REVIEW ARTICLE

# Association of Drugs with Psoriasis: A Review of Literature

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**Summary:**

***Psoriasis is a common disorder in dermatologic practice. Though its exact etiology is still unknown but there are many internal and external factors contributing to the clinical course of the disease. There are several drugs described in the literature that have been associated with the initiation, exacerbation and aggravation of psoriasis. Depending on the relation to induction or exacerbation of psoriasis the drugs may be classified as drugs with strong casual relation with psoriasis, drugs with considerable but insufficient evidence of association and drugs with occasional association with aggravation or induction of the disease. Understanding of underlying pathogenesis is very important in the management of drug related psoriasis. This review included the most common causative agents in relation to psoriasis, their underlying pathogenesis, clinical manifestations and management of such cases.***

***Key words: psoriasis, etiologic agents of psoriasis, drugs related to psoriasis.***

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## Introduction:

Psoriasis is a chronic, noncontagious, multisystem, inflammatory disorder with a reported prevalence of 0.1 percent to 11.8 percent in different population.[1,2] Psoriasis involves hyperproliferation of the keratinocytes in the epidermis, with an increase in the epidermal cell turnover rate. The cause of the loss of control of keratinocyte turnover is unknown. However, environmental, genetic, and immunologic factors appear to play a role.[1] Some factors known to trigger psoriasis include smoking, alcohol consumption, body mass index (BMI), trauma, infection, endocrine disorders, drugs, and acute withdrawal of systemic or potent topical corticosteroids.[3] Drug intake is a major concern in this respect, as new drugs are constantly being added to the list of factors that may influence the course of the disease.[4] Analysis of comedication in a study of 1,203 psoriasis patients revealed 23.2 percent of patients were taking more than three systemic medications, and of these patients, 11.1 percent were taking more than 10 medications. Further analysis demonstrated that comorbid cardiac and metabolic disorders are common in these individuals with a high prevalence of hypertension (28.2%), diabetes (10.5%), and dyslipidemia (12.5%).[3] With this in mind, many psoriasis patients can be on multi-drug regimens; therefore, careful analysis of medications that can exacerbate the disease is prudent.

## Effect of drug on clinical course of psoriasis

Drug intake may affect the clinical course of psoriasis in the following ways

- Precipitation of de novo psoriasis in persons with or without a family history or predisposition of the condition.
- Exacerbation of pre-existing psoriasis
- Induction of psoriatic lesions on clinically normal skin in patients with psoriasis.[4]

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**Types of cutaneous eruptions in relation to drugs**

Psoriasiform drug eruption and Drug-provoked psoriasis are the two forms of cutaneous eruption that related to ingestion of several drugs. Psoriasiform drug eruption is a heterogeneous group of disorders that clinically and/or histologically simulate psoriasis at some point during the course of the disease. It may be a reaction to either the internal or the external environmental, allergic, infective, parasitic, bacterial, fungal, viral and/or malignant stimuli. These psoriasiform reactions are elicited by inflammatory events that cause dysregulation of cytokines, growth factors, and abnormal keratinocyte proliferation.[3,5] Drug-provoked psoriasis can be divided into two categories, drug-induced psoriasis and drug-triggered or aggravated psoriasis (Table-1). [3]

**Table-I**

*Characteristics of drug induced and drug aggravated psoriasis.* [3, 4, 6]

| Drug induced psoriasis | Drug-triggered or aggravated psoriasis |
|---|---|
| Discontinuation of the drug will stop further progression of the disease. | The disease progresses even after discontinuation of the drug. |
| Tends to occur in a de-novo fashion in patients with no family or previous history of psoriasis. | Exhibits a propensity to occur in patients with a history of psoriasis or with a genetic predisposition for the disease. |
| The clinical presentation often mimic the pustular variant of psoriasis, often with no nail involvement or associated arthritis. | Patients can have exacerbation of pre-existing psoriatic lesions or develop new lesions in previously uninvolved skin. |
| There is an absence of Munro microabscesses, few macrophages, and sparse vascular changes on histology. | Histology reveals typical characteristic of psoriasis vulgaris. |

**Classification of Drugs in the development of psoriasis**

Drugs can be divided into 3 categories in view of their relationship to drug-provoked psoriasis (Table II). [4]

**Table-II**

*Drugs and their relationship in the development of psoriasis*

| Category | Drugs/drug classes |
|---|---|
| Drugs with undoubted causal relationship to psoriasis | β-Blockers, lithium, syntheticantimalarials, nonsteroidal anti-inflammatory drugs, tetracyclines |
| Drugs about which there are considerable but insufficient data supporting induction or aggravation of psoriasis | ACE inhibitors, interferons, terbinafine |
| Drugs occasionally reportedto be associated with induction or aggravation of psoriasis | Clonidine, digoxin, amiodarone, quinidine, dihydropyridine calcium antagonists, carbamazepine, valproic acid (sodium valproate), fluoxetine, acetazolamide, sulfonamides, penicillin, amoxicillin, ampicillin, morphine, procaine, cimetidine, ranitidine, gold, mercury, oxandrolone, progesterone, gemfibrozil, potassium iodide, granulocyte-macrophage colony-stimulating factors |

**Beta-blocker**

β-blockers are the most common drugs encountered in the exacerbation of psoriasis. β-blockers are classified as noncardioselective and cardioselective, according to interact selectively with β1 and β2 adrenergic receptors[7].

- Cardioselective β-blocker- Practolol is the earliest in this group and has been most commonly cited in association with psoriasis. This drug was withdrawn because of many side effects including dermatological ones[8-12]. Metoprolol[13], Atenolol[14] also reported to induce similar eruption.
- Noncardioselective β-blocker- Propranolon was reported to cause histologic changes in guinea pigs similar to those in psoriatic human skin. The eruptions described with propranolol use include psoriasis, psoriasiform dermatitis, eczematous and lichenoid rashes.[15,16] Cetamolol[17], nadolol[18] also reported to cause similar eruption. Topical application of timolol, in the treatment of chronic open angle glaucoma was reported to induce psoriasis and to transform psoriasis vulgaris into psoriatic erythroderma.[19,20,21]
- There is cross reactivity between b-blockers and probably every β-blocker is able to provoke psoriasiform eruptions, aggravation or induction of the condition.

**Clinical findings**

1. Latency period- Latency periods vary from several days to 12 months. Latency period is shorter in case of de novo pustular psoriasis and exacerbation of pre-existing psoriasis [7].
2. β-blockers are responsible for the provocation of various clinical types of psoriasis. Psoriasiform eruptions are the most common consequences.[4,21]. Aggravation of classical psoriasis vulgaris and guttate psoriasis, transformation of plaque-type psoriasis into localized and generalized pustular psoriasis and rarely induction of classical plaque psoriasis. [19, 22-24]

**Pathogenesis**

The precise pathogenic mechanism of the influence of â-blockers on the course of psoriasis is unknown. Several hypotheses have been proposed and investigated. These include decrease in intra-epidermal cyclic adenosine monophosphate (cAMP) (it is the most reliable hypothesis so far), delayed type hypersensitivity, immunologic mechanism, impaired lymphocyte transformation.[25, 26, 27]

β-adrenergic receptors are present in the skin and these receptors are blocked by β-blockers. Normal beta agonists' attachment to beta receptors resulting in increased cAMP levels is blocked by the beta antagonists. Cyclic AMP (cAMP), an intracellular messenger, stimulates proteins responsible for differentiation and inhibition of proliferation. A decrease in cAMP levels leads to a decrease in calcium and an up-regulation of keratinocyte proliferation, lack of differentiation, as well as an increase in lymphocyte motility seen in psoriasis.[3, 4, 11, 28, 29] There is increased proteolytic enzymes released by macrophages, neutrophils, and lymphocytes. Proteolytic enzymes have been associated with keratinocyte hyperproliferation and psoriasiform eruptions.[30]

**Lithium**

Lithium is a metal ion that has been used extensively in the treatment of manic-depressive disorder and in urology practice. The first association of lithium with psoriasis was suspected in 1972, and since then there have been several reports of lithium-induced psoriasis described in individuals with no personal or family history. Lithium-provoked psoriasis was first reported in 1976.[31,32, 33]. Psoriasiform eruptions are the most frequently reported cutaneous adverse effects of lithium treatment and reported to occur in 3.4 to 45 percent of patients treated with lithium.[31]

**Clinical features**

1. Latency period- Development of psoriatic lesions after the initiation of lithium treatment is variable and ranges from a few weeks to several months. The latency period is few weeks to months (average 20 weeks). [7, 34]
2. Clinical manifestations of psoriasis aggravated or induced by lithium carbonate- Most common presentation is classic plaque-type psoriasis. Generalized psoriasis, erythroderma, palmoplantar psoriasis, generalized pustular psoriasis, scalp and nail psoriasis, psoriasiform dermatitis and psoriatic arthropathy all have been reported in association with lithium therapy.[6,34] The clinical features and histopathology of lithium-related psoriasis do not differ considerably from those of idiopathic psoriasis. [35]

**Pathogenesis**

Different mechanisms have been involved in the pathogenesis of lithium induced psoriasis. It has been suggested that lithium may influence the pathogenesis of psoriasis at both molecular and cellular level. [36]

A) Pathogenesis at molecular level

- Adenyl cyclease system hypothesis- In the past, researchers theorized that the decrease in cAMP from lithium treatment caused low intracellular levels of calcium, leading to a lack of differentiation, increased proliferation of keratinocytes, and enhanced chemotaxis and phagocytic activity of polymorphonuclear leukocytes. But studies showed that the short-term use of lithium leads to diminution of intracellular cAMP, but long-term lithium treatment causes just the opposite response through a compensatory mechanism.[3, 37]
- Inositol depletion hypothesis- Proposed mechanisms is the decreased levels of inositol in the skin may lead to the triggering or the exacerbation of psoriasis. Inositol is a component of the intracellular second messenger system linked to various neuro-transmitters effecting cell function, growth, and differentiation. The pathway is dependent on the phosphatidyl inositol 3,4-diphosphate (PIP2). Receptor-activated phospholipase C hydrolyzes PIP2 in the cell membrane to inositol phosphate 1,4,5-triphosphate (IP3) and diacylgylcerol (DAG). IP3 induces the release of calcium from intracellular stores and DAG activates protein kinase C. An important source for the recycling of inositol to form PIP2 is the hydrolysis of inositol monophosphate to inositol and inorganic phosphate. This reaction, catalyzed by the enzyme monophosphatase, is inhibited by therapeutic doses of lithium. By blocking this recycling reaction, the PIP2 form of inositol is depleted and the intracellular signaling pathway described above is concomitantly blocked.[31-36,38].

B) Pathogenesis at cellular level-

- Recent studies established that lithium affects the 'psoriatic cytokine network' by triggering the secretion of TNF- $\alpha$, interleukin-2, interleukin-6, and interferon-$\gamma$. The dysregulation in the production of these cytokines has been linked to the induction of psoriatic lesions.[6, 38, 39]

**Antimalarials**

The synthetic oral antimalarial (AM) agents have been used in the prophylaxis and treatment of malaria and several dermatological disorders for many years. The most commonly used oral AMs are chloroquine and hydroxychloroquine.[38] At least three indications for the use of antimalarials in patient with psoriasis have been reported. These are psoriatic arthropathy, coexistent lupus erythematosus (LE) and antimalarial prophylaxis for travel to an endemic area.[7] The exacerbation and induction of psoriasis during treatment with AMs has been widely acknowledged.[4] It is estimated that up to 31 percent of patient with psoriasis would develop an exacerbation of their disease following antimalarial therapy.[40] The use of chloroquine and hydroxy-chloroquine in patients with psoriasis is considered by some to be a contraindication.[4]

**Clinical features**

1. Latency periods- Psoriatic skin lesions most often occur with a latency of 2 to 12 weeks (average of 3 weeks) after starting AMs. Longer latency period of about 40.5 weeks, especially in cases of pustular eruptions.[4]
2. Clinical form of psoriasis eruption caused by antimalarials- Most common is the aggravation of preexisting psoriasis. Induction of pustular eruption may occur in preexisting psoriasis but de novo pustular psoriasis is uncommon. [4, 7, 41, 42]

**Pathogenesis**

The chemical structure of the antimalarial drugs is very similar to that of dansylputrescine, a potent transglutaminase inhibitor. Transglutaminase is involved in the pathogenetic epidermal proliferation of psoriasis. Therefore antimalarial drugs probably trigger psoriasis through changes in the activity of the enzyme transglutaminase.[43]

**Nonsteroidal anti-inflammatory drugs (NSAIDs)**

NSAIDs are a class of medications used for treatment of pain and arthritides. NSAIDs are frequently used by patients who have psoriasis as well as psoriatic arthritis. The evidence that NSAIDs exacerbate or induce psoriasis is not strong.[7] Nevertheless, in some patients, exacerbation of psoriasis and arthritis may coincidently occur simultaneously with the use of NSAIDs. Naproxen was the most common culprit in one study[44].

Indomethacin, both topical and oral indomethacin is found to associated with exacerbation of psoriasis.[45,46]. Generalized pustular psoriasis developed in a patient with phenylbutazone.[47] The experience of many dermatologists does not suggest that NSAIDs have any obvious adverse effect on psoriasis. The effects of NSAIDs have a short latency period, 1.6 weeks on average without significant variations between the different subsets of drug-provoked psoriasis[4].

**Pathogenesis**

NSAIDs inhibit the metabolism of arachidonic acid by the cycloxygenase pathway, leading to an accumulation of leukotrienes, which have been postulated to aggravate psoriasis. Elevated levels of these inflammatory mediators in psoriatic skin were found or indirectly confirmed in a number of studies. [48]

**Antibiotics**

The influence of antibacterials on the course of psoriasis is controversial. The antibiotics that have been implicated in psoriasis are tetracyclines, including doxycycline, penicillin, amoxicillin and ampicillin[49, 50]. In one study, investigators reported that 4.11 percent of patients experienced exacerbation of psoriasis as a consequence of tetracycline use[4]. It has also been suggested that tetracyclines should be avoided in patients with clinical evidence of psoriasis, as well as in healthy individuals with a genetic predisposition for psoriasis. Macrolides and penicillin derivatives were associated with psoriasis in one multivariate case-control model in patients less than 50 years of age.[49] Reports suggest that exacerbation of psoriasis by penicillin derivatives is rare and may actually represent acute generalized exanthematous pustulosis and not true drug-provoked psoriasis.[50, 51]

Clinical features- There has been no detailed study on the latency period of tetracyclines. Antibiotics may be associated with onset or exacerbation of already existing psoriasis.[4]

Pathogenesis- Tetracyclines provoke psoriasis probably via the reduction of intracellular cAMP or by the interaction of the drug with arachidonic acid and its metabolites. Tetracyclines accumulate in higher concentrations in psoriatic lesions than in clinically uninvolved skin. It is well established that they are photosensitizing agents. Predisposed and psoriatic patients may undergo a Koebner phenomenon as a result of the photosensitizing properties of tetracyclines.[3, 52, 53]

**Diagnosis of drug related psoriasis**

There are 5 important points for the diagnosis

- Detailed history of when drug treatment started, dosage regimen, and therapy duration
- Absence of additional triggering factors (stress, trauma, infections)
- Clinical relationship between the introduction of the drug and the onset of cutaneous manifestation
- Withdrawal of the drug followed by improvement of dermatologic status
- Histologic findings. Average values of the various histologic parameters (hyperkeratosis, parakeratosis, hypogranulosis, acanthosis, spongiosis, edema, and infiltration) measured for both drug-related psoriasis and controls with early eruptive psoriasis showed statistically significant differences for hyperkeratosis in the control group ($p < 0.05$) and spongiosis in the drug-related psoriasis group ($p < 0.05$). [4]

**Guideline for the management of drug-related psoriasis**

Management of drug-provoked psoriasis includes detailed personal, social, and family history. The absence of additional triggering factors should always be ruled out first. Patients should be encouraged to avoid alcohol, excessive sun exposure, smoking, stress and other factors that can all affect the clinical course of the disease. The distinction between drug-induced and drug-triggered psoriasis is of crucial importance for appropriate management. Incase of drug induced psoriasis withdrawal of the implicated drug is followed by clinical improvement and can be managed with emollients alone. Management of drug-triggered psoriasis is difficult and required full range of topical and systemic modalities of treatment of idiopathic psoriasis [4].

**Treatment of β-blockers induced or provoked psoriasis-**

Cardiologists may underestimate the fact that â-blockers worsen the course of psoriasis. Consultation by a dermatologist is advisable in such cases for the benefit of the patient. Psoriasiform eruptions regress rapidly after discontinuation of the drug. Exacerbation of psoriasis by β-blockers is resistant to treatment unless the drugs are discontinued[4]. If psoriasis is present only in localized areas, emollients alone can be helpful.

Unresponsive cases of drug provoked psoriasis needs use of conventional therapeutic agents that include topical and systemic agents used in the treatment of psoriasis vulgaris[3]. Hospitalization is required for beta-blocker induced erythroderma to monitor hypovolemia and hemodynamic instability, aggressive fluid resuscitation. Aggressive treatment with systemic and topical agents in concordance with discontinuation of the offending drug is also necessary[3,4].

Treatment of Lithium-induced or -exacerbated psoriasis-

Many therapeutic modalities have been used with variable success, and conventional topical treatment has become less effective as lithium-induced or -exacerbated psoriasis is often recalcitrant to treatment.[4,32, 54] Discontinuation of lithium results in disappearance of the lesions within 6 months but skin changes are reversible, and most often readministration of lithium is followed by a rebound flare.[36, 54]

Inositol supplementation in diet- Peripheral inositols received in the form of dietary consumption do not cross the blood-brain barrier and therefore do not alter lithium effects on mood stabilization. Significant improvement after 6g of daily inositol supplementation by mouth is noticed with "dramatic improvement" within 48 to 72 hours. [55]

In some cases, patients can develop treatment-resistant psoriasis, which may warrant discontinuation of lithium with change to another mood-stabilizing agent depending on the severity of cutaneous involvement. Reduction in dosage of lithium is an additional option for treatment-resistant cases.[54] TNF-á inhibitors, such as etanercept, in the treatment of severe, recalcitrant, lithium-provoked psoriasis.[56]

**Treatment of Antimalarial and tetracycline induced psoriasis-**

Resolution of psoriatic lesions usually occurs within one month of discontinuing the AM agent.

Tetracyclines should be avoided in patients with clinical evidence of psoriasis as well as in healthy persons with genetic predisposition for psoriasis[4, 38].

**Conclusion:**

Several drugs have been associated with drug-provoked psoriasis. Why provocation of psoriasis occurs in some individuals and not others who are exposed to a specific drug remains unclear. Understanding the pathogenesis of drug-provoked psoriasis not only helps to achieve a greater appreciation of the disease process, but is also useful in providing guideline for treatment methodologies. Drugs that are considered to have a strong potential risk factor for psoriasis development should be avoided after weighing the risk and benefits of the agent. Fortunately, there are only a few drugs that demonstrate a well-documented, direct, causal relationship with the development of psoriasis or psoriasiform eruptions, and alternative therapeutic options are frequently available.

**References:**


1. Meffert J, O'Connor RE. Psoriasis. http://emedicine.medscape.com/article/1943419-overview (5/9/2011).
2. Gudjonsson JE. Elder JT. Pathology and Clinical Aspects of Pruritus. In: Wolff, K., Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ. Fitzpatric's Dermatology in General Medicine. New York: The Mc Graw Hill Companies; 2007.p169.
3. Grace K, Kim DO, James Q, DelRosso, DO. Drug-Provoked Psoriasis: Is It Drug Induced or Drug Aggravated? Understanding Pathophysiology and Clinical Relevance. The Journal of Clinical and Aesthetic Dermatology 2010 January; 3(1): 32–38.
4. Nikolai T, Irena A and Jana K. Drug-Induced Psoriasis:Recognition and Management. Am J Clin Dermatol 2000 May-Jun; 1 (3): 159-165.
5. Sehgal V, Dogra S, Srivastava G, et al. Psoriasiform dermatoses. Indian J Dermatol Venereol Leprol. 2008;74:94–99.
6. O'Brian M, Koo J. The mechanism of lithium and beta-blocker agents in inducing and exacerbating psoriasis. J Drugs Dermatol. 2006;5:426–433.
7. Basavaraj KH, Ashok NM, Rashmi R, and Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. International Journal of Dermatology 2010; 49: 1351-1361.
8. Assem ESK, Banks RA. Practolol induced drug eruptions. Proc R Soc Med 1973; 66: 179-81.
9. Cohran R, Thomson J, Fleming K. The psoriasiform eruption induced by practolol: a clinicopathological study. J Cutan Pathol 1975; 2: 314-8.
10. Wright P. Untoward effects associated with practolol administration: oculo-mucocutaneous syndrome. BMJ 1975; 1: 595-8.
11. Kauppinen K, Niemi KM, Salo OP. Cutaneous reactions to practolol. Clinical and histopathological study. Ann Clin Res 1976; 8: 232-40.

12. Sondergaard J, Vadskov S, Jensen He, et al. Aggravation of psoriasis and occurrence of psoriasiform cutaneous eruptions induced by practolol (Eraldin). Acta Dermatovenereol 1976; 56: 239-43.

13. Neumann HAM, van Joost T. Adverse reactions of the skin to metoprolol and other beta-adrenoreceptor blocking agents. Dermatologica 1981; 162: 330-5.

14. Gawkrodger DJ, Beveridge GW. Psoriasiform reaction to atenolol. Clin Exp Dermatol 1984; 9: 92-4.

15. Gaylarde PM, Brocq AP, Sarkany I. Psoriasiform changes in guinea pig skin from propranolol. Clin Exp Dermatol 1978; 3: 157-60.

16. Wolf R, Shechter H, Brenner S. Induction of psoriasiform changes in guinea pig skin by propranolol. Int J Dermatol 1994; 33: 811-4.

17. White WB, Schulman P, McCabe EJ. Psoriasiform cutaneous eruptions induced by cetamolol hydrochloride. Arch Dermatol 1986; 122: 857-8.

18. Gold MH, Holy AK, Roenigk HH. Beta-blocking drugs and psoriasis. J Am Acad Dermatol 1988; 19: 837-41.

19. Puig L, Goni FJ, Roque AM, et al. Psoriasis induced by ophthalmic timolol preparations. Am J Ophthalmol 1989; 108: 455-6.

20. Coignet M, Sayag J. Collyre beta-bloquant et psoriasis. Nouv Dermatol 1990; 9: 552

21. Jenson H, Mikkelsen I, Wadskov F, et al. Cutaneous reactions to propranolol (Inderal) Acta Med Scad. 1976;199:363–367.

22. Hu CH, Miller CM, Pepperkorn R, et al. Generalized pustular psoriasis provoked by propranolol. Arch Dermatol. 1985;121:1326–1327.

23. Brauchli YB, Jick SS, Meier C. Association between beta-blockers, other antihypertensive drugs and psoriasis: population-based case-control study. Br J Dermatol. 2008;158:1299–1307.

24. Waqar S, Sarkar P. Exacerbation of psoriasis with beta blocker therapy. CMAJ. 2009;181:1–2.

25. Assem ESK, Banks RA. Practolol induced drug eruptions. Proc R Soc Med. 1973;66:179–181.

26. Halevy S, Livni E. Psoriasis and psoriasiform eruptions associated with propranolol—the role of an immunological mechanism. Arch Dermatol Res. 1991;238:472–473.

27. Raftery EB, Denman AM. Systemic lupus erythematosus syndrome induced by practolol. BMJ. 1973;2:452–455.

28. Voorhees JJ, Duell EA. Psoriasis as a possible defect of the adenyl cyclase-cyclic AMP cascade; a defective chalone mechanism? Arch.Dermatol 1971; 104:352-8.

29. Voorhees JJ. Psoriasis as a possible defect of the adenyl cyclase-cyclic AMP cascade. Arch.Dermatol 1982; 118: 862-8.

30. Heng MC, Heng MK. Beta-adrenoceptor antagonist-induced psoriasiform eruption Clinical and pathogenetic aspects. Int J Dermatol. 1988; 27(9):619–627.

31. Carter TN. The relationship of lithium carbonate to psoriasis. Psychosomatics 1972; 13: 325-7.

32. Skott A, Mobacken H, Starmark JE. Exacerbation of psoriasis during lithium treatment. Br J Dermatol 1977; 96: 445-8.

33. Bakker JB, Pepplinkhuitzen L. More about the relationship of lithium to psoriasis. Psychosomatics 1976; 17: 143-6

34. Jafferany M. Lithium and psoriasis: what primary care and family physicians should know. Prim Care Companion J Clin Psychiatry. 2008;10:435–439.

35. Abel EA, DiCicco LM, Orenberg EK, et al. Drugs in exacerbation of psoriasis. J Am Acad Dermatol. 1986;15:1007–1022.

36. Paduart O, Heenen M. Pharmacological action of lithium in the pathogenesis of psoriasis. Eur J Dermatol 1995; 5: 413-5

37. Voorhees JJ, Marcelo CL, Duell EA. Cyclic AMP, cyclic GMP and glucocorticoids as potential metabolic regulators of epidermal proliferation and differentiation. J Invest Dermatol. 1975;65(1):179–190.

38. Lionel F, Baker B. Triggering psoriasis: the role of infections and medications. Clin Dermatol. 2007;25:606–615.

39. Ockenfels HM, Wanger SN, Klim-Maas C, et al. Lithium and Psoriasis: cytokinemodulation of cultured lymphocytes and psoriatic keratinocytes by lithium. Arch Dermatol Res 1996; 288: 173-178.

40. Slagel GA, James WD. Plaquenil induced erythroderma. J Am Acad Dermatol 1985; 12: 857-62

41. Baker H. The influence of chloroquine and related drugs on psoriasis and keratoderma blenorrhagicum. Br J Dermatol 1966; 78: 161-6

42. Friedman SS. Pustular psoriasis associated with hydroxy chloroquine. J Am Acad Dermatol 1987; 16: 1256-7

43. Wolf R, Schiavo AL. Is transglutaminase the mediator between antimalarial drugs and psoriasis. Int J Dermatol. 1997;36: 10–13.

44. Grau R. Drug-induced psoriasis—A retrospective chart review performed at the University of Oklahoma Department of Dermatology. J Am Acad Dermatol. 2008;59:P2647.

45. Ellis CN, Fallon JD, Heezen JL, et al. Topical indomethacin exacerbates lesions of psoriasis. J Invest Dermatol. 1983;80:362.

46. Cohen AD, Bonneh DY, Reuveni M, et al. Drug exposure and psoriasis vulgaris: case-control and case-crossover studies. Acta Derm Venereol. 2005;85:299–303.

47. Reshod H, Hargreaves GK, Vickers CF. Generalized pustular psoriasis precipitated by phenylbutazone and oxyphenylbutazone. Br J Dermatol 1983; 109:111-3

48. Lammers AM, Van de Kerkof PCM. Leucotriene B4 fails to induce penetration of polymorphonuclear leucocytes into psoriatic lesions. Br J Dermatol 1987; 117: 541-4

49. Katz M, Seidenbaum M, Weinrauch L. Penicillin-induced generalized pustular psoriasis. J Am Acad Dermatol. 1987;17:918–920.

50. Sidoroff A, Halevy S, Bowes-Bavinck JN, et al. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction patter. J Cutan Pathol. 2001;28:113–119.

51. Cohen A, Bonneh D, Reuveni H, et al. Drug exposure and psoriasis vulgaris: case-control and case-crossover studies. Acta Derm Venereol. 2005;85:299–303.

52. Boothe JH. The tetracyclines. In: Hlavka JJ. Handbook of Experimental Pharmacology. Vol 78. Berlin: Springer-Verlag; 1985. p. 451.

53. Wright AL, Colver GB. Tetracyclines-how safe are they? Clin Exper Dermatol. 1988;13:57–61.

54. Skoven I, Thormann J. Lithium compound treatment and psoriasis. Arch Dermatol 1979; 115: 1185-7

55. Grisaru N, Blemaker RH. Ltihium dosage and inositol levels. Br J Psychiatry. 1994;164(1):133–134.

56. Watchter T, Murach WM, Brocker EB, et al. Recalcitrant lithium-induced psoriasis in a suicidal patient alleviated by tumor necrosis factor-alpha inhibition. Br J Dermatol. 2007;157(3):627–629.