010)
Time to Market: 10-15 years

U.S. FDA drug approvals

The FDA approved 22 novel drugs in 2016.

NUMBER OF APPROVALS



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Newest Drugs by Therapeutic Class:

Steroids & NSAIDs:

- Vivlodex (meloxicam) OA pain-2015
- Duexis (ibuprofen & famotidine) OA & RA pain ↓ Ulcer-2011
- Vimovo (naproxen & esomeprazole) joint pain ↓ Ulcer-2010

Antimicrobial & Antibiotics:

- Vaxchora (cholera vaccine) Cholera Immunization-2016
- Jublia (efinaconazole) Onychomycosis toenails-2014
- Luzu (luliconazole) Tinea pedis, cruris & coporis-2013
- Taflaro (ceftaroline fosamil) Bacterial skin infections-2010

<https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2010-2017>

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Newest Drugs Cont'd:

Antineoplastics & Immunosuppressive:

- Taltz (ixekizumab) 2016, Cosentyx (secukinumab) 2015, Otezla (apremilast) 2014 ALL for plaque psoriasis
- Ilaris (canakinumab) 2013, Actrema (ocilizumab) 2013, Xeljanz (tofacitinib) 2012 All for rheumatoid or juvenile arthritis

Antihypertensives:

- Prestalia (perindopril arginine & amlodipine besylate) ACE inhibitor & calcium channel blocker for HTN-2015

<https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2010-2017>

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Newest Drugs Cont'd:

Anticoagulants & Antihypotensives:

- Eliquis (apixaban) prevents embolism/stroke-2012
- Xarelto (rivaroxaban) prevents DVT/emboli/stroke-2011
- Pradaxa (abigatran etexilate mesylate) decrease stroke/emboli due to A-fib- 2010

Analgesics/Opioids:

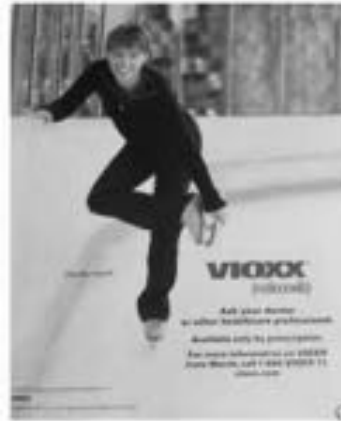
- Troxyca (oxycodone & naltrexone) opioid & opioid agonist for severe pain-2016
- Bunavail (buprenorphine & naloxone) opioid agonist for Rx of opioid dependence-2014
- Lyrica (pregabalin) neuropathic pain-2012

<https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2010-2017>

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Drugs removed from market by FDA

- › “Darvon” or Darvocet-propoxyphene on market from 1955-2010. Cardiac toxicity resulted in > 2,110 deaths.
- › “Vioxx” or Rofecoxib-NSAID- on market from 1999-2004 caused heart attacks, stroke and sudden cardiac death >60,000 deaths. Earliest known DTC advertisement.



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Drug Classifications their MOA, ADRs and Effect on Integument/Wound Healing

Clinical Cases and Most Likely to List

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Steroids

MOA

- Block the release of arachidonic acid, and the production of leukotrienes & prostaglandins
- Inhibit the synthesis of interleukins and tumor necrosis factor (tnf)

ADRs affecting Rehab

- Thinned skin, easy bruising, muscle wasting & weakness
- Hypertension & water/salt retention
- Steroid induced immunosuppression and diabetes (assess for hyperglycemia)

Integumentary considerations

- Inhibit fibroblast production which impedes wound contraction
- Decreased collagen production reduces tensile strength of remodeled tissue

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NSAIDS (Anti-Inflammatories)

MOA

- Reduce PGE2 (inflammatory prostaglandin) production
- Inhibit the Cyclooxygenase (COX) Inhibitors varying effect on COX 1 & 2

ADRs affecting Rehab

- GI discomfort & bleeding
- Nausea & vomiting, dyspepsia or constipation

Integumentary considerations

- Decrease the normal granulocytic inflammatory effect (combine with NO can prevent negative impact)
- Significantly reduces fibroblasts thereby inhibiting proliferation of granulation tissue

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Clinical Case

- › 78 y/o female 1 week s/p TKA.
- › **PMH:** Type 2 DM, HTN, polyarticular osteoarthritis and morbidly obese.
- › **Medications:** Metformin 25 mg PO q 6-8 hrs. Atenolol 30 mg PO QD. Methylprednisone 10 mg PO BID. Naproxen sodium 275 mg PO BID.
- › **Function:** Mod-max assist for all mobility.
- › **Findings:** Surgical site with lower area showing signs of inflammation and dehiscence with excessive serous exudate.



© My Knee Guide, used with permission

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Clinical Decision Making Process:

- › Treat? What is therapy plan of care?
- › Refer? What is not in our scope of practice?
- › Refer and Treat..... Differentiate what is beyond our scope.

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Antineoplastics & Immunosuppressives

MOA

- Inhibit cell division & growth, blocks angiogenesis
- Inhibit T-cell response, block transcription of cellular components

ADRs affecting Rehab

- Seizures, weakness, thrombocytopenia and leukopenia
- Depressed immune response

Integumentary considerations

- Delay inflammatory phase, decreased fibrin deposition & collagen deposition and delayed wound contraction
- Decreased availability of oxygen & nutrients to cells, tissue

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Clinical Case

- › 55 y/o male s/p bone marrow transplant for ALL.
- › **PMH/PSH:** Hypercholesterolemia, HTN and multiple allergic reactions since BMT.
- › **Medications:** Atorvastatin 40 mg PO QD. Atenolol 30 mg PO QD.
- › **Induction** chemo: Vincristine, prednisone, anthracycline, cyclophosphamide, and L - asparaginase given over the course of 4-6 weeks.
- › **Maintenance** chemo: Methotrexate
- › **Function:** Min assist for all mobility & easily fatigued with even walking across a room.
- › **Findings:** Maculopapular rash on palms of hands and soles of feet.



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Allergic reaction

- › Heightened immune response to pathogens or medications
- › IgE antibody response with histamine production
- › Often mild with minor rash and repeated exposures can either heighten or dampen response
- › Children and elderly often at higher risk
- › Anaphylaxis can be life threatening
- › Recent Epinephrine pen scandal

GVHD

- › Alloantigen T-cells destroy tissue
- › Acute: Very quick onset with 15-40% mortality rate in hematopoietic cell transplant patients
- › Inflammatory cytokines causing cytokine storm
- › Maculopapular rash palms/soles
- › Chronic: 3 months after transplant and multi organ system symptoms likely

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Clinical Decision Making Process:

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Antimicrobials & Antibiotics

MOA

- Inhibit bacterial DNA synthesis
- Inhibit glucan & synthesis of fungal cell walls

ADRs affecting Rehab

- GI upset (c-diff connection); topical irritations and rashes
- Allergic reactions including anaphylaxis
- Tendonitis/rupture & recently AAA disease/dissection (**Fluoroquinolone Class**)

Integumentary considerations

- Multi-drug resistance (MDR) and photosynthetic rashes
- Decreased collagen synthesis and increased collagen lysis for remodeling and tensile strength

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Clinical Case

- › 42 y/o female 2 weeks s/p Achilles tendon repair
- › **PMH/PSH:** Frequent UTI's, Laproscopic cholecystectomy
- › **Medications:** Ciprofloxacin 500 mg PO q 12 hours, Ibuprofen 800 mg q 4-6 hours or PRN for pain
- › **Function:** Mod. Indep with crutches
- › **Findings:** Abdominal pain x 2 days "getting worse"



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Clinical Decision Making Process:

- › Treat? What is therapy plan of care?
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Anticoagulants & Antihypotensives

MOA

- Potentiates inhibitory effect of antithrombin of factor Xa & thrombin, inhibit platelet aggregation
- Stimulate alpha-1 & beta-2 adrenergic receptors to cause vasodilation of blood vessels-lowering blood pressure "vasopressors"

ADRs affecting Rehab

- Bleeding, anemia, thrombocytopenia, hair loss & osteoporosis w/long term use
- Angina, arrhythmias, hypertension, tachycardia, tremors, N & V

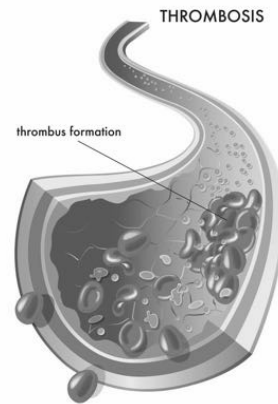
Integumentary considerations

- Inability to clot can impair hemostasis & subsequent phases
- Vasopressors in ICU patients: Increased rate of DTIs and pressure injuries

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Clinical Case

- › 84 y/o female in SNF/Rehab unit
- › **PMH:** Dementia, DJD, CAD w/stent 20 yrs ago; gastric ulcers w/recent GI bleed and L groin and LLQ abdominal surgical wounds for exploratory surgery.
- › **Medications:** Donepezil 10 mg QD, Clopidogrel 75 mg QD, Ibuprofen 800 mg PRN, aspirin was recently stopped after GI bleed & started Sucralfate 2 g BID.
- › **Function:** Mod-Max assist for OOB & standing; not able to fully WB left LE
- › **Findings:** L LE from groin to knee & LLQ abdomen swollen no calor or rubor.



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Clinical Decision Making Process:

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Antihypertensives

MOA

- Beta-blockers reduce heart rate & cardiac output. ACE inhibitors block endothelin receptors.
- Diuretics decrease blood volume & vasodilators relax vascular smooth muscle.

ADRs affecting Rehab

- Severe lowering of BP and syncopal episodes
- Orthostatic hypotension and dehydration; use caution on initial standing and offer fluids.

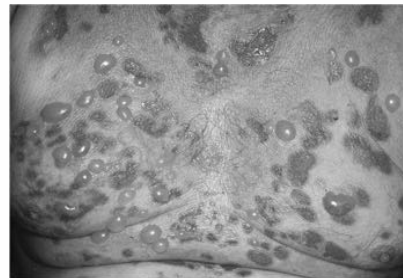
Integumentary considerations

- ACE Inhibitors "Captopril" or diuretics "furosemide/Lasix" can cause autoimmune blistering skin disorders

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Clinical Case

- › 67 y/o male accountant lives at home with wife & 2 dogs.
- › **PMH/PSH:** Type 2 DM, HTN, GERD, R TKA, multiple lumbar surgeries including fusion L2-L4 and morbidly obese.
- › **Medications:** Glipizide 10 mg QD, Captopril 50 mg TID, Omeprazole 20 mg QD and NSAIDs PRN for back pain & OA pain.
- › **Findings:** Recent rapid onset of rash which had started in his mouth and is now covering upper torso; not itching just very painful.



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Bullous pemphigoid or Pemphigus vulgaris

- | | |
|--|--|
| › Nikolsky's sign negative | › Nikolsky's sign positive |
| › No "tombstoning" of keratinocytes histologically | › Tombstoning of keratinocytes does occur |
| › Pathology at dermal & epidermal junction (DEJ) | › Pathology stays in epidermis between keratinocytes |
| › Highly correlated with penicillamines and ACE inhibitors | › > 70 y/o and 14 cases per million per year (rare) |
| › Middle age and above at .68 per 100,000 cases per year | › Painful but rarely pruritic |
| | › Diagnose all pemphoid diseases w/biopsy |

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Clinical Decision Making Process:

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Analgesics/Opioids

MOA

- Opioids: Binding or blocking opiate receptors (mu, delta or kappa) in brain, can be full or partial agonist or agonist-antagonist
- Non-opioids: inhibit production of prostaglandins

ADRs affecting Rehab

- Physiology of pain: highly complex, #ChoosePT campaign
- Sedation, decreased respirations and cognition, truncal rigidity, hypotension, N & V, brady or tachycardia

Integumentary considerations

- Pruritis, hypo or hyperthermia and allergic reactions including rashes

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Clinical Case

- › 32 y/o male factory worker lives with wife and 3 children.
- › **PMH/PSH:** GERD, Allergies, R shoulder RTC repair & occasional athlete's foot in high school. Recent sore throat & fever.
- › **Medications:** Omeprazole 20 mg QD, Cetirizine 10 mg QD, Azithromycin 250-500 mg QD x 5 days & Dexamethasone 5 mg IM.
- › **Findings:** Pustules & rash plantar surface B feet, no pruritis or burning x 2 days since started Z-pack & got steroid shot.



Podiatry Today online case by Saleena Niehaus, DPM Feb 1, 2017

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Clinical Decision Making Process:

- › Treat? What is therapy plan of care?
- › Refer? What is not in our scope of practice?
- › Refer and Treat..... Differentiate what is beyond our scope.

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Disease Process

- › Cancerous lesions (ABCDE)
- › “Phlebitis” type rashes with vascular ulcers
- › Dermatologic disorders; contact, atopic or dyshidrotic dermatitis
- › Rheumatologic diseases: “Skin is the MAP”
- › STDs (multiple) and HSV1-2 or VSV “shingles”

Adverse Drug Reaction

- › Rashes, hives and pruritis (location, location, location)
- › Hemorrhage, petechiae or ecchymosis
- › Nail bed: Photo-onycholysis or Beau’s lines
- › Photosensitivity: Antibiotics, NSAIDs, Hypoglycemics
- › Poor wound repair

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Non-Prescription Agents:

Illicit, Vitamins/Minerals & OTC

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ILLICIT DRUGS, TOBACCO & ALCOHOL

Effects of ALL street drugs on Integumentary system is not well represented in the literature.

Many of similar MOA to “analgesics” or they are barbiturates & opioids.



- › Nicotine is a plant alkaloid which is poisonous to many cells and also a known carcinogen.
- › Alcohol increases insulin resistance & decreases nutrient absorption effecting blood sugars increases protein malnutrition.
- › Both negatively effect ALL phases of wound healing: decreased neutrophil & macrophage activity, impaired angiogenesis, increased tissue hypoxia, decreased remodeling & tensile strength.
- › These patients often have higher rates of surgical wound dehiscence and hospital acquired infections.

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VITAMINS & MINERALS

Zinc, Iron & Copper are Key minerals: Zinc most studied & essential for DNA synthesis

Meet D.B. CAKE:

- D- Produced in Integument; promotes proliferation & differentiation of cells
- B1, 2 & 5- Required for collagen cross-linking
- C- Increase leukocyte/macrophage activity
- A- Required for epithelialization
- K- Clotting factors
- E- Consumers use widely; inconclusive evidence
- ACE are used systemically and topically with strong research evidence
- C & B: Water-soluble (↓ toxicity) A, D, K & E: Fat-soluble (↑ toxicity)

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OVER THE COUNTER PRODUCTS

- › NSAIDs and other analgesics (see counterparts in prescribed agents)
- › Allergy relief: oral, topical or inhaled (mostly antihistamine or anti inflammatory)
- › Gastrointestinal care
- › Cold & Flu medications
- › Genito-urinary products: male & female; topical & oral
- › Antimicrobials: yeast, fungus, bacteria

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FINAL CLINICAL CASE STUDY DISCUSSION

- POC Template and Case Provided
- Review and type in any questions???
- Develop PT Plan of Care per Template

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Clinical Connection Case Study

Pt is a 62 y/o female in ICU with multiple traumatic injuries after a car accident 12 days ago. Left LE wound has been surgically debrided 2 days previous; today is initial dressing take down and there is a PT referral for "Mobility and Wound Care".

PMH/PSH: Polyarticular DJD w/R TKA 5 years ago, HTN, CVA 3 years ago w/ residual mild RUE hypertonicity, hypercholesterolemia, seizure disorder, depression and morbidly obese.

Recent medical complications secondary to MVA: Chest contusions, Grade III liver laceration, acute respiratory failure w/fluid overload just extubated yesterday and right sided facial fractures with orbital edema causing visual deficit in right eye field of vision, extensive facial and abdominal/trunk bruising and 3 small areas of sutures on right side of face.

Medications:

Daily/Routine: Clopidogrel 75 mg QD, Clonazepam 1 mg TID, Lisinoprel 30 mg QD, Atorvastatin 40 mg QD, Celocoxib 100 mg BID and Fluoxetine 90 mg weekly.

Hospital Stay: Vasopressin then switch to Dobutamine x 10 days, Morphine drip x 7 days, Lorazepam IV q 4 hours until extubation and Carbapenem IV q 12 hours x 5 days. Hydrocodone/ibuprofen PO 10 mg q 4 hours.

Personal/Home: Pt is widowed and lives in an "apartment" within the home of her daughter, son-in law and their children. Used a single tip cane for community ambulation only, otherwise Indep or Modif Indep with all mobility, ADL's and was still driving and volunteered 3 days a week at local charities.

Wound is packed with gauze that was impregnated with Iodosorb. Wound was surgically debrided yesterday; this is first dressing change. Wound has approximately 30% slough and 70% beefy red tissue.



Physical Therapy POC & Goals: Template

1. Functional Mobility
2. Integument/Wound Care
3. Education
4. Prevention & Health Promotion
5. What are possible ADRs or “Red Flags”?

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“Words are; of course, the most powerful drug used by mankind. Not only do words infect, ergotise, narcotise, and paralyse, but they enter into and colour the minutest cells of the brain.”

Kipling, 1923
Royal College of Surgeons

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References

- Anderson K, Hamm RL. Review Article: Factors That Impair Wound Healing. *Journal Of The American College Of Clinical Wound Specialists*, 2012;484-91. doi:10.1016/j.jccw.2014.03.001
- Boateng JS, Matthews KH, Stevens HNE & Eccleston GM. Wound healing dressings and drug delivery systems: A review. *J. Pharm. Sci.*, 2008;97: 2892–2923. doi:10.1002/jps.21210
- Bootun, R. Effects of immunosuppressive therapy on wound healing. *International Wound Journal*, 2013;10(1), 98-104 7p. doi:10.1111/j.1742-481X.2012.00950.x
- Bosanquet D, Rangaraj A, Richards A, Riddell A, Saravolac V, & Harding K. Topical steroids for chronic wounds displaying abnormal inflammation. *Annals of The Royal College of Surgeons of England*, 2013;95(4), 291–296. <http://doi.org/10.1308/003588413X13629960045634>
- Bradford WD1, Kleit AN, Nietert PJ, Steyer T, McIlwain T, Ornstein S. How direct-to-consumer television advertising for osteoarthritis drugs affects physicians' prescribing behavior. 2006 Sep-Oct;25(5):1371-7.
- Choron RL, Chang S, Khan S, Villalobos MA, Zhang P, Carpenter JP, Liu, Y. Wound Healing/Plastic Surgery: Paclitaxel impairs adipose stem cell proliferation and differentiation. *Journal Of Surgical Research*, 2015;196404-415. doi:10.1016/j.jss.2015.03.026
- Ciccone CD. *Davis's Drug Guide for Rehabilitation Professionals*. Philadelphia, PA. FA Davis & Company; 2013.
- Curtis BJ, Hlavin S, Brubaker AL, Kovacs EJ, & Radek KA. Episodic Binge Ethanol Exposure Impairs Murine Macrophage Infiltration and Delays Wound Closure by Promoting Defects in Early Innate Immune Responses. *Alcoholism: Clinical & Experimental Research*, 2014;38(5), 1347-1355 9p. doi:10.1111/acer.12369
- Fox AJ, Schär MO, Wanivenhaus F, Chen T, Attia E, Binder N, Rodeo SA. Fluoroquinolones Impair Tendon Healing in a Rat Rotator Cuff Repair Model: A Preliminary Study. *American Journal Of Sports Medicine*, 2014;42(12), 2851-2859.

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References Cont'd

- Gladson B. *Pharmacology for Rehabilitation Professionals*. St Louis, MO. Elsevier Health Sciences; 2014.
- Goodman CC, Snyder TE. *Differential Diagnosis for Physical therapists: Screening for Referral*. 5th Ed. St Louis MO. Elsevier; 2013.
- Gottrup F, Apelqvist J, Bjarnsholt T, Cooper R, Moore Z, Peters, EG, & Probst S. Antimicrobials and Non-Healing Wounds. Evidence, controversies and suggestions—key messages. *Journal Of Wound Care*. 2014;23(10), 477-482 6p. doi:10.12968/jowc.2014.23.10.477
- Hamed S, Bennett CL, Demiot C, Ullman Teot L & Desmouliere A. Erythropoietin, a novel repurposed drug: An innovative treatment for wound healing in patients with diabetes mellitus. *Wound Repair and Regeneration*. 2014;22; 23-33.
- He Y, Shimoda M, Ono Y, Villalobos IB, Mitra A, Konia T, Grando SA et al. Persistence of autoreactive IgA-secreting B cells despite multiple immunosuppressive medications including Rituximab. *JAMA Dermatology*, 2015;151(6):646-650.
- Koh Y, Yap CW, Li S-C. Development of a combined system for identification and classification of adverse drug reactions: Alerts Based on ADR Causality and Severity (ABACUS). *Journal of the American Medical Informatics Association : JAMIA*. 2010;17(6):720-722. doi:10.1136/jamia.2010.006882
- Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *British Medical Journal*, 2008;337;180.
- MacKay D, Miller AL. Nutritional support for wound healing. *Alternative Medicine Review*. 2003;8(4):359-377.
- Niehaus S. A closer look at pustular tinea pedis. *Podiatry Today* via online access February 1, 2017.
- Sandberg O, Eliasson P, Andersson T, Agholme F, & Aspenberg P. Etanercept does not impair healing in rat models of tendon or metaphyseal bone injury. *Acta Orthopaedica*, 2012;83(3), 305-310 6p. doi:10.3109/17453674.2012.693018.
- Serra R, Gallelli L, Buffone G, Molinari V, Stillitano DM, Palmieri C. and de Francis S. (2015), Doxycycline speeds up healing of chronic venous ulcers. *Int Wound J*, 12: 179–184. doi:10.1111/iwj.12077
- Sussman C, Bates-Jensen BM. *Wound Care: A Collaborative Practice manual for Physical therapists and Nurses*. 4th Ed. Philadelphia PA. Lippincott, Williams & Wilkins; 2012.

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