# Systemic Drug Therapy in Dermatology - I

## Basic principles

- Medications – Can target the skin by either topical/ intralesional/ systemic routes
- Intralesional administration – Additional option for very localized lesions *e.g.* IL steroids in keloids, AA *etc*.
- *Topical* application – Often a very effective therapeutic modality (frequently successful alone) for dermatological disease
- Will be ineffective *if* physical properties of drug leads to problem with passive diffusion from the skin surface

- Systemic medications – Distributed via the cutaneous vasculature
- Have the potential to exert pharmacological actions on *all* elements of the skin – therapeutic efficacy
- Not only the skin but also most of the other organs are exposed to the drug
- Therefore, systemic therapies may have potential for significant adverse effects
- Sometimes life-threatening

- One of the basic principles of medical *ethics*
- *L.* '*primum non nocere*', *i.e.* 'first, do no harm'
- Before considering systemic options – The clinician always to consider possibility of unwanted consequences of any therapeutic intervention

- Clinician – To use systemic medications safely

- Also – Appreciate the patient's perspective
- Assess the detrimental impact of a skin disorder on the patient's quality of life (QoL; DQLI)
- Assess the risk–benefit balance of a particular medication
- Best – A shared & informed decision between patient & dermatologist

# Standards of care

- No *perfect* medical management plan in all cases
- The competent clinician – Follow peer-determined & approved standards of care, *e.g.* in evidence-based/ National guidelines *etc.*

➢The Indian Association of Dermatologists, Venereologists & Leprologists (IADVL)

➢The British Association of Dermatologists (BAD)

➢The American Academy of Dermatology (AAD)

➢The National Institute for Health and Care Excellence (NICE)

➢The European Academy of Dermadology & Venereology (EADV)

➢For STIs: CDC guidelines *etc.*

# Drug-drug interactions

- Clinicians – To exclude *potential* interactions with the patient's existing medication
- To provide the patient with a *list of drugs* that may interact with the new drug
- To ensure the patient makes the prescribers of any *future* medication aware of the medicines they are already taking

# Immunomodulatory/ Immunosuppresive drugs

- Many (but *not* all) of the systemic agents – Immunomodulatory or (potent) immunosuppressive
- Require - Pre-treatment screening & subsequent monitoring
- Prior to initiation – Patients to be carefully counselled about the risk/ benefit aspects
- Written information - <u>Preferable</u>
- Particular regard – To infection, systemic & cutaneous malignancy, bone marrow suppression & conception-related issues

- Women – Adequate contraceptive guidance if applicable
- Cervical cytology screening history if applicable
- A h/o malignancy in any organ - Seek appropriate specialist advice
- The entire skin – Examine to exclude the presence of dysplastic/ neoplastic lesions
- Minimize the risk of reactivation of infections – Screen for latent blood-borne viruses (*e.g.* hepatitis B and C & HIV), latent tuberculosis
- Review vaccinations

**Box 19.1 Suggested pre-treatment checklist for cytotoxic and immunosuppressive therapy**

- Patient information leaflet
- Risk counselling
  - Infection
  - Bone marrow suppression
  - Skin malignancy
  - Lymphoma
  - Conception-related hazards
- Contraception
- Cervical screening concordance (pre-treatment gynaecological review if there is a history of dysplastic change)
- Sun protection measures
- General skin examination for dysplastic and neoplastic lesions
- Blood tests
  - Full blood count
  - Urea and electrolytes
  - Liver function tests
  - Hepatitis B and C serology
  - HIV serology (if there are positive risk factors)
  - Varicella zoster virus serology (if chickenpox history is uncertain)
- Vaccinations
  - Pneumococcal vaccination
  - Seasonal influenza vaccination
  - Hepatitis B (if seronegative)
  - Varicella zoster virus vaccination (if seronegative – several weeks prior to commencing treatment as vaccine is live)
  - Consider travel-related vaccinations

- Periodic follow-up visits – Regular investigations with regard to particular as per guidelines
- Occasional GPE – With a view to excluding lymphoma & cutaneous neoplasia

# Antihistamines

- H1 antihistamines - Mainstay of treatment for
  - ➢Chronic urticaria & angio-oedema
  - ➢Physical urticarias,
  - ➢Urticarial vasculitis,
  - ➢Cutaneous mastocytosis,
  - ➢Insect bite reactions,
  - ➢Anaphylaxis & allergic reactions to drugs

- Effectiveness in atopic eczema – Sedating H 1antihistamines - a role in the management of nocturnal pruritus
- The combination of H1 & H2 antihistamines – The treatment of urticaria

# Formula and structure

- H1 antihistamines – 6 Structural classes:
  - Alkylamines
  - Ethanolamines
  - Ethylenediamines
  - Phenothiazines
  - Piperidines
  - Piperazines

- 1st generation of antihistamines – Representatives in each structural group
- Majority of 2nd generation antihistamines – Piperidines or piperazines
- Doxepin – Tricyclic antidepressant with antihistamine activity

# Pharmacodynamics

- Traditionally, antihistamines – Considered reversible competitive inhibitors of histamine
- However, histamine receptors have an *intrinsic* level of activity
- H1 and H2 antihistamines are now best regarded as inverse agonists,
- Not just simply block the interaction of histamine with its receptors
- Also induce an <u>opposite pharmacological response</u> by decreasing the constitutive activity of the receptors

## Adverse Effects of $H_1$ Antihistamines

- Sedation[a]
- Other CNS disturbances[a]
  - Dizziness
  - Tinnitus
  - Blurred vision
  - Irritability or nervousness
  - Insomnia
  - Tremor
- GI complaints (rare)[a]
  - Nausea and vomiting
  - Diarrhea or constipation
  - Anorexia
- Anticholinergic effects[a]
  - Dry mucous membranes
  - Urinary retention
  - Postural hypotension
- Cardiac arrhythmias (particularly prolongation of the QT interval, ventricular arrhythmias, torsades de pointes) (rare)[a]
- Hypersensitivity reactions (rare)

# Dose & regimens

- If recommended dose of individual antihistamines – Not clinically effective → May prescribe higher doses *i.e.* updosing (limited evidence for the efficacy & safety)
- Combination of two or more antihistamines – Can be more effective than monotherapy
- The combination of H1 & H2 antihistamines

## TABLE 189-3
### Dosing Regimens for $H_1$ Antihistamines[1,6,15,18,33,81]

| DRUG | FORMULATION | DOSAGE | CONDITIONS REQUIRING DOSAGE ADJUSTMENT |
|---|---|---|---|
| **First-generation $H_1$ Antihistamines** | | | |
| Chlorpheniramine | 2-, 4-, 8-, 12-mg tablet | Adult: 4 mg thrice daily, 4 times daily; 8-12 mg twice daily | Hepatic impairment |
| | 2 mg/5 mL syrup | Age 6-11 years: 2 mg q4-6h | |
| Cyproheptadine | 4-mg tablet | Adult: 4 mg thrice daily, 4 times daily | Hepatic impairment |
| | 2 mg/5 mL syrup | Age 7-14 years: 4 mg twice daily, thrice daily | |
| Diphenhydramine | 25-, 50-mg tablet | Adult: 25-50 mg q4-6h | Hepatic impairment |
| | 12.5 mg/5 mL syrup | Age 6-12 years: 12.5-25 mg q4-6h | |
| | 50 mg/15 mL syrup | Age <6 years: 6.25-12.5 mg q4-6h | |
| | 6.25 mg/5 mL syrup | | |
| | 12.5 mg/5 mL syrup | | |
| Hydroxyzine | 10-, 25-, 50-, 100-mg tablet | Age ≥6 years: 25-50 mg q6-8h or at bedtime | Hepatic impairment |
| | 10 mg/5 mL syrup | Age <6 years: 25-50 mg daily | |
| Tripelennamine | 25-, 50-, 100-mg tablets | Adult: 25-50 mg q4-6h | Hepatic impairment |

## TABLE 189-3
### Dosing Regimens for $H_1$ Antihistamines[1,6,15,18,33,81] (*Continued*)

| DRUG | FORMULATION | DOSAGE | CONDITIONS REQUIRING DOSAGE ADJUSTMENT |
|---|---|---|---|
| **Second-generation $H_1$ Antihistamines** | | | |
| Acrivastine[a] | 8-mg tablet | Adult: 8 mg thrice daily | Renal impairment |
| Azelastine | 2-mg tablet[b] | Adult: 2-4 mg twice daily | Renal and hepatic impairment |
| | 0.1% nasal spray | Age 6-12 years: 1-2 mg twice daily | |
| | | 2 sprays/nostril twice daily | |
| Cetirizine | 5-, 10-mg tablet | Age ≥6 years: 5-10 mg daily | Renal and hepatic impairment |
| | 5 mg/mL syrup | Age 2-6 years: 5 mg daily | |
| | | Age 6 months to 2 years: 2.5 mg daily | |
| Desloratadine | 2.5-, 5-mg tablet | Age ≥12 years: 5 mg daily | Renal and hepatic impairment |
| | 5 mg/mL syrup | Age 6-12 years: 2.5 mg daily | |
| | | Age 1-6 years: 1.25 mg daily | |
| | | Age 6-12 months: 1 mg daily | |
| Ebastine[b] | 10-mg tablet | Age ≥6 years: 10-20 mg daily | Renal impairment |
| | | Age 6-12 years: 5 mg daily | |
| | | Age 2-5 years: 2.5 mg daily | |
| Fexofenadine | 30-, 60-, 120-, 180-mg tablet | Age ≥12 years: 60 mg daily, twice daily; 120-180 mg daily | Renal impairment |
| | | Age 6-12 years: 30 mg daily, twice daily | |
| Levocetirizine | 5-mg tablet | Age ≥6 years: 5 mg daily | Renal and hepatic impairment |
| Loratadine | 10-mg tablet | Age ≥6 years: 10 mg daily | Renal and hepatic impairment |
| | 5 mg/mL suspension | Age 2-9 years: 5 mg daily | |
| Mizolastine[b] | 10-mg tablet | Adult: 10 mg daily | Hepatic impairment |

## Factors for Risk-to-Benefit Assessment of First-generation $H_1$ Antihistamine Therapy

- Risks
  - History of cardiac arrhythmias, particularly ventricular arrhythmias
  - First trimester of pregnancy
  - Prostatic hypertrophy
- Contraindications
  - Narrow-angle glaucoma
  - Concomitant use of monoamine oxidase inhibitors

# Pregnancy

- Limited guidelines for use of H1 antihistamines in pregnancy
- Most – Classified as Food & Drug Administration (FDA) pregnancy category *B* or *C*
- Earlier reports – Link H1 antihistamines to fetal malformations (*e.g.* particularly cleft palate)
- Usually avoided in the first trimester of pregnancy
- Newer studies – (including a meta-analysis of 200,000 first-trimester exposures to first-generation antihistamines) – <u>No</u> increased risk of congenital malformations

# Breastfeeding

- No formal studies – During breastfeeding
- Theoretically – May diminish milk supply via anticholinergic effects
- Many e.g. diphenhydramine, promethazine, cetirizine, loratadine,
- fexofenadine, levocetirizine etc. - Excreted in breastmilk
- However, effects on the nursing infants – Not studied

# Tricyclic antidepressants

- TCAs – Bind to both H1 & H2 receptors
- TCA MC used in dermatology – doxepin – about 800 times more potent than diphenhydramine
- Uses:
  - Refractory CSU
  - Physical urticarias
  - Pruritus associated with systemic conditions
- Sedation is the most common adverse effect - some patients *may* develop tolerance with regular use
- Oral doxepin - FDA as a pregnancy category *C*
- Use with caution in elderly - May be more susceptible to its anticholinergic effects, including urinary retention & blurred vision

# Antifungal drugs

- The systemic antifungal drugs – Broadly classified by *MoA*

❖Act on the fungal wall or cell membrane

❖Act intracellularly

- The fungal wall/cell membrane agents - Subdivided

✓Inhibit ergosterol (integral part of fungal cell membrane) function

✓Inhibit β-glucan synthase

- *<u>The ergosterol inhibitors</u>*
  - <u>Azoles</u> (inhibit lanosterol 14-α demethylase, essential for the synthesis of ergosterol)
  - ➢*Imidazoles* (5-membered aromatic ring with 2 nitrogen & 3 carbon atoms) *e.g.* ketoconazole
  - ➢*Triazoles* (5-membered aromatic ring with 3 nitrogen & 2 carbon atoms) *e.g.* fluconazole, itraconazole, posaconazole, voriconazole
  - <u>Allylamines</u> (inhibit squalene epoxidase, essential in ergosterol synthesis) *e.g.* terbinafine
  - <u>Polyenes</u> (bind to ergosterol & interfere with fungal cell membrane) *e.g.* nystatin & amphotericin B

- *Β-glucan synthase inhibitors* - Interfere with the synthesis of glucan (component of the fungal cell wall) *e.g*. echinocandin antifungals caspofungin, micafungin
- *Intracellular MoA*
- Flucytosine - A pyrimidine analogue, inhibits fungal DNA & RNA synthesis
- Griseofulvin – A spiro-benzo[b]furan - inhibits fungal mitosis by binding to tubulin thus disrupting microtubule function

**Trade Names and Formulations of Representative Systemic Antifungals**

| DRUG/CLASS | TRADE NAMES | USUAL FORMULATION | INDICATIONS | DOSING REGIME | | PREGNANCY CATEGORY |
|---|---|---|---|---|---|---|
| | | | | ADULT | PEDIATRIC | |
| **Allylamines** | | | | | | |
| Terbinafine | Lamisil, Terbinex | 1. Tablets 250 mg<br>2. Oral granules | Tinea unguium[a] | Continuous 250 mg/d >20 kg<br>Fingernail for 6 wk<br>Toenail for 9-12 wk<br>Pulse 500 mg/d for 1 wk/m for same duration | Continuous >20 kg<br>62.5 mg/d<br>20-40 kg<br>125 mg/d for same duration | B |
| | | | T. capitis[a] | 250 mg/d for 2-8 wk | 5 mg/kg/d[c] for 2-4 wk | |
| | | | T. pedis, cruris, corporis[b] | 250 mg/d 2-4 wk | | |
| | | | Seborrheic dermatitis[b] | 250 mg/d 4-6 wk | | |

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| **Azoles** | | | | | | |
| ***Triazoles*** | | | | | | |
| Fluconazole | Diflucan | 1. Capsule 150 mg<br>2. Tablets 150 mg<br>3. Solution for IV infusion | 1. Esophageal candidiasis[a] | 150 mg/d for 2-3 wk after clinical improvement | 6 mg/kg/d until clinical improvement, then 3 mg/kg/d for 2 wk | C |
| | | | 2. Vaginal candidiasis[a] | 150 mg once<br>Recurrence<br>150 mg/wk for 6 mo | | |
| | | | 3. Cutaneous, mucocutaneous candidiasis[a] | 300 mg/wk for 2 wk | | |
| | | | 4. T. capitis[b] | | 6 mg/kg/d<br>*Trichophyton tonsurans* for 20 d<br>*Microsporum canis* 2 wk | |
| | | | 5. Onychomycosis[b] | 150-300 mg/wk<br>Fingernail for 6-9 mo<br>Toenail for 9-15 mo | 3-6 mg/kg/d<br>Fingernail 12-16 wk<br>Toenail 18-26 wk | |
| | | | 6. Tinea pedis, cruris, corporis, barbae[b] | 150 mg/wk for 2-6 wk | | |
| | | | 7. Tinea versicolor[b] | 300 mg/wk for 2 wk | | |

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|---|---|---|---|---|---|---|
| **Azoles** | | | | | | |
| ***Triazoles*** | | | | | | |
| Itraconazole | Sporanox | | 1. Onychomycosis[a] | **Continuous** | | C |
| | Sporanox pluspak<br>Onmel | 1. Capsules 100 mg<br>2. Cyclodextrin oral solution | | 200 mg/d<br>Fingernail for 6 wk<br>Toenail for 12 wk<br>**Pulse**<br>400 mg/d for 1 wk/mo<br>Fingernail 2 pulses<br>Toenail 3 pulses | **Pulse**<br>5 mg/kg/d for 1 wk/mo<br>Fingernail 2 pulses<br>Toenail 3 pulses | |
| | | | 2. Oropharyngeal candidiasis[a] | Oral solution<br>100-200 mg/d for 1-2 wk after clinical improvement | >15 kg 100 mg/d<br>15-30 kg<br>100 mg/d<br>alternating with<br>200 mg/d<br>30-45 kg<br>200 mg/d<br>same duration as adults | |
| | | | 3. T. capitis[b] | 200 mg/d for 2-8 wk | 5 mg/kg/d<br>*T. tonsurans* for 2-4 wk<br>*M. canis* for 4-8 wk | |
| | | | 4. T. pedis, cruris, corporis[b] | 200 mg/d for 1 wk | | |
| | | | 5. Pityriasis versicolor[b] | TTT<br>200 mg/d for 1 wk<br>Prophylaxis<br>400 mg once every month | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Other** | | | | | | |
| Griseofulvin | Griseofulicin<br>Griseofulvic<br>Gris-PEG<br>Grifulvin V | 1. Tablets Microsize 250, 500 mg Ultramicro-size 125, 165, 250 mg<br>2. Oral suspen-sion 125 mg/5 mL | 1. T. capitis[a] | Microsize 500 mg/d or ultramicrosize 300-375 mg/d for 4-8 wk | Microsize 15-2 0 mg/kg/d or ultramicrosize 5-10 mg/kg/d for 6-12 wk | C |
| | | | 2. T. cruris,[a] corporis | Same doses as above for 2-4 wk | Same doses as above for 2-4 wk | |
| | | | 3. T. pedis[a] | Microsize 750-1000 mg/d or ultramicrosize 660-750 mg/d for 4-8 wk | Microsize 10-20 mg/kg/d or ultramicro-size 5-10 mg/kg/d for 4-8 wk | |

## Side Effects, Contraindications, and Monitoring of Representative Systemic Antifungals

| DRUG | SIDE EFFECTS | PRECAUTIONS/CONTRAINDICATIONS | MONITORING |
|---|---|---|---|
| **Terbinafine** | 1. Ageusia (altered taste), loss of smell, and tongue discoloration+<br>2. Hepatotoxicity, hematologic disorders ++<br>3. GIT upset, aggravate psoriasis, lupus erythematosus | 1. Hepatic disease (chronic or active)<br>2. Renal impairment (creatinine clearance <50 mL/min) | 1. Baseline LFTs<br>2. Full CBC<br>3. BUN, creatinine<br>4. Plasma level of CYP2D6-metabolized drugs |
| **Fluconazole** | 1. Cardiac abnormalities (torsade de pointes), exfoliative skin reactions, anaphylactic reactions++<br>2. Headache, myalgia, dizziness, GIT upset+++<br>3. Hepatic, renal functions abnormalities | 1. Hepatic and renal impairment<br>2. In patients with risk for arrhythmias<br>3. Coadministration with astemizole, terfenadine, cisapride (increased risk of developing torsade de pointes)<br>4. Coadministration with statins (increased myopathy) | 1. Baseline LFTs<br>2. Full CBC<br>3. Regular LFTs<br>4. Close monitor of oral hypoglycemic, and blood glucose |
| **Itraconazole** | 1. Triad of hypertension, hypokalemia, &edema in elderly+<br>2. Negative inotropic fulminant hepatitis, Stevens–Johnson syndrome; Anaphylaxis++<br>3. GIT upset, esp. odious taste with cyclo-dextrin solution+++<br>4. Headache, rhinitis, sinusitis, hepatic, renal impairment | 1. Heart failure<br>2. Liver disease<br>3. Patients with hypersensitivity to other azoles (use with caution) | 1. Patients with risk factors for CHF for developing signs or symptoms of CHF<br>2. Baseline LFTs<br>3. Regular LFTs<br>4. Blood glucose in patients using oral hypoglycemic<br>5. Plasma level of drugs metabolized with by CYP3A4 |
| **Griseofulvin** | 1. Hetaotoxicity, pancytopenia++<br>2. Hypersensitivity skin eruptions, Photosensitivity,<br>3. GIT upset+++<br>4. Neurologic problems | 1. Porphyria<br>2. LCF<br>3. Patients with penicillin sensitivity (use with cautious)<br>4. Females using OCP should change the contraceptive method or add another form | 1. Liver enzymes after 8 wk of continuous use<br>2. BUN, creatinine after 8 wk of continuous use |

# Thank you