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A REVIEW ON DRUG-INDUCED PHOTOSENSITIVITY

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Abstract

Drug-induced photosensitivity is the term used for the cutaneous adverse drug reaction that results from interaction between UV radiations and drug molecule. The majority of photosensitivity reactions occurs in the ultraviolet-A spectrum. Drug-induced phototoxic reactions and Drug-induced photoallergic reactions are two main types of Drug-induced photosensitivity (DIP) reactions. Drug-induced photoallergic reactions are immune mediated, while Drug-induced phototoxic reactions are caused by direct cellular death. The onset of Drug-induced phototoxic responses (DI-PTRs) can happen anywhere from 30 minutes to 24 hours following sun exposure. The symptoms may subside quickly or persist for up to four days. Nonetheless, a few days following exposure, a rash that is itchyand eczematous develops in Drug-induced photoallergic reactions (DI-PARs). This paper includes a thorough definition of Drug- induced photosensitivity(DIP), a discussion of its causative medications, and its subtypes. We discussed how doctors can identify and treat Drug-induced photosensitivity (DIP) early on. We offered recommendations on how to help patients who runthe risk of developing Drug-induced photosensitivity (DIP) modifytheir sun exposure habits.

Keywords: Photosensitivity, Cutaneous adverse drug reaction, UV radiations, Drug molecule, Ultraviolet-Aspectrum, Phototoxic reactions, Photoallergic reactions, immune mediated.

INTRODUCTION

Drug-induced photosensitivity is the term used for the cutaneous adverse drug reaction that results from interaction between UV radiations and drug molecule.[1,125] From all over the adverse drug reactions, the 8% of ADR are attributed to Drug-induced photosensitivity (DIP).[2,125] Photosensitivity reactions primarily occurs in the ultraviolet-A region (the wavelength may range from 315-400 nm).[3] The drug which is responsible for Drug-induced photosensitivity is called 'Photosensitizer' and procedure called 'Photosensitization'.[1,125]

According to their suggested mechanisms of action, Drug-induced photosensitivity reactions are traditionally divided into phototoxic and photoallergic reactions (Table 1).[39]

Drug-induced phototoxic reactions and Drug induced photoallergic reactions are two main different categories of Drug-induced photosensitivity (DIP) reactions. Direct cellular destruction causes Drug-induced phototoxic reactions, whereas an immune mediated method of action causes the Drug-induced photoallergic reactions.[4,132]

Drugs absorb UVA light and release it into the skin in case of Drug-induced phototoxic reactions, which causes damage to cells. In contrast, Drug-induced photoallergic reactions are caused by light-induced structural changes in drug, which cause the drug to bind proteins and become a photoallergen, which triggers an immune response by activating T cells.[5,6,125]

Depending on the type of photosensitizer, clinical signs of Drug-induced phototoxic reactions may commence half an hour to 24 hours after sun exposure.[1] On the other hand Drug-induced photoallergic reactions develop an itchy, eczematous rash a few days after exposure.[1]

An eruption of a medication must satisfy certain requirements in order to be classified as photosensitive;[133]

- It happens only in relation to radiations.
- When exposed to radiations, the medicine or its metabolities need to be in the skin.
- Radiation absorption is a requirement for drugs or their metabolites.

The mechanism of action of various Drug-induced Photosensitivity subtypes i.e Hyperpigmentation, Pseudoporphyria, Photo-onycholysis, Emergent Telangiectasia, Pellagra like reaction, Lichenoid reaction, Photodistributed Erthema Multiforme, Lupus Erythematosusare given in Fig 1.

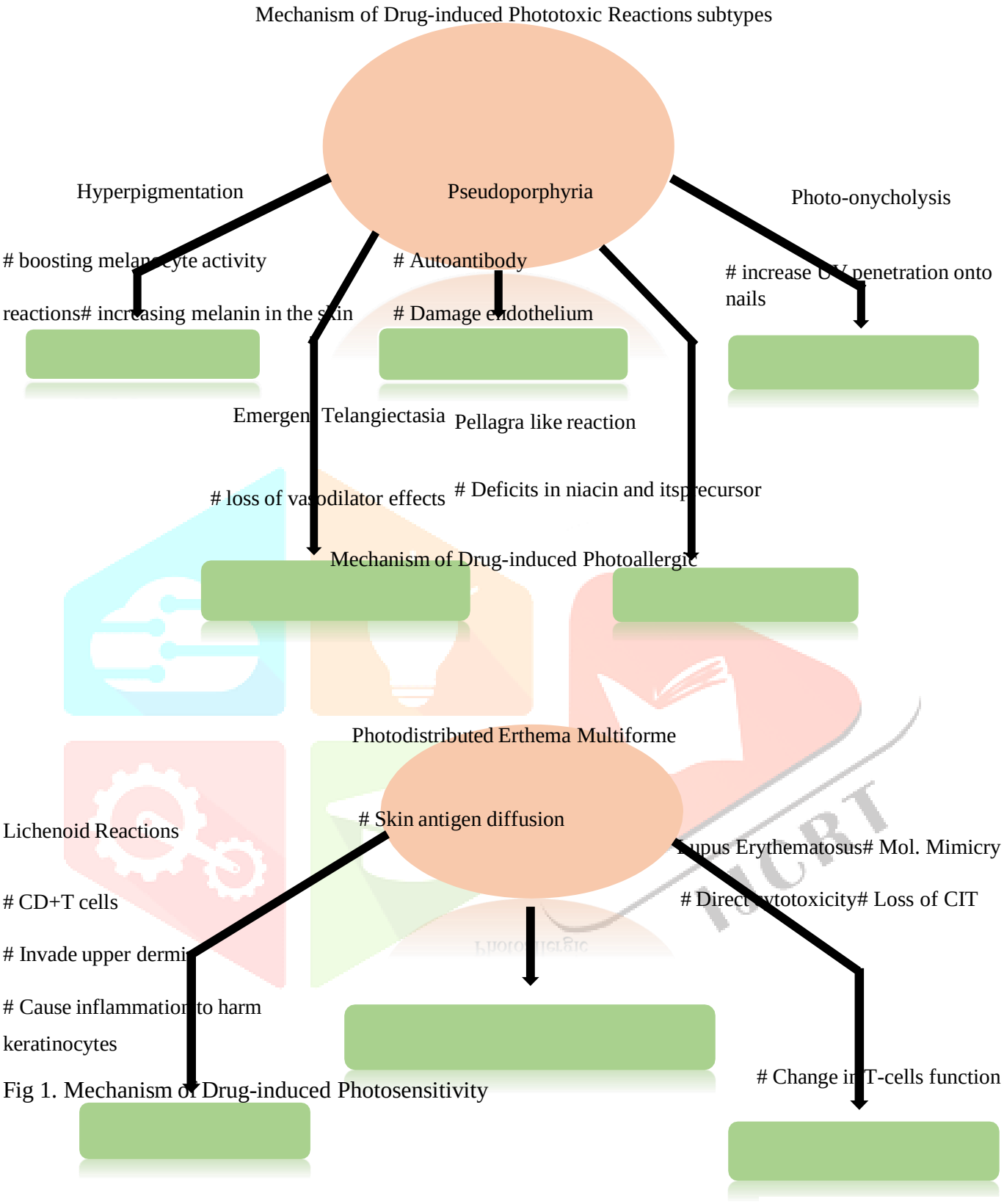

Fig 1. Mechanism of Drug-induced Photosensitivity

The difference between Drug-induced phototoxic and photoallergic reactions are[39]

Features	Drug-induced phototoxic reaction	Drug-induced photoallergic reaction
Incidence	High	Low
Pathogenesis	Direct cellular destruction	Immune-mediated
Dose of Medication	High	Low
Radiation intensity	High	Low
Onset	Half an hour to 24 hours after exposure	Few days after exposure
Clinical Appearance	Sunburn reactions	Eczematous rash
Localization	Exposed area	May spread outside the exposed area
Other Manifestations	Hyperpigmentation Pseudoporphyria Photo-oncycholysis Emergent Telangiectasia Pellagra like reaction	Lichenoid reaction Erthema Multiforme Lupus Erythematosus
Pigmentary Changes	Frequent	Unusual

Tab 1. Difference between DI-PTRs and DI-PARs

TYPES OF DRUG-INDUCED PHOTOSENSITIVITY

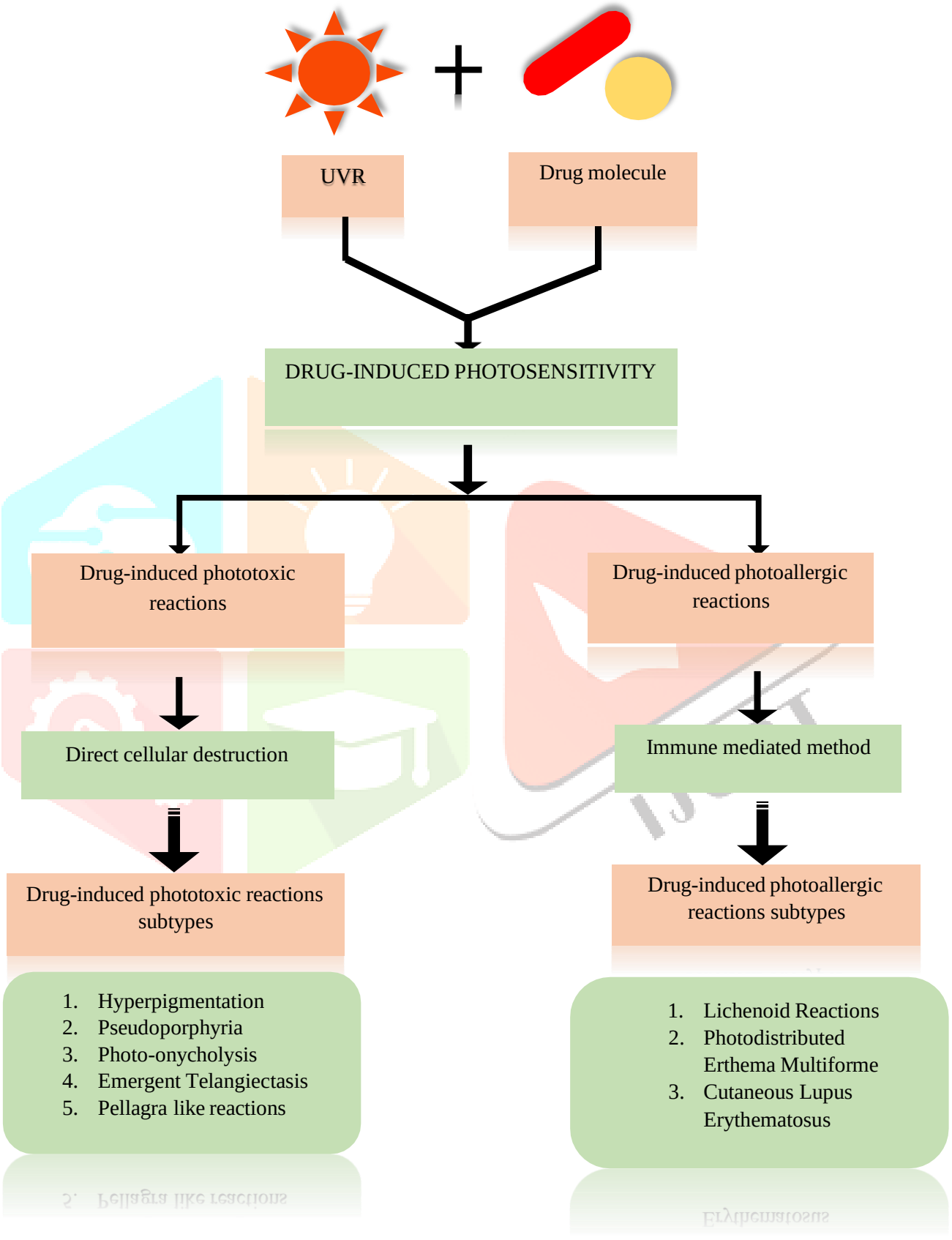

Fig 2. Types of Drug-Induced Photosensitivity

DRUG-INDUCED PHOTOTOXIC REACTIONS SUBTYPES

Hyperpigmentation

One of the most frequent side effects of several medications is skin hyperpigmentation.[7] It might happen following severe phototoxic reactions.[8] In clinics, 10-20% cases of hyperpigmentation are related to Drug-induced photosensitivity.[9]According to suspected drugs, the rate might range from rare occurrences to 25% of people who take the medication.[10]

Numerous reports have been linked to the occurrence of it. This includes cytotoxic substances, analgesics, anti-arrhythmics, coagulants, anti-epileptics, anti-microbials, anti-retrovirals, metals, prostaglandin analogues, and psychoactive substances, among other things.[9]

By boosting melanocyte activity and causing melanin to build up in the skin, photosensitizing medications may result in skin hyperpigmentation.[11] Amiodarone-induced photosensitivity, may determine hyperpigmentation.[12]

Fig 3. Pathogenesis of Hyperpigmentation

Pseudoporphyria

Pseudoporphyria (PP), resemble porphyria via clinically, histopathologically, and immunologically.[13,14] NSAIDs, Tetracycline, Quinolones, Anti-fungal drugs, Diuretics, Anti- arrhythmic and cyclosporines are medications that are frequently linked to pseudoporphyria.[15]

The process driving the formation of blisters in both porphyria and pseudoporphyria may entail physiological autoantibody reactions to damage endothelium. However, pathophysiology of both diseases is still poorly understood.[16] Recent research has focused on pseudoporphyria brought on by imatinib.[17]

Fig 4. Pathogenesis of Pseudoporphyria

Photo-onycholysis

Drug-induced photo-onycholysis, which may be unpleasant, often starts at least two weeks after the initial drug intake.[18,19] During photo-onycholysis, the distal part of the nail is split off from the nail bed[126]. Anti-malarials, NSAIDs, Quinolones, Anti-metabolites, Anti- microbial are the medications responsible for photo-onycholysis.[20]

Currently, 4 distinct clinical subgroups have been identified.[19,21]Type A has half-moon shape and splitting of distal edge of nail.Type B has round notch on nail.Type C has round, yellow discoloration in the center of the nail bed, after 5 to 10 days, turns scarlet.Type D, patients with bullae under the nails have been documented.

Normal fingernails can be penetrated by 3-20% of UV rays. Nails being act as a lens, increase UV penetration and leads to splitting off the nail from nail bed.[21] Unknown pathophysiology may require prolonged exposure to very bright sunshine in order to cause photo-onycholysis.[22]

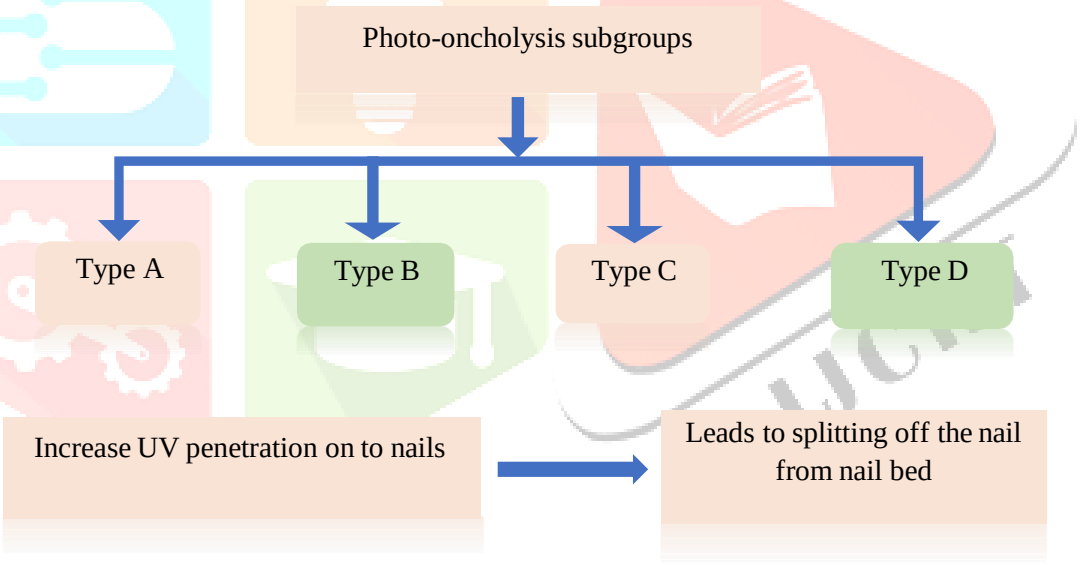

Fig 5. Pathogenesis of Photo-oncholysis

Emergent Telangiectasia

Telangiectasias, sometimes called spider veins, are swollen blood vessels that are located near the surface of the skin or mucous membranes. Often, they appear as tiny pink or red lines that briefly turn white when touched. Iatrogenic injury or drug-related telangiectasias are quite uncommon.[23]

However, the usage of Calcium Channel Blockers is generally associated with telangiectasias. Telangiectasias also occur in sun-exposed locations.[24,25] A class of medications known as

Calcium Channel Blockers are used to treat heart related problems like ischemic heart disease, systemic hypertension etc. All Calcium Channel Blockers (CCBs) associated with photodistributed telangiectasias belong to the dihydropyridine family.[26]

Its genesis and pathogenic mechanisms remain obscure. It has been hypothesized that sunlight may have a substantial impact on how it appears. Loss of vasodilator effects on cutaneous blood vessels by Calcium Channel Blockers as a result of UV radiations.[23,26,129]

Fig 6. Pathogenesis of E. Telangiectasia

Pellagra like reaction

Deficits in niacin and its precursor tryptophan are the main contributors to pellagra. Among its clinical characteristics are diarrhea, dementia, and dermatitis.[27] The pathology of pellagra like reaction is unknown[108].

The lack of cutaneous L-histidine intermediate,[28,29] the accumulation of metabolites of L- tryptophan,[28,30] the deficit of nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate,[31] and the defect in metabolism of porphyrin[32] are other potential causes.

The medications that cause pellagrous dermatitis can act as NAD analogs and impede the synthesis of niacin from dietary tryptophan, interfering with niacin/NAD metabolism.[27]

Pellagra is commonly brought on by chemotherapeutic drugs such as 6-mercaptopurine, 5- fluorouracil, and azathioprine. Aside from these medications, ethionamide, phenobarbital, chloramphenicol, and isoniazid have also been linked to pellagra.[33,34]

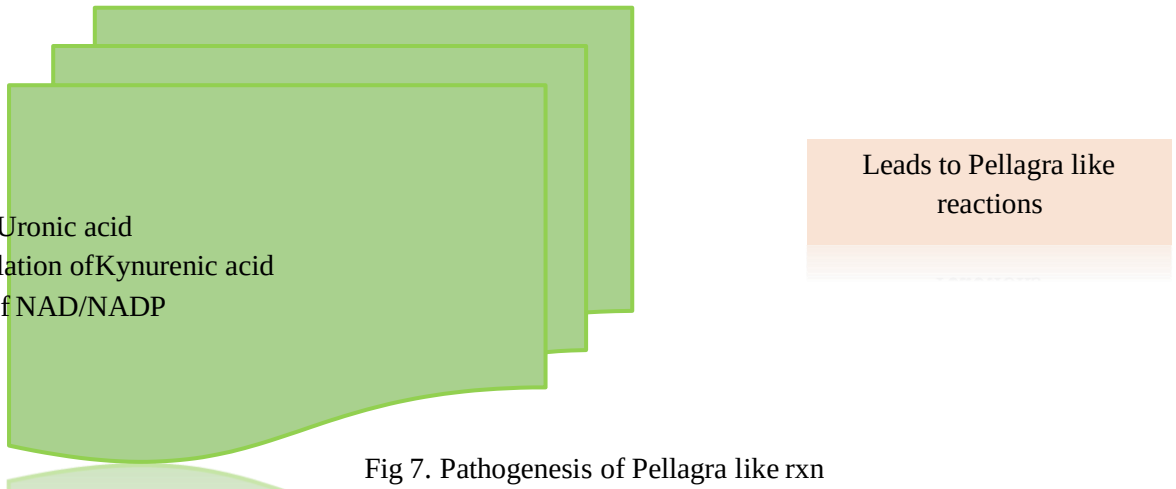

Fig 7. Pathogenesis of Pellagra like rxn

DRUG-INDUCED PHOTOALLERGIC REACTIONS SUBYPES

Lichenoid Reaction

Lichenoid reaction is rare cutaneous ADR.[35-38] Without affecting mucosal membranes, lichenoid reactions manifest as scaling violaceous erythema or violaceous papules with wickhams striae in sun-exposed regions.[39] These reactions may surface months or even yearsafter taking a medication.[40]

NSAIDs, thiazide diuretics and beta blockers, penicillamine, anti-malarial medications, hypolipidemic treatments, phenothiazine, and different antibiotics are a few of the medications known to frequently cause lichenoid reactions.[41]

In lichenoid reactions, CD+T cells would be active; they would invade the upper dermis and cause inflammation to harm keratinocytes.[42,43]

Fig 8. Pathogenesis of Lichenoid rxn

Photodistributed Erthema Multiforme

It is believed that erythema multiform (EM) is a hypersensitivity response to several antigenicstimuli, the most common is Herpes Simplex Virus.[44-48] Phenylbutazone,[49] trichlocarban,[50]

ofloqualone,[51] bufexamac,[52] paclitaxel,[53,54] simvastin, pravastatin,[55] paroxetine,[56] and naproxene[57] were among the medications involved.

Photodistributed erythema multiforme (PEM) is a particular type of erythema multiforme (EM) that is characterized by lesions that are limited to sun-exposed areas and clearly separate from unexposed areas. UV radiations can help skin antigens diffuse into the circulation in photodistributed erythema multiforme.[58]

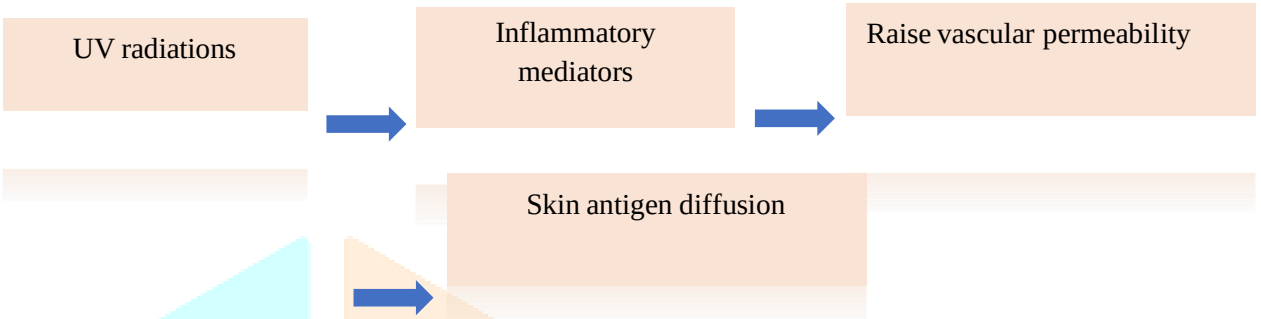

Fig 9. Pathogenesis of E. Multiforme

Lupus Erythematosus

Lupus erythematosus is characterized by immunological pathologic serum results and clinicalsigns comparable to those of idiopathic lupus; however, it is caused by ongoing drug exposure and clears up if the offending medicines are stopped using.[59,132]

The two drugs that most frequently cause lupus erythematosus are procainamide and hydralazine[128]. lupus erythematosus has been linked to all anti-TNF medications, with etanercept and infliximab carrying a larger risk.[60-62]

Lupus erythematosus is caused by a number of processes, some of which may be light independent. Molecular mimicry, direct cytotoxicity, loss of CIT and hypomethylation-induced changes in T-cell function are some of these processes.[59]

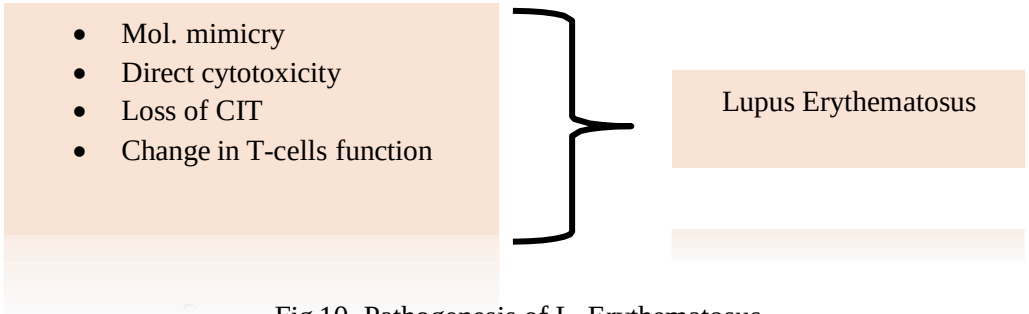

Fig 10. Pathogenesis of L. Erythematosus

PHOTOSENSITIZING AGENTS

CLASS	SUBCLASS	DRUGS
Adrenergicantagonist	Beta-blockers[41,63,64]	Bisoprolol[4,65] Atenolol[4,65]
2. NSAIDs[41]	Non-selective COXinhibitors	Naproxen[15,57,66,67,68] Ketoprofen[69] Phenylbutazone[49]
	Preferential COX-2inhibitors	Diclofenac[70]
3. Anti-epileptics[9]		Levetiracetam[71] Carbamazepine[72]
Anti-psychoticdrugs[9]	Phenothiazines[41]	Chlorpromazine[73,74] Thioridazine[75]
	Atypical Anti-psychotics	Olanzapine[18,76] Aripiprazole[18]
	Butyrophenones	Haloperidol[77]
5. Anti-depressants	Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine[56] Citalopram[78] Escitalopram[79]

	Tricyclic Anti-depressants (TCAs)	Imipramine[80] Amitriptyline[81]
	Serotonin and nor-adrenaline reuptake inhibitors (SNRIs)	Venlafaxine[24,25]
6. ACEs inhibitors		Enalapril[82]
Anti-arrhythmicdrugs[9]	Class III	Amiodarone[12,15,83,84,85]
	Class I	Quinidine[86]
Calcium channelblockers[63,64]	Benzothiazepine	Diltiazem[87]
	Dihydropyridines[26]	Amlodipine[26]
9. Diuretics[63,64]	Loop diuretics	Furosemide[15,88]
	Thiazide diuretics[41,89]	Indapamide[90] Chlorthalidone[15] Hydrochlorothiazide[15,91]
	Potassium sparing diuretics	Triamterene[15,91]
10. Anti-platelet drugs		Clopidogrel[92]
Hypolipidemicdrugs[41]	Statins	Simvastatin[55]Pravastatin[55]
	Fibrates	Fenofibrate[93]
Gastric acid secretioninhibitors	Proton pump inhibitors[94]	Omeprazole[94-98] Esomeprazole[97] Pantoprazole[94-97] Lansoprazole[94-96]

	H_2 Anti-histamines	Cimetidine[99]Ranitidine[100]
13. Antimicrobials[9]	Quinolones	Nalidixic acids[101] Sparfloxacin[43,102]
	Cephalosporines	Cefotaxime[24,25]
	Tetracyclines	Tetracycline[15,20,103] Doxycycline[104-106] Demeclocycline[107]
		Chloramphenicol[20,33,34]
14. Anti-tubercular agents	1st line drug	Isoniazid[27,33,34,42]
	2nd line drug	Ethinonamide[33,34,108]
15. Anti-fungal drugs		Griseofulvin[63,64,109] Itraconazole[110] Voriconazole[15,111,112] Terbinafine[63,64]
16. Anti-malarial drugs[41]		Quinine[20,113]
Anti-cancer drugs[9,114]	Antimetabolites	6-mercaptopurine[33,34] Azathioprine[33,34,115,116]5-fluorouracil[33,34,117] Capecitabine[118]
	Taxanes	Paclitaxel[53,54]
	Kinase inhibitors	Imatinib[17]

18. Immunosuppressants	Calcineurin inhibitors	Cyclosporine[15]
	TNF-alpha inhibitors	Etanercept[60,61,62,119,120] Infliximab[60,61,62,119,120]

Tab 2. List of Photosensitizing agents

MANAGEMENT

Medical professionals should be able to identify Drug-induced photosensitivity (DIP) early on and differentiate between Drug-induced phototoxic reactions and Drug-induced photoallergic reactions. The diagnosis of Drug-induced photosensitivity is implied by the history of systemic or topical photosensitizer exposure. Both photopatch test and monochromator phototesting canverify it.[42,121]

Patients who have had a photosensitivity reaction should take the following measures:-

1. Use sunscreens that block both UVB and UVA rays, as light with a wavelength of between 315 and 400 nm is the primary source of drug-induced photosensitivity (DIPs). It is recommended to use sunscreens with SPF of 50 or greater, as they offer protection against UVB and UVA rays. They ought to be administered an hour before being exposed to the sun and again an hour later.[122]
2. Patients should always dress modestly. The Ultraviolet Protection Factor (UPF), which indicates how much UV light may pass through fabric, is a useful tool when selecting apparel. Patients who are susceptible to Drug-induced photosensitivity should wear clothes that block at least 40% of UV radiation and can transmit less than 5% of it.[123,133,134]
3. The most crucial part of treatment is stopping the medicine as soon as Drug-induced photosensitivity is diagnosed and the offending medication is found.[4,136]
4. Topical or systemic corticosteroids may be useful in treating Drug-induced photosensitivity if a rash appears, if stopping the medication is not feasible or for symptomatic patients.[1,4,43,137]
5. If the pharmacokinetic characteristics permit, taking medication at night.[10,124]
6. Patients frequently utilize drugs without first talking to their doctor and are rarely informed of the possibility of having an unpleasant skin reactions. Therefore, it is essential to inform and educate patients about photosensitivity.[136,138]

CONCLUSION

Even though it is unclear how frequently drugs cause photosensitivity, it is relatively prevalent for various drugs. With the help of diagnostic tests like phototesting and photopatch test we can diagnose Drug-induced photo eruptions[131]. In this, a vast number of drugs are listed as photosensitivity triggers[127]. To educate both the doctor and patient on Drug-induced photosensitivity and photosensitizing drugs, a thorough narrative review has been put together. This review adds to the expanding body of knowledge on the subject. To begin potentially photosensitizing drugs and assess any drug-induced rashes, follow the recommendations in this guide. To accurately diagnose and treat these eruptions, doctors must be able to identify their causes. Before beginning treatment with drugs known to be strong photosensitizers, patients should be educate about this[130].

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