GI Health and Its Effect On the Skin Part II

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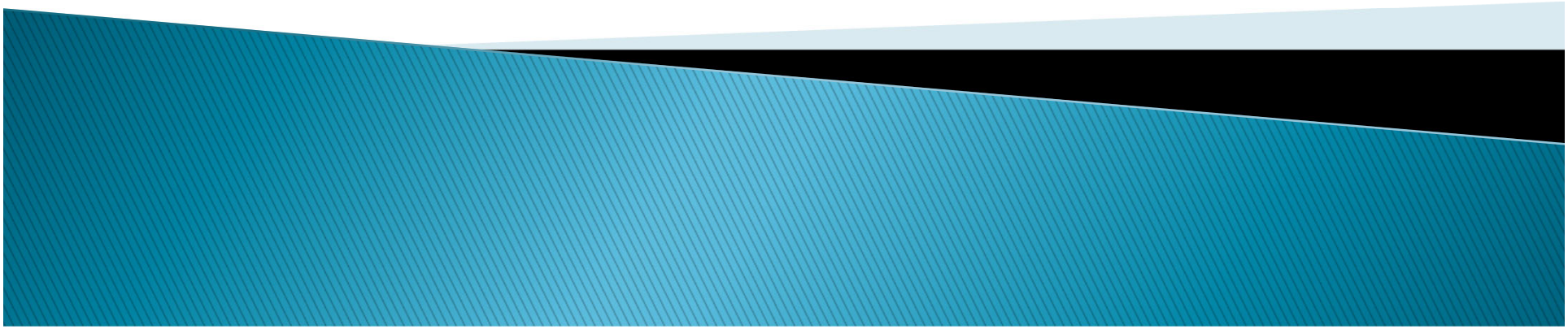
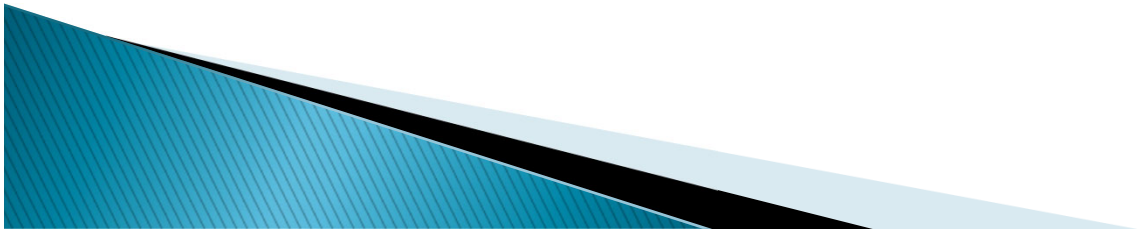


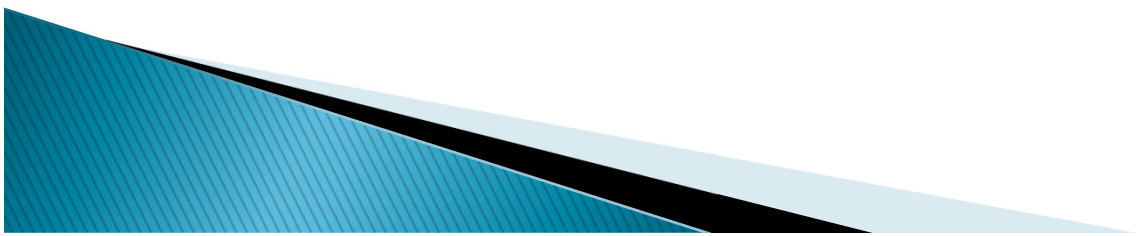
Disclosures

- Disclosure of Financial Relationships:
  - Speaker for Genova, ZRT, Microbiome
- Off-Label Usage
  - None



Objectives

- Understand the connection between the health of the GI tract and skin disorders.
- Review the etiologies of psoriasis.
- Learn conventional and metabolic therapies for psoriasis.
- Examine the use of low-dose naltrexone in patients with psoriasis.



References

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- Gaby, A., Psoriasis. In Nutritional Medicine. Concord, NH: Fritz Perlberg Publishing, 2017.
- Pagano, J., Healing Psoriasis. Hoboken, NJ: Wiley & Sons, 2009.

Psoriasis

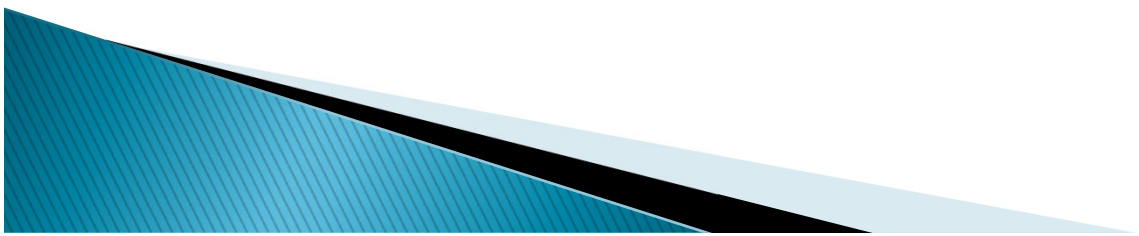
- Psoriasis is a chronic inflammatory skin disease that is an autoimmune process in which abnormal differentiation and hyper-proliferation of the epidermis occurs with redness and scaling.
- It affects 2% of the general population in the world which is 100 million people.
- In the U.S. 4-6 million people have psoriasis.
- 150,00 new cases are diagnosed each year in the U.S.
  - van de Kerkhof, P., "Psoriasis," in Bolognia, J., et al., (Eds.) Dermatology. St. Louise: Mosby 2003.

Psoriasis (Cont.)

- In Sweden 3 % of the population have it.
- In Italy and Russia, 4% of the people have psoriasis.
- Peak onset is between 20 and 30 years and between 50 and 60 years.
- It occurs in males and females equally and is more common in white patients and rare in North and South American Indians.
- In the U.S. the annual outlay of outpatient costs is $1.6 to $3.2 billion.
- Every year, about 400 people die of psoriasis-related causes.
- Over 1.5 million people each year see their physician for psoriasis.
  - National Psoriasis Foundation
  - National Institutes of Health

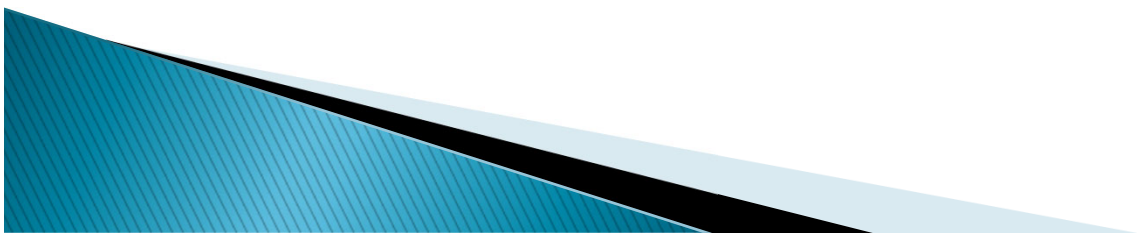
Psoriasis (Cont.)

- Psoriasis is an autoimmune process driven by abnormally activated helper T cells.
  - Activation of the T cells can occur through specific interactions with antigen-presenting cells (APCs)
    - Require costimulatory signals which are membrane-bound or secreted products of accessory cells that are required for signal transduction.
  - Activation of the T cells can also occur through nonspecific super-antigen interactions.



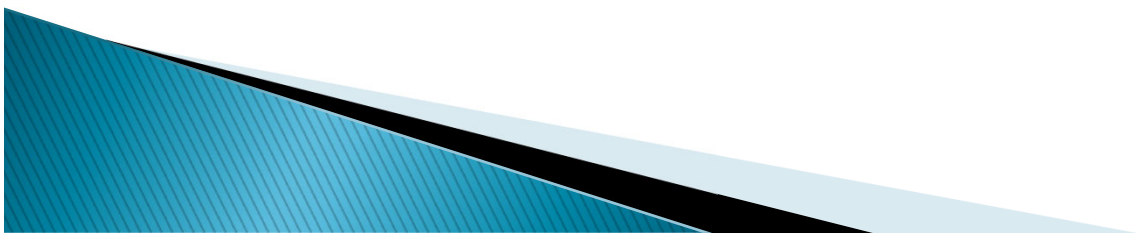
Psoriasis (Cont.)

- Autoimmune process (cont.)
  - Once activated, psoriatic T cells produce a type 1 helper T cell (Th1) dominant cytokine profile that includes
    - Interleukin-2 (IL-2)
    - TNF-alpha
    - IFN-gamma
    - IL-8
      - Ibid., Bodemer.



Psoriasis (Cont.)

- Autoimmune process (cont.)
  - The cytokines act to attract and activate neutrophils which cause inflammation.
  - Other factors that attract neutrophils
    - Complement split products (C5a)
    - Leukotrienes (arachidonic acid metabolites from the 5-lipoxygenase pathway)
      - Schroder, J., et al., "Neutrophil-activating proteins in psoriasis," Jour Invest Dermatol 1992; 98:241-47.



Causes of Psoriasis: Multifactorial

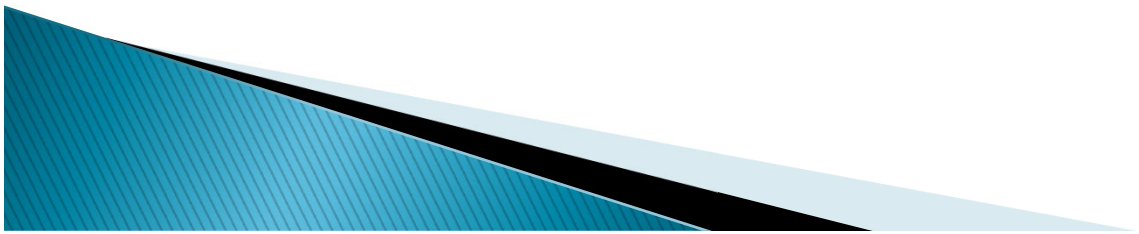
- Genetic
  - If one parent has psoriasis the risk of a child having it is 14%.
  - If both parents have psoriasis the risk of a child having the disease is 41%.
    - Ibid., van de Kerkhof.

Causes of Psoriasis: Multifactorial (Cont.)

- Genetic (cont.)
  - HLAs that have been associated with psoriasis
    - HLA-B13
    - HLA-B17
    - HLA-B27
    - HLA-Cw6
      - Strongest connection
      - Earlier onset disease
      - Harder to treat
    - HLA-DR7
      - Ibid., Bodemer.

Causes of Psoriasis: Multifactorial (Cont.)

- Genetic (cont.)
  - Several genetic loci have been linked
    - PSORSI is the major gene associated with psoriasis.
      - Ibid., Bodemer.
      - Ibid., van de Kerkhof.

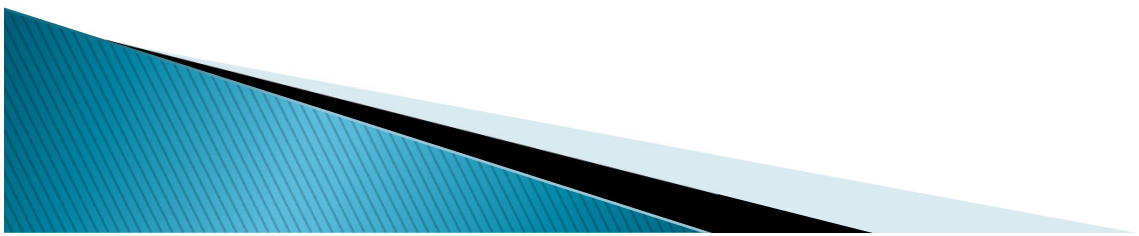


Causes of Psoriasis: Multifactorial (Cont.)

- Environmental
  - Physical trauma
    - Isomorphic or Koebner phenomenon
  - Infections
    - Streptococcal pharyngitis
  - Hypocalcemia
  - Stress
- Rapid weight changes
- ETOH consumption
- Tobacco
  - Ibid., Bodemer.

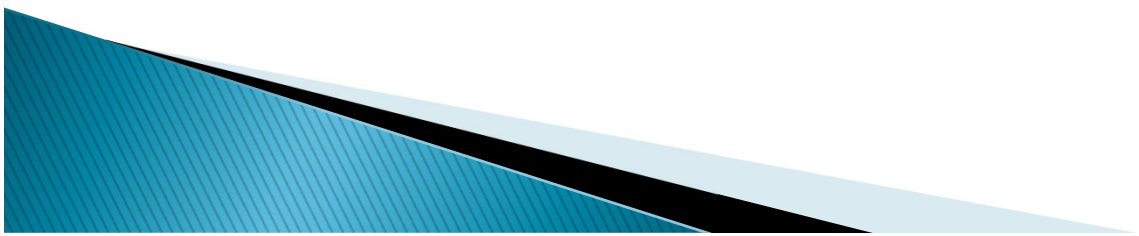
Causes of Psoriasis: Multifactorial (Cont.)

- Environmental (cont.)
  - Medications
    - Lithium
    - Beta blockers
    - Antimalarials
    - Interferon
    - Rapid tapers of systemic corticosteroids
      - Ibid., Bodemer.



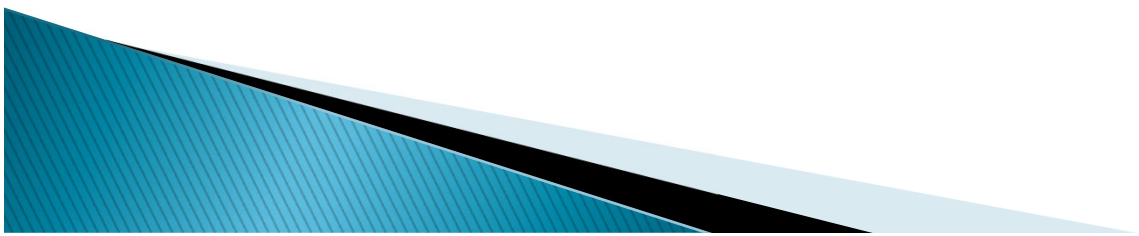
Subtypes of Psoriasis

- Chronic plaque: (most common 90%)
- Guttate: second most common (2%)
- Inverse
- Erythrodermic
- Pustular (can be life-threatening)



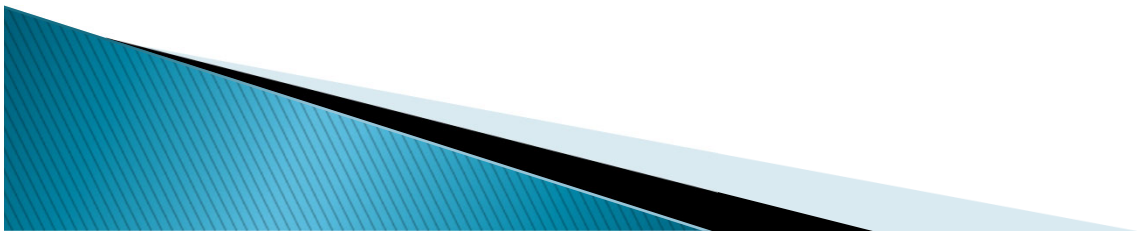
Psoriasis

- Besides skin findings, nail abnormalities are common which occur in up to 55% of people.
  - Pits
  - Oil slicks
  - Subungual hyperkeratosis
  - Onycholysis
    - Ibid., Bodemer.



Conventional Therapies

- Skin care
- Phototherapy
- Methotrexate
- Cyclosporine
- Acitretin
- Biologic immune response modifiers
- Topical pharmaceuticals



Skin Care

- Bathing in cool to tepid water with gentle cleaners such as Cetaphil
- Apply emollients
- Colloidal oatmeal in bath form
  - Aveeno
  - Oatmeal baths can be made by putting whole oats in a blender and grinding to a fine powder. Then add water to half cup of the oat flour to make a loose slurry that can be added to the bath water.
  - A thicker paste can be made and applied transdermally as a poultice to the affect area.
    - Ibid., Bodemer.

Skin Care (Cont.)

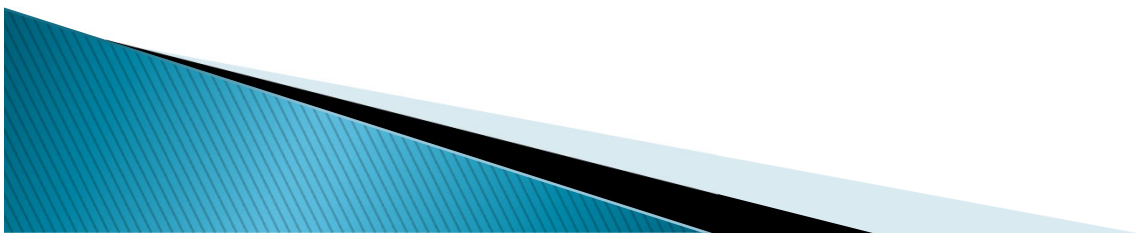
- Natural oils
  - Avocado
  - Almond
  - Olive
    - Ibid., Bodemer.

Phototherapy

- Psoriasis improves in the summer due to exposure to UV light.
- Ultraviolet B therapy
  - Consists of radiation with wavelengths between 290 and 320 nm with narrow-band (between 308 and 313 nm) being the most effective
  - Decreases DNA synthesis
  - Has Immunosuppressive effects
  - Decreases inflammation
    - Honigsmann, H., et al., "Ultraviolet light therapy," in Bolognia, J., et al., (Eds.) Dermatology. St. Louis: Mosby, 2003.
    - Honigsmann, H., "Phototherapy for psoriasis," Clin Exp Dermatol 2001; 26:343-50.

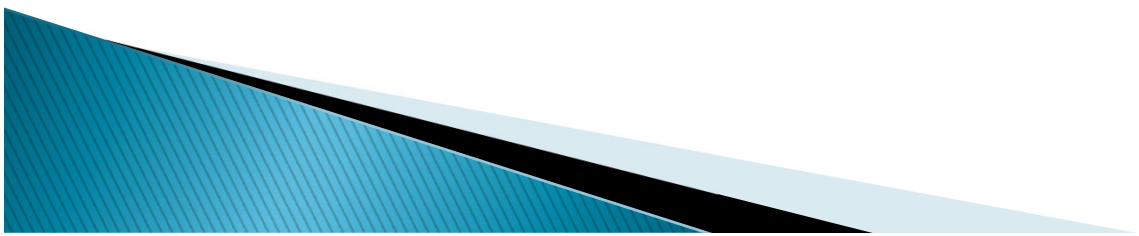
Phototherapy (Cont.)

- Possible side effects of ultraviolet B
  - Short-term
    - Erythema, xerosis, pruritus, higher frequency of herpes simplex outbreaks
  - Long-term
    - Photoaging
    - Perhaps increased risk of skin cancers
      - Ibid., Bodemer.



Phototherapy (Cont.)

- Ultraviolet A and Psoralen therapy (PUVA)
- Psoralens
  - Are furocoumarins found in limes, parsley, figs, and celery.
  - Can be used orally or topically
  - Incorporate DNA strands and absorb photons in the range of 320 to 400 nm which causes DNA cross-linkage, causes cell cycle arrest
  - Also interact with ROS to cause cell membrane damage
    - Runger, T., "Ultraviolet light," in Bolognia, J., et al., (Eds) Dermatology. St. Louis: Mosby, 2003.

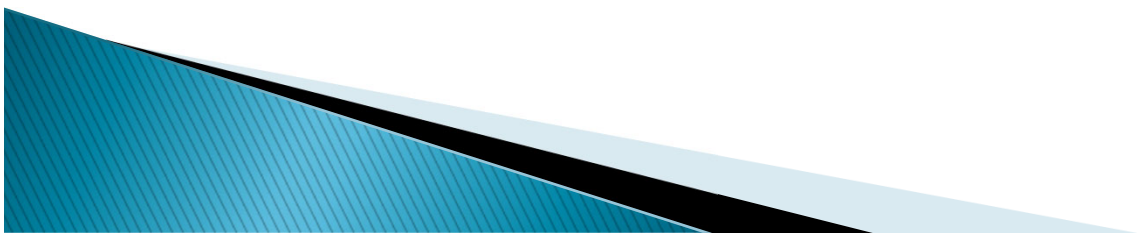


Phototherapy (Cont.)

- Possible side effects
  - Erythema at site
  - Psoralens lasts for 24 hours so patients must wear protective eyewear avoid the sun with strict photo protection.
  - Do not use in patients with renal or liver disease
  - Oral psoralens
    - Nausea and vomiting
    - Sunburn
    - Persistent pruritus
      - Ibid., Bodemer.

Phototherapy (Cont.)

- Possible side effects (cont.)
  - Increased risk of developing squamous call carcinoma of the skin
    - Later treating with immunosuppressive therapy increases the risk
    - Morison, W., et al., “Consensus workshop on the toxic effects of long-term PUVA therapy,” Arch Dermatol 1998; 134:595-98.



Phototherapy (Cont.)

- Possible side effects (cont.)
  - Also an increased risk of developing basal cell carcinomas of the trunk or extremities
  - Also increased risk of developing melanoma
    - Ibid., Bodemer.
    - Stem, R., et al., "Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA): the PUVA Follow-Up Study," NEJM 1997; 336:1041-45.
  - Increased risk of developing lymphoma if patients used PUVA and methotrexate
    - Stem, R., et al., "The carcinogenic risk of treatments for severe psoriasis," Cancer 1994; 73:2759-64.

Phototherapy (Cont.)

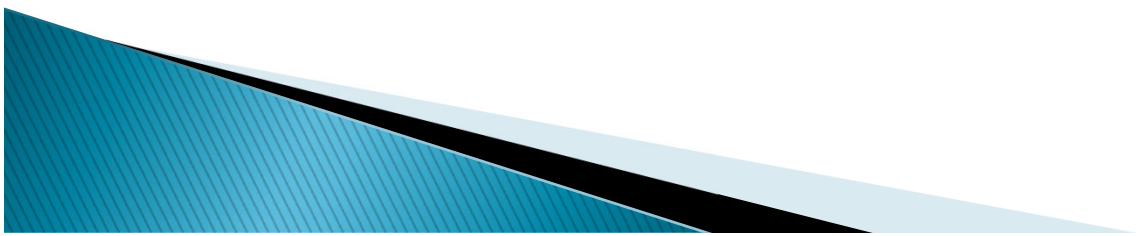
- Phototherapy is now also used successfully with biologic agents as combination therapy to treat recalcitrant psoriasis.
- Recent studies have identified specific immunologic effects of phototherapy that may underlie phototherapy efficacy.
- Furthermore, recent advancements have been made in developing safe and effective targeted phototherapy modalities for difficult-to-treat areas such as scalp psoriasis.
- Therefore, though one of the oldest therapeutic modalities for psoriasis, phototherapy remains a mainstay treatment with promise for further advancement.
  - Nakamura, M., et al., "Recent advances in phototherapy for psoriasis," F1000Res 2016; 5:F1000Faculty Rev-1684.

Methotrexate

- It is a folic acid antagonist which blocks the formation of the building blocks needed for DNA synthesis and leads to cell cycle death.
- It is immunosuppressive and anti-inflammatory raising tissue levels of adenosine.
- Add 1 mg of folic acid daily for patients to take qd.
  - West, J., et al., "Safety and efficacy of methotrexate in psoriasis: A meta-analysis of published trials," PLoS One 2016; 11(5):e0153740.

Methotrexate

- Possible side effects
  - GI symptoms: are the most common side effect
  - Pancytopenia: most dangerous side effect
  - Hepatotoxicity
  - Pulmonary fibrosis
  - Cancer
    - Occurs more frequently if methotrexate is combined with PUVA
  - Teratogenicity
  - Need to monitor CBC, renal, and liver function
  - Liver Bx needs to be done after cumulative dose of 1.5 to 2 grams
    - Ibid., Bodemer.

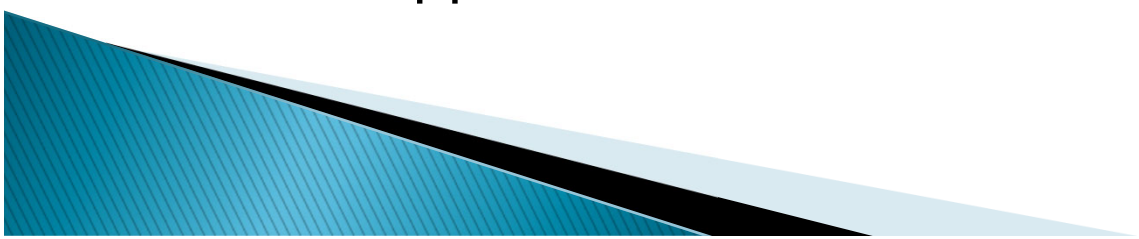


Cyclosporine

- Cyclosporine initially isolated from the soil fungus Tolypocladium inflatum.
- It inhibits IL-2 gene transcription and leads to decreased T-cell proliferation and activation.
- It inhibits the transcription of various pro-inflammatory cytokines.
  - Lim, K., et al., "Cyclosporine in the treatment of dermatologic disease: an update," Mayo Clin Proc 1996; 71:1182-91.
  - Koo, Y., et al., "Cyclosporine and related drugs," in Wolverton, S., (Ed.) Comprehensive Dermatologic Drug Therapy. Philadelphia: Saunders 2001.

Cyclosporine (Cont.)

- Possible side effects
  - Renal dysfunction
  - HTN
  - Hypertrichosis
  - Gingival hyperplasia
  - GI upset
  - Headache, tremor, paresthesias
  - Electrolyte imbalances
  - Sleep disturbances
  - Acneiform eruptions
  - Hypertriglyceridemia
  - Decreased seizure threshold
  - BM suppression



Cyclosporine (Cont.)

- Possible side effects (cont.)
  - Need to monitor
    - BP
    - Renal function including urinalysis
    - CBC
    - Liver function tests
    - Magnesium, potassium, uric acid
    - Cleared through the P-450 CYP3A4 enzyme system so can interact with other medications and herbal therapies
      - Soleymani, T., et al., "Comparison of guidelines for the use of cyclosporine for psoriasis" A critical appraisal and comprehensive review," Jour Drugs Dermatol 2016; 15(3):293-301.

Acitretin

- Is an oral retinoid
- Has anti-proliferative action
- Has anti-inflammatory effects
- Can reduce lymphocyte proliferation
- Can decrease arachidonic acid metabolism
- Used for rapid control of pustular psoriasis
- Dosage: 10, 25, 50 mg qd with good

Acitretin (Cont.)

- Possible side effects
  - Since acitretin is a retinoid it is teratogenic
  - Can cause drying of skin and mucous membranes
  - Decreased night vision
  - Pseudotumor cerebri especially if given with tetracycline
  - Arthralgias
  - Myalgias
  - Bony changes (hyperostosis)
  - Poor wound healing
  - GI symptoms
  - Elevation of liver enzymes rarely toxic hepatitis
  - Elevation of cholesterol and triglycerides

References

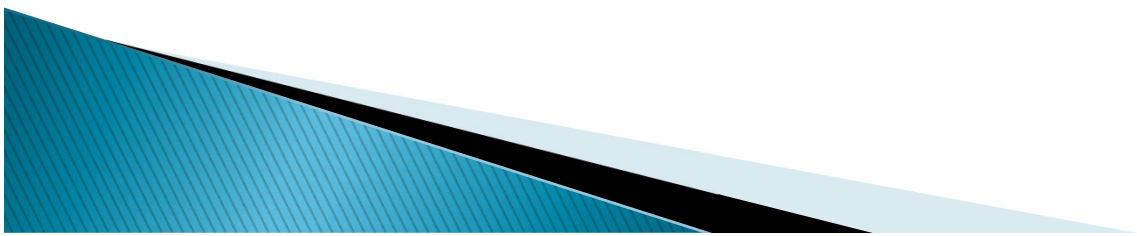
- Dunn, L., et al., “Acitretin in dermatology: A review,” Jour Drugs Dermatol 2011; 10(7):772-82.
- Yamauchi, P., et al., “Current systemic therapies for psoriasis: where are we now?” Jour Amer Acad Dermatol 2003; 49:66-77.
- Nguyen, E., et al., “Systemic retinoids,” in Wolverton, S., (Ed.) Comprehensive Dermatologic Drug Therapy. Philadelphia: Saunders, 2001.

Acitretin (Cont.)

- Possible side effects (cont.)
  - Dry skin may be improved by the use of 800 IU of vitamin E daily
    - Lebwohl, M., et al., "Treatment of psoriasis. Part 2. Systemic therapies," Jour Amer Acad Dermatol 2001; 45:649-61.
- Possible side effects (cont.)
  - Need to monitor
    - Pregnancy tests
    - Lipid panel
    - Liver function tests
    - CBC with platelets
    - Renal function tests
    - Creatine phosphokinase
      - Ibid., Bodemer.

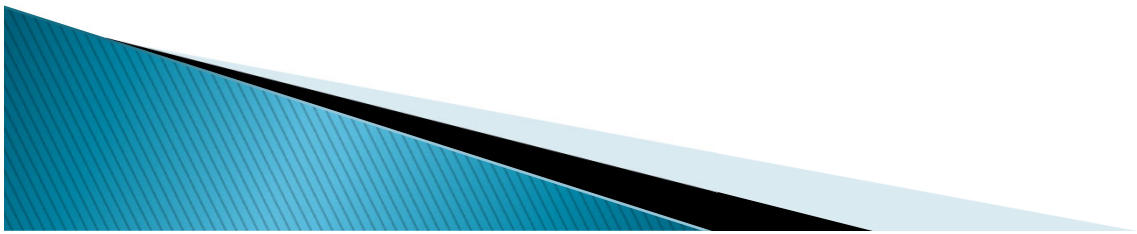
Biologic Immune Response Modifiers

- They are directed specifically at neutralizing cytokines.
- They block costimulatory messages important for the activation of T cells.
  - Costimulatory messages are membrane-bound or secreted products of accessory cells that are required for signal transduction.



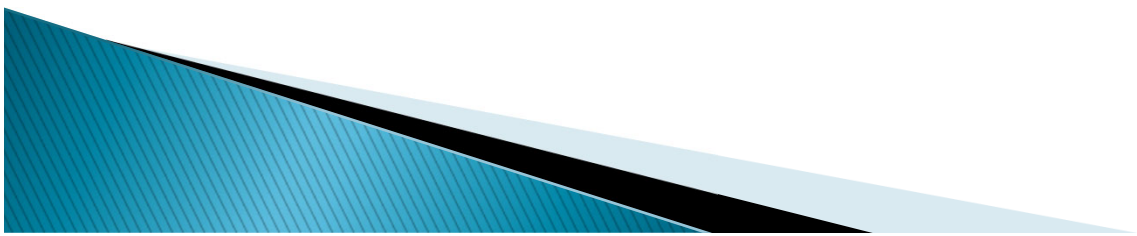
Biologic Immune Response Modifiers (Cont.)

- Alefacept
  - Is a fusion protein
  - Blocks the costimulatory signal between leukocyte function-associated antigen 3 (LEA-3) and CD2 needed for antigen-mediated T-cell activation
- Etanercept
  - A humanized chimeric monoclonal antibody to TNF-alpha
    - Ibid., Bodemer.



Biologic Immune Response Modifiers (Cont.)

- Efalizumab
  - A monoclonal antibody directed against CD11a (a component of LEA-1)
  - Blocks the costimulatory interaction between LEA-1 and intercellular adhesion molecule-1 (ICAM-1) which prevents T-cell activation
- Infliximab
  - A monoclonal antibody
  - Neutralizes TNF-alpha by binding to both soluble and transmembrane TNF-alpha
  - Induces apoptosis of TNF-alpha-expressing cells
  - Inhibits other pro-inflammatory cytokines which decreases keratinocyte proliferation
    - Ibid., Bodemer.



Biologic Immune Response Modifiers (Cont.)

- Ustekinumab
  - A human monoclonal antibody
  - Blocks both IL-12 and IL-23 which causes naïve CD4' T cells to differentiate into types 1 and 17 helper cells that are key mediators in psoriasis
    - Ibid., Bodemer.

Biologic Immune Response Modifiers (Cont.)

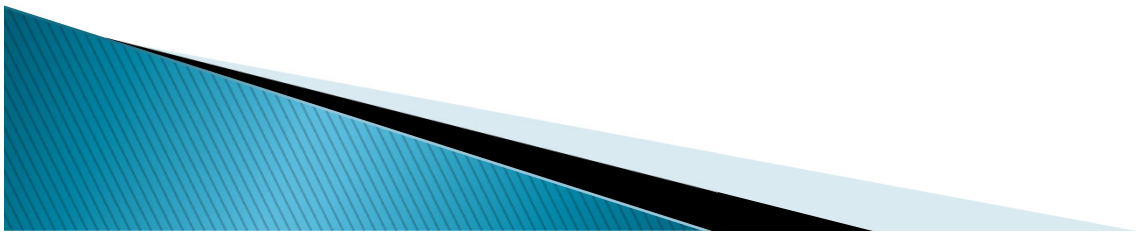
- All of these medications require thorough baseline evaluation including P/E and blood work and then constant monitoring of these values.
- Patients are advised to have any needed vaccinations before beginning therapy.
  - Lebwohl, M., et al., "From the Medical Board of the National Psoriasis Foundation: monitoring and vaccinations in patients treated with biologics for psoriasis," Jour Amer Acad Dermatol 2008; 58:94-105.

Topical Pharmaceuticals

- Keratolytics
  - Keratolytics decrease the thickness of the psoriatic plaques.
  - If the plaques are thinner, then the patient has more comfort and there is enhanced penetration of other topical therapies.
    - Such as salicylic acid (2% to 10%)
    - Urea (up to 40%)
    - Alpha-hydroxy acid
      - Glycolic acid
      - Lactic acid
        - Ibid., Bodemer.

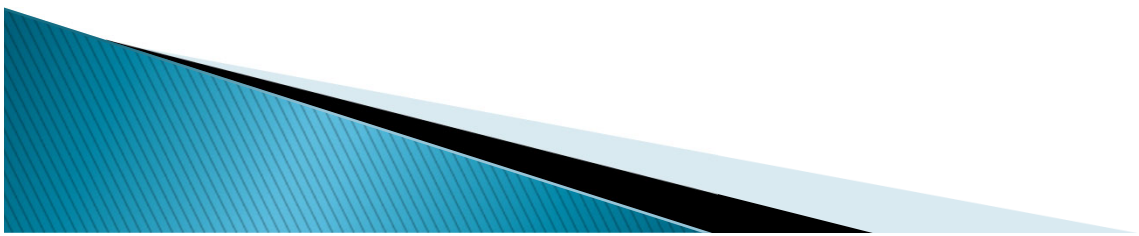
Topical Pharmaceuticals (Cont.)

- Keratolytics (cont.)
  - Salicylic acid should not be applied extensively on the body, particularly in children
  - Systemic absorption can lead to salicylism
    - Tinnitus
    - Nausea
    - Vomiting
      - Chiricozzi, A., et al., "Treatment of psoriasis with topical agents: Recommendations from a Tuscany Consensus," Dermatol Ther 2017; 30(6).



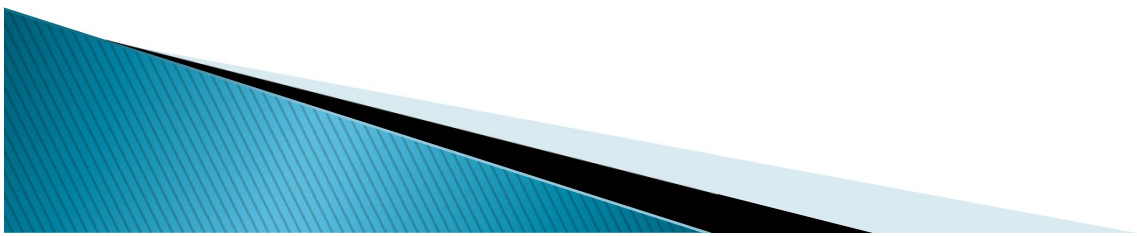
Topical Pharmaceuticals (Cont.)

- Coal tar
  - Is created from the gasses produced during the distillation of coal that are condensed and undergo ammonia extraction
  - This results in a dark liquid.
  - Contains 10,000 different chemical compounds
    - Polycyclic aromatic hydrocarbons
    - Phenols
    - Nitrogen bases
      - Ibid., Bodemer.



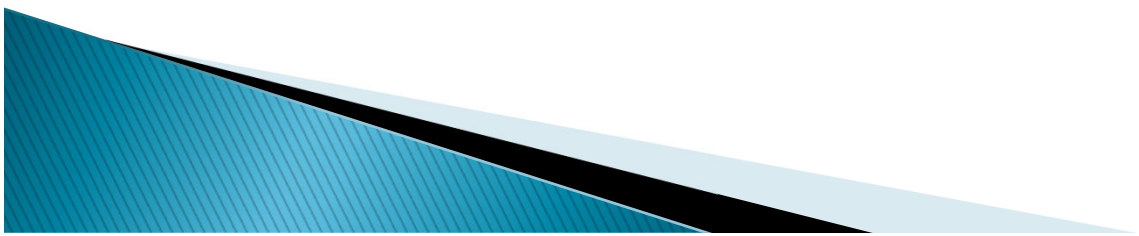
Topical Pharmaceuticals (Cont.)

- Coal tar (cont.)
  - Coal tar has anti-proliferative activity.
  - It also has anti-inflammatory activity.
    - Sekhon, S., et al., "Review of the mechanism of action of coal tar in psoriasis," Jour Dermatol Treat 2018; 29(3):230-32.
    - Federman, D., et al., "Topical psoriasis therapy," Amer Fam Physician 1999; 59:957-62.
    - Hessel, A., et al., "Agents used for treatment of hyperkeratosis," in Wolverton, S., (Ed.) Comprehensive Dermatologic Drug Therapy," Philadelphia: Saunders, 2001.



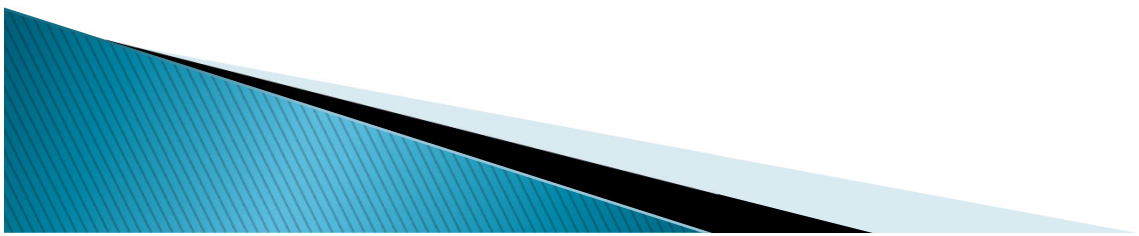
Topical Pharmaceuticals (Cont.)

- Coal tar (cont.)
  - Dosage: 5% to 20% preparations
  - Coal tar + UV radiation increases the patient's risk of developing skin cancer.
  - Other side effects
    - Phototoxicity
    - Contact allergy
    - Irritant dermatitis
    - Acneiform eruptions
      - Ibid., Bodemer.



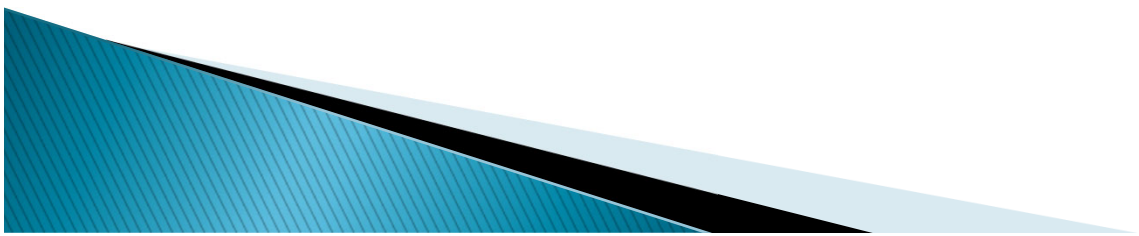
Topical Pharmaceuticals (Cont.)

- Anthralin
  - It is a synthetic derivative of chrysarobin which is found in Goa powder from the park of the araroba tree.
  - It inhibits cell growth and promotes cell differentiation.
  - Dosage: 0.5% to 1% preparation applied for 10–30 minutes then washed off qd or BID
    - Ibid., Bodemer.



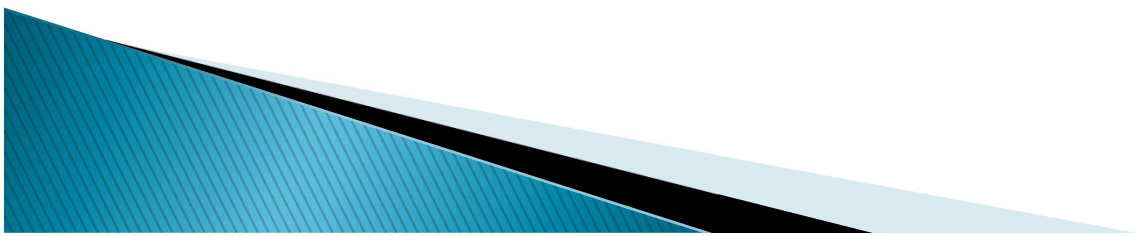
Topical Pharmaceuticals (Cont.)

- Anthralin (cont.)
  - Irritation to normal skin can be decreased by protection with petrolatum or zinc oxide around psoriatic plaques.
  - It is messy and can stain hair, skin, nails, clothing and bedding a brownish to purplish color. Hair discoloration can be decreased by using neutral henna powder to coat the hair.
    - Ibid., Bodmer.



Topical Pharmaceuticals (Cont.)

- Calcipotriene
  - The bioactive form (1,25-dihydroxycholecalciferol) inhibits keratinocyte proliferation and promotes keratinocyte differentiation.
    - Sachs, D., et al., "Topical vitamin D3," in Wolverton, S., (Ed.) Comprehensive Dermatologic Drug Therapy. Philadelphia: Saunders, 2001.
    - Highton, A., Calcipotriene ointment 0.005% for psoriasis: a safety and efficacy study. Calcipotriene Study Group," Jour Amer Acad Dermatol 1995; 32(1):67-72.



Topical Pharmaceuticals (Cont.)

- Calcipotriene (cont.)
  - Locally metabolized very quickly so there is less interference with calcium metabolism.
  - Measure vitamin D levels to make sure that adequate oral supplementation is being given.
  - Dosage: 0.005% cream, ointment, or lotion applied BID
  - Possible side effects
    - Self-limited irritant dermatitis is the most common
    - Photosensitivity can develop in people who receive UVB after calcipotriene.
    - Hypercalcemia is the most significant potential risk but is usually not a problem if the dose is kept at less than 100 grams week.

Reference

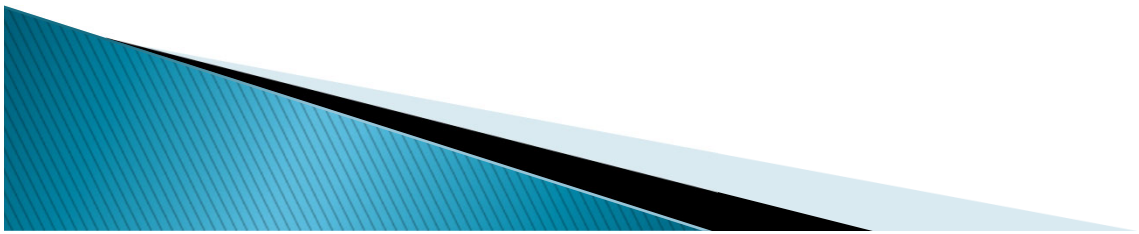
- Bourke, J., et al., “The effects of topical calcipotriol on systemic calcium homeostasis in patients with chronic plaque psoriasis,” Jour Amer Acad Dermatol 1997; 37:929-34.

Topical Pharmaceuticals (Cont.)

- Tazarotene gel
  - It is a topical retinoid (vitamin A derivative) that is applied daily.
  - It increases differentiation of keratinocytes.
  - Dosage: 0.05% or 0.1% gel can be used with a topical steroid
  - Possible side effects
    - Local skin irritation and pruritus can occur
    - Can be teratogenic
      - Ibid., Bodemer.

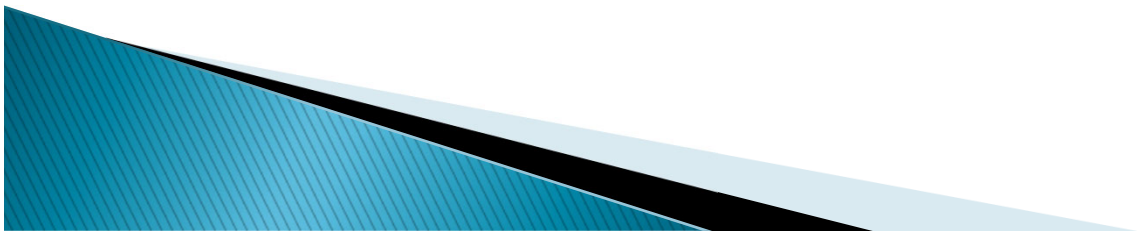
Topical Pharmaceuticals (Cont.)

- Topical steroids
  - Its actions are mediated by alterations in gene transcription.
    - Anti-inflammatory
    - Immunosuppressive
    - Anti-proliferative
      - Ibid., Bodemer.



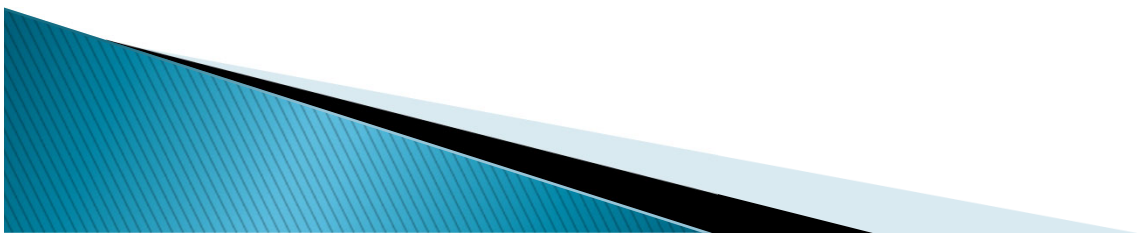
Topical Pharmaceuticals (Cont.)

- Topical steroids (cont.)
  - Are associated with tachyphylaxis which is less efficacy with continual use. Combining topical steroids with other topical pharmaceuticals minimizes this issue
  - Local side affects increase with dosage.
    - Atrophy
    - Acne
    - Localized hypertrichosis
- Systemic absorption can occur and may cause side effects that are similar to oral steroids if topic steroids are used frequently or long-term.



Topical Pharmaceuticals (Cont.)

- A combination of a vitamin D analog and a corticosteroid into a two-compound topical formulation has increased efficacy compared with either drug administered alone according to several studies.
  - Shepard, J., et al., "Once-daily topical treatment for psoriasis calcipotriene+ betamethasone two-compound topical formulation," Clin Cosmet Investig Dermatol 2014; 7:19-22.
  - Rogalski, C., Calcipotriol/betamethasone for the treatment of psoriasis: efficacy, safety, and patient acceptability," Psoriasis (Auckl) 2015; 5:97-107.



Topical Pharmaceuticals (Cont.)

- The combination of calcipotriol and corticosteroid efficiently disrupts the IL-36 and IL-23/IL-17 positive feedback loop, thus revealing a mechanism underlying the efficacy of calcipotriol and corticosteroid combination therapy for psoriasis.
  - German, B., et al., "Disrupting the IL-36 and IL-23/IL-17 loop underlies the efficacy of calcipotriol and corticosteroid therapy for psoriasis," JCI Insight 2019; 4(2):e123390.

Metabolic Therapies for Psoriasis

- Diet
- EPA/DHA
- Nutrients
- Topical botanicals
- Systemic botanicals
- Meditation
- Hypnosis
- Chinese medicine
- Acupuncture
- Climatotherapy
- Balneophototherapy
- Lifestyle
- Detoxification
- Homeopathy
- Herbal teas
- Compounded formulas
- GI health

  - Ibid., Bodemer.

Diet

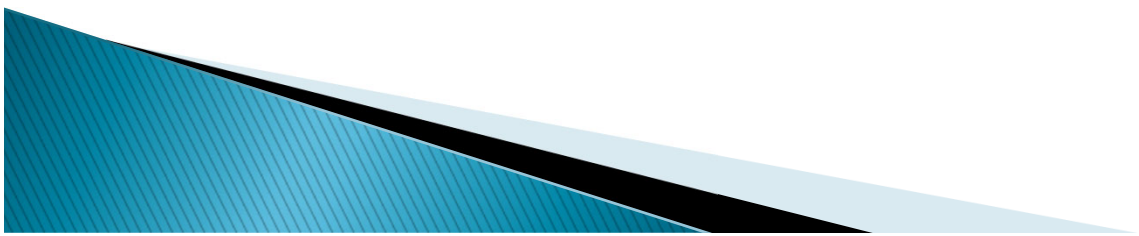
- Have the patient remove pro-inflammatory foods from their diet.
- For meat select: fish, fowl, and lamb
- Avoid acid forming foods (see handout)
- Avoid pizza
- Avoid all salad dressings that contain wine or grain vinegar
- Avoid all white products including white rice
- Avoid shellfish
  - Ibid., Pagano.

Diet (Cont.)

- Instruct the patient to avoid foods in the nightshade family.
  - Tomatoes (and their derivatives)
  - Tobacco: 25% of patient with psoriasis smoke or use to smoke
  - Eggplant
  - White potatoes
  - Peppers
  - Paprika
    - Ibid., Pagano.

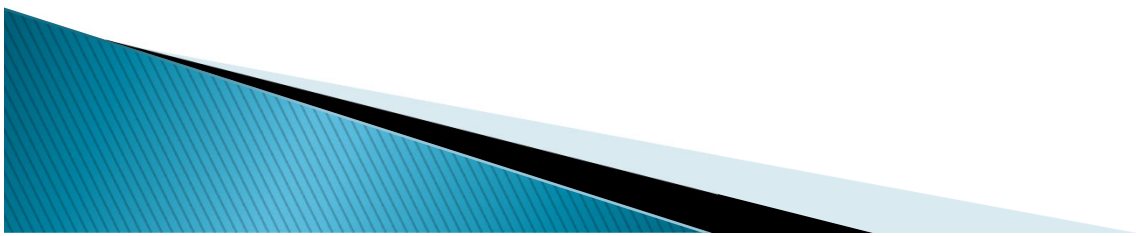
Diet (Cont.)

- Avoid sugary foods including carob
- Avoid soft drinks
- Drink a lot of water
- Eliminate all ETOH
- Avoid foods the patient is allergic to



Diet (Cont.)

- Among the risk factors for psoriasis, evidence is accumulating that nutrition plays a major role in psoriasis pathogenesis.
- In particular; body weight, nutrition, and diet may exacerbate the clinical manifestations, or even trigger the disease.
  - Barrea, L., et al., “Environmental risk factors in psoriasis: the point of view of the nutritionist,” Int Jour Environ Res Public Health 2016; 13(5):743.



Diet (Cont.)

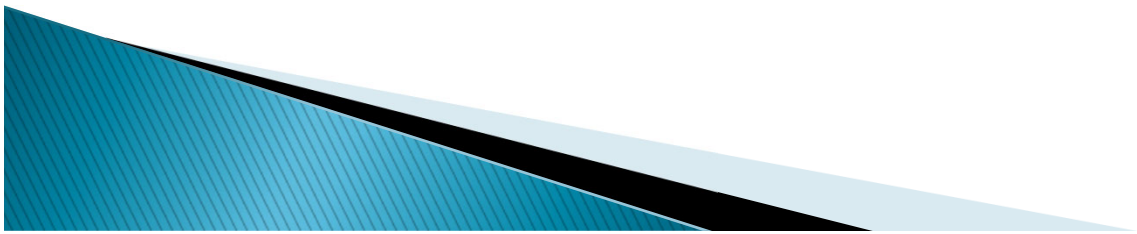
- Another article pointed out that obesity has been associated with a proinflammatory state and several studies have demonstrated a relationship between body mass index and psoriasis severity.
  - Debbaneh, M., et al., “Diet and psoriasis, part I: Impact of weight loss interventions,” Jour Amer Acad Dermatol 2014; 71(1):133-40.

Diet (Cont.)

- Even if the patient is taking a medication, a study showed the positive effect of weight reduction by dietary control on treatment efficacy of biologics in obese patients as indicated by the Psoriasis Area and Severity Index (PASI) score.
  - Al-Mutairi, N., et al., "The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial," Expert Opin Biol Ther 2014; 14(6):749-56.

Nutrients

- EPA/DHA
- Zinc
- Inositol
- Lecithin
- Vitamin D
- Compounded nutrients

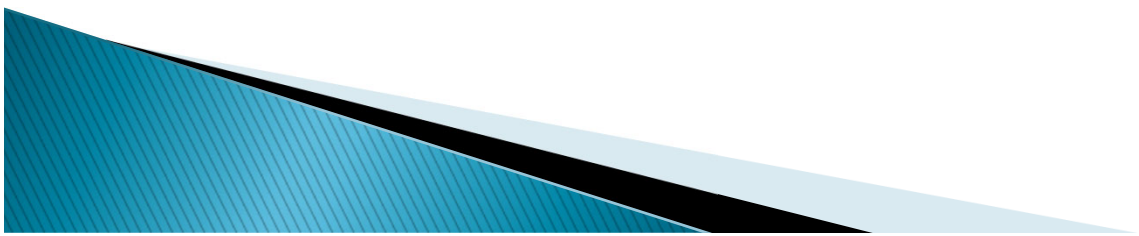


Supplements and Psoriasis

- In this review they examined the extent to which each of common nutritional interventions has been studied for the treatment of psoriasis.
- The evidence of benefit was highest for fish oils.
- For other supplements, there was suggested a need for additional large, randomized clinical trials to establish evidence of efficacy.
  - Millsop, J., et al., "Diet and psoriasis: Part 3: Role of nutritional supplements," Jour Amer Acad Dermatol 2014; 71(3):561-59.

EPA/DHA

- In vitro studies support the use of EPA/DHA in the therapy of psoriasis since it inhibits the inflammatory cytokines IL-6 and TNF-alpha.
- EPA/DHA also decreases levels of leukotrienes.
  - Simopoulos, A., "Omega-3-fatty acids in inflammation and autoimmune diseases," Jour Amer Coll Nutr 2002; 21:495-505.



EPA/DHA (Cont.)

- One study looked at the effect of consumption of oily fish compared with white fish on chronic plaque psoriasis.
- The individuals that ate the oily fish (6 oz/day for 6 weeks) had an improvement in their psoriasis.
  - Collier, P., et al., "Effect of regular consumption of oily fish compared with white fish on chronic plaque psoriasis," Eur Jour Clin Nutr 1993; 47:251-54.

EPA/DHA (Cont.)

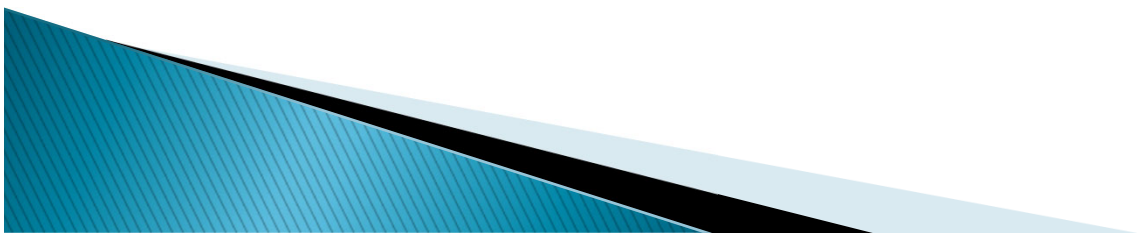
- A double-blind, placebo-controlled trial using high dose fish oil compared to olive oil capsules found that the patients had less itching, scaling, and erythema in the group that used the fish oil.
  - Bittiner, S., et al., "A double-blind, randomized, placebo-controlled trial of fish oil in psoriasis," Lancet 1988; 1:378-80.

EPA/DHA (Cont.)

- Another medical trial that was randomized, double-blind, placebo-controlled looked at patients that were in the hospital with guttate psoriasis that had at least 10% of their body involved.
- They were given IV omega-3-fatty acids vs. IV omega-6-fatty acids.
- Both groups improved, but the patients in the IV omega-3-fatty acid group did better.
  - Grimminger, F., et al., "A double-blind randomized, placebo-controlled trial of omega-3-fatty acid-based lipid infusion in acute, extended guttate psoriasis," Clin Investig 1993; 71:6334-43.

EPA/DHA (Cont.)

- A similar trial that was randomized, double-blind, placebo-controlled using IV EPA/DHA.
- Improvement was seen with the use of IV EPA/DHA.
  - Maser, P., et al., "Omega-3-fatty acid-based lipid infusion in patients with chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, multicenter trial," Jour Amer Acad Dermatol 1998; 38:539-47.



EPA/DHA (Cont.)

- Other studies did not show improvement with the use of EPA/DHA or it was nonconclusive.
  - Upala, S., et al., “Effect of omega-3 fatty acids on disease severity in patients with psoriasis: A systematic review ,” Int Jour Rheum Dis 2017; 20(4):442-50.
  - Bjornboe, A., et al., “Effect of dietary supplementation with n-3 fatty acids on clinical manifestations of psoriasis,” Brit Jour Dermatol 1988; 118:77-83.
  - Soyland, E., et al., “Effect of dietary supplementation with very long chain n-3 fatty acids in patients with psoriasis,” NEJM 1993; 328:1812-16.

EPA/DHA (Cont.)

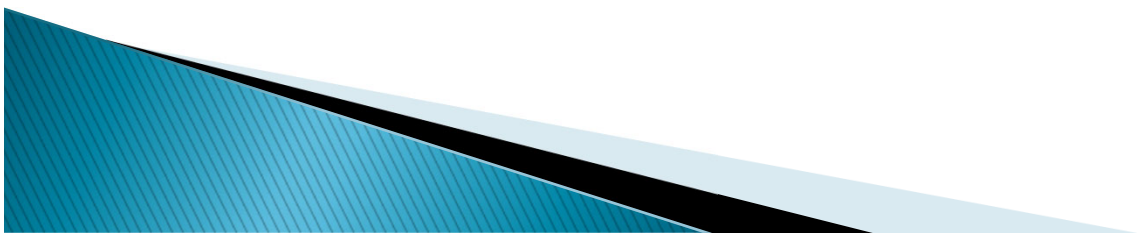
- The use of EPA/DHA may decrease the side effects of mediations such as retinoids by lowering triglyceride and cholesterol levels.
  - Lowe, N., et al., “Fish oil consumption reduces hypertriglyceridemia in psoriatic patients during etretinate therapy,” Arch Dermatol 1988; 124:177.

EPA/DHA (Cont.)

- EPA/DHA may also decrease the risk of nephrotoxicity that is associated with the use of cyclosporine.
  - Ibid., Simopoulos.

EPA/DHA (Cont.)

- In doses greater than 3,000 mg, EPA/DHA is a blood thinner. Therefore more than 3,000 mg a day of EPA/DHA should not be used in patients on anticoagulants.
- EPA/DHA can also lower blood pressure, so if a patient is already on an anti-hypertensive agent then carefully monitor their BP.

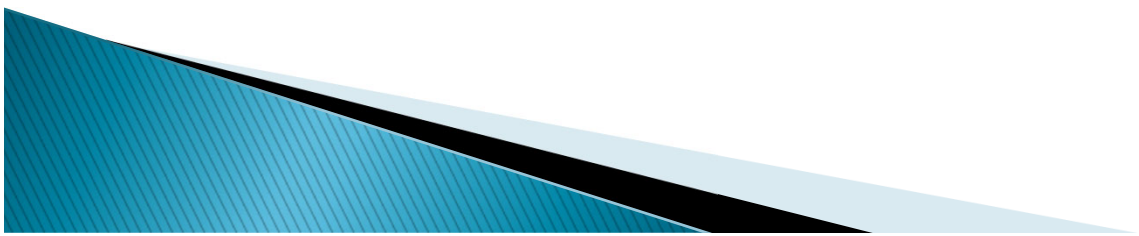


Zinc

- Patients with psoriasis may have low zinc levels.
- Dosage: 15 mg of zinc with 1 mg of copper
  - Paulsen, E., et al., “A double-blind, placebo-controlled study of a commercial aloe vera gel in the treatment of slight to moderate psoriasis vulgaris,” Jour Eur Acad Dermatol Venereol 2005; 19:326-31.

Zinc (Cont.)

- Potential side effects of zinc supplementation
  - Nausea
  - Vomiting
  - Metallic taste in mouth
  - Higher doses patient may become zinc toxic
    - Watery diarrhea
    - Irritation and erosion of the GI tract
    - Acute renal tubular necrosis
    - Interstitial nephritis
    - Flu-like syndrome
      - Ibid., Bodemer.



Inositol

- Lithium can worsen psoriasis since lithium depletes the body of inositol.
- Study showed that patients taking lithium if they also took inositol (6 grams/day) had improvement in their symptoms of psoriasis.
  - Allan, S., et al., "The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial," Brit Jour Dermatol 2004; 150:966-69.

Vitamin D

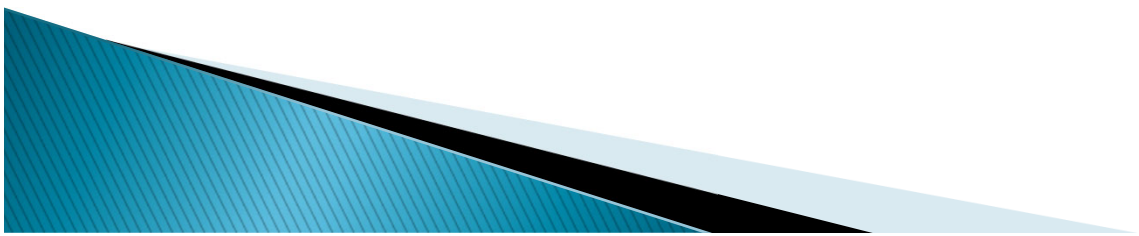
- A meta-analysis that was the first study to establish the relation between vitamin D and psoriasis found a significant relationship between low 25(OH) D levels and psoriasis. However, no causal relationship was found.
- Measure levels of 25(OH) vitamin D in your patients with psoriasis and replace according to lab results.
  - Pitukweerakul, S., et al., "Hypovitaminosis D is associated with psoriasis: A systematic review and meta-analysis," Kans Jour Med 2019; 12(4):103-08.

Vitamin D (Cont.)

- Vitamin D supplementation has been shown to reduce the clinical severity of psoriasis.
  - Barrea, L., "Vitamin D and its role in psoriasis: An overview of the dermatologist and nutritionist," Rev Endocr Metab Disord 2017; 18(2):195-205.
  - Smith, E., et al., "A novel approach for the evaluation and treatment of psoriasis. Oral or topical use of 1,25-dihydroxyvitamin D3 can be a safe and effective therapy for psoriasis," Jour Amer Acad Dermatol 1988; 19:516-28.
  - Takamoto, S., et al., "Effect of 1 alpha-hydroxycholecalciferol on psoriasis vulgaris: a pilot study," Calcif Tissue Int 1986; 39:360-64.

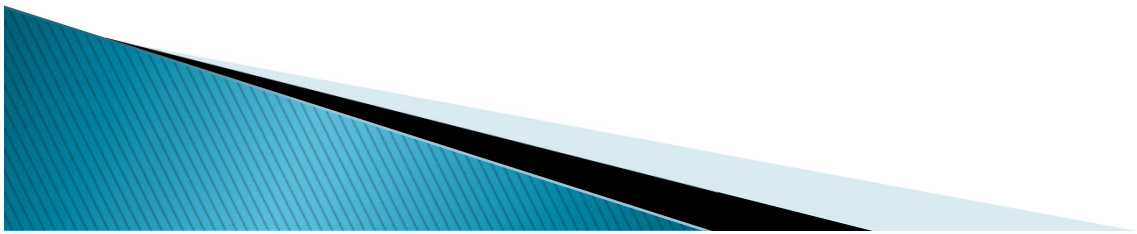
Lecithin

- Some practitioners have had success with giving the patient lecithin.
- Dosage: one tablespoon TID, 5 days a week
- Do not give to patients that are allergic to soy or soy products.
  - Ibid., Pagano.



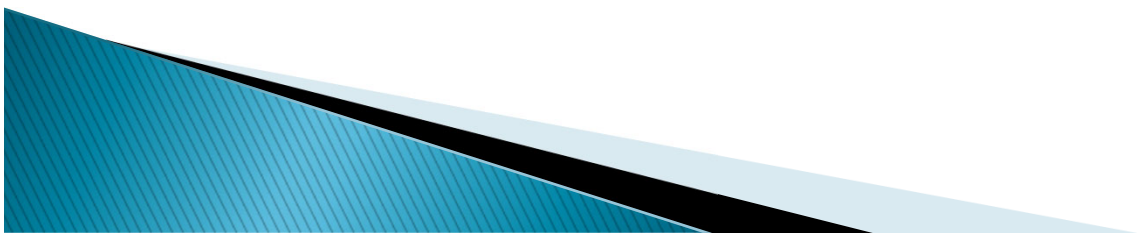
Topical Botanicals

- A total of 27 controlled and uncontrolled clinical trials addressing the use of topical botanical agents for psoriasis were assessed in this review.
- The most highly studied and most efficacious topical botanical therapeutics were Mahonia aquifolium, indigo naturalis, aloe vera, and capsaicin.
- The most commonly reported adverse effects were local skin irritation, erythema, pruritus, burning, and pain.
  - Farahnik, B., et al., "Topical botanical agents for the treatment of psoriasis: A systematic review," Amer Jour Clin Dermatol 2017; 18(4):451-68.



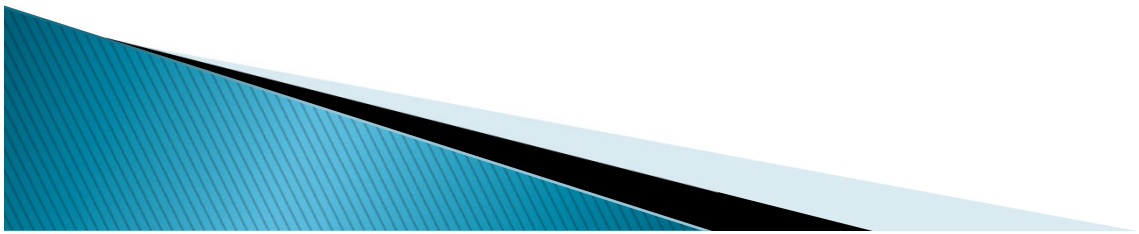
Topical Botanicals (Cont.)

- Capsaicin (cont.)
  - Neuropeptide substance P is elevated in psoriatic skin which up-regulates the expression of adhesion molecules important in the activation and recruitment of leukocytes.
    - Lotz, M., et al., "Effect of neuropeptides on production of inflammatory cytokines by human monocytes," Science 1988; 241:1218-21.



Topical Botanicals (Cont.)

- Capsaicin (cont.)
  - Also substance P is known to elicit itching when applied to normal skin.
    - Nakamura, M., et al., "Pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors," Brit Jour Dermatol 2003; 149:718-30.
  - Itching is a major issue in patients with psoriasis.
    - Naukkarinen, A., et al., "Quantification of cutaneous sensory nerves and their substance P content in psoriasis," Jour Invest Dermatol 1989; 92:126-29.

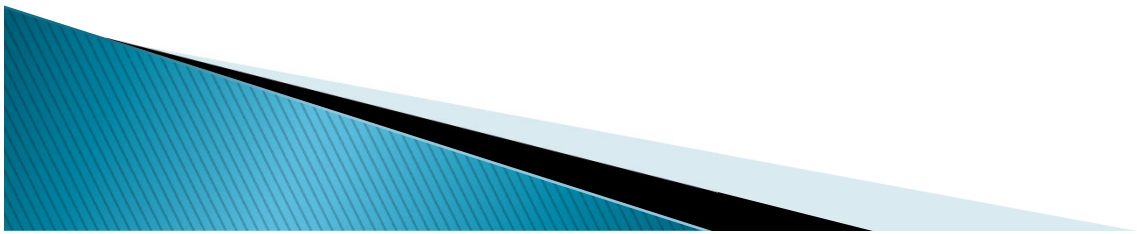


Topical Botanicals (Cont.)

- Capsaicin (cont.)
  - Capsaicin is an extract of chili peppers that acts by depleting substance P locally.
  - Double-blind, placebo-controlled trial using capsaicin QID for 6 weeks.
  - The treatment group had better overall improvement, greater relief of itching and a decrease in psoriasis severity scores. The study was not statistically significant though.
    - Ellis, C., et al., "A double blind evaluation of topical capsaicin in pruritc psoriasis," Jour Amer Acad Dermatol 1993; 29:438-42.

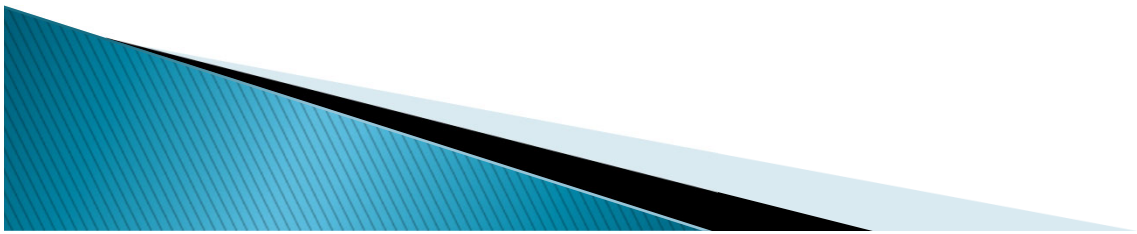
Topical Botanicals (Cont.)

- Capsaicin (cont.)
  - Dosage: 0.025% or 0.075% capsaicin cream applied TID to QID
  - The patient may have some burning during initial application which resolves with regular use.
  - Instuct patients to wash their hands after usage and instruct them not to rub their eyes after using capsaicin.
    - Ibid., Bodemer.



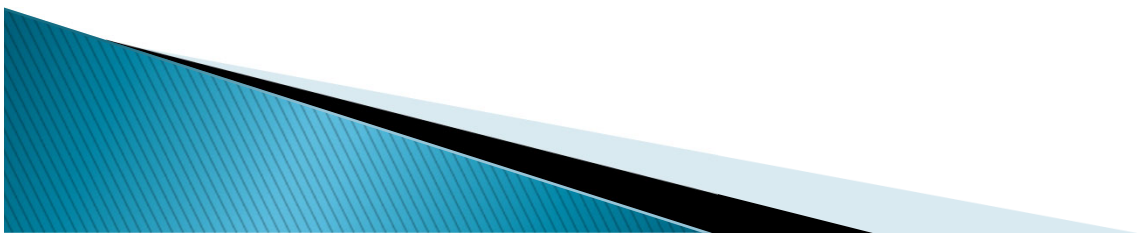
Topical Botanicals (Cont.)

- Aloe vera
  - Topically aloe vera reduces desquamation, erythema, and infiltration associate with psoriatic plagues.
    - Surjushe, A., et al., "Aloe vera: a short review," Indian Jour Dermatol 2008; 53(4):163-66.
  - Results from controlled trials have varied.
    - Syed, T., et al., "Management of psoriasis with aloe vera extract in a hydrophilic cream" a placebo-controlled, double-blind study," Trop Med Int Health 1996; 1:505-09.
    - Paulsen, E., et al., "A double-blind, placebo-controlled study of a commercial aloe vera gel in the treatment of slight to moderate psoriasis vulgaris," Jour Eur Acad Dermatol Venerol 2005; 19:326-31.



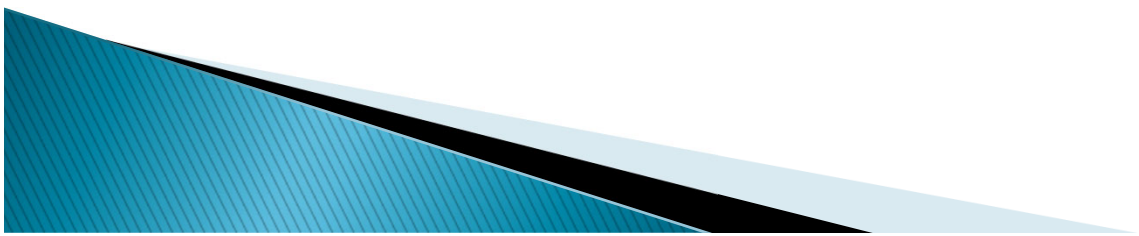
Topical Botanicals (Cont.)

- Glycyrrhetinic acid (Licorice)
  - In the skin, cortisol is inactivated by the enzyme, 11beta-hydroxysteroid dehydrogenase.
  - This enzyme is inhibited by glycyrrhetinic acid which is found in licorice.
  - Topical glycyrrhetinic acid potentiates the action of hydrocortisone.
    - Teelucksingh, S., et al., "Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid," Lancet 1990; 335:1060-63.



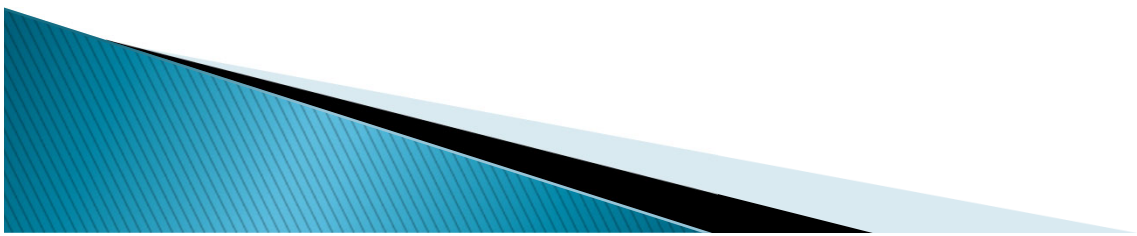
Topical Botanicals (Cont.)

- Glycyrrhetinic acid (Licorice) (cont.)
  - Compound
    - Glycyrrhetinic acid 1-2% in VersaBase with or without a steroid
    - #30 grams
    - Sig: apply to affected area qd
  - Studies need to be done using glycyrrhetinic acid in psoriasis.
    - Ibid., Bodemer.



Topical Botanicals (Cont.)

- Mahonia aquifolium
  - It was found to be effective and well tolerated in patients with mild to moderate psoriasis demonstrated in a randomized, double-blind, placebo-controlled study of 200 participants for 12 weeks.
  - The side effects reported were infrequent with the most common being a rash, burning sensation with application, and clothing stain.
    - Bernstein, S., et al., "Treatment of mild to moderate psoriasis with Reliéva, a Mahonia aquifolium extract--a double-blind, placebo-controlled study ," Amer Jour Ther 2006; 13(2):121-26.

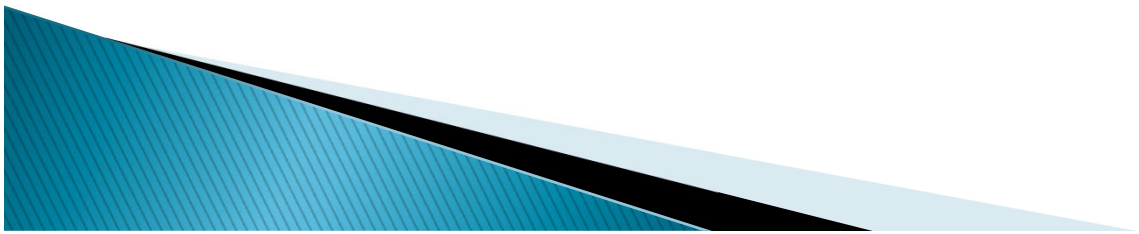


Topical Botanicals (Cont.)

- M. aquifolium (cont.)
  - Another article reviewed the efficacy of Mahonia aquifolium and showed that it resulted in a statistically significant improvement of symptoms in psoriasis and atopic dermatitis with minimal side effects.
    - Janeczek, M., et al., "Review of the efficacy and safety of topical Mahonia equifolium for the treatment of psoriasis and atopic dermatitis," Jour Clin Aesthetic Dermatol 2018; 11(12):42-7.

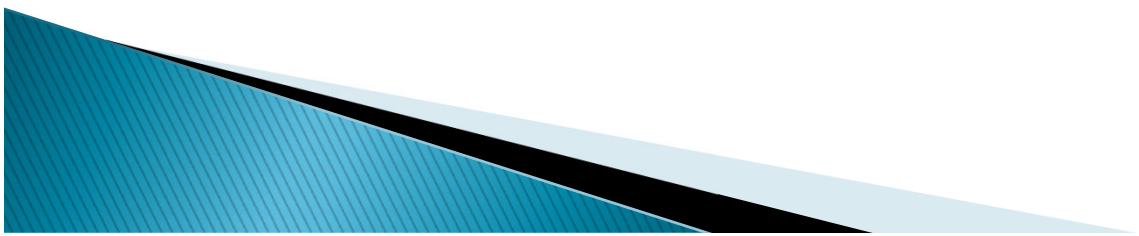
Systemic Botanicals

- Curcumin
  - The active component of turmeric
  - Inhibits pro-inflammatory pathways
    - Kurd, S., et al., "Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: a prospective clinical trial," Jour Amer Acad Dermatol 2008; 58:625-31.



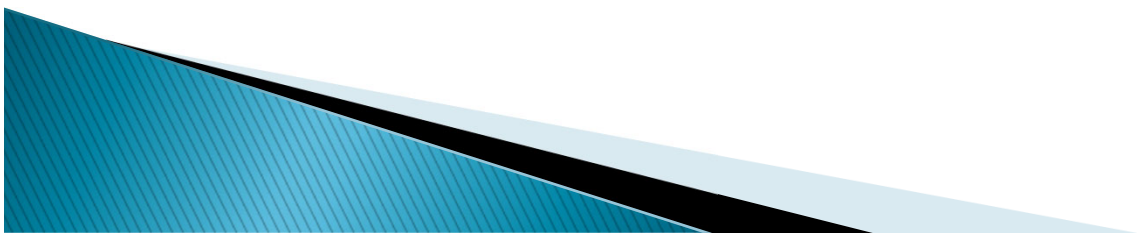
Systemic Botanicals (Cont.)

- Curcumin (cont.)
  - A small study used 500 mg of curcuminoid complex that contained 95% curcuminoids.
  - Patients took 3 capsules TID for 12 weeks.
  - Some patients had an excellent response.
  - Larger study is needed.
    - O'Hara, M., et al., "A review of 12 commonly used medicinal herbs," Arch Fam Med 1998; 7:523-36.



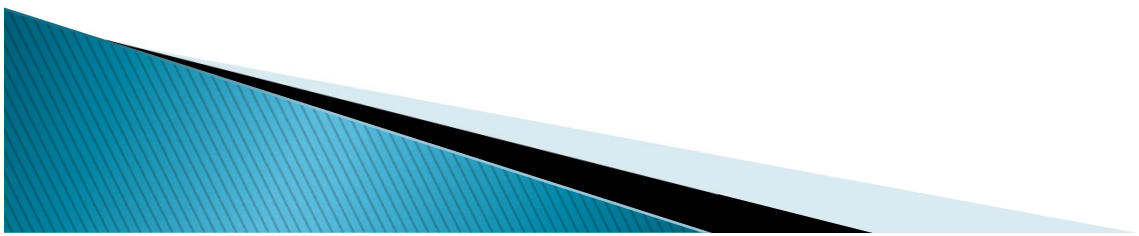
Systemic Botanicals (Cont.)

- Milk thistle (Silybum marianum)
  - Milk thistle protects against hepatotoxicity seen with methotrexate.
  - It acts as an antioxidant by scavenging free radicals and inhibiting lipid peroxidation.
  - It may protect against DNA injury and increase hepatocyte protein synthesis.
  - Dosage: 140 mg (70% silymarin) BID or TID
    - It increases insulin sensitivity in some individuals. Therefore, watch blood sugar if the patient is on a hypoglycemic agent.
    - Ibid., Bodemer.
    - Flora, K., et al., "Milk thistle (Silybum marianum) for the therapy of liver disease," Amer Jour Gastroenterol 1998; 93:139–43.



Meditation

- Study showed that patients that listened to a meditation tape during PUV or UVB therapy for psoriasis improved faster than patients that did not listen to the tape.
  - Kabat-Zinn, J., et al., "Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA)," Psychosom Med 1998; 60:625-32.



Hypnosis

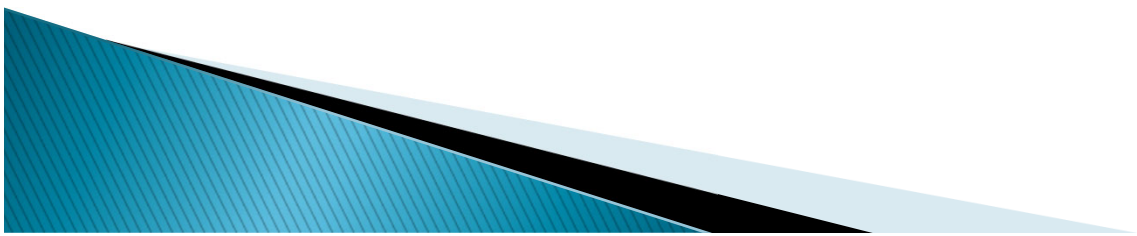
- In a three month, randomized, blind-controlled study showed that individuals that were highly hypnotizable had benefit from adding hypnosis to their treatment.
  - Tausk, F., et al., “A pilot study of hypnosis in the treatment of patients with psoriasis,” Psychother Psychosom 1999; 68:221-25.

Chinese Medicine

- According to Chinese medicine the main cause of papulosquamous skin eruptions is an inadequate supply of nutrients to the skin.
- Inadequacies include
  - External pathogenic wind-heat and wind-cold
  - Accumulation of blood-heat resulting from dietary or emotional influences
  - Qi stagnation and blood stasis from retention of pathogenic wind, damp, and heat
  - Yin deficiency of the liver and kidneys
    - Yihou, X., Dermatology in Traditional Chinese Medicine. London, Donica, 2004.

Chinese Medicine (Cont.)

- Topical preparations
  - Must make sure they are free of contamination
- Systemic herbs
  - 174 herbs have been studied
  - The following are the top 10.
    - Tse, T., "Use of common Chinese herbs in the treatment of psoriasis," Clin Dermatol 2003; 28:469–75.



Chinese Medicine Chinese (Cont.)

- Top 10 herbs for psoriasis
  - Rehmannia glutinosa (dried root)
  - Angelica sinensis (root)
  - Salvia militiorrhiza (root)
  - Dictamnus dasycarpus (root cortex)
  - Smilax glabra (underground stem)
  - Oldenlandia diffusa (whole plant)
  - Lithospermum erythrorhizon (root)
  - Paeonia lactiflora (root)
  - Carthamus tinctorius (flower)
  - Glycyrrhiza uralensis (rrot)

Chinese Medicine (Cont.)

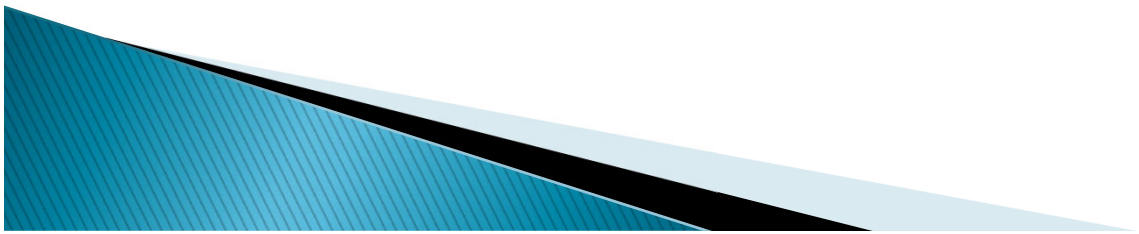
- Herbal preparations are not regulated so there is a risk of hepatotoxicity from the herbs themselves or from contaminants.
  - Perharic, L., et al., "Possible association of liver damage with the use of Chinese herbal medicine for skin disease," Vet Hum Toxicol 1995; 37:562-66.

Acupuncture

- The acupuncture points depend on the patterns of psoriasis.
- In a case series, patients with psoriasis that did not respond to conventional therapy were treated with acupuncture from 1 to 15 sessions.
  - ½ of the patients had total or almost complete clearance and many more had a significant improvement.
    - Liao, S., et al., "Acupuncture treatment for psoriasis: a retrospective case report," Acupunct Electrother Res 1992; 17:195-208.

Climatotherapy

- Climatotherapy means to move to a climate that is more favorable to treat the disease.
- Patients that move to sunny, dry climates do better with their psoriasis.



Balneophototherapy

- Balneophototherapy is a therapy with water and sun in a spa setting.
- Some patients use Dead Sea therapy by going to the Dead Sea and they are exposed to the water and the sun.
- Studies have shown significant improvement.
  - It may be due to more exposure there to UVB wavelengths.
  - Also, the water content has a high mineral count which may have an anti-proliferative effect.
    - Harari, M., et al., "Demographic evaluation of successful antipsoriatic climatotherapy at the Dead Sea DMZ clinic," Int Jour Dermatol 1997; 36:304-08.

Lifestyle

- The links between psoriasis and stress are complex.
- This article showed that in 31-88% of cases, patients reported stress as being a trigger for their psoriasis.
- There was also a reported higher incidence of psoriasis in subjects who had a stressful event the previous year, suggesting that stress may have a role in triggering the disease in predisposed individuals.
- Stress is also a consequence of psoriasis outbreaks.
  - Rousset, L., et al., "Stress and psoriasis," Int Jour Dermatol 2018; 57(10):1165-72.

Lifestyle (Cont.)

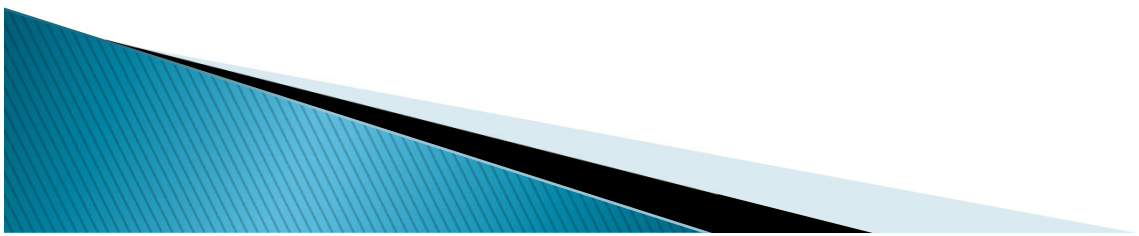
- How stress affects psoriasis?
  - Epidermal barrier is impaired by psychological stress
  - Injury to the epidermis promotes higher levels of keratinocyte growth stimulators like substance P and vasoactive intestinal peptide
  - Epidermal injury increases neural proliferation that may stimulate Langerhans cell activity
  - May change the level of tolerance for physical insult or may prolong epidermal recovery time
    - Garg, A., et al., "Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders," Arch Dermatol 2001; 137:53-59.

Lifestyle (Cont.)

- Stress can also affect treatment outcomes negatively.
- A study using PUVA phototherapy found that stress was the only significant predictor of time taken for the treatment to work.
  - Fortune, D., et al., "Psychological distress impairs clearance of psoriasis in patients treated with photochemotherapy," Arch Dermatol 2003; 139:752-56.

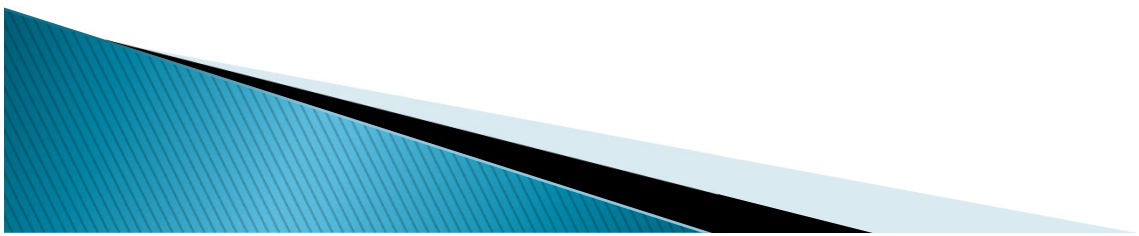
Lifestyle (Cont.)

- Improving stress levels may increase the positive affects of therapy whether it is conventional or metabolic.
  - Winchell, S., et al., “Relaxation therapies in the treatment of psoriasis and possible pathophysiologic mechanisms,” Jour Amer Acad Dermatol 1988; 18:101-04.
  - Zachariae, R., et al., “Effects of psychologic intervention on psoriasis: a preliminary report,” Jour Amer Acad Dermatol 1996; 34:1008-15.



Lifestyle (Cont.)

- Several controlled studies have demonstrated that relaxation, hypnosis, biofeedback, homeopathy, and behavioral and cognitive stress management therapies have been effective in people with psoriasis.
  - Basavaraj, K., et al., “Stress and quality of life in psoriasis: an update,” Int Jour Dermatol 2011; 50(7):783-92.



Herbal Teas

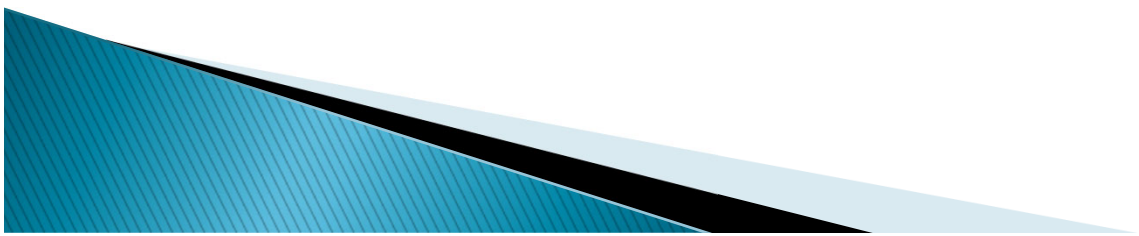
- Herbal teas have been found to be effective therapy for psoriasis. Patient should not use if they are pregnant.
  - American yellow saffron
  - Slippery elm
  - Chamomile
  - Mullein
  - Watermelon seed tea
  - Oolong tea
    - Ibid., Pagano.

Topical Applications for Symptoms

- Olive oil–peanut mixture
- Castor oil
- Cuticura soap, ointment, and shampoo
- Resinol
- Vaseline (white) and Vaseline cocoa butter, Baker's P&S Liquid, Ray's Ointment (for the hair line)
- Vitamin E
- Epsom or Dead Sea salts baths
  - Ibid., Pagano.

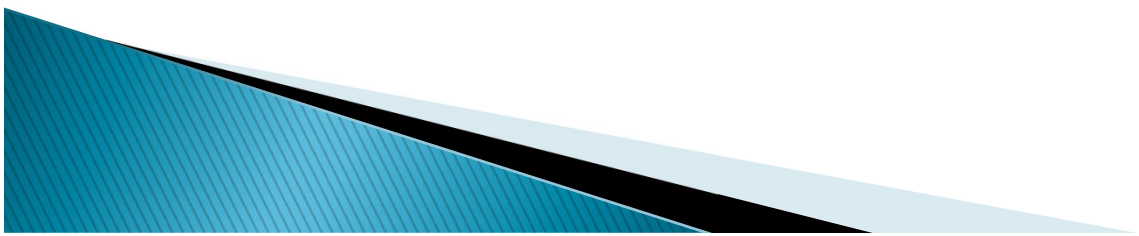
Topical Applications for Symptoms (Cont.)

- Fume and/or steam baths, wet sauna
- Sunlight and ultraviolet light
- Sodium bicarbonate (baking soda) baths and Aveeno baths
- Witch hazel, Listerine, Glyco-Thymoline, Sitz bath for the genital area
- Electrical stimulation and ultrasound (professionally applied)
  - Ibid., Pagano.



Topical Applications for Symptoms (Cont.)

- Olive oil–tincture of myrrh massage
- Hydrophilic ointment
- Physiotherapy at home
  - Whirlpool
  - Steam bath cabinet
  - Electrical heat caps, mitts, and boots
  - Humidifier
  - Ultraviolet lamp
- Pure, organic coconut oil
  - Ibid., Pagano.

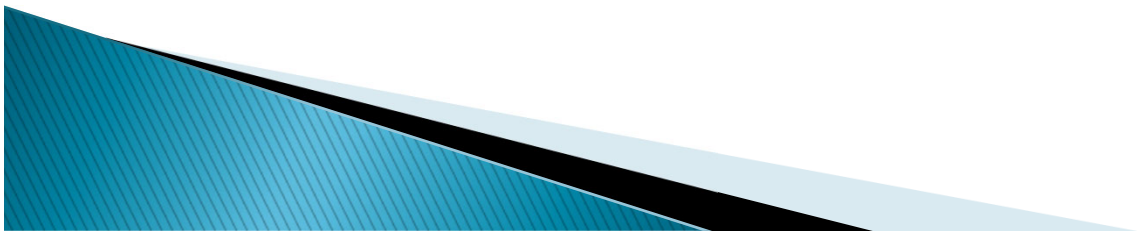


Clothing

- Synthetic or nylon undergarments may cause the psoriasis to become worse.
  - Ibid., Pagano.

Compound For Psoriasis #1

- Zinc pyrithione 0.2%/Clobetasol propionate 0.05%/Cyanocobalamin 0.07% in Topical Cream
- #90-120 grams
- Sig: apply to affected area qd

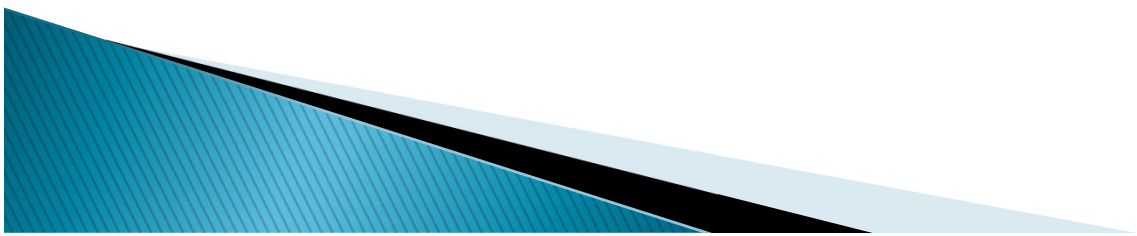


Compound For Psoriasis #2

- Clobetasol propionate 0.05%/Zinc pyrithione 0.2% as a Topical Spray
- #4oz.
- Sig: apply to affected area qd

Compound For Psoriasis #3

- Salicylic acid 1%/Coal tar topical solution 10% in Topical Cream
- #90 grams
- Sig: apply to affected area qd

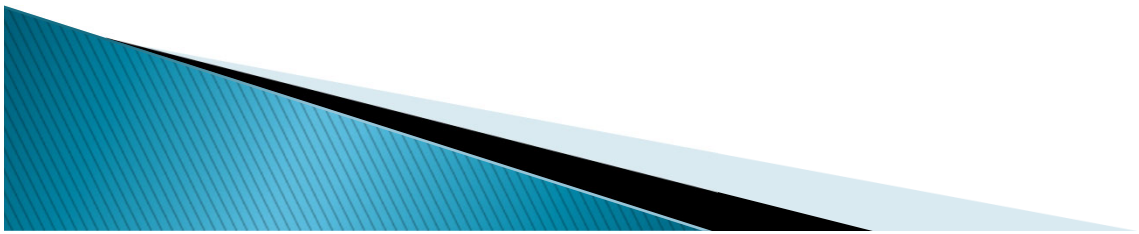


Compound For Psoriasis #4

- Compounded Formulation
  - Tacrolimus 0.1%/Cyanocobalamin 0.07%/Zinc Pyrithione 0.2% in Topical Cream
  - # 90 grams
  - Sig: apply to affected area qd

Compound For Psoriasis #5

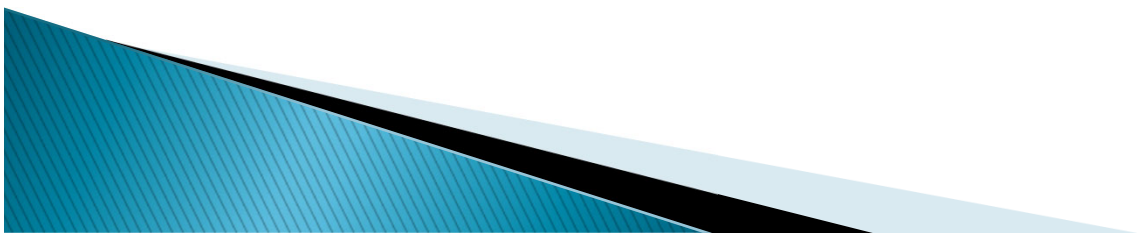
- Compounded Formulation
  - Zinc Pyrithione 0.8%/Clobetasol Propionate 0.05%/Coal Tar Topical Solution 5% in Topical Cream
  - # 90 grams
  - Sig: apply to affected area qd



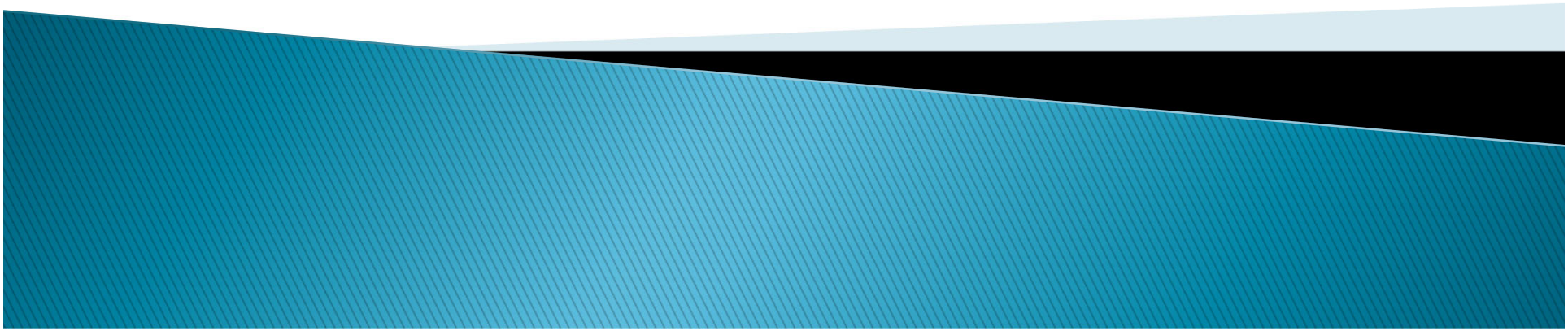
Compound For Psoriasis #6

- Compounded Formulation
  - Ketotifen 0.05%/Cyanocobalamin 0.07% in Topical Cream
  - # 90 grams
  - Sig: apply to affected area qd

  - Rotate away from Tacrolimus or steroids.

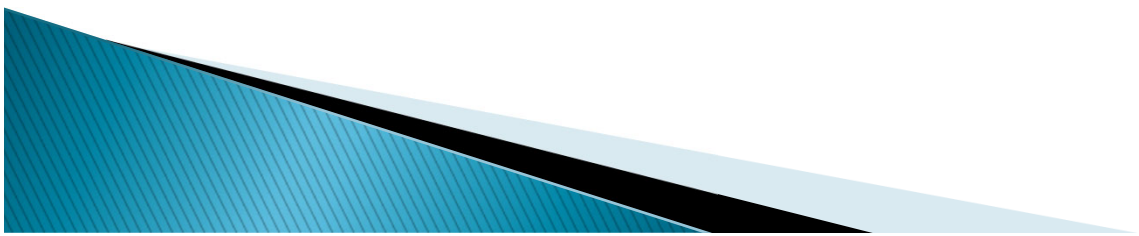


GI Health and Psoriasis



GI Health

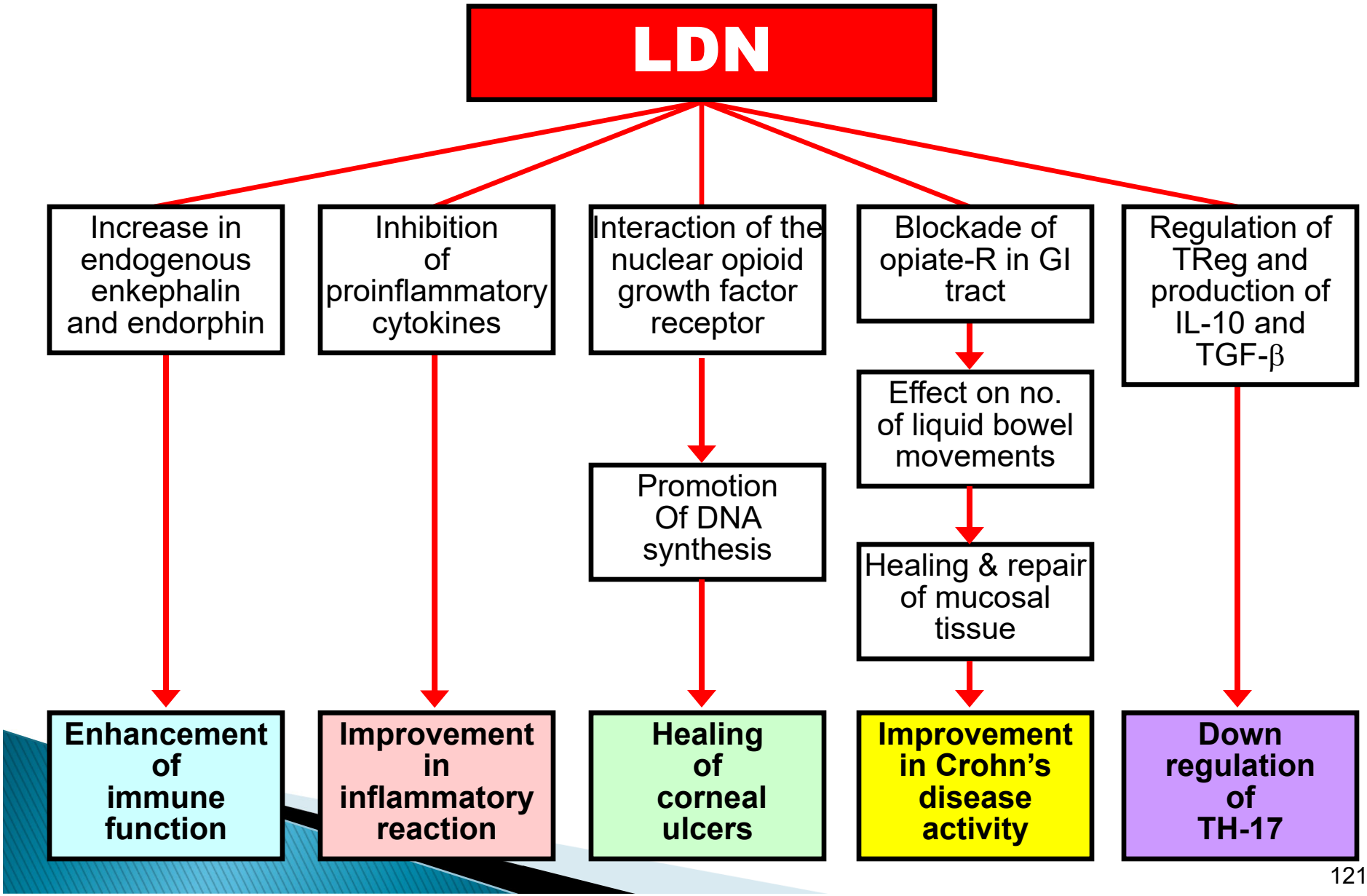
- As with any autoimmune process, always start with the gut.
  - 5R program
    - Remove
    - Replace
    - Re-inoculate
    - Repair
    - Rebalance
- Avoid all gluten
- LDN



LDN For Psoriasis

- LDN is effective for all autoimmune diseases including psoriasis.
- For mild cases
  - Use topical naltrexone to affect immune system: 1% cream base for itching
- For severe cases
  - One 1.5 mg capsule qhs x 7 days
  - Two 1.5 mg capsules qhs x 7 days
  - Three 1.5 mg capsules qhs x 7 days
  - Then 4.5 mg thereafter as a single capsule

MECHANISM OF ACTION OF LDN



Contraindications

- Acute hepatitis
- Liver failure
- Recent or current opioid/alcohol ingestion

Potential Short-Term Side effects

- Insomnia—most common
- Vivid dreams
- Fatigue
- Loss of appetite
- Nausea
- Hair thinning
- Mood swings
- Mild disorientation

Potential Long-Term Side effects

- Possible liver and kidney toxicity
- Possible tolerance to the beneficial rebound effect
- Other unknown sequelae
  - There is a long history of use of naltrexone at FDA approved doses (much higher than used in LDN)

Psoriasis and Cardiovascular Disease

- Although psoriasis is predominantly a chronic inflammatory skin disorder, it has been known to be associated with cardiovascular disease. In other words, patients with psoriasis, particularly with moderate to severe forms, present with an increased rate of cardiovascular mortality, myocardial infarction, and stroke.
- In addition, chronic inflammation may be considered a solid link between psoriasis and related cardiovascular events. Several cytokines and inflammatory cells play a pivotal role in the development of psoriatic lesions, resulting in angiogenesis and endothelial dysfunction.
- Furthermore, the imbalance between oxidative stress and antioxidant mechanisms in psoriatic patients may contribute to explain the pathogenesis of increased reactive oxygen species and the formation of atherosclerotic plaque.
- The early detection of specific markers of cardiovascular impairment, such as N-terminal pro B-type natriuretic peptide, homocysteine and YKL-40, may enable psoriatic patients at higher cardiovascular risk to be identified as rapidly as possible.

Reference

- Cozzani, E., et al., “Psoriasis as a cardiovascular risk factor: updates and algorithmic approach,” G Ital Dermatol Venereol 2018; 153(5):659-65.

Conclusion

- The good news is that there are both traditional and metabolic therapies that have been shown to be effective for psoriasis used alone or in conjunction with each other.
- Therefore, patients now has many personalized medicine choices to positively affect their disease process.