

EXPANDING TREATMENT OPTIONS FOR PSORIASIS: UNDERSTANDING THE ROLE OF TOPICAL VITAMIN D DERIVATIVES.

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LEARNING OBJECTIVES

- 1.** Understand the inflammatory mechanisms of psoriasis that characterize its chronic nature and shape the goals of treatment.
- 2.** Critically assess the different topical pharmacologic approaches for psoriasis and revisit the potential side effects associated with their use, including prolonged topical corticosteroid use.
- 3.** Become familiar with the suitability of Vitamin D derivatives for the long-term management of psoriasis.



This educational resource has been reviewed by Continuing Professional Development, Schulich School of Medicine & Dentistry, The University of Western Ontario and deemed to be appropriate for self-directed, independent learning.

For time spent in this activity, members of the Royal College of Physicians and Surgeons of Canada may claim a total of one credit under Section 2 of the Maintenance of Certification framework of CPD options. Specialists may also incorporate information obtained from this activity into a Personal Learning Project (PLP) and claim two credits per hour under Section 2. Members of The College of Family Physicians of Canada may refer to www.cfpc.ca/education

to find options for claiming time spent in this self-directed learning activity. Members may also complete a Linking Learning to Practice or PEARLS exercise and generate Mainpro-C credits.

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PSORIASIS IS A CHRONIC, INFLAMMATORY SKIN CONDITION PRONE TO PERIODIC FLARES

Psoriasis is a complex and multifactorial disease, brought on by various environmental triggers including trauma, stress and infections. In genetically predisposed individuals, these triggers may induce the activation of an exaggerated and poorly controlled immune inflammatory response in the skin leading to excessive keratinocyte proliferation.¹ The result is the manifestation of visible plaques of psoriasis on the skin, varying from minimal involvement to a high degree of body surface area being involved. Of the 1 to 3% of the population worldwide that is affected by psoriasis, over 80% of patients are classified as having plaque-type psoriasis vulgaris, characterized by well-defined erythematous scaly plaques, typically observed on extensor surfaces such as the elbows, knees, scalp and buttocks.¹

Previously, psoriasis was viewed as a chronic disease of dysregulated epidermal keratinocytes. Today, it is felt that the epidermal hyperproliferation is the result of a dysregulated cutaneous immune response. Clinical flare-ups and disfiguring lesions in visible skin areas, lead to a high-degree of morbidity and decreased quality of life in psoriasis patients.¹ Complications of the chronic inflammatory state of psoriasis result in cardiovascular and metabolic complications and comorbidities, such as cardiovascular diseases and diabetes; depression and suicide are more common as well, potentially brought on by the various psychosocial problems that psoriasis patients encounter.²

With approximately half a million Canadians affected by psoriasis, there is a definite need for effective therapeutic strategies at the primary care level that employ a patient-centered approach.³ As with other disease areas, treatment efficacy largely hinges on the patients' ability to manage their disease and adhere to the prescribed course of treatment. It is noted that in the general psoriasis population, up to 73% of patients are found to be non-adherent, even when patients classify their own psoriasis as severe and greatly impacting their quality of life.³ Compounded with the chronic nature of psoriasis pathophysiology, non-adherence can limit optimal patient outcomes (Figure 1). Patients often become frustrated if their therapy is ineffective, and then stop therapy as a result, further lowering the chance for treatment success.^{3,4} Most often, patients attribute non-adherence to frustration with medication efficacy, inconvenience of administration and fear of long-term side effects.^{3,4} Thus, it is vital that physicians, especially those at a primary care level, discuss these issues with their patients to choose a course of treatment that is best suited to their patient's needs.³

According to the Canadian Guidelines for the Management of Plaque Psoriasis, a physician should first identify therapies that are effective, safe and well suited to the symptoms of their patient. Second, and equally important, physicians should choose an appropriate therapeutic option that the patient is most likely to use consistently, over the long-term, to achieve and maintain control of their psoriasis.^{3,4}

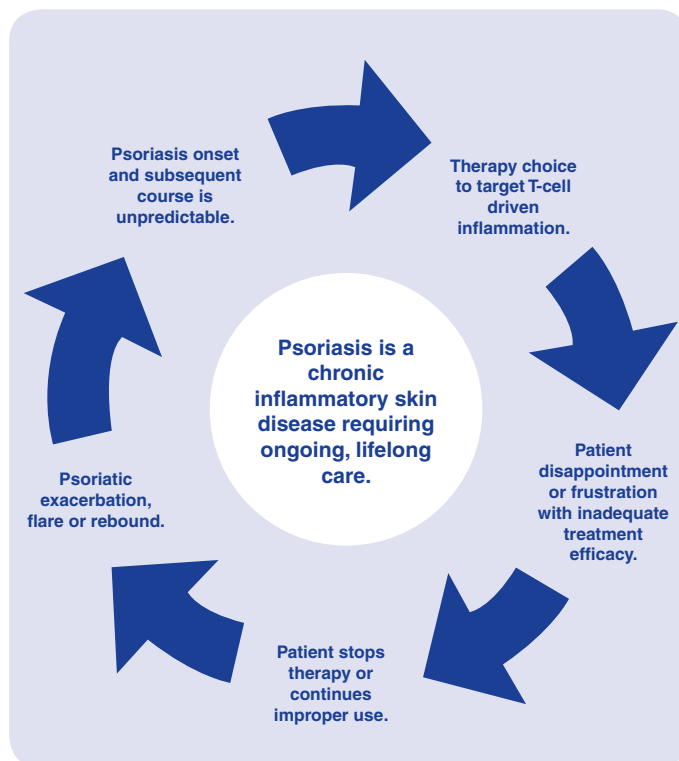


Figure 1. The vicious cycle.^{3,4}

CURRENT TREATMENT PARADIGMS

Due to the wide variability of psoriasis presentations, tailoring therapy to the individual needs of the patient must be made on a basis that is well suited to the nature and the extent of the disease. This includes assessment of the affected anatomical location, patient expected outcomes including quality of life implications and the patient's commitment to a treatment regimen as well considering the costs of various treatments.⁵ Topical therapy remains the cornerstone of treatment for patients with plaque psoriasis. While topical therapies have been established as effective for use on individual plaques, they can be time consuming to apply depending on the affected body surface area, and vary in their cosmetic acceptability.

There are a variety of topical formulations available for the treatment of psoriasis. The choice of vehicle has a notable impact on the use and the penetration of the medication, and therefore can greatly influence efficacy.⁴ Ointments, creams, lotions, solutions, gels, foams and sprays are among the numerous vehicle options available. The optimal choice, then, is generally the vehicle the individual patient would prefer to use.⁴

Topical corticosteroids remain the most widely prescribed first-line treatment for psoriasis.⁵ Typically, more potent topical corticosteroids provide rapid efficacy, cosmetic acceptability, and versatility in use.⁵ Among class I and class II topical steroids, when used for 2 to 4 weeks, efficacy rates vary widely among agents. This is, in part, due to the specifics of primary endpoints studied. Halobetasol propionate 0.05% ointment (class I), for example, has demonstrated a 92% improvement in physician's global assessment compared with 39% of vehicle treated patients ($P<0.0003$), during a 2-week, double-blind, vehicle-controlled trial of 204 patients with moderate to severe psoriasis.⁵ Comparatively, with 0.25% desoximetasone cream (class II), the results from a double-blind, vehicle-controlled study of 35 patients with psoriasis treated for 3 weeks, showed that 68% of desoximetasone treated patients improved in their mean overall evaluation score compared to 23% of vehicle-treated patients ($P<0.001$).⁵

As a cream and ointment alternative, clobetasol propionate spray 0.05% (class I), is a unique formulation of topical clobetasol for the treatment of moderate to severe plaque psoriasis. Studied in the first large community-based clinical trial for plaque psoriasis, *Clobex® Spray Community-Based Research Assessment (COBRA)*, it has been established as an effective psoriasis treatment as both monotherapy and as an add-on to existing therapies.⁶ In the monotherapy study, by week 4, 80% of subjects achieved target plaque severity (TPS) success, defined by a rating of clear or almost clear on the TPS scale or an improvement in severity of 2 grades, when twice-daily clobetasol spray was applied to target lesions ($P<0.001$).^{6,7,8} These results were mirrored in the add-on study ($P<0.001$).^{6,7,8}

Calcipotriol 0.005%/betamethasone dipropionate 0.05% (C-BD) ointment is another highly prescribed topical corticosteroid (class I) for the treatment of plaque psoriasis, indicated for use up to 4 weeks.¹⁰ Efficacy between the steroid components has been previously evaluated. In 193 patients with moderate-to-severe scalp psoriasis, 0.05% betamethasone dipropionate lotion demonstrated similar efficacy to that of 0.05% clobetasol propionate solution. Betamethasone dipropionate did, however, provide faster onset of action than clobetasol, which can be potentially attributed to the difference in vehicle.¹⁵ The individual reports of efficacy success for clobetasol 0.05% spray and C-BD ointment have been similar. Though, success rate measures are often determined by different assessments making direct comparison difficult.

Clobetasol spray and C-BD have been directly compared for efficacy, safety, quality of life and patient satisfaction with treatment.⁹ In one study, twice daily clobetasol spray, or once-daily C-BD ointment was used to treat stable plaque psoriasis up to 4 weeks, as per each product's approved label. Observing overall disease severity in the per-protocol population revealed that at the end of the 4 week treatment period significantly more clobetasol spray treated patients (75%) had treatment success (clear or almost clear) compared to C-BD ointment patients (45%) ($P=0.003$).⁹ Four weeks following completion of treatment, the percent of clear or almost clear patients returned to near baseline levels (14% and 8%, clobetasol spray and CB-D respectively) (Figure 2).⁹ In addition, more patients were satisfied with clobetasol spray treatment than were with C-BD ointment, with similar compliance in both treatment groups.⁹

Coal tar and, much less commonly, anthralin are additional topical treatments for psoriasis, but their use in clinical practice has been declining given tolerability issues associated with their use and the advent of more cosmetically acceptable treatment options.⁵

Vitamin D₃ derivative agents, such as calcitriol or calcipotriol (calcipotriene), are newer to the physician's armamentarium for plaque psoriasis treatment. Although clinical responses with Vitamin D₃ therapies are often slower than high potency corticosteroid agents, their long-term safety profile makes them a valuable treatment choice for maintenance therapy.⁵

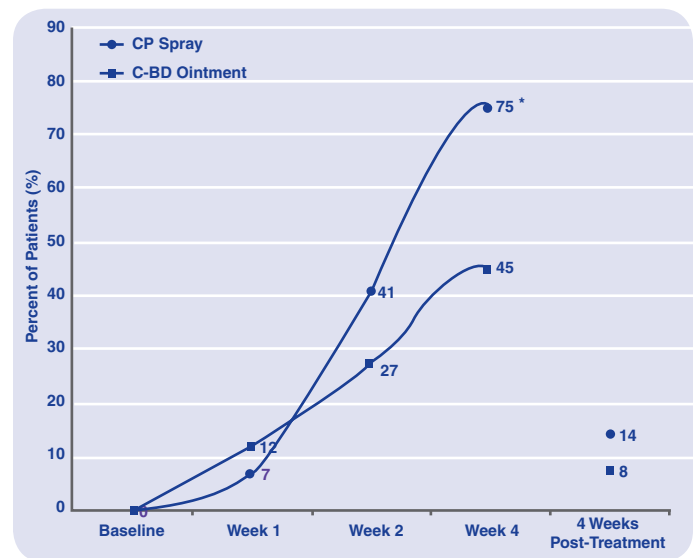


Figure 2. Treatment success by overall disease severity scale, per protocol population. CP=Clobetasol propionate spray, CB-D=Calcipotriol/betamethasone dipropionate. * $P=0.003$.⁹

SHIFTING FOCUS TO LONG-TERM MANAGEMENT

Topical corticosteroids are associated with potential cutaneous side effects that can limit their use over the long-term.⁹ These include skin atrophy, telangiectases, striae distensae, acne, folliculitis and purpura.⁹ Additionally, there are concerns that topical corticosteroids may cause rebound of psoriatic flares, wherein the disease recurs worse than the pretreatment baseline after the topical corticosteroid is discontinued.⁹ Many topical corticosteroids, including clobetasol spray and C-BD are limited for use up to 4 weeks to minimize long-term complications (Table 1). Though, it appears patients are unaware of this.

One study asked patients how long they were instructed to use their most recent topical steroid for psoriasis and found that in over half of the subjects, the duration of treatment was not defined.¹⁷ Only one quarter of the subjects were instructed to continue treatment for less than 8 weeks, yet 11% were unsure when to stop their treatment and 6% were instructed to continue their topical corticosteroid longer than 8 weeks.¹⁷ The use of topical steroids in this way may lead to unintended prolonged treatment.

Traditionally, the goal of psoriasis therapy has focused on the short-term management of isolated outbreaks.⁶ Since 1986, there has been a large increase in the amount of potent topical corticosteroids prescribed.¹⁸ This is most likely due, in part, to a demand from patients for quicker rates of plaque clearing and the availability of new treatment options. However, statistics as recent as 2004 reveal that more than 1 million patients report that their psoriasis was poorly controlled.¹⁸ Despite a wide variety of topical steroid treatment options available, there is a need for new treatment strategies.

In recent years a new paradigm has emerged shifting the emphasis from short-term strategies to the maintenance of continuous long-term control. This has sparked the development of a variety of creative therapeutic approaches, such as those involving sequential, combination, and rotational treatment regimens that utilize both topical and systemic medications as well as phototherapy.^{6,17} Employing regimens with non-steroidal products, including calcineurin inhibitors and vitamin D derivatives can decrease the potential for flares when topical steroids are cycled off.¹⁹

The vitamin D analog calcipotriol and corticosteroid betamethasone dipropionate are well known topical treatments for psoriasis and have been studied for safe, long-term use under regimen type approaches. One study has reported the randomization of 19 patients to one of three different regimens, applied once-daily, as needed, for up to 52-weeks.²⁰ All patients received an initial 4 week treatment with the

two-compound ointment (calcipotriol/betamethasone dipropionate), and subsequently received either the two-compound ointment, the two-compound ointment alternating every 4 weeks with the calcipotriol ointment, or the calcipotriol ointment.²⁰ None of the patients reported adrenal suppression over the 52-week treatment period.²⁰

Another regimen approach, sequential therapy, was developed to maximize the short-term efficacy of topical corticosteroids, while minimizing the side-effects associated with their long-term use.^{19,21,22} This approach differs from the latter, in that psoriasis is treated preventatively, rather than as-needed. Recently studied in subjects with moderate to severe plaque psoriasis, treatment consisted of clobetasol propionate 0.05% spray twice daily for up to 4 weeks, followed by calcitriol 3 µg/g treatment twice daily until the end of the 12 week trial period. This sequential regimen was efficacious with a success rate of 84.1% at week 12, defined as an improvement of at least one grade from baseline in overall disease severity at week 12.¹⁹ Mean percent of body surface area affected improved rapidly after two weeks of treatment, and was sustained throughout the 8 week calcitriol ointment treatment period (Figure 3).¹⁹ Adverse events were limited, reported in only 32.8% of patients and were mostly unrelated (69.7%) to study medications.¹⁹ Moreover, after 12 weeks less than 1% of patients were reported as having any signs of skin atrophy. While further investigation is required to assess the safety and efficacy of repeated cycles of this sequential regimen, this study offers a new treatment strategy that uses a very high potent steroid followed by a steroid-sparing therapy to achieve effective treatment for plaque psoriasis over 12 weeks.

The flexibility of topical agents allows for their use both intermittently and long-term. In general, it has been recommended that more potent agents be used on a short-term basis to gain control of psoriasis plaques, after which patients should be instructed to use these agents intermittently or to transition to a therapy suitable for maintenance.⁹ Additionally, when patients understand these strategies, their fear of topical steroids, for initial therapy use, may decrease.¹⁷ This strategy may confer less risk of side effects than continuous treatment with a potent steroidal therapy.⁹

Table 1. Indication of Class I topical corticosteroids approved for use in Canada.

| Generic name | Brand Name | Indication |
|---|-----------------------|---|
| Calcipotriol 0.005%/betamethasone dipropionate 0.05% ointment ¹⁰ | Dovobet® | For the topical treatment of psoriasis vulgaris for up to 4 weeks. Should not be used on the face. |
| Clobetasol propionate 0.05% spray ¹¹ | Clobex® Spray | For the treatment of moderate to severe plaque psoriasis. Not for long-term use, treatment should be limited to a maximum of 4 consecutive weeks. |
| Betamethasone dipropionate 0.05% ointment ¹² | Diprosone®/Diprolene® | For anti-inflammatory, antipruritic and anti-allergic activity in the topical management of corticosteroid-responsive dermatoses. Such disorders include: psoriasis, allergic contact dermatitis, atopic dermatitis, neurodermatitis, dyshidrotic eczema, seborrheic dermatitis, exfoliative dermatitis, stasis dermatitis, anogenital and senile pruritus. |
| Halobetasol propionate 0.05% cream or ointment ¹³ | Ultravate® | For the relief of inflammatory manifestations of resistant or severe psoriasis and corticosteroid-responsive dermatoses. The duration of therapy should not exceed 2 weeks without patient re-evaluation. |

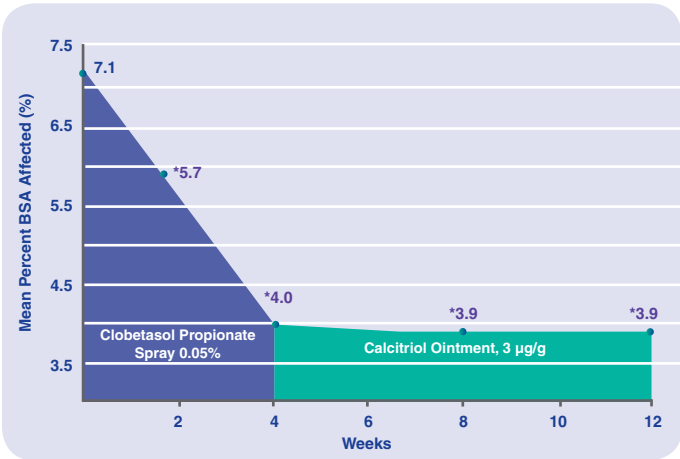


Figure 3. Sequential treatment regimen. Mean % of body surface area affected. * $P<0.001$ (comparison to baseline value).¹⁹

THE VALUE OF VITAMIN D₃ THERAPIES

Topical vitamin D derivatives are among the most widely used medications for the treatment of psoriasis.^{23,24} Although the exact mechanism to which vitamin D modulators improves psoriasis is not completely understood, they have been shown to inhibit keratinocyte proliferation, promote keratinocyte differentiation and decrease the expression of proinflammatory cytokines that stimulate T-cell proliferation and cutaneous inflammation.^{14,16,24,25}

Calcipotriol, a synthetic analog of vitamin D, is a commonly prescribed medication for psoriasis. In placebo-controlled short-term clinical efficacy trials, calcipotriol treated patients have shown better reductions in overall disease severity ranging from 52 to 59% versus 16 to 35% with placebo. Moreover, a greater percentage of calcipotriol-treated patients have achieved $\geq 75\%$ improvement in severity of psoriasis or complete clearance, than that of placebo (59 to 74% versus 12 to 19% respectively).²⁶ Long-term evaluations have indicated that improvements in disease severity demonstrated in the short-term can be maintained up to 1 year in adult patients.²⁶ In addition, calcipotriol treated patients generally experience clinically superior benefits on psoriasis severity when compared to betamethasone valerate (1 to 1.2 mg/g twice-daily) or once-daily dithranol (1 to 20 mg/g).²⁶ When combined with phototherapy, one small study observed the effects of calcipotriol in combination with phototherapy, and reported that, when compared to placebo, the addition of calcipotriol led to a more rapid clearance of psoriasis plaques and a 26.5% reduction in the dose of phototherapy required.²⁵

Calcitriol 3 µg/g ointment, a vitamin D derivative new to the Canadian market, is a naturally occurring and biologically active metabolite of vitamin D₃, in contrast to synthetic vitamin D products such as calcipotriol.^{14,16,21} While both calcitriol and calcipotriol are considered to be equally effective vitamin D analogs, calcitriol has the advantage of increased tolerability in sensitive regions, such as the face, hairline, and postauricular and flexural areas.²³

In two separate studies, calcitriol 3 µg/g ointment was used to treat mild to moderate chronic plaque psoriasis, twice daily over 8 weeks compared to vehicle only.²⁷ Combined efficacy results, defined as no or minimal psoriasis, in a total of 839 subjects (419 in the calcitriol group, 420 in the vehicle group) showed a calcitriol success rate of 34.4% in study one and 33.3% in study two, and for placebo 22.5% and 12.3% for studies one and two respectively, ($P=0.005$ and $P<0.001$).²⁷ The difference of mean change in the dermatological sum score in both studies was statistically significant ($P\leq 0.001$) in favor of calcitriol by week 8, particularly efficacious on bony prominences (Figure 4). Therapeutic effect of calcitriol was rapid with significantly observable results at 2 weeks, which was sustained until the end of treatment in both studies.²⁷

Two additional studies reported calcitriol use in moderate to severe lesions of chronic plaque psoriasis in sensitive skin areas including the face, hairline, or retroauricular areas. The first study reported use for 8 weeks with improvement in scaling, erythema, induration and pruritus seen by week 4 and continuing to the end of the study.²⁸ At the study endpoint, 74% of the patients were classified as better or improved.²⁸ In the second study patients applied calcitriol 3 µg/g ointment for 6 weeks to the same sensitive skin areas, and similar clinical outcomes were observed. In both studies, the cosmetic acceptability of treatment was judged as good by the majority of patients.²⁸ An additional 6 week study in patients with mild to moderate severe plaque psoriasis, directly compared the efficacy and safety of twice-daily calcitriol 3 µg/g ointment with twice-daily calcipotriol 50 µg/g ointment in sensitive skin areas including the face, hairline, retroauricular and flexural areas.²⁹ The greatest efficacy difference during the trial was observed in flexural areas, where 67% of calcitriol subjects reported clearing compared to only 33% of calcipotriol treated patients (Figure 5). The subjects' evaluation of local tolerability was significantly in favor of calcitriol ($P<0.0001$).²⁹ The use of calcitriol in sensitive skin areas may minimize the need for corticosteroids and allow for better individualization in developing a patient tailored psoriasis management regimen.²³

It has been demonstrated that topical calcitriol has less irritancy, sensitization, phototoxicity and photoallergic potentials.^{30,31,32} The long-term topical and systemic safety of calcitriol 3 µg/g ointment has been studied up to 78 weeks. When calcitriol was applied twice-daily to all psoriatic lesions, except those on the head, for up to 18 months, only 14.6% of patients report transient skin irritation reactions.³¹ Additionally, from baseline to endpoint there were no relevant changes in mean serum level of total calcium, albumin-adjusted total calcium, phosphorus, urea, creatinine, PTH, mean creatinine clearance values and mean plasma calcitriol levels.³¹ These results mirror the safety data reported in a 52 week study.³² Hypercalcemia was the primary laboratory outcome measure evaluated during this study, and only 3.1% of participants experienced one episode of hypercalcemia, defined as serum total albumin-adjusted calcium level greater than 2.55 mmol/L. None of the cases of hypercalcemia were considered clinically significant by the primary investigator or led to discontinuation of the study medication.³² Together, these reports demonstrate calcitriol as safe for long-term use, reiterating its value as a treatment choice for maintenance therapy, following the withdrawal of a flare controlling agent.^{5,31,32}

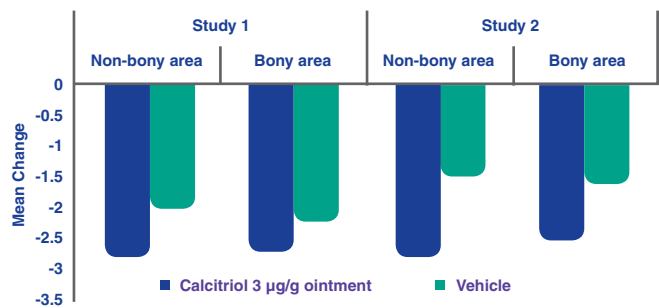


Figure 4. Dermatological sum scores after 8 weeks. $P<0.001$ in favor of calcitriol 3 µg/g ointment.²⁷



Figure 5. Results after 2 and 4 weeks of treatment.²⁹

FUTURE CONSIDERATIONS IN THE TREATMENT OF PSORIASIS

Treating psoriasis at the primary care level is often a challenge because of the chronic course of the disease, compounded by patient non-adherence and fear of long-term side effects. Patients with psoriasis experience a reduction in their quality of life similar to, or in some cases worse than, patients with other chronic diseases, such as ischemic heart disease and diabetes.^{1,33}

Thus, the treatment of psoriasis must be equally focused on both reducing the physical manifestation of symptoms over the long-term and individualizing treatment approaches to allow quality of life improvement. Individualized approaches are vital to the management of psoriasis due to the wide variation in patients' psoriatic presentations, and their personal opinions on what necessitates acceptable treatments. While topical corticosteroids will continue to be an important treatment agent for the immediate control of psoriatic flares, non-steroidal options such as vitamin D derivatives, may be particularly valuable for long-term maintenance. Physicians should use their understanding of available treatment options to develop a personalized therapeutic strategy that is tailored to the individual patient's needs.

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