

Lithium and Psoriasis: What Primary Care and Family Physicians Should Know

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Objective: This review focuses on the association of lithium treatment and psoriasis. The mechanism of action of lithium in causing psoriasis and the clinical presentation of psoriasis secondary to lithium treatment are considered.

Data Sources: A search of the literature from 1949 to 2007 was performed using MEDLINE, with the following search terms: *lithium, psoriasis, skin, dermatology*, and *psychodermatology*.

Data Synthesis: Lithium is involved in a variety of cutaneous reactions including psoriasis, which may present as exacerbation of preexisting psoriasis, induction of de novo psoriasis, pustular psoriasis, nail changes, and psoriatic arthropathy. The appearance of psoriatic lesions may occur at normal therapeutic serum lithium levels. The refractory period for the development of psoriatic lesions is variable and generally longer in induction and shorter in exacerbation of psoriasis. Lithium-induced psoriasis is often resistant to conventional treatment modalities, and some cases may require dose reduction or discontinuation of lithium treatment.

Conclusion: Lithium is the mainstay of treatment in bipolar disorder and is associated with a variety of cutaneous side effects including psoriasis. Primary care providers and family physicians should be knowledgeable about the association of lithium and its dermatologic side effects. Early recognition and management could be beneficial in avoiding the issues of noncompliance and further deterioration of mood symptoms secondary to obviously disfiguring skin appearance. Primary care, psychiatry, and dermatology liaison services will prove helpful in managing these patients.

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Bipolar disorder is a mood disorder characterized by an elevated, expansive, or irritable mood lasting at least 1 week and accompanied by at least 3 of the following: grandiosity, decreased need for sleep, pressured speech or over-talkativeness, flight of ideas, distractibility, and increase in goal-directed activity and high-risk behavior.¹ Lithium is the mainstay of treatment of bipolar disorder and is an effective mood stabilizer that has been used for more than 5 decades. Despite its superior efficacy in the treatment of bipolar disorder, lithium has a wide range of systemic side effects affecting several body systems including skin. The reported prevalence of cutaneous side effects varies from 3.4% to 45% in different studies.²⁻⁴ Psoriasis and psoriasiform rash are among the major cutaneous side effects of lithium and have resulted in severe emotional distress and noncompliance in patients with bipolar disorder treated with lithium. It should be kept in mind that not all patients with preexisting psoriasis will develop flare in their lesions on lithium treatment, and psoriasis is not considered a contraindication to lithium therapy in patients with bipolar disorder.

This review focuses on the association of lithium treatment and psoriasis. A search of the literature from 1949 to 2007 was performed using MEDLINE, with the following search terms: *lithium, psoriasis, skin, dermatology*, and *psychodermatology*. The mechanism of action of lithium in causing psoriasis and the clinical presentation of psoriasis secondary to lithium treatment are considered.

HISTORY OF LITHIUM

The name *lithium* was derived from the Greek word *lithos*, meaning stone. Lithium was first discovered as an element by Johan August Arfvedson in 1817.⁵ Lithium's use in modern medicine dates back to the mid-19th century, when it was used to treat various metabolic derangements including bladder stones. In 1948, lithium was withdrawn from the U.S. market after reports of toxicity leading to several deaths secondary to its use as a salt substitute. In 1949, John Cade in Australia reported successful use of lithium in patients with manic episodes.⁶ Use of lithium was approved by the U.S. Food and Drug Administration (FDA) in 1970 for the treatment of acute mania and in 1974 for the maintenance therapy and prophylaxis of patients with bipolar disorder.

PHARMACOLOGY OF LITHIUM

Lithium is an alkali metal and a monovalent cation. The half-life of lithium is about 24 hours, and it is excreted unchanged by the kidneys. The normal therapeutic window for serum concentration in different laboratories ranges from 0.5 to 1.5 mEq/L. Due to the narrow therapeutic window of lithium, monitoring of levels is required throughout the course of treatment. Lithium is available in multiple formulations in carbonate, citrate, and immediate- and extended-release forms. Peak plasma concentration may be achieved after 1 to 2 hours with immediate-release preparations and 4 to 5 hours with extended-release forms.

INCIDENCE OF PSORIASIS

The first description of association of lithium with psoriasis was by Carter in 1972,⁷ and since then several reports of lithium-induced psoriasis or exacerbation of preexisting psoriasis have been published in literature. Lithium-provoked psoriasis was first reported in 1976 by Bakker and Peplinkhuizen.⁸ The incidence of psoriasis secondary to lithium treatment has been reported to be from 1.8% to 6%.^{3,4}

MECHANISM OF ACTION

The mechanism by which lithium induces or exacerbates psoriasis is not exactly known, but its role in modulating second messenger systems such as adenylyl cyclase and inositol monophosphatase-mediated pathways, resulting in alteration in calcium homeostasis,^{9,10} and its effect on serotonergic function^{11,12} have been implicated. The decrease in cyclic adenosine monophosphate (cAMP) and inositol that results from lithium treatment causes low intracellular levels of calcium, leading to lack of differentiation and increased proliferation of keratinocytes, enhanced chemotaxis, and phagocytic activity of polymorphonuclear leukocytes.^{13,14} Inositol supplementation in psoriatic patients on lithium treatment has demonstrated beneficial effects.^{15,16} Decreased cAMP is also implicated in the inhibition of prostaglandin synthesis, thus stimulating neutrophil proliferation.¹⁷

Lithium is also involved in the dysregulation of the proinflammatory cytokines. Ockenfels and colleagues¹⁸ demonstrated that lithium influences the cellular communications of psoriatic keratinocytes when cultured with HUT-78 lymphocytes by triggering the secretion of transforming growth factor (TGF)- α , interferon gamma, and interleukin-2 levels in the skin of patients with psoriasis after lithium treatment. However, some authors have argued the precise role of proinflammatory cytokines in the production of lithium-induced psoriasis and suggested 2 separate mechanisms for the production of

psoriatic lesions in patients taking lithium and patients not taking lithium.¹⁹ In vitro studies of culture of normal human skin with lithium have demonstrated lithium's direct role in epidermal hyperproliferation and indirect role in altering epidermal barrier function and generating signals to the nucleated layer of the epidermis to proliferate in an attempt to restore the barrier, increasing cell turnover, intercellular edema, and vacuolar alteration with formation of small cavities in the upper dermis.²⁰ Some authors have described the importance of the role of increased intracellular tyrosine phosphorylation in psoriatic T cells compared to control T cells.²¹ In animal models, topical application of lithium carbonate has produced lesions characterized by epidermal thickening and dermal infiltration of mononuclear and polymorphonuclear cells.²²

CLINICAL PICTURE

Lithium has been implicated in a variety of clinical and morphological presentations of psoriasis. Its role in exacerbation of preexisting psoriasis, induction of psoriasis on previously unaffected skin of psoriatic patients, and triggering of psoriasis for the first time in patients with no personal or family history of psoriasis is well documented.^{23,24} A definite temporal relationship exists between exacerbation of psoriasis when lithium treatment is initiated and improvement when lithium is stopped.²⁵ The appearance of psoriatic lesions in patients on lithium treatment has been reported to occur at therapeutic serum levels.²⁶ It is unclear whether the relationship of lithium to the appearance of psoriatic lesion is dose related. The majority of authors have not noticed any dose dependency in the production or exacerbation of psoriatic lesions.^{23,25,27} However, some authors have described a dose-dependent relationship of lithium in induction of psoriasis.²⁸ The refractory period for the development of psoriatic lesions after the initiation of lithium treatment is variable and ranges from a few weeks to several months. Generally, it is longer for induction and shorter for exacerbation of psoriasis lesions.²⁹ De novo plaque-type psoriasis generally takes longer to develop compared to production of pustular psoriasis.³⁰ It has also been suggested that exacerbation of preexisting psoriasis is more common than induction of new psoriasis lesions.^{3,29}

Since the association of depression with psoriasis has been well documented,³¹ the treating physician should be careful and aware of the complexity of situations in which a patient with preexisting ordinary psoriasis is in a depressive phase of bipolar illness and is started on lithium treatment. The production of psoriatic lesions is temporally related to the improvement in mood symptoms, probably indicating complete cellular saturation with lithium ions. What influences the induction or

Table 1. Clinical Manifestations of Lithium-Induced Psoriasis

Generalized psoriasis ^{7,29,40}
Plaque-type psoriasis ^{25,29}
Pustular psoriasis ^{27,33,34}
Palmoplantar pustulosis ³⁴
Nail psoriasis ³⁵⁻³⁷
Scalp psoriasis ²⁹
Exfoliative (erythrodermic) psoriasis ³⁸
Psoriasiform dermatitis ⁴¹
Psoriatic arthropathy ^{24,26}

exacerbation of psoriasis in some patients on lithium treatment and not in others is not clearly known; however, the significance of the role of individual host factors has been emphasized in the production of psoriatic lesions in predisposed patients.²³ Psoriasis that has flared and exacerbated with lithium is generally more resistant to standard treatment methods, and in several cases discontinuation of lithium has proved helpful. Patients who have a positive family history of psoriasis should be carefully evaluated for potential development of psoriasis later during the course of treatment.³²

The common presentation of psoriasis secondary to lithium treatment is typical plaque-type lesions, but other manifestations may also occur and include pustular psoriasis,^{27,33,34} fingernail abnormalities,³⁵⁻³⁷ erythroderma,³⁸ nonspecific psoriasiform dermatitis,³⁹ and psoriatic arthropathy.^{24,26} Table 1 shows the clinical presentation of psoriasis secondary to lithium therapy. The clinical and histopathologic picture of lithium-induced psoriasis is compatible with that of ordinary psoriasis,³⁹ and there are no specific histopathologic differences. Some authors have described a psoriasiform dermatitis-like picture with nonspecific histopathologic findings.⁴¹ New-onset pustular psoriasis, palmoplantar pustulosis, and transformation of ordinary stable plaque-type psoriasis to generalized pustular psoriasis have all been reported in patients on lithium treatment.^{34,42} Psoriasis in lithium-treated patients may sometimes initially appear as a scalp lesion that is resistant to conventional treatment and may spread all over the body.²⁹ Some patients on lithium treatment may experience roughening, yellowing, opaqueness, and pitting on nails, the features commonly encountered in psoriatic nails. In one study, such lesions were reversible upon discontinuation of lithium.³⁵ Erythroderma or exfoliative dermatitis secondary to lithium treatment is a relatively uncommon presentation. When present, the psoriatic lesions gradually spread over the scalp, trunk, and extremities, and discontinuation of lithium has proved useful in ameliorating the condition.³⁸ Lithium-induced psoriasis has been reported to progress to psoriatic arthritis.²⁴ Interestingly, increased adherence of polymorphonuclear leukocytes, which correlates positively with the extent of ordinary psoriasis and psoriatic arthritis, has not been found in lithium-treated patients.⁴³

MANAGEMENT

In evaluating the lithium-treated patient with exacerbation of psoriasis, the role of stress and other psychological factors as well as concomitant medications should be thoroughly evaluated, since the exacerbation of psoriasis with certain medications, stress, and psychological factors is common and has been well documented.^{31,44,45} Psoriasis induced or exacerbated by lithium could be managed with conventional treatment methods such as topical steroids, keratolytics, vitamin D analogues, oral retinoids, PUVA (psoralen and ultraviolet A) therapy, and methotrexate. However, in most cases these treatments may not be very effective,^{29,46} and in such resistant cases, lithium discontinuation may be considered and the patient may be switched to another mood stabilizer.^{5,26} Reduction in dose is another reasonable option and is worth trying. The psoriatic lesions generally disappear within a few months' time after discontinuation of lithium treatment.

Some newer therapeutic agents used specifically in the treatment of lithium-induced psoriasis include omega-3 fatty acids, tumor necrosis factor (TNF)- α inhibitors, and inositol. These agents are not routinely used in lithium-induced psoriasis, since the majority of lesions disappear or are controlled with either conventional methods or discontinuation of lithium. In a double-blind, placebo-controlled trial, omega-3 fatty acid was found to be very useful in clearing lithium-induced psoriasis,⁴⁷ and some authors have successfully used TNF- α inhibitors (etanercept) in the treatment of severe recalcitrant lithium-induced psoriasis not responding to other treatment modalities.⁴⁸ TNF- α inhibitors are novel agents in the treatment of a variety of chronic inflammatory and rheumatic disorders. Three drugs in this class that are currently in use are etanercept, infliximab, and adalimumab. These drugs are associated with numerous side effects that include development of opportunistic infections, lymphoproliferative disorders, reactivation of demyelinating diseases, systemic lupus erythematosus-like syndrome, and aggravation of congestive heart failure.⁴⁹

In a randomized, double-blind, placebo-controlled crossover trial,¹⁶ inositol supplementation was found to have a beneficial effect on psoriasis in patients who were taking lithium compared to those who were not taking lithium. The beneficial effect of inositol is related to lithium's "inositol depletion hypothesis" in the pathogenesis of lithium-induced psoriasis.^{15,16,40} Since inositol taken by mouth does not cross the blood-brain barrier, inositol supplementation will not interfere with lithium's mood-stabilizing effects in patients with lithium-aggravated psoriasis.²³

Preexisting psoriasis should not be regarded as a contraindication to lithium treatment, as not all patients on lithium treatment will develop exacerbation. Careful monitoring and a psychodermatology consultation could

Table 2. Management Guidelines for Lithium-Induced Production or Exacerbation of Psoriasis

Detailed personal, social, and family history and history of psoriasis before considering lithium therapy
Psychodermatologic evaluations at frequent intervals during the treatment course to recognize psoriatic lesions and address potential issues with low self-esteem and treatment compliance
Mild to moderate disease: conventional treatment such as topical steroids, vitamin D analogues, retinoids, methotrexate, and PUVA (psoralen and ultraviolet A) therapy
Severe disease: discontinue lithium treatment and request dermatology/psychodermatology consult. Reduction of dose could be another option reasonable and worth trying in these cases
Consistent liaison among primary care physician, psychiatrist, and dermatologist regarding the management of psoriasis
Patient and family education regarding the association of lithium and psoriasis and provision of alternative medications

be helpful at the initiation of treatment, during the course of the treatment, and after the production or exacerbation of psoriatic lesions. Table 2 summarizes the management guidelines for lithium-induced production or exacerbation of psoriasis.

CONCLUSION

Lithium is the most commonly prescribed medication for patients with bipolar disorder and is associated with a wide range of cutaneous side effects. Treating providers should closely monitor psoriasis and other cutaneous lesions in patients on lithium treatment. Psoriasis induced and exacerbated by lithium treatment sometimes becomes very resistant to conventional treatment and could manifest as a source of frustration and anger on the part of both patient and providers. Early recognition and management will help avoid issues of noncompliance and further deterioration of mood symptoms in these patients. Psychiatry, dermatology, and primary care liaison services could prove very helpful in the management of these patients.

Drug names: adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), lithium (Eskalith, Lithobid, and others), methotrexate (Trexall and others).

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