
ADVERSE
DRUG
REACTIONS
DR PRADNYA ROTITHOR
causation
proposed
effect
clinical
factor
haemorrhage
dosage
criteria
reaction
discontinuation
headache
pharmacologic
abates
inherited
missed
hepatic
impairment
normal
cytochrome
binding
lipoproteins
medication
glycoprotein

WHAT ADVICE A DOCTOR GIVES TO PATIENTS--

- ***For severe types of reactions patient should avoid taking that drug in future***
- **Type A reduce the dose**
- **Type B reactions Stop the drug**
- **Avoid in future**
- ***Instruct patient to report other doctors he/she visits in future***
- **Type C -use safest drug at lowest possible dose for minimum duration**
- **Type D –use only if essential**
- **Type E –taper the dose before stopping**


Report
Drug
Adverse
Reactions

- India – 'Suspected Adverse Drug Reaction Reporting Form'
- UK – 'Yellow Card', since 1964
- Australia – 'Blue Card' , since 1964
- US – 'Med Watch'
  - Form FDA 3500 – voluntary reporting
  - Form FDA 3500A - mandatory reporting

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

INDIAN PHARM ACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
www.ipc.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique

A. PATIENT INFORMATION

1. Patient Initials
2. Age at time of Event or date of birth
3. Sex ☐ M ☐ F
4. Weight _____ Kgs

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

ADR REPORTING FORM IN INDIA

12. Relevant tests / laboratory data with dates

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction
- ☐ Death (dd/mm/yyyy)
- ☐ Life threatening
- ☐ Hospitalization/prolonged
- ☐ Disability
- ☐ Congenital anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

Outcomes
- ☐ Fatal
- ☐ Recovering
- ☐ Unknown
- ☐ Continuing
- ☐ Recovered
- ☐ Other (specify)

C. SUSPECTED MEDICATION(S)

S.No	8. Name (brand and/ or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known, give duration) Date started	Date stopped	Reason for use of prescribed for
i.										
ii.										
iii.										
iv.										

S.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. REPORTER (see confidentiality section on first page)

16. Name and Professional Address : _____

Pin code: _____ E-mail _____

Tel. No. (with STD code): _____

Occupation _____ Signature _____

17. Causality Assessment

18. Date of this report (dd/mm/yyyy)

Pharmacovigilance

collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of drugs

Major goal of pharmacovigilance is to detect a signal on an unknown serious adverse drug reaction as soon as possible

WHO DEFINITION

- Unwanted effects of drugs caused by therapeutic doses.
- Noxious, Unintended response to a drug that occurs at usual doses in human beings
- (prophylaxis, diagnosis, and therapy) or for modification of physiological state

- Types –A B C D E

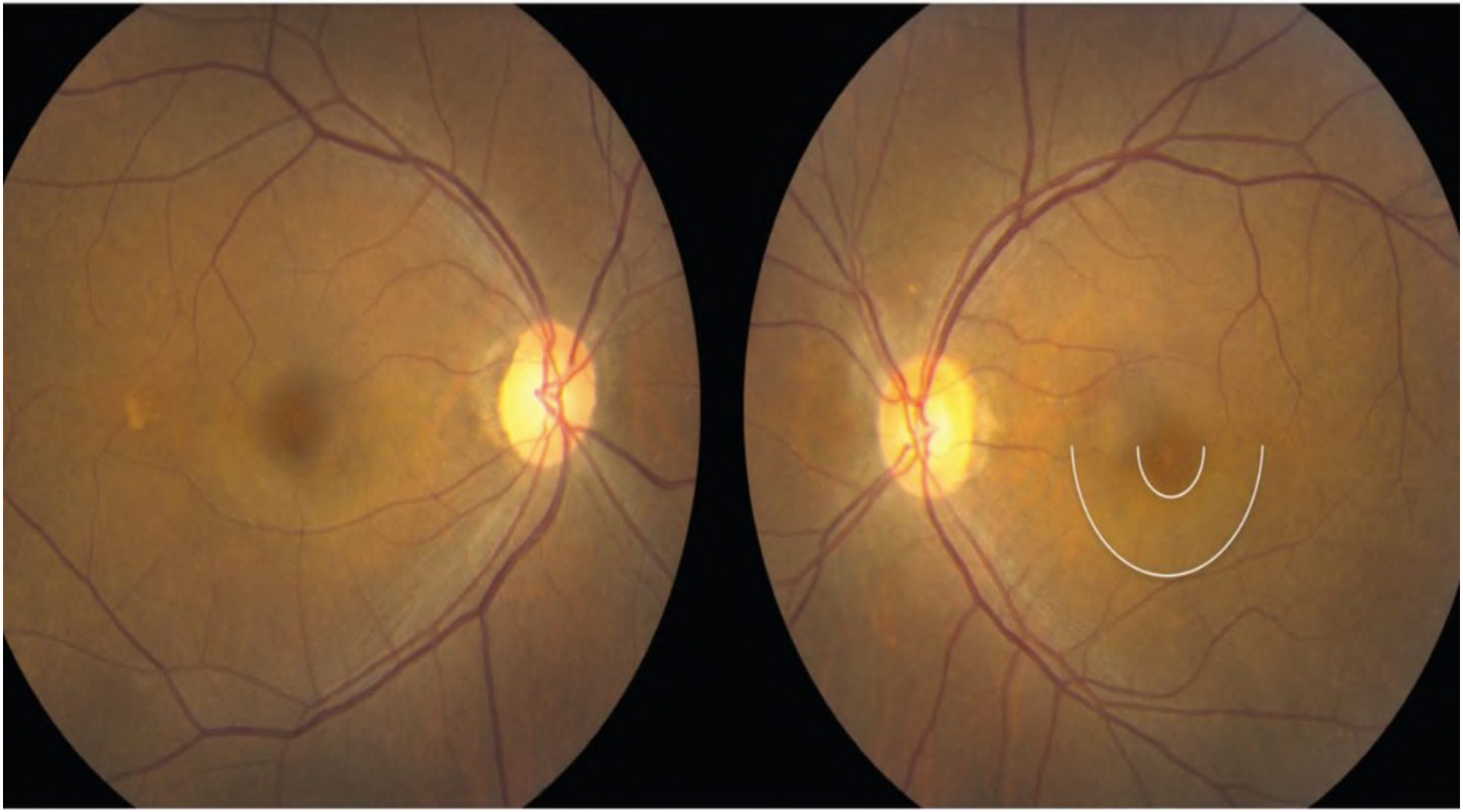
Classification--MCQ

- Type A Augmented dose related
- ----------
- Type B Bizarre abnormal
- ----------
- Type C Cumulative time & dose
- ----------
- Type D Delayed time
- ----------
- Type E End of dose after stoppage

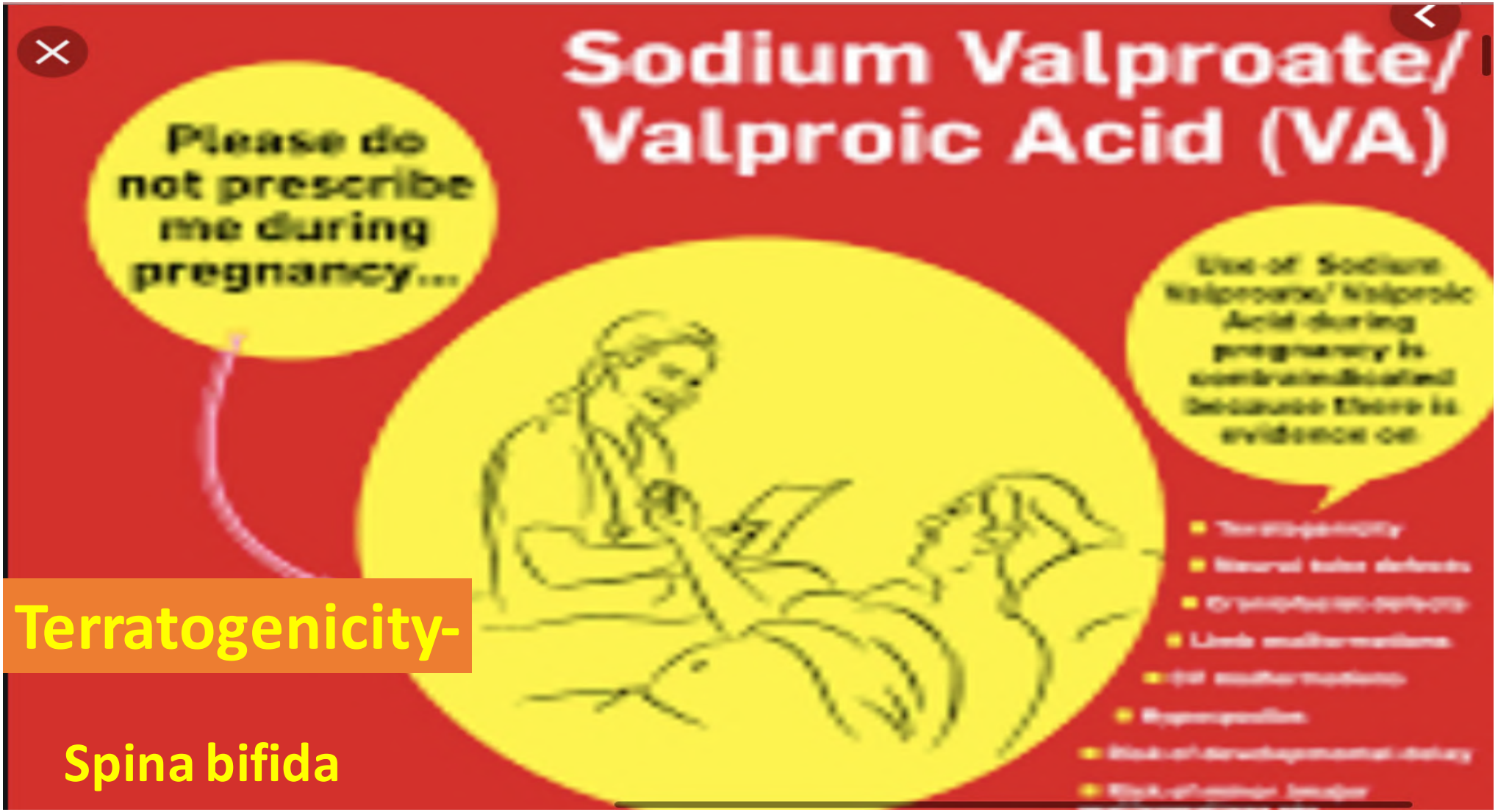
Type	name	description
A	**AUGMENTED**	**Extension of pharmacological action**
B	**BIZARRE**	**Hypersensitivity/allergy** **-Idiosyncrasy**
C	**CONTINUOUS REACTION**	**Due to long term use** **-Antipsychotics – Tardive dyskinesia** **-Analgesics – Nephropathy** **PHENYTOIN -gingivitis**
D	**DELAYED REACTIONS**	**Carcinogenicity, Mutagenicity, Teratogenicity**
E	END OF USE REACTIONS	**WITHDRAWAL / DISCONTINUATION – steroids, beta blockers, benzodiazepines**

Type A and Type C

- **Augmented and Continuous**
- **Most common ADRs Dose dependent**
- **Extension of pharmacological actions**
- **Ex-hypoglycaemia due to insulin**
- **dryness of mouth due to atropine**
- **Occur due to repeated or continuous /long term use of drugs**
- **Mostly seen with drugs having low Therapeutic index TI having less margin of safety**
- **Or occurs due to drugs which cumulate of in certain tissues—**
- **Organ specific/structural damage**
- **Ex –analgesic nephropathy ,retinal toxicity due to chloroquine**



Alopecia –anticancer drugs


Sodium Valproate/
Valproic Acid (VA)
Please do not prescribe me during pregnancy...
Use of Sodium Valproate/ Valproic Acid during pregnancy is contraindicated because there is evidence of
Terratogenicity-
Spina bifida

Other adverse drug reactions

Toxic effect	Overdose / poisoning
Intolerance	Exaggerated effect even with small dose (Gaussian distribution – Extreme end)
Drug dependence	Compulsive, chronic, nontherapeutic drug administration
Secondary effects	Indirect consequence of drug action – tetracyclines – destruction of commensal flora – superinfection

TYPE A quantitative Dose dependent

- **Augmented & Predictable**

pharmacological properties –drug related

- More common, dose related ,preventable and reversible
- 80% of ADR
- Augmentation of normal action of drug
- Or less safe drugs

- Severity --mild to moderate

TYPE B qualitative independent of dose

- **Bizarre & mostly Unpredictable**

peculiarities of **patient** and not on drug –person related

- rare, non dose related ,more serious ,only few can be prevented
- 1:1000 –1:10000
- Hypersensitivity/allergy
- immunologic
- Genetic basis /off target reactions
- idiosyncrasy
- severe to lethal

Adverse drug reactions (ADR)

Type A (Augmented) (Quantitative)	Type B (Bizzare) (Qualitative)
High incidence Low mortality	Low incidence Considerable mortality
Dose reduction needed	Drug has to be discontinued
B blockers - Bradycardia Atropine – Dry mouth Glipizide – Hypoglycemia Warfarin – Bleeding Digoxin – Nausea	Pen G – Anaphylaxis Primaquine – Hemolysis Chloramphenicol – aplastic anemia
Mild - Side effects Severe – Untoward effects	

Qualitative intolerance (Type B – Bizzare)
(Non-dose related)

- **HYPERSENSITIVITY**
- **IDIOSYNCRASY**

•HYPERSENSITIVITY REACTIONS

- HUMORAL
- **Anaphylactic** --type 1 IgE AB mast cells release 5HT Prostaglandins leukotrines
- Urticaria itching angioedema bronchospasm anaphylactic shock
- Cytolytic type 2 IgG IgM
- drug + specific tissue cell act as AG
- Thrombocytopenia aplastic anaemia haemolysis organ damage

- Retarded type 3 IgG circulating antibodies
- Causing inflammatory damage to vascular endothelium –
- Steven Johnson syndrome serum sickness

- **CELL MEDIATED**
- **Type 4 sensitized T lymphocytes carry receptors for AG .**
- **On contact with AG lymphokines are produced which cause**
- **inflammatory damage**
- **Ex –photosensitivity rashes fever contact dermatitis**

- **Dentist –contact dermatitis on repeated exposure to procaine**

Hypersensitivity reactions (Allergy)

Type I Immediate	Humoral IgE- mast cell	Anaphylaxis Penicillins, cephalosporins
Type II Immediate	Humoral IgE, IgM	Cytolytic reaction – complement fixation - Pen, cepha, methyldopa, quinine – Coomb's positive hemolytic anemia
Type III - Immediate	Humoral Mostly IgG Circulating immune complexes	(Retarded) Arthus reaction -serum sickness, glomerulonephritis, eosinophilia, drug fever, urticaria, rash, polyarteritis nodosa, SLE-like syn - Peni, Cotrim, strepto, PTU, amiodarone, hydralazine. [Steven-Johnson Syndrome – Sulfa, aspirin, carbamazepine]
Type IV Delayed	*Cell mediated immunity* *T cells*	Contact dermatitis – Peni, neomycin Maculopapular rash - Ampicillin Photosensitivity - (Amiodarone, tetracyclines, Chlorpromazine, Ciprofloxacin) Fixed drug eruption – Sulfa

Anaphylaxis

Qualitative intolerance

- **HYPERSENSITIVITY (I,II,III, IV)**

-Immediate

Anaphylactic reaction (penicillin),

Steven-Johnson Syndrome (sulfa, sulfones)

-Delayed

Maculopapular skin eruption (ampicillin)

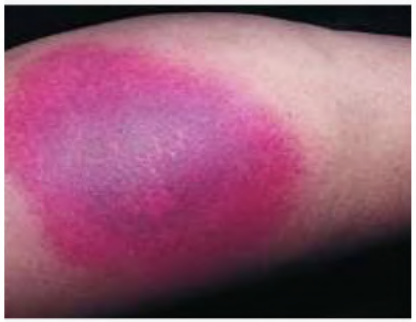
Fixed drug eruption (sulfa)

Qualitative intolerance (Type B – Bizarre)
(Non-dose related)

- **IDIOSYNCRASY**
- **Bone marrow suppression, agranulocytosis:**
  Chloramphenicol
- **Hemolysis in G6PD deficient patients:**
- **Sulfa drugs, primaquine, quinolones, cephalosporins, dapsone, metronidazole**

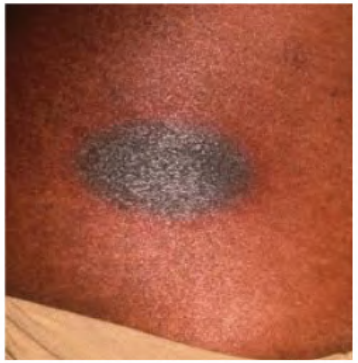
Quantitative intolerance

Side effect	Untoward effect	Toxic effect
Therapeutic dose	Therapeutic dose	Acute overdose / Chronic administration
Mild	Severe, the patient feels like stopping the drug	Severe

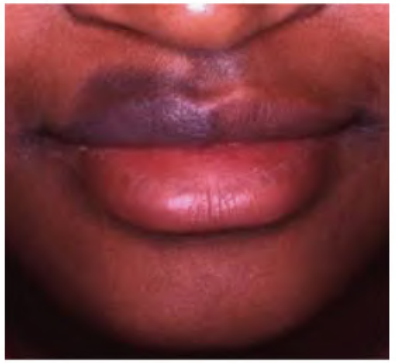


Fixed drug eruption | definition o...
medical-dictionary.thefreedictionary...

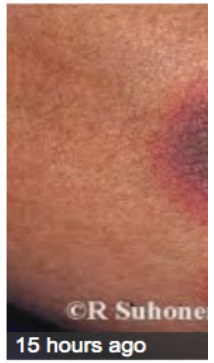
Fixed drug eruption | DermNet NZ
dermnetnz.org



Fixed Drug Eruptions Clini...
emedicine.medscape.com

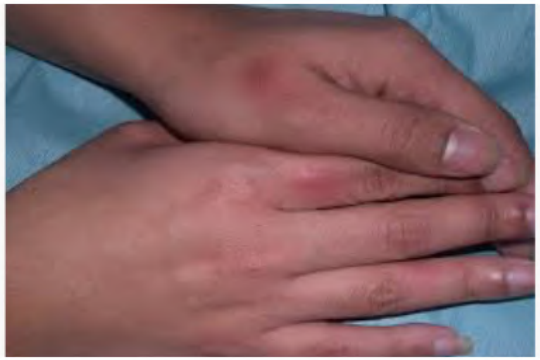


Fixed Drug Eruptions Clinical ...
emedicine.medscape.com

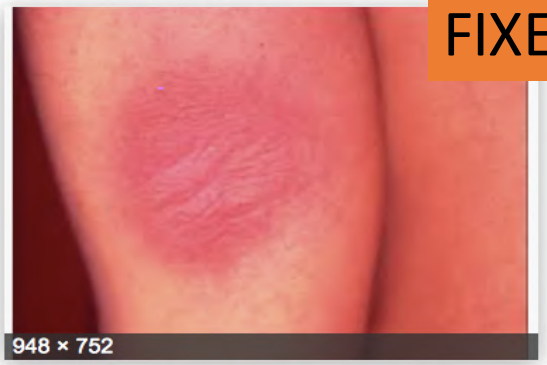


Fixed drug erupti
dermnetnz.org

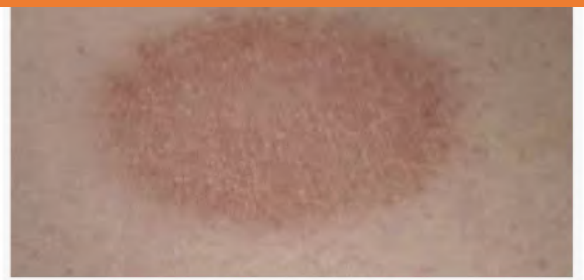
FIXED DRUG ERUPTIONS



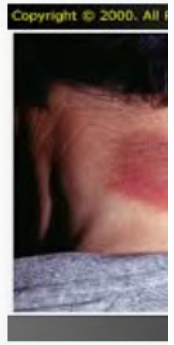
Fixed Drug Eruption (FDE) - Clinical ...
clinicalpainadvisor.com



Bullous Fixed Drug Eruption Induced by ...
jamanetwork.com



Fixed drug eruptions | Chemist+Druggist
chemistanddruggist.co.uk



Drug eruptions
dermweb.com

Type iv delayed –CELL MEDIATED

Stevens-Johnson Syndrome. Image Credit (Left) http://www.rash-pictures.com/category/93 (Middle) Source Unknown. (Right) http://www.drguide.mohp.gov.eg/newsite/E-Learning/SuperCourses/Dermatology2.asp

Steven johnson's syndrome

Type III IG-CIRCULATING IMMUNE COMPLEXES

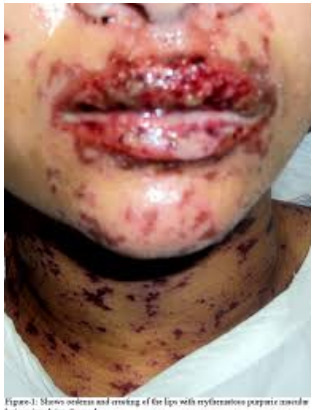
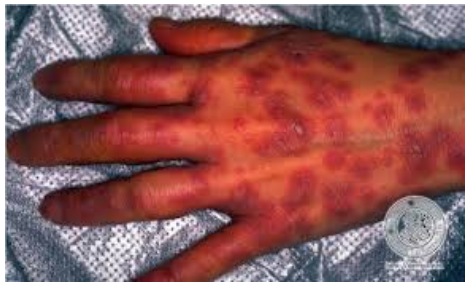
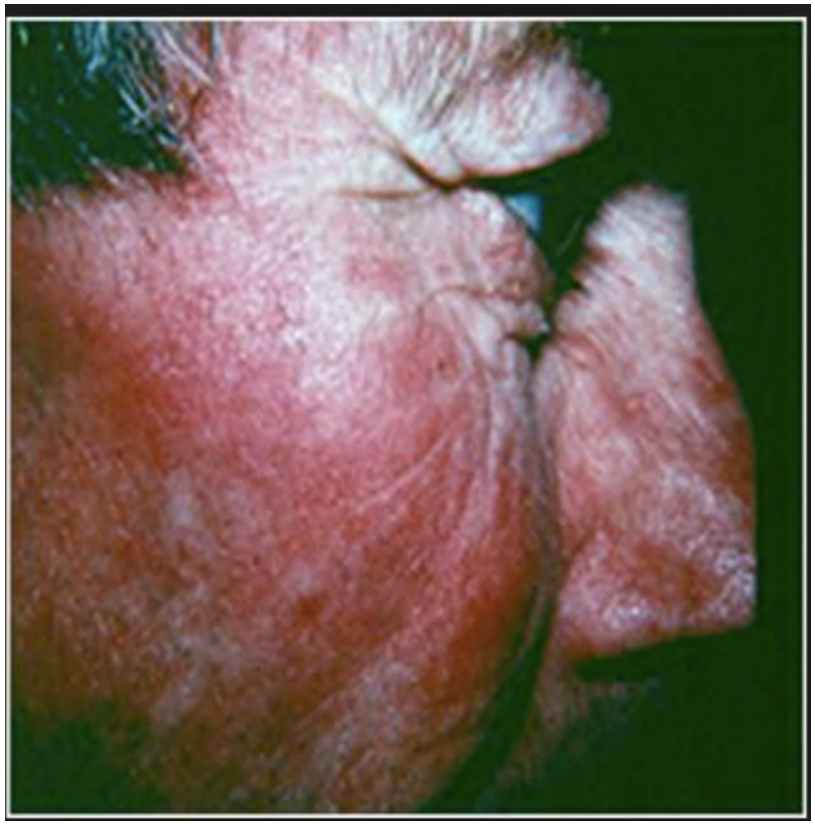


Figure-1: Shows oedema and crusting of the lips with erythematous purpuric macular lesion involving the cheek.





Contact dermatitis photosensitivity

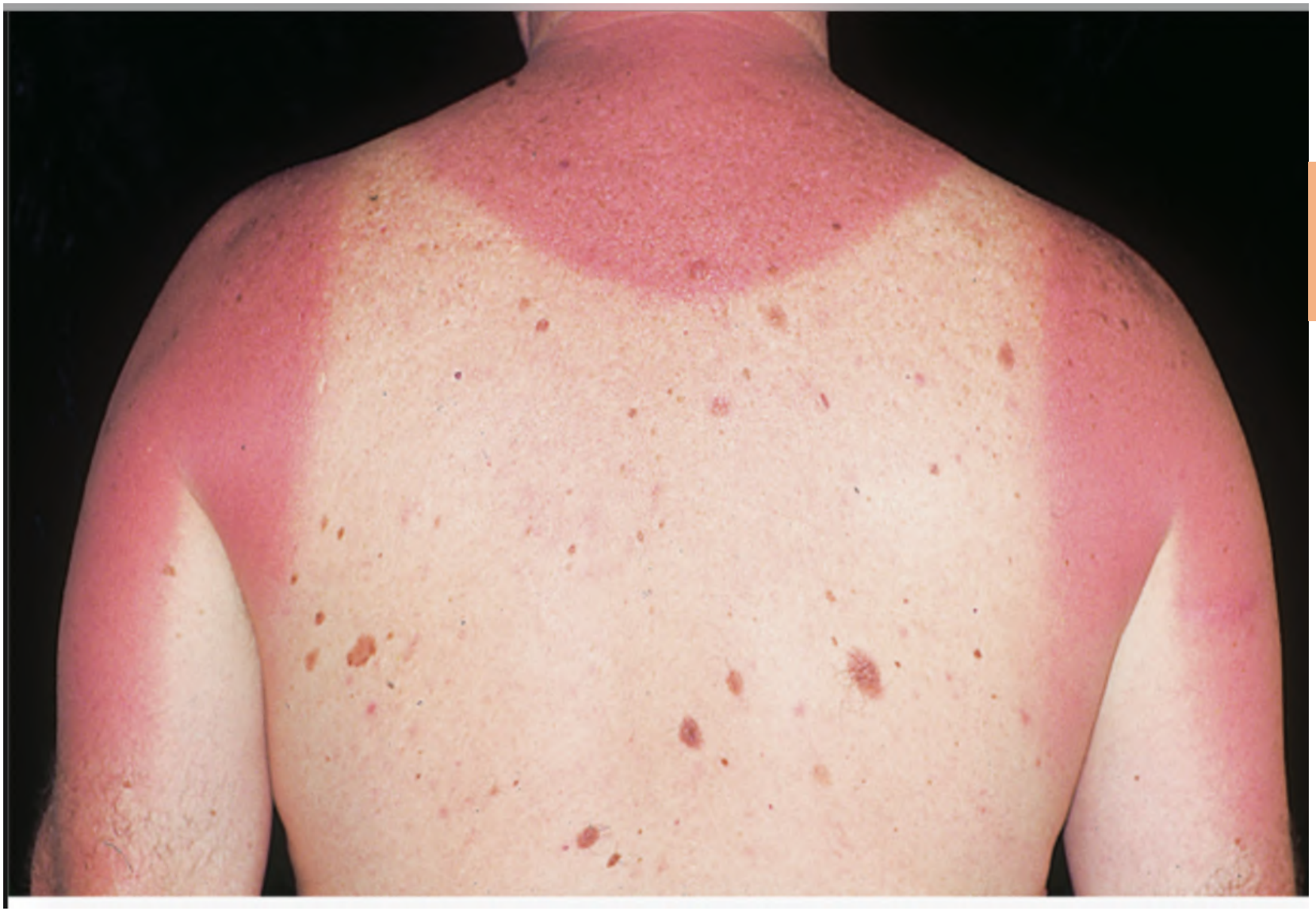
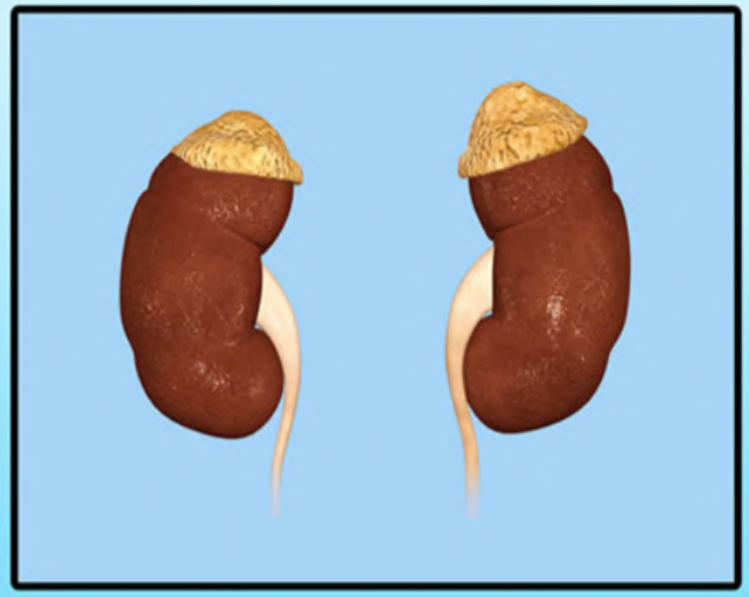


photo allergy

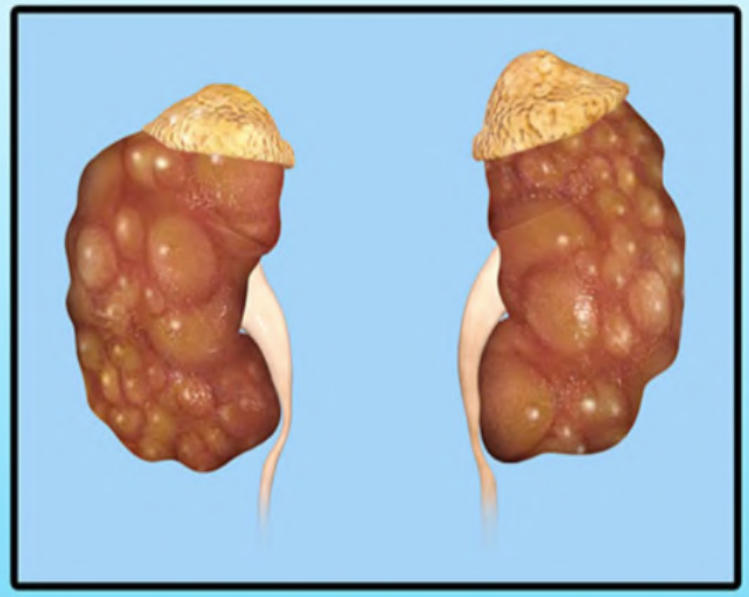
Organ toxicity

Kidneys	Aminoglycosides, cisplatin, Amphotericin B, Analgesics, NRTIs
Heart	Digoxin, emetine,
Liver	INH, pyrazinamide, rifampicin
Retina	Chloroquine (retina), Ethambutol (Optic Nerve)
Thyroid	Amiodarone, lithium
Peptic ulcer	NSAIDs, steroids
Bones	Tetracyclines, steroids
Bone marrow	Anticancer drugs, NRTIs

Analgesic Nephropathy



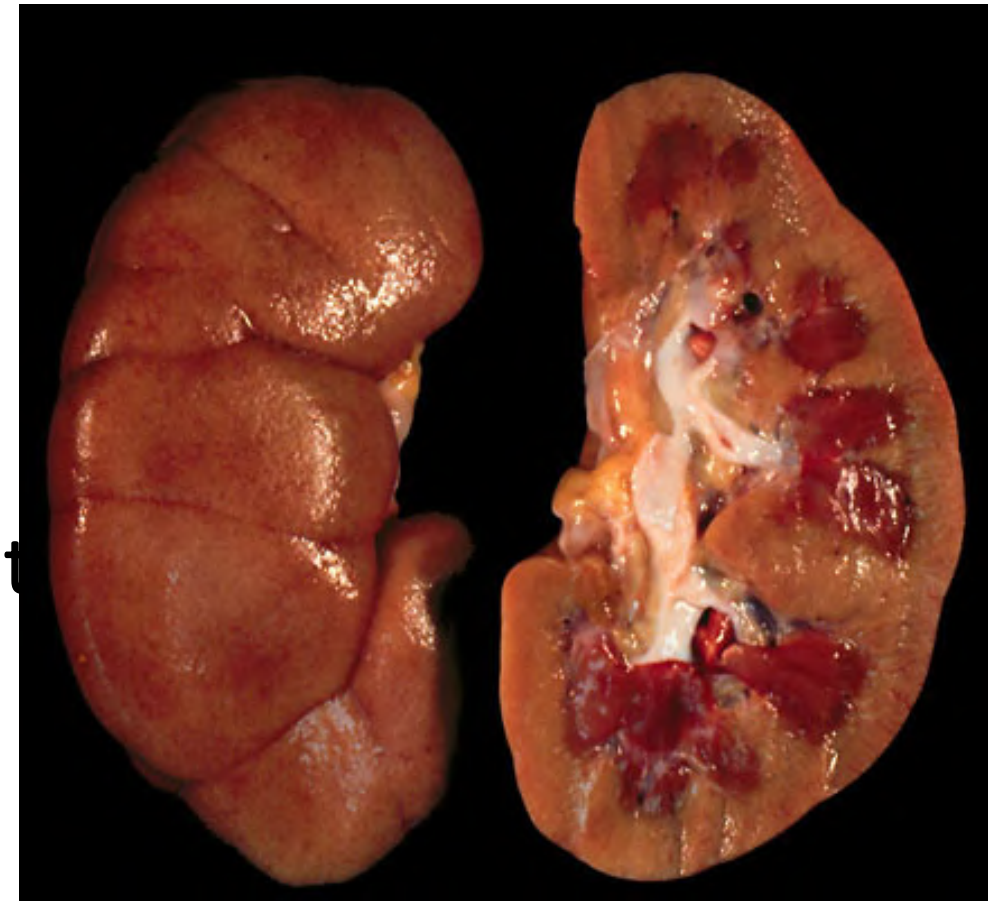
Normal Kidney



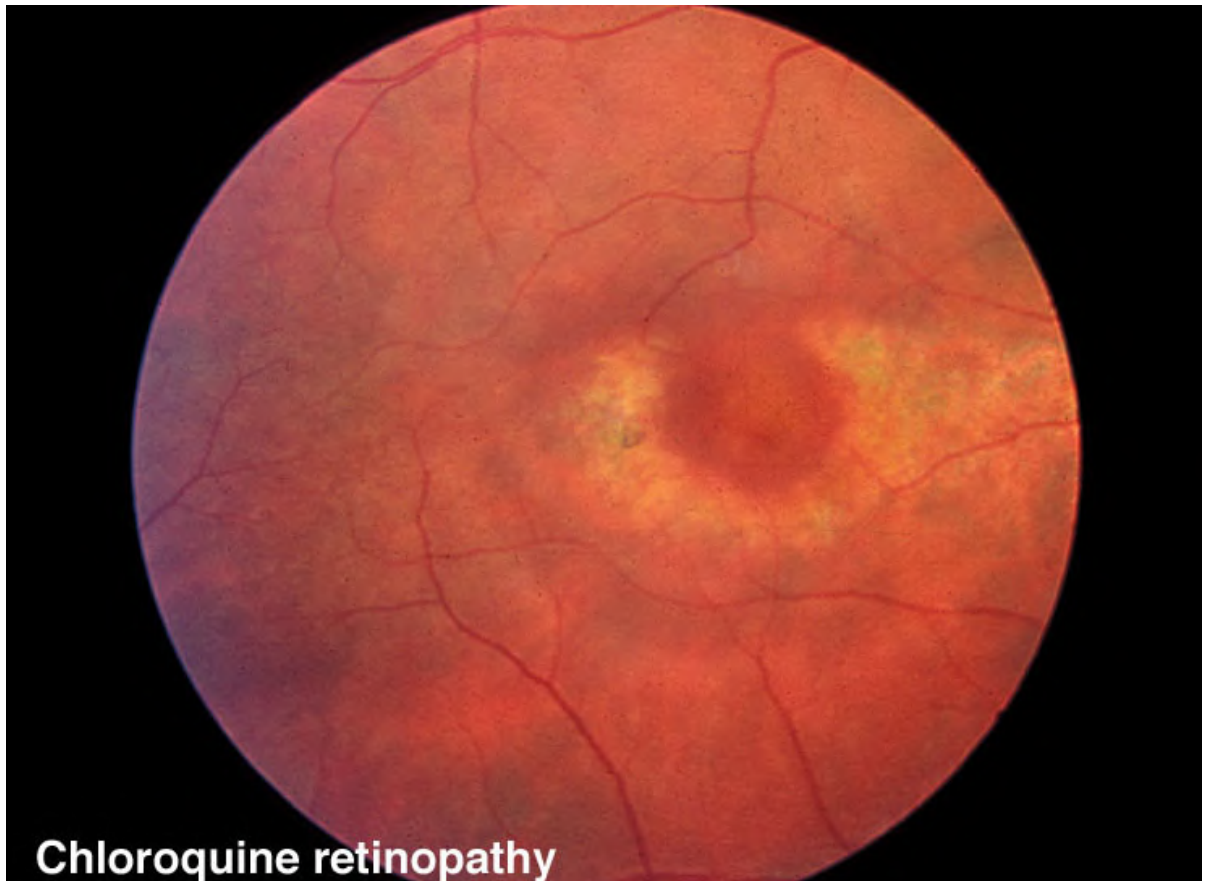
Analgesic Nephropathy

GENTAMICIN NEPHROTOXICITY

Gent



Chloroquine - Retinopathy



Margin of Safety

- **Therapeutic Index = $\frac{\text{LD50}}{\text{ED50}}$**

LD50: Median lethal dose

ED50: Median effective dose

Higher the value safer the drug

Drugs with high T.I.

- -Penicillins
- -Cephalosporins
- -Macrolide antibiotics
- -Aspirin
- -Ibuprofen
- -Paracetamol
- ondensetran

Drugs with low T. I. viva Q

- Morphine, Barbiturates
- General anaesthetic agents
- Digoxin, Digitoxin
- Phenytoin
- Antiarrhythmics
- Tetracyclines, Chloramphenicol
- Aminoglycosides
- Lithium

Therapeutic drug monitoring TDM

- ---not required for most drugs
- For drugs with low TI and narrow therapeutic window
- EX- phenytoin digoxin warfarin sodium valproate
- Actually measuring plasma concentration of drug
- In order to---
- Determine the highest possible tolerable levels
- Or
- Concentrations at which dangerous ADR start appearing


THANK YOU