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Medications and Wound Healing/Wound Generation:
Systemic and Topical Therapies

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Objectives

Participants will:

1) Discuss chronic illnesses and polypharmacy of wound patients in health care.
2) Describe data around the effects of common systemic and topical medications on the inhibition or stimulation of wound healing
3) Discuss clinical practices that can mitigate the inhibitory effects of certain medications on wound healing
Major Topics

1) Introduction and Background
2) Polypharmacy in Wound Care
3) Medications’ Effects on Wound Healing: Literature-Based Data
   – Oral systemic and topical (traditional and alternative) therapies
4) Clinical Approaches to Promoting Wound Healing
Normal Wound Healing

- Human body “wired” to heal
- Despite many obstacles, most wounds heal
- Not here to discuss this comforting reality
- Here to discuss pharmacologic impact on wound healing and wound generation
Normal Wound Healing

- Four phases overlapping/special cells (keratinocytes, fibroblasts, endothelial cells, macrophages, platelets)
- **Hemostasis** – platelets, growth factors (immediate)
- **Inflammation** – macrophages, leukocytes, mast cells (day 1–4)
- **Proliferation** – fibroblasts, myofibroblasts, endothelial cells
- **Remodeling** (maturation) (Day 21 – 2 years) (80% of original strength)
Stages of Wound Healing

**Hemostasis** (Injury)
- Vascular constriction
- Platelet activation
- Blood clotting cascade (PDGF, TGF-B, TGF-A, EGF)

**Inflammation**
- Cell recruitment (neutrophil, monocyte, lymphocytes, macrophage)
- Phagocytosis
- Debridement (PDGF, TGF-B, TGF-A, IL-2, IFN, EGF, TNF-A)

**Proliferation**
- Release of cytokines
- Cell growth and activation (epithelial cells, fibroblasts, endothelial cells)
- Neovascularization (angiogenesis)
- Granulation tissue formation (PGDF, TGF-B, FGF, IGF, IFN, TGF-A, EGF)

**Maturation**
- Wound contraction
- Fibroblasts, epithelial cells
- Vascular maturation and regression
- Remodeling (TNF-A, IL-1, PDGF, TGF-B, EGF)
Chronic Wound
(Armstrong & Meyr, UptoDate, 2018)

- Defined as wound that is physiologically impaired due to:
  - Inadequate angiogenesis
  - Impaired innervation
  - Impaired cellular migration

- Medications can affect *any* aspect of wound healing
In 2015, top 10 leading causes of death accounted for approximately 75% of all US deaths

In 2015, 2,712,630 Americans died (86,212 more than 2014) (CDC, 2018)
Top 10 Causes of Death

1) Heart Disease*
2) Cancer*
3) Chronic Lower Respiratory Disease*
4) Unintentional injuries
5) Stroke*
6) Alzheimer’s Disease*
7) Diabetes*
8) Influenza/pneumonia
9) Kidney Disease*
10) Suicide

*Chronic Disorders

(CDC, 2018)
As of 2012, half of all American adults had one or more chronic diseases
Constitutes 117 million Americans
Obesity – serious health disorder – approaching 50% are obese or overweight
Diabetes mellitus type 2 – pandemic
Risk behaviors: Little or no exercise, poor dietary habits (fat, calories, salt), smoking (1 in 5 adults), alcohol abuse (CDC, 2018)
Arthritis affects 53 million Americans
86% of all US healthcare spending in 2010 was for people with one or more chronic diseases.

In Americans over 65, 3 of 4 have multiple chronic conditions.

93% of total Medicare spending in 2012 was for people with multiple chronic conditions (CDC, 2018; CMS, 2012)
Aging Consequences

- More than 36 million are edentulous
- 120 million more are missing one or more teeth
- In next 15 years, tooth loss will affect 200 million Americans
- Medications/disease can affect implant osteointegration (Aghaloo et al, 2019)
- SSRIs and PPIs increase odds for implant failure
Chronic Wounds

- Pressure injuries – focus of today’s conference
- Venous ulcers
- Arterial ulcers
- Neuropathic (diabetic) ulcers
- Vasculitic and “other” ulcers
- Just about ALL wound patients are receiving medication therapy
Wound healing affected by many drugs and disease processes

Nearly 50% of Americans take one prescription drug monthly

Twenty percent take three drugs or more a month

Eleven percent take five or more drugs (CDC, 2017)

Thirty-six million Americans use herbals yearly (Ranade & Collins, 2014)

U.S. herbal use grew for 12th straight year (Crane, 2016)
Medications Associated with Wound Healing Delays

- Anticoagulants
- Antimicrobials
- Aspirin/NSAIDs
  - NSAIDs impair fibroblasts; weaken wound contraction with long-term use
    - (Guo et al, 2010)
- Povidone/Iodine
- Colchicine
- Dakin’s solution
  - Useful and safe if used diluted and for short-term
- Glucocorticoids
- Immunosuppressive agents
- Anti-angiogenesis agents
- Anticoagulants – Warfarin, Dabigatran
Antineoplastic agents
◦ Reduce RBC and WBC presence
◦ Damage keratinocyte
◦ May decrease VEGF and angiogenesis

Colchicine
◦ Reduces granulocyte migration
◦ Reduces fibroblast synthesis

Beta blockers – help skin diseases of vascular origin (Chen et al, 2018)

Vasoconstrictors
◦ Decrease tissue perfusion

Anti–rheumatoid drugs
◦ Methotrexate: cytotoxic to T cells and macrophages

Nicotine and smoking (But NRT does NOT impair healing)
DMARDS and SSI/Delayed Wound Healing

- Looked at risk factors for SSI and DWH
- Risk factors were foot/ankle surgery, total knee arthroplasty, and rheumatoid arthritis (RA) disease duration
- Looked at conventional synthetic DMARDs; looked at biologic DMARDs as variables
- Neither were risk factors
- Why?? – drugs stopped 2–4 weeks before surgery
- Restarted infliximab in 4 weeks after surgery; others (Entanercept, Adalimumab, Tocilizumab, Golimumab) restarted after healing of surgical wounds
Gaucher et al, 2017

53-year-old male with sarcoidosis and steroid-induced diabetes

Receiving methotrexate and prednisone

Developed LLE cellulitis

Stopped prednisone

Treated cellulitis

Four rounds of skin grafting: stopped methotrexate

Fifth skin graft was successful
Cancer Chemotherapy: Antiangiogenics (Choueiri & Sonpavde, 2018; McIntyre, 2015)

- Use is expanding
  - Bevacizumab (Monoclonal antibody; VEGF–A inhibitor)
  - Aflibercept (VEGF–A, VEGF–B)
  - Sunitinib (Tyrosine kinase inhibitor)
- Can cause impaired wound healing, osteo–necrosis of jaw, hand–foot skin reaction, hand–foot syndrome, and bleeding
Notorious inhibitors of wound healing
Notorious for systemic effects (hyperglycemia, osteoporosis, mood changes)
Steroids affect cells by altering gene expression after crossing cell membrane
Consequently affect almost every phase of wound healing
Degree of inhibition related to potency of steroid
Long-term usage impact is the challenge: bottom line is immune modulation (and associated derived risks)
Steroids: Specific Effects

- Delay in removal of bacteria and foreign bodies
  - Decreased neutrophil and macrophage activity
- Decrease in epithelial regeneration and granulation activity (caused by steroids anti-mitotic activity)
- Decrease in fibroblast activity
- Over time thinned epidermis inhibits wound contraction

Yet **no problem** with acute surgical healing if not long-term use (Treadwell, 2013; Wang et al, 2013)

And when used topically may *help* healing (e.g., stasis dermatitis)
Glucocorticoids, Vitamin A, and Neurosurgery

- Glucocorticoids used to decrease inflammatory response in neurosurgery
- Vitamin A known to reverse steroid effects
- Vitamin A in large doses causes increased ICP
- Not good for neurosurgical patients (Berry et al, 2019)
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

- Work by inhibiting Cyclooxygenase (COX)
- COX affects arachidonic acid and prostaglandins; blocking has serious effects
- NSAIDs – have well known effect on delaying bone healing
- Krischak et al (2007): Found diclofenac inhibited fibroblasts after use in 10 rats (lab testing)
- Can affect ligament health too
Retrospective study of all orthopedic patients with femur, tibia, and/or humerus fractures between October 2009 and September 2011 – University of Tennessee Level 1 Trauma Center

1,901 patients with LBFs

Assessed for complications: Nonunion/malunion, infection

60 patients had complications

Logistic regression calculated ORs

Patient more likely to have complication if received NSAIDs postop (OR 2.17) or if they were smokers (OR 3.19)

Recommend avoidance of NSAID use in traumatic LBF
Large retrospective study of adult GI surgery patients between 2008 and 2012

Among 398,752 patients, 55% underwent colorectal surgery and 45% had non–colorectal GI surgery.

Five percent of all received ketorolac (IV)

These patients had higher odds of re–intervention (OR 1.20), emergency room visit (OR 1.44) and 30–day readmission (OR 1.11) and readmission for anastomotic complications (OR 1.2)

Use great caution when using IV ketorolac in patients undergoing GI surgery

- Tested 42 rats with **oral** sildenafil (10mg/kg) in 1cc distilled water via NG tube vs. sodium chloride injection in intraperitoneum (21 exp; 21 control)
- Created an ischemic skin wound on rats’ abdomens
- Checked healing at days 3, 5, 10 on 7 rats in each group
- Theoretically sildenafil (PDE-5 inhibitor) should **help** healing
- Sildenafil significantly **reduced** re-epithelialization, neovascularization, granulation tissue and number of inflammatory cells on day 3
- **Increased** inflammatory cells on day 10
- **Oral** vs. **Topical** sildenafil: have differential effects on wounds
Animal Studies Inform Care

- Leise (2018) noted that tap water is cytotoxic to equine wounds (okay for humans) (weird but true)
- Veterinarians use saline
- Vets use topical antiseptics (Povidone or CHG) but diluted
- Aloe vera works for both animals and humans
Other Side Of The Coin
Medications Improving Wound Healing

- Hemorrheologics (e.g., pentoxifylline (Trental))
- Hormones (estrogen): Topical
- Hormones: Insulin parenteral (Levine, 2018)
- Phenytoin (think gums): topical (Cochrane Review by Hao et al, 2017)
- Prostaglandins
- Zinc (need correct balance)
- Vitamins A and C
- Hormones: Testosterone (oxandrolone)
- Metformin – cardioprotectant and anti-atherosclerotic (Marmolejo et al, 2019)
Medications *Improving* Wound Healing

- **Topical “Natural” Medications** (more later)
  - Aloe vera
  - Curcumin
  - Ginger
  - Medicinal Honey (Cooper, 2017)
  - Mucilage (in Slippery Elm)
  - Witch Hazel

- **Off Label** Topical Traditional Drugs (more later)
  - Calcium Channel Blockers
  - Topical Regular Insulin (Shridharan et al, 2017)
  - Topical Nitroglycerin
  - Topical doxycycline on DFUs (Gabrielle et al, 2019)
Medications Improving Wound Healing

- **Off Label** Topical Traditional Drugs
  - Topical Dilantin (Phenytoin) (Hao et al, 2017)
  - Topical Hemoglobin (Hunt, 2017)
  - Topical Timolol (0.5%) (Chen et al, 2018)
  - Topical Tadalafil (Cialis) (Davenport et al, 2015)
  - Topical Tacrolimus (Ginocchio et al, 2017)
  - Topical Sucralfate (Godhi et al, 2017)
  - Topical Propanolol (1%) (Zileng et al, 2017)
  - Topical Metformin (Zhad et al, 2017)
  - Topical Enalapril (Less scarring) (Mohammadi et al, 2018)
Periodontal Patients

- 19 patients with IBD had anti–TNF alpha therapy
- Had 14 control patients
- Underwent dental surgery including root canal
- Patients with IBD on anti–TNF alpha meds healed *better* \((p < .05)\) Cotti, et al, 2018)
Clinical Wake Up Call

- Polypharmacy is the norm
- Co-morbidities are common
- Drugs involved in all wound patients care
Case Study From Real World

- 94-year-old female admitted from home; cared for by son who is devoted to her; sits at bedside; multiple co-morbidities including dementia, poor nutrition, immobility and frailty
- Consultation for wound care team: has pressure injuries on sacrum, bilateral hips and sternum
- Also has “rash” on extremities and trunk
- Multiple medications; nothing new except recently began Aricept (donepezil)
Drugs Can “Break Bad”
Drugs Can CAUSE Wounds
Cutaneous Adverse Drug Reactions

- One of most common adverse reactions
- Overall incidence rate of 2–3% in hospitalized patients
- Almost any (1:1000 hospitalized patients (Ijaz, 2015)) medication can induce skin reactions
- Selected drug classes have rates as high as 5% (Lee & Thomson)
- Some reactions are immunological; most are *not* (thankfully)
- Categorized by predictability (pharmacological) or immune basis
Type A/Type B Categories

Type A: 85–90% of adverse drug reactions (ADEs); *predictable* from known pharmacologic properties of a drug. Examples:

- Diarrhea – Antibiotics
- Gastritis – NSAIDS
- Kidney toxicity – Aminoglycosides (Kaniwa et al, 2013)
Type A/Type B Categories

Type B: 10–15% of ADEs hypersensitivity: Immunologic or other patho–mechanisms; have signs/symptoms different from action of drug usually not predictable. Examples: Exaggerated sensitivity to known drug reactions – tinnitus from low dose aspirin (Kaniwa et al, 2013)
Immunological (Hypersensitivity) Reactions

Type I: Cased by drug/antigen specific IgE that links with mast cells and basophils – immediate release of histamine/leukotrienes get urticaria, angioedema, anaphylaxis (aspirin, penicillins)

Type II: Cytotoxic reactions based on IgG or IgM – mediated mechanisms antibody ruptures cell (blood cell dyscrasias like hemolytic anemia and thrombocytopenia)
Immunologic (Hypersensitivity) Reactions

**Type III:** Mediated by intravascular immune complexes. Antibodies and drug antigens in circulation. Phagocytes remove complexes and ends up in skin, kidneys, etc. (serum sickness, vasculitis)

**Type IV:** Mediated by T cells; cause “delayed” hypersensitivity (contact dermatitis, SJS and TENS)
## Uncommon Drug Offenders (Rarely Cause Skin Eruptions)

<table>
<thead>
<tr>
<th>Medication</th>
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<tbody>
<tr>
<td>Antacids</td>
<td>Muscle Relaxants</td>
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<td>Antihistamines (oral)</td>
<td>Nitrates</td>
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<tr>
<td>Atropine</td>
<td>Nystatin</td>
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<td>Benzodiazepines</td>
<td>Oral Contraceptives</td>
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<td>Corticosteroids</td>
<td>Propanolol</td>
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<td>Digoxin</td>
<td>Spironolactone</td>
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<td>Ferrous Sulfate</td>
<td>Theophylline</td>
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<td>Insulin</td>
<td>Thyroid Hormones</td>
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<tr>
<td>Laxatives</td>
<td>Vitamins</td>
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<tr>
<td>Local Anesthetics</td>
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Type of Skin ADEs

- Exanthems
- Fixed Drug Eruptions (Allergic)
- Blistering
- Psoriasiform
- Immune Mediated (SJS and TEN)
- Hematologic/Vasculitic
Risk Factors for Skin ADE

- History of atopy
- Viral infections (e.g., HIV, Hepatitis C)
- Female gender
- Genetic polymorphism
- Connective tissue disorders
- Solid organ cancers (Ijaz, 2015)
Exanthem Response
Blistering: Bullous Pemphigoid
Hematologic: Warfarin Necrosis
Common Drug Offenders: Exanthems

- Allopurinol
- Antimicrobials (PCN, Cephalosporins, Erythromycin, Gentamicin, Anti-TB Drugs, Nitrofurantoin, Sulfa)
- Barbiturates
- Captopril
- Carbamazepine
- Furosemide
- Gold Salts
- Lithium
- Phenothiazine
- Phenytoin
- Thiazides
Common Drug Offenders
(Fixed Drug Eruption – Same Site*)

- ACE Inhibitors
- Allopurinol
- Antimicrobials (Sulfa, Tetracyclines, Cephalosporins, PCN, Clindamycin, Trimethoprim, metronidazole)
- Barbiturates
- Benzodiazepines
- Calcium Channel Blockers
- Carbamazepine
- Fluconazole
- Lamotrigine
- NSAIDs
- Paclitaxel
- Proton Pump Inhibitors (Omeprazole, Lansoprazole)
- Salicylates
- Terbinafine

*Reaction at same site or sites each time drug is taken
Common Drug Offenders
Blistering Reactions

- ACE Inhibitors (captopril, enalapril)
- antibiotics (cephalosporins, penicillins, sulfa agents, tetracyclines, vancomycin)
- gold/sodium aurothiolamar
- lithium
- loop diuretics (eg, furosemide, bumetanide)
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- penicillamine
- thiazide diuretics (eg, hydrochlorothiazide)
Common Drug Offenders Causing Psoriasiform Eruptions

- ACE–I
- Beta Blockers
- Chloroquine
- Digoxin
- Gold
- Interferons
- Lithium
- NSAIDs
- Terbinafine
- Tetracyclines
- TNF–Alpha Antagonists
TENS
## Common Drug Offenders (SJS/TEN)

<table>
<thead>
<tr>
<th>SJS</th>
<th>TEN</th>
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<tr>
<td>Barbiturates*</td>
<td>Allopurinol</td>
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<tr>
<td>Beta–Lactams</td>
<td>Anti–TB Drugs</td>
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<tr>
<td>Carbamazepine*</td>
<td>Barbiturates*</td>
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<tr>
<td>Chloropropamide</td>
<td>Carbamazepine*</td>
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<td>Co–Trimoxazole</td>
<td>Gold*</td>
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<td>Gold*</td>
<td>Griseofulvin</td>
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<td>H2 Antagonists</td>
<td>Lamotrigine*</td>
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<td>Lamotrigine*</td>
<td>Leflunomide*</td>
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<td>Leflunomide*</td>
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<tr>
<td>Macrolides</td>
<td>Nitrofurantoin</td>
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<td>NSAIDs</td>
<td>NSAIDs*</td>
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<td>Phenothiazines</td>
<td>Penicillins</td>
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<td>Phenytoin*</td>
<td>Phenytoin*</td>
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<tr>
<td>Rifampicin</td>
<td>Salicylates</td>
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<td>Sulfonamides*</td>
<td>Sulfonamides*</td>
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<td>Tetracyclines*</td>
<td>Tetracyclines*</td>
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<tr>
<td>Thiazides</td>
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</tbody>
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* Can cause **both** SJS and TEN
Common Drug Offenders (Vasculitis Reactions)

- Allopurinol
- Aspirin
- Beta–Lactam Antibiotics
- Carbamazepine
- Co-trimoxazole
- Diltiazem
- Erythromycin
- Furosemide
- Gold
- Hydralazine
- Methotrexate
- NSAIDs
- PTU
- Sulfasalazine
- Sulfonamides
- Thiazides
- Thrombolytic Agents
WISN: Warfarin–induced skin necrosis
HIT Syndrome
WISN: occurs 3 to 5 days after dose of warfarin; often in patient with Protein C and Protein S deficiencies
Red painful plaques
Progress possibly to hemorrhagic blisters, ulcers, necrosis (Clinard et al)
Warfarin Necrosis
Warfarin Necrosis
Hematologic ADR of Skin

➢ HIT Syndrome (Specifically HIT II)
  o Get loss of heparin due to Immune complex (HIT antibodies)
  o Get destruction of platelets from antibody complexes (Trautman et al, 2010)
  o Decreased platelets < 150,000
  o Get arterial and venous thrombosis
  o Necrosis of skin in fatty areas as abdomen, thighs
    – can also be blisters, purpura
  o Diagnosis: Use “4Ts Score” (Thrombocytopenia, timing of platelet fall, thrombosis and sequelae, other causes for thrombocytopenia) (Coutre, 2018)
HIT Skin Necrosis
Heparin-Induced Thrombocytopenia Lesions
General Management Points SKIN ADEs

- Examine skin eruption closely and determine if drug–related
- Educate patient about avoidance of drug in future; record clearly in history
- If serious enough, Medic Alert bracelet
- Notify pertinent regulatory authorities if serious reaction (FDA FAERS (Federal adverse Event Reporting System: www.fda.gov))

- Total of 180 ADEs in 125 patients (27%)
- Of these 74 (41%) were preventable; 95% caused temporary harm
- Most common ADE was abnormal blood potassium
- Risk was increased by duration of care and polypharmacy
Literature describes off label use of traditional medication topically

Literature describes topical application of non–traditional medications (called by various names: ethnopharmacology, herbals, phytotherapy, ethnobotanicals, phytomedicine)
Topical Medications and Wound Healing

- All descriptions are variations on themes
- Both off label traditional and topical phytotherapy (phytochemicals) have common effects:
  - Anti-oxidative
  - Anti-inflammatory
  - Anti-microbial
  - Adaptogenic
  - Tissue regeneration (upregulates growth factors (e.g., VEGF))
Topical Medications and Wound Healing

- Substantive amount of literature on phytotherapy from developing countries (low resource communities)
  - Iran
  - Turkey
  - China
  - Brazil
  - Bolivia
  - Panama
  - Balkans of Europe

- We have the opportunity to capitalize on reverse science: to learn from those countries
80% of world’s population depends on “traditional” (not Western) medicine

In developed nations like the USA and the UK, 25% of medical drugs are based on plants and their derivatives (Alam et al, 2011)
Topical Phytotherapy

- Trigonella Folenum
- Terminalia Bellirica
- Veronia Arborea
- Sesamum Indicum
- Lantana Camara

- Helianthus Annus
- Tridax Procumbens
- Hydnocarpus Wightiana
- Lepidum Sativum
Topical Phytotherapy

- Achillea Millefolium (Yarrow) (Imtiyaz et al, 2017; Mohammadhosseini et al, 2017)
- Turmeric (Curcumin) (Bahramsojani et al, 2017; Wound Healing Group, 2017)
- Propolis (Cao 2017)
Topical Phytotherapy

- Aloe Vera (Liliaceae) (Gebreseskel et al, 2018; Fox et al, 2017; Lobine et al, 2018)
- Sphaeranthus Indicus (Aster)
- Ageratum Conyzoides
- Hyptus suaveoulenus
- Sambucus Ebolus (Dwarf Elder) (Jabbarie et al, 2017)
Topical Phytotherapy

- Tectona Gradis
- Carica Papaya
- Allium Cepa
- Tribulus Terrestris
- Morinda (Noni) (Chin et al, 2018; Torres et al, 2017)
- Anthocephalus Cadamba
- Piper (Piperaceae) (Durant–Archibold et al, 2018)
Topical Phytotherapy

- Achyranthes (Chaff Flower) (He et al, 2017)
- Dracorhodin (Dragon’s Blood) (Jiang et al, 2017)
- Ephedra Alata (Kittana et al, 2017)
- Cymboporon Nardus (Poaceae) (Kandimalla et al, 2016)
- Ligularia (Liu et al, 2018)
- Zingiber (Liu et al 2017)
- Calendula (Pot Marigold) (Nicolaus et al, 2017)
- Pinus Pinaster (Maritime Pine) (Tumen, 2018)
Topical Phytotherapy

- Henna, Pomegranate, Myrrh (Elzayat et al, 2018)
- Salve and burdock (Actium weed) (Amish): Salve is honey, lanolin oil, wheat germ oil, marshmallow rot, aloe vera gel, wormwood, comfrey root, white oak bark, lobelia, beeswax, myrrh) (Flurry et al, 2017)
- Mimosa Tenuiflora (Freitas et al, 2017)
- Copaifera Oil (DeAlbuquerque et al, 2017; Ricardo et al, 2018)
Topical Phytotherapy (Elzayat et al)

- Rat model testing Henna, Pomegranate, Myrrh vs Gentamycin (N = 30)
- Used in ointment formulations solely and combined for full thickness wounds
- Combined extracts worked best and was comparable to gentamicin for epithelialization and contraction
- Combined extract had antimicrobial activity (Candida, staph aureus)
Topical Phytotherapy

- Hypericum Perforatum (St. John’s Wort) (Yucel, 2017)
- Acalypha Indica (Zahidin et al, 2017)
- Frankincense and Myrrh Oils (Grbic et al, 2018)
- Aromatherapy: Damask Rose Essence (Graner–Wizard, 2017)
Clinical Implications for Wound Professionals

- Take detailed accurate medication history
- Note use of all OTC medications especially herbals
- Note injections – including vaccines or contrast media
- Note time of medication relative to onset of wound/skin problems (ADE)
- Take detailed medical history: Any history of drug sensitivity, contact dermatitis, connective tissue disease, atopy (asthma, eczema), previous wound healing delays
Addressing Wound Healing Inhibiting Factors

- Consider impact of hidden malnutrition (Protein insufficiency) on drug metabolism (protein binding and drug toxicities); does patient have fatigue, pain, mouth ulcers?
- Consider common drugs of age groups treated (in wound care and wound clinics mostly older)
  - Rheumatoid diseases and DMARDS (methotrexate and sulfasalazine etc.)
- Consider polypharmacy and need for “deprescribing”
Effects of **Aging** on Drug Metabolism and Excretion

- With aging, liver function decreases by 40% so drugs can be “stored” and cause toxicity
- Kidney function decreases with age; better to use creatinine clearance rather than creatinine level in elderly to monitor levels; affects drug excretion
- Selected drugs with greater harm in elderly:
  - Antipsychotics (haloperidol)
  - Hypnotics (diazepam)
  - Diuretics (furosemide) (Kaufman, 2015)
Addressing Other Wound Healing Inhibitors

- Usage of other “traditional” therapies
  1) Need to ask if patient is consuming any herbal products (teas, liquid extracts, capsules)
  2) Need to ask patient is applying any herbal topical preparation to wound
  3) Potential for herbal–drug interaction: “Natural” does not mean safe
  4) Does the patient space herbals away in time from other drugs (St. John’s Wort, Ginkgo biloba, etc.)
Herbal Medicines and Wound Healing (Maver et al, 2015)

- Plant–based systems continue to play role in healthcare of 80% of world’s developing countries
- Called “phytomedicines”
- Affordable and usually no to minimal side effects
- Level of evidence varies greatly
- Trying to develop a science base for topical natural medicines (Sushma et al, 2018; Wen et al, 2018)
Top 10 Selling Herbals in USA (2012)

- Cranberry
- Garlic
- Saw Palmetto
- Soy
- Ginkgo Biloba
- Milk Thistle
- Black Cohosh
- Echinacea
- St. John’s Wort
- Ginseng

- Flax seeds
- Wheat and Barley grass
- Turmeric
- Aloe Vera
- Blue Green Algae
- Milk Thistle
- Elderberry
- Saw Palmetto
- Echinacea
- Cranberry

Mainstream Markets

Natural/Health Markets
Practice Implications: Wound Care

- Need to identify detailed information on herbals used (dose, form, topical etc.)
- Need to identify “red-flag” medications for potential interactions (warfarin, digoxin, lithium, cyclosporine, protease inhibitors)
- Educate patient with wounds on safety, dosing, and potential toxicities of non-prescription pharmaceuticals (Ranade and Collins, 2014)
- Need to understand how drug delivered matters
  - Metformin systemically helpful
  - Topical metformin—deleterious (Stuermer et al, 2019)
Reduce polypharmacy for wound patients by “de-prescribing”; interact with primary care provider.

Remember that polypharmacy is not only removing excess drugs but that polypharmacy is also *going to more than one pharmacy* (Gillette et al, 2015); educate patients about the risk.

Put on your ARMOR and *LOOK* at the wound patient.
Practice Implications: ARMOR

- A: Assess
- R: Review
- M: Minimize
- O: Optimize
- R: Reassess

- A: Beers criteria; Beta blockers, Pain meds; Antipsychotics
- R: D-drug interaction; D-disease interaction; ADEs
- M: #of meds related to functional status
- O: for renal/hepatic status
- R: functional/cognitive status in one week from any changes and periodically

Mnemonic

Meaning (Haque, 2008)
Practice Implications: Wound Care

- Update oneself about alternative adjuncts to wound healing
- Repurposed approved drugs: Erythropoietin (EPO); excellent review of animal studies using exogenous EPO (Hamed et al, 2014); topical EPO accelerates wound healing
- Phyto-extracts in wound healing—excellent overview (Ghosh and Gaba, 2013) 450 plant species have wound healing properties
- Hydralazine has anti-angiogenesis effects (study done in rats and chicken models) (Zheng et al, 2016)
Summary

- Discussed multiple chronic conditions affecting wound patients
- Explored selected data for drugs that impair or assist wound healing
- Topical and Systemic therapies
- Offered implications for informed clinical practice
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