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Review

Oral and Topical Vitamin D, Sunshine, and UVB Phototherapy Safely Control Psoriasis in Patients with Normal Pretreatment Serum 25-Hydroxyvitamin D Concentrations: A Literature Review and Discussion of Health Implications

Patrick J. McCullough [1,2,*], William P. McCullough [3], Douglas Lehrer [2], Jeffrey B. Travers [4] and Steven J. Repas [5]

[1] Medical Services Department, Summit Behavioral Healthcare, Ohio Department of Mental Health and Addiction Services, 1101 Summit Rd, Cincinnati, OH 45237, USA
[2] Department of Psychiatry, Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Hwy, Dayton, OH 45435, USA; Douglas.lehrer@wright.edu
[3] Rose-Hulman Institute of Technology, 5500 Wabash Ave, Terre Haute, IN 47803, USA; mcculloughw1999@gmail.com
[4] Department of Pharmacology & Toxicology, Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Hwy, Dayton, OH 45435, USA; jeffrey.travers@wright.edu
[5] Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Hwy, Dayton, OH 45435, USA; repas.3@wright.edu
* Correspondence: Patrick.mccullough@mha.ohio.gov; Tel.: +1-513-948-3600

Abstract: Vitamin D, sunshine and UVB phototherapy were first reported in the early 1900s to control psoriasis, cure rickets and cure tuberculosis (TB). Vitamin D also controlled asthma and rheumatoid arthritis with intakes ranging from 60,000 to 600,000 International Units (IU)/day. In the 1980s, interest in treating psoriasis with vitamin D rekindled. Since 1985 four different oral forms of vitamin D (D_2, D_3, 1-hydroxyvitaminD_3 (1(OH)D_3) and 1,25-dihydroxyvitaminD_3 (calcitriol)) and several topical formulations have been reported safe and effective treatments for psoriasis—as has UVB phototherapy and sunshine. In this review we show that many pre-treatment serum 25(OH)D concentrations fall within the current range of normal, while many post-treatment concentrations fall outside the upper limit of this normal (100 ng/mL). Yet, psoriasis patients showed significant clinical improvement without complications using these treatments. Current estimates of vitamin D sufficiency appear to underestimate serum 25(OH)D concentrations required for optimal health in psoriasis patients, while concentrations associated with adverse events appear to be much higher than current estimates of safe serum 25(OH)D concentrations. Based on these observations, the therapeutic index for vitamin D needs to be reexamined in the treatment of psoriasis and other diseases strongly linked to vitamin D deficiency, including COVID-19 infections, which may also improve safely with sufficient vitamin D intake or UVB exposure.

Keywords: vitamin D_3; D_2; calcitriol; oral; topical; serum 25-hydroxyvitamin D; psoriasis; skin diseases; UVB; phototherapy; sunshine; COVID-19; regulatory T lymphocytes

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1. Introduction

Psoriasis is the most common autoimmune disease in the United States, estimated to affect over 8 million people [1]. The total cost of health care in the US for psoriasis was estimated to be USD 135 billion per year in 2013 [2] and is likely much higher today. A wide variety of treatment options are currently available, classified by the National Psoriasis Foundation (NPF) as biologic drugs, bio-similar medicines, oral treatments, traditional systemic medications, UVB phototherapy and sunshine, and topically applied medications (corticosteroids, vitamin D analogues, others), and are summarized on the

NPF website [3–9]. In addition, the American Academy of Dermatology (AAD) and the National Psoriasis Foundation released two guidelines in 2019 outlining best practices for managing this inflammatory skin disease [10,11]. One guideline extensively reviews the use of the relatively newly developed biologic agents that target specific components of the inflammatory process causing psoriasis [10], and the other focuses on the management and treatment of psoriasis with awareness of and attention to comorbidities [11]. Neither of these two references mentions the use of oral vitamin D.

While topical vitamin D is included in the list of recommended treatments by the NPF, oral vitamin D is not discussed, other than a brief comment stating, "Research on the use of vitamin D dietary supplements for treating psoriasis is limited . . . We recommend speaking with your health care provider about taking a vitamin D supplement" (page 11, 2018 Topical Treatments handbook) [9]. The reason for the exclusion of oral vitamin D as a recommended treatment for psoriasis by both the NPF and AAD is unclear. Four different forms of oral vitamin D have been shown to be safe treatments for psoriasis dating back to the 1930s [12–28], when oral vitamin D_2 was first found to be effective in treating a number of diseases in addition to psoriasis, including asthma [29], rheumatoid arthritis [30,31], rickets [32] and tuberculosis [33–39]. Sunshine, UVB phototherapy and cod liver oil, a concentrated food source of vitamin D, were also noted to be effective treatments for psoriasis [12,40–44], rickets [45,46] and TB [39,47–54] during that era.

There is currently much debate as to what constitutes vitamin D deficiency, insufficiency, sufficiency and toxicity, and what diseases are responsive to vitamin D supplementation. A serum 25(OH)D concentration > 20 ng/mL was defined as sufficient for the vast majority of the population by the Institute of Medicine (IOM) in 2011 [55], while serum 25(OH)D concentrations < 30 ng/mL were defined as insufficient by the Endocrine Society in 2011 [56]. A serum 25(OH)D concentration > 50 ng/mL was cited as a cause for concern by the IOM in 2011 [55], while the Endocrine Society set a serum 25(OH)D concentration of 100 ng/mL as the upper limit of normal in 2011 [56]. The risk for toxicity has been variably thought to occur with serum 25(OH)D concentrations above 150 ng/mL in 1999 [57], 240 ng/mL in 2007 [58], 300 ng/mL in 2008 [59] and 400 ng/mL in 2011 [60].

In this report we review clinical research studies that reported serum 25(OH)D concentrations in psoriasis patients who responded safely to treatment with either oral $1(OH)D_3$ [14], oral or topical calcitriol [14,19,21,22], oral vitamin D_3 [25,26], oral vitamin D_2 [28], UVB phototherapy [61–64] or sunshine [64]. We will summarize the serum 25(OH)D concentrations obtained before and after treatment in each report as they relate to current definitions of vitamin D deficiency, sufficiency and toxicity, as well as the safety and efficacy of the treatments. We will show that psoriasis patients commonly have normal serum 25OHD concentrations prior to treatment with vitamin D yet show significant clinical improvement after treatment, while those treated with UVB phototherapy often have serum 25(OH)D concentrations greater that 100 ng/mL post treatment without complications.

The data reviewed in this report was never mentioned in reports published in 2011 by the IOM [55] and the Endocrine Society [56] when they issued separate recommendations for what constitutes vitamin D deficiency, insufficiency, sufficiency and toxicity. The vitamin D clinical research studies will be listed in Section 2, and the UVB phototherapy and sunshine clinical research studies listed in Section 3, along with a brief description of the design of each study. A detailed analysis of each report is provided in the Supplementary Materials Section. A summary of the key findings from these reports is presented in Section 4. A discussion of the implications of our findings in this review for the treatment of psoriasis and other diseases strongly linked to vitamin D deficiency using vitamin D, including COVID-19 infections, is included in Sections 5 and 6. Numerous recent reports have shown a strong link between adverse outcomes from COVID-19 infections and vitamin D deficiency [65–80], with at least one pilot study showing clinical efficacy in reducing intensive care unit admissions and mortality among patients hospitalized for COVID-19 after treatment with calcitriol [80].

2. Oral Vitamin D_2, Oral 1 Alpha-HydroxyvitaminD_3 (1(OH)D_3), Oral Calcitriol, Topical Calcitriol and Oral Vitamin D_3 Safely Treat Psoriasis—1930s to 2019

2.1. Sunshine and Oral Vitamin D_2 in the 1930s—Krafka

In 1936, a report documented the use of oral vitamin D_2 to clear psoriasis plaques in three psoriasis patients, two of which were long-standing cases [12].

Other reports describing variable results from the use of vitamin D in treating psoriasis were also published in that era, but unfortunately the use of oral vitamin D to treat psoriasis and other diseases soon fell out of favor due to concerns of toxicity from hypercalcemia which was observed with the supraphysiogical doses of vitamin D then used [29–31,33–39].

Published reports on the use of vitamin D in the treatment of psoriasis did not resume again until the 1980′s, when a serendipitous observation was made in a psoriasis patient who was being treated with oral 1-hydroxyvitamin D_3 (1(OH)D_3) for osteoporosis, whose skin showed remarkable clinical improvement [13]. This observation led to the resurrection of research into the use of vitamin D in treating psoriasis, which continues through today [12–28,81–109].

2.2. Oral 1 Alpha-HydroxyvitaminD_3, Oral Calcitriol and Topical Calcitriol in the 1980s—Morimoto

The impetus for this study was the chance observation made the year before by two of the investigators when they were using 1(OH)D_3 as a treatment for osteoporosis in a patient who happened to have psoriasis, and whose skin cleared completely [13]. "This observation prompted us to confirm the effect by an open-design study" [14].

In the open-design study, both oral 1(OH)D_3, and oral and topically applied calcitriol were found to be safe and effective in clearing psoriasis skin lesions [14]. A total of 40 patients were studied: (a) 17 with oral 1(OH)D_3, (b) 4 with oral calcitriol, and (c) 19 with topical calcitriol.

Morimoto and colleagues published the results of 3 other clinical trials in the 1980s with similar results [15,16], and a review of their experience in 1989 [17]. In their review, they concluded: "These data suggest that exogenous active forms of vitamin D_3 are effective for the treatment of psoriasis, and that the endogenous 1,25-dihydroxyvitamin D level also may be involved in the development of this disease".

In the 1980s several important discoveries were made regarding vitamin D and the skin leading to the realization that the skin is both the site of production of vitamin D and a target organ for its actions:

(a) Calcitriol could be synthesized in the skin
(b) Vitamin D receptors are present in the skin
(c) Vitamin D inhibited the proliferation of cultured keratinocytes and induced them to terminally differentiate [18–20,83,84,90].

2.3. Oral and Topical Calcitriol in the 1980s and 1990s—Smith, Huckins, Perez and Holick

Reports published beginning in 1987 by Holick et al. described the safe and effective use of oral calcitriol in treating psoriasis [18–23]. One report also examined the use of topical calcitriol and found it to be safe and effective as well [19].

2.4. Oral and Topical Calcitriol 12-Month Study, 1988—Smith

In 1988 [19] calcitriol was tested in three different ways:

(a) On cultures of fibroblasts and keratinocytes from patients with psoriasis
(b) Orally in 14 patients with moderate to severe psoriasis
(c) Topically in 3 patients with psoriasis.

The authors concluded their report stating: "Topical or oral use of 1,25-$(OH)_2D_3$ heralds a new mode of treatment that appears to be both safe and effective for the treatment of psoriasis". And as was shown by Morimoto, many patients with active psoriasis had baseline serum 25(OH)D_3 concentrations > 20 ng/mL and improved significantly after treatment with oral or topical vitamin D_3.

2.5. Oral Calcitriol 6-Month Study in Psoriatic Arthritis, 1990—Huckins

In 1990 ten patients with active psoriatic arthritis were treated daily with oral calcitriol for 6 months in an open label trial. The goal of the study was to determine if the treatment would be beneficial for the arthritis, and if so, was there a correlation between the improvement in the skin lesions and the improvement in the arthritis. The dose of calcitriol was titrated from 0.5 μg/day to a maximum of 2 μg/day.

"It often took 2–3 months for improvement to occur, and improvement never occurred at a dosage < 1.5 ug/day". Five patients chose to stay on the treatment at the end of the study.

2.6. Oral Calcitriol 3-Year Dose Titration Safety Study, 1996—Perez

In 1996, a three-year follow-up study of 88 patients with plaque type psoriasis involving at least 15% of their body surface who were treated with oral calcitriol was published. The doses of calcitriol used ranged from 0.5 μg/day to 4.0 μg/day. The mean calcitriol dose was 2.1 μg/day at 24 months, and 2.4 μg/day at 36 months. A total of 88% of the patients noted some degree of improvement in their disease. Complete clearing occurred in 26.5%, moderate improvement occurred in 36.2%, and slight improvement occurred in 25.3%. A total of 12% of the patients had no change in their disease severity.

The mean baseline serum 25(OH)D_3 concentration was 31.8 ± 14 ng/mL, indicating that many of the 88 patients had pre-treatment serum 25(OH)D_3 concentrations > 20 ng/mL (exact number not provided). The mean serum 25(OH)D_3 concentration was not affected by calcitriol supplementation and did not change significantly over time. The fact that serum 25(OH)D_3 concentrations did not change was as expected, as calcitriol is the active hormone form of vitamin D and is not metabolized into serum 25(OH)D_3. At the end of the opening summary paragraph, the authors concluded "Oral calcitriol is effective and safe for the treatment of psoriasis".

These 5 studies [12,14,19,21,22] detail the safe and effective use of oral vitamin D_2 (1936), oral 1(OH)D_3 (1986), oral calcitriol (1986,1988,1990,1996), and topical calcitriol (1986,1988) in treating psoriasis. There are very few reports published in the past 30 years describing the use of oral vitamin D_2 or oral vitamin D_3 (the precursors to serum 25(OH)D_3 and calcitriol) in treating psoriasis. Three relatively recent reports [25,26,28] that do describe the use of oral vitamin D_3 (2012, 2013) and oral vitamin D_2 (2019) in successfully controlling plaque psoriasis will be reviewed next. These reports show similar clinical benefits and safety as the previous reports showed, even though much higher post-treatment serum 25(OH)D_3 concentrations were observed as would be expected, as both vitamin D_2 and vitamin D_3 are metabolized into 25(OH)D_3 prior to forming calcitriol.

2.7. Serum 25(OH)D_3 Concentrations in 2 Patients with Plaque Psoriasis after 5 Months' Oral Vitamin D_3 in 2012—McCullough

In 2012, one of the authors (PM) presented a poster describing the results of using oral vitamin D_3 to successfully control chronic plaque psoriasis in 2 patients at the 15th Workshop on Vitamin D in Houston, Texas [25]. The patients were provided with over the counter 5000 IU vitamin D_3 gel caps and were instructed to take 40,000 IU/day for 2 weeks, and then reduce the dose to 10,000 IU/day.

No adverse reactions were noted, and both patients reported marked clinical improvement in their skin and in their quality of life. Both patients later experienced recurrence of the plaques within a month after stopping oral vitamin D_3 intake, and both were able to achieve clear skin again after resuming the oral vitamin D_3. The recurrence of psoriasis with cessation of oral vitamin D intake and clearing again with resumption of oral vitamin D intake was also previously reported by Smith et al. in 1988 [19].

2.8. Serum 25(OH)D_3 Concentrations after 6 Months of Taking 35,000 IU/Day of Oral Vitamin D_3 in 25 Patients with Either Plaque Psoriasis or Vitiligo, 2013—Finamor

In 2013, results from a 6-month follow-up study using 35,000 IU/day of oral vitamin D_3 to treat 9 patients with psoriasis and 16 patients with vitiligo were published [26]. The PASI score significantly improved in all nine patients with psoriasis. Fourteen of 16 patients with vitiligo had 25–75% repigmentation. A significant negative correlation was observed between the PASI scores and serum 25(OH)D_3 concentrations.

In the psoriasis group, mean serum 25(OH)D_3 concentrations increased from 14.9 ± 7.4 ng/mL at baseline to 106.3 ± 31.9 ng/mL at 6 months. In the vitiligo group, mean serum 25(OH)D_3 concentrations increased from 18.4 ± 8.9 ng/mL at baseline to 132.5 ± 37.0 ng/mL at 6 months. The authors noted that "Laboratory or clinical signs of toxicity (hypercalcemia, hypercalciuria or kidney dysfunction) were not observed in any of the 25 participants, including a patient with vitiligo who reached a serum concentration of 25OHD_3 of 202 ng/mL".

The authors' main conclusion was "In summary, the present study suggests that, at least for patients with autoimmune disorders like vitiligo and psoriasis, a daily dose of 35,000 IU of vitamin D_3 is a safe and effective therapeutic approach for reducing disease activity". The yearly cost of treatment with oral vitamin D_3 at a dose of 35,000 IU/day is around USD 98 per year, based on currently available over the counter pricing at USD 14/bottle for a USP verified bottle of 400 gel caps with 5000 IU/cap.

2.9. Serum 25(OH)D_2 Concentrations in a Patient with Plaque Psoriasis after 42 Months of Taking 50,000 IU/Day of Oral Vitamin D_2, 2019—McCullough

In 2019, a paper describing results from supplementing long-term hospitalized patients with 5000 IU/day to 50,000 IU/day of vitamin D_3 for over 7 years was published by one of the authors (PM), who made it a standard of care beginning in April 2009 to offer all long-term hospitalized patients under his care supplementation with oral vitamin D_3 in doses of either 5000 IU/day or 10,000 IU/day [28]. This was done for several reasons:

(a) patients receive very little sunshine in the hospital
(b) there is very little vitamin D in the food they eat
(c) serum 25-hydroxyvitamin D (25(OH)D) production in the skin from UVB phototherapy was first estimated in the 1970s to range from 10,000 to 25,000 IU/day [39,53,56,110–113]
(d) vitamin D, sunshine and UVB phototherapy were shown to be effective treatments for several diseases in the 1930s and 1940s, and again beginning in the 1980s as discussed earlier [12–39,45–54]. In addition, several patients received daily doses of vitamin D_2 or vitamin D_3 ranging from 20,000 to 50,000 IU/day based on specific disease concerns.

There have been over 6000 admissions to SBH since 2011. A recent sampling of patients not on vitamin D_3 (n = 777; combination of new admissions and long-term patients who declined supplementation) showed a mean serum 25(OH)D_3 concentration of 27.1 ng/mL (range 4.9 to 74.8 ng/mL). Patients on vitamin D_3 long enough to develop serum 25(OH)D_3 concentrations > 74.4 ng/mL (n = 418) had a mean serum 25(OH)D_3 concentration of 118.9 ng/mL (range 74.4 to 384.8 ng/mL). The highest serum 25(OH)D_3 concentrations observed on 10,000 IU/day was 202 ng/mL.

The mean and range of serum calcium concentrations were almost identical in the two groups, despite the wide disparity in serum 25(OH)D_3 concentrations. The average serum calcium concentrations were 9.5 mg/dL (no D_3) vs. 9.6 mg/dL (D_3), with ranges of 8.4 mg/dL to 10.7 mg/dL (no D_3) vs. 8.6 mg/dL to 10.7 mg/dL (D_3), after excluding patients with other causes of hypercalcemia.

There were no adverse events observed in any patients taking 5000 to 10,000 IU/day for several years, in spite of serum 25(OH)D_3 concentrations reaching as high as 202 ng/mL. In addition, several patients, as well one of the authors, having taken daily oral doses of vitamin D ranging from 20,000 to 60,000 IU/day for 2 to 6 years, achieved serum 25(OH)D_3 concentrations as high as 384 ng/mL without any complications [28,114].

In our 2019 report we included a case report of a patient admitted with poorly controlled plaque psoriasis whose skin improved dramatically within a few months of starting 50,000 IU/day of oral vitamin D_2 and has remained clear for many months. His serum calcium and iPTH concentrations have been checked numerous times and have remained normal. No adverse events related to vitamin D supplementation have been observed. His quality of life has improved significantly. The yearly cost for the vitamin D_2 used was USD 36.50, as we are able to obtain 50,000 IU capsules of vitamin D_2, with 100 capsules/bottle for USD 10 a bottle.

Table 1 shows the study year, type of vitamin D, route, dose used, number of patients treated, study duration and number of patients showing significant clinical improvement following treatment in the clinical trials and case reports reviewed.

Table 1. Study year, type of vitamin D, route, dose, duration of treatment, number of patients treated, and number showing significant improvement in the oral vitamin D clinical trials and case reports reviewed.

Study Year	Type of Vit D	Route	Dose/Day	*N*	100% Improv	Signif Improv	Study Duration
1936	D2	oral	NA	3	2	3	6 mos
1986	1(OH)D3	oral	1 μg	17	5	13	6 mos
	calcitriol	oral	0.5 μg	4	0	1	6 mos
	calcitriol	topical	0.5 μg/gm	19	3	16	6 mos
1988	calcitriol	oral	0.5 to 2 μg	14	3	10	12 mos
	calcitriol	topical	3 μg/gm	3	3	3	6 weeks
1990	calcitriol	oral	0.5 to 2 μg	9	0	7	6 mos+
1996	calcitriol	oral	0.5 to 4 μg	85	20	47	36 mos
2012	D3	oral	40,000 IU	2	1	2	5 mos
2013	D3	oral	35,000 IU	9	1	9	6 mos
2019	D2	oral	50,000 IU	1	1	1	2+ years
			Total	166	39	112	

Note: NA = not available, *N* = number of patients treated, Signif Improv = significant improvement reported.

As shown in the table, all four forms of oral vitamin D and topical calcitriol were effective in treating psoriasis. No serious safety concerns were reported in any of the clinical trials or case reports. See the Supplementary Materials for more information on safety monitoring in each clinical trial and case report. This will also be reviewed in more detail in Section 4.

Table 2 summarizes the baseline mean serum 25(OH)D concentrations, range at baseline if indicated, number (*N*) greater than 20 ng/mL at baseline, number (*N*) greater than 50 ng/mL at baseline, and peak serum 25(OH)D concentrations post-treatment in the oral vitamin D clinical trials and case reports reviewed.

As seen in the table, numerous pre-treatment serum 25(OH)D concentrations were above 20 ng/mL, ranging as high as high as 67 ng/mL (where data was provided), yet the patients psoriasis improved following treatment with the four forms of vitamin D used. No significant change over time was noted in serum 25(OH)D concentrations in patients treated with 1(OH)D and calcitriol, as neither compound is metabolized into 25(OH)D.

In contrast, significant increases in serum 25(OH)D concentrations were noted in patients following daily treatment with 35,000 units of vitamin D_3 for 6 months and 50,000 units of vitamin D_2, for over 2 years, with peak serum 25(OH)D concentrations of 202 ng/mL and 308 ng/mL reported without complication.

In the next section we will review four clinical phototherapy trials in patients with plaque psoriasis which show results very similar to and consistent with those just reviewed in the nine oral vitamin D plaque psoriasis clinical trials and case reports.

Table 2. Baseline mean serum 25(OH)D concentrations, range at baseline, number greater than 20 ng/mL at baseline, number greater than 50 ng/mL at baseline, and peak serum 25(OH)D concentrations post-treatment in the vitamin D clinical trials and case reports reviewed.

			Baseline	Baseline	Baseline	Baseline	Post-Tx
Study	**Type of**		**25(OH)D**	**25(OH)D**	**25(OH)D**	**25(OH)D**	**25(OH)D**
Year	**Vit D**	***N***	**Mean**	**Range**	***N* > 20**	***N* > 50**	**Peak ng/mL**
1936	D2	3	NA	NA	NA	NA	NA
1986	1(OH)D3	17	23 ± 12	NR	sig #	NR	NR
	calcitriol	4	17 ± 5	NR	sig #	NR	NR
	calcitriol	19	20 ± 10	NR	sig #	NR	NR
1988	calcitriol	14	32.8	8 to 67	9	3	NR
	calcitriol	3	48.5	30 to 67	2	1	NR
1990	calcitriol	9	NR	NR	NR	NR	NR
1996	calcitriol	85	32 ± 18	NR	sig #	sig #	NR
2012	D3	2	26	23 to 29	2	0	
2013	D3	9	15 ± 7	NR	NR	NR	202
2019	D2	1	70	NA	1	1	308
		166					

Note: NA = not available; NR = not reported; 25(OH)D = ng/mL, *N* > is number of measurements above 20 ng/mL or 50 ng/mL, sig # = significant number based on mean ± standard deviation (actual number not reported).

3. Changes in Serum 25(OH)D_3 Concentrations in Psoriasis Patients Treated with UVB Phototherapy and Sunshine—1996, 2009, and 2010

The use of phototherapy to treat disease dates back to the 1890s when Finsen developed a method to cure TB with refracted light rays from an electric arc lamp [28,39–44,48–50,52,54]. Several recent reviews give an excellent overview of the evolution of the use of phototherapy for treating human disease, including psoriasis [40–44]. The first documented use of UVB phototherapy in treating psoriasis dates back to Gockerman in the 1920s [41–43]. UVB phototherapy is now a well-established, relatively safe and cost-effective option for treating psoriasis [40–44,61–64,115–131].

In this section, we will briefly review four UVB phototherapy psoriasis treatment studies that provided baseline and post-treatment serum 25(OH)D_3 concentrations [61–64]. A more detailed review of each study is provided in the Supplementary Materials.

Significant increases in 25(OH)D_3 from baseline were noted in the UVB phototherapy studies, with several patients obtaining serum 25(OH)D_3 concentrations > 100 ng/mL without any adverse effects while observing significant improvement in their skin. As noted in the oral vitamin D studies, baseline serum 25(OH)D_3 concentrations > 20 ng/mL were also commonly observed in these reports and increased after treatment. One study also included a group of patients treated with sunshine, in which the observed changes in serum 25(OH)D_3 concentrations were significantly lower than those after treatment with UVB therapy [64].

3.1. Serum 25(OH)D_3 Concentrations in Psoriasis Patients after 8 Weeks of UVB Phototherapy, 1996—Prystowsky

In 1996 changes in serum 25(OH)D_3 concentrations were assessed in 15 patients with plaque-type psoriasis treated with UVB phototherapy [61]. Seven of these patients were treated with oral calcitriol (0.5 to 2 ug/day), and eight with placebo. Serum concentrations of 25(OH)D_3 and calcitriol were measured before, during and after treatment in 13 patients. Serum chemistry and hematology laboratory evaluations were also done.

All patients treated with phototherapy showed significant increases in their serum 25(OH)D_3 concentrations. Significant improvement was noted in disease severity in all patients in both groups, with no significant difference between groups.

Post-treatment 10 of 13 (77%) had a serum 25(OH)D_3 concentrations > 50 ng/mL, and 3 patients (23%) had serum 25(OH)D_3 concentrations > 100 ng/mL, two in the placebo group and one in the calcitriol group. Their serum 25(OH)D_3 concentrations ranged from 123 ng/mL to 159 ng/mL.

The authors noted that "because phototherapy for psoriatic plaques produces changes in keratinocytes similar to those described for 1,25-(OH)2D3 (i.e., slowed proliferation and enhanced differentiation), this raises the possibility that one of the mechanisms of action of UVB may be through enhanced vitamin D metabolism".

3.2. Serum 25(OH)D_3 Concentrations in Psoriasis Patients after 1–4 Months of NB-UVB Phototherapy, 2010—Ryan

In a 2010 report, serum 25(OH)D_3, ionized calcium, intact parathyroid hormone (iPTH) and alkaline phosphatase concentrations were assessed in 30 patients with plaque psoriasis before and after treatment with narrowband (NB) UVB phototherapy [62]. Comparison was made to a matched untreated control group of 30 patients with plaque psoriasis. Patients in the treatment group received NB-UVB phototherapy 2 to 3 times a week. Treatment continued until essentially complete clearing of the psoriasis occurred, which took between 25 to 118 days (median 51 days).

In the NB-UVB group baseline serum 25(OH)D_3 concentrations ranged from 9 ng/mL to 46 ng/mL (median 23 ng/mL). Post-NB-UVB phototherapy, after complete skin clearing, the range of serum 25(OH)D_3 concentrations increased to 32 to 112 ng/mL (median 59 ng/mL).

3.3. Serum 25(OH)D_3 Concentrations in Psoriasis Patients after 8–12 Weeks of NB-UVB and BB-UVB Phototherapy, 2009—Osmancevic

In a 2009 report, serum 25(OH)D_3, calcitriol, iPTH, calcium and creatinine concentrations were measured in 68 patients with plaque psoriasis before and after treatment with either broadband UVB (BB-UVB, n = 26) or NB-UVB (n = 42) phototherapy [63]. All patients were treated with whole body exposure for 8 to 12 weeks, with the doses of UVB adjusted based on the skin phenotype and the erythemal response noted during treatment.

The purpose of the study was to determine if there was a difference in vitamin D production with NB-UVB versus BB-UVB phototherapy. The use of oral or topical vitamin D, vitamin D analogues, or any biologics was prohibited. Patients were treated either in the spring (n = 39) or in the winter (n = 29).

There was no significant difference in the total number of treatments needed, but the treatment time was four times longer in the NB-UVB group compared to the BB-UVB group. Psoriasis plaques improved in all patients in both groups.

Serum 25(OH)D_3 concentrations increased in both groups, with a more pronounced increase noted in the BB-UVB versus NB-UVB group. In the BB-UVB group, the baseline mean serum 25(OH)D_3 concentration was 37.9 $\pm$ 16.9 ng/mL and increased to 69.4 $\pm$ 19.7 ng/mL after treatment. In the NB-UVB group, the baseline mean serum 25(OH)D_3 concentration was 34.8 $\pm$ 11.9 ng/mL and increased to 55.3 $\pm$ 17.6 ng/mL after phototherapy.

A line plot of individual serum 25(OH)D_3 concentrations before and after treatment for the two groups showed that at least 3 patients in the BB-UVB group had serum 25(OH)D_3 concentrations > 100 ng/mL post-treatment, but the actual values were not indicated.

3.4. Serum 25(OH)D_3 Concentrations in Psoriasis Patients after 15 Days of Sunshine or 8–12 Weeks of NB-UVB or BB-UVB Phototherapy, 2010—Osmancevic

In a 2010 report, serum 25(OH)D_3, calcitriol, PTH, calcium and creatinine concentrations in psoriasis patients were measured before and after treatment with sunshine, NB-UVB and BB-UVB phototherapy [64]. This report was a discussion of data aggregated from 3 studies, including data in the previously discussed report [63]. The two additional studies included a group of 24 post-menopausal women with psoriasis who were treated with whole body BB-UVB phototherapy 2 to 3 times a week for 8 to 12 weeks, and a group

20 psoriasis patients who were treated with whole body heliotherapy (sunshine) daily for 2 weeks. The authors stated that they had 2 main aims:

(a) To increase the knowledge about the effects of phototherapy on vitamin D production during the treatment of psoriasis,
(b) To see if there were differences between the effect of BB-UVB, NB-UVB and heliotherapy on vitamin D synthesis in psoriasis patients.

A similar efficacy was reported with each treatment. An improvement in the PASI score of about 75% was observed in each group. However, the group treated with sunshine required only two weeks to achieve the same clinical improvement as seen after 2 to 3 months of UVB phototherapy.

Serum 25(OH)D_3 concentrations increased in each group. The range of serum 25(OH)D_3 concentrations after treatment with sunshine was much lower than in the UVB groups. This may be due to the shorter duration of treatment, as well as the fact that the patients used sunscreen on areas of their body susceptible to sunburn.

Table 3 shows the study year, type of phototherapy used, the number of patients treated, study duration, and number of patients showing significant improvement following treatment in each clinical trial reviewed.

Table 3. Study year, type of phototherapy of used in each study, number of patients treated, study duration and number of patients showing significant improvement following treatment.

Study			100%	Signif	Study
Year	**Group**	***N***	**Improv**	**Improv**	**Duration**
1996	UVB + Placebo	7	NR	7	8 weeks
	UVB + Calcitirol	6	NR	6	8 weeks
2010	UVB	29	29	29	4 mos
	No UVB	29	0	0	4 mos
2009	BB-UVB	26	NR	26	8 to 12 weeks
	NB-UVB	42	NR	42	8 to 12 weeks
2010	BB-UVB	24	NR	24	8 to 12 weeks
	Sunshine	20	NR	20	2 weeks
	Total	183	29	154	

Note: *N* = number of patients treated, NR = not reported, Signif Improv = significant improvement reported.

As shown in the table, all three forms of phototherapy were effective in treating plaque psoriasis. No serious safety concerns were reported in any of the clinical trials. See the Supplementary Materials for more information on safety monitoring in each clinical trial. This will also be reviewed in more detail in Section 4.

Table 4 summarizes the baseline and post-treatment mean serum 25(OH)D concentrations, and baseline and post-treatment range at of serum 25(OH)D concentrations in the phototherapy clinical studies reviewed.

As seen in the table, numerous pre-treatment serum 25(OH)D concentrations were above 20 ng/mL, ranging to as high as 88 ng/mL, yet the patients' psoriasis improved following treatment with the three forms of phototherapy used. This is consistent with the data reported in the oral vitamin D clinical trials and case reports reviewed in Section 2. The total number of baseline serum 25(OH)D concentrations greater than 20 ng/mL and 50 ng/mL in each clinical trial are reported in Table 5.

Table 4. Study year, type of phototherapy of used, number of patients treated, baseline and post treatment mean serum 25(OH)D concentrations, and baseline and posttreatment range at of serum 25(OH)D concentrations in the phototherapy clinical trials reviewed.

			Baseline	Post-Tx	Baseline	Post-Tx
Study			**25(OH)D**	**25(OH)D**	**25(OH)D**	**25(OH)D**
Year	**Group**	***N***	**Mean**	**Mean**	**Range ****	**Range ****
1996	UVB + Placebo	7	37.9	96.1	20 to 80	45 to 159
	UVB + Calcitirol	6	27.3	67.1	15 to 40	45 to 123
2010	UVB	29	23 *	51 *	9 to 46	32 to 112
	No UVB	29	12 *	13 *	7 to 42	7 to 33
2009	BB-UVB	26	38 ± 17	69 ± 20	17 to 82	45 to 118
	NB-UVB	42	35 ± 12	55 ± 18	15 to 73	28 to 98
2010	BB-UVB	24	37 ± 17	60 ± 19	18 to 88	25 to 90
	Sunshine	20	23 ± 6	42 ± 6	18 to 42	30 to 60
	Total	183				

Note: *N* = number of patients, * = median, ** = range estimated from figure in manuscript.

Table 5. Distribution of serum 25(OH)D concentrations greater than 20 ng/mL, 50 ng/mL and 100 ng/mL at baseline and post-treatment in each phototherapy clinical trial.

			Baseline	Baseline	Post-Tx	Post-Tx	Post-Tx
Study			**25(OH)D**	**25(OH)D**	**25(OH)D**	**25(OH)D**	**25(OH)D**
Year	**Group**	***N***	***N* > 20 ng/mL**	***N* > 50 ng/mL**	***N* > 20 ng/mL**	***N* > 50 ng/mL**	***N* > 100 ng/mL**
1996	UVB + Placebo	7	7	2	7	6	2
	UVB + Calcitirol	6	4	0	6	4	1
2010	UVB	29	19	0	29	15	1+
	No UVB	29	NR	0	7	0	0
2009	BB-UVB	26	65	5	68	48	3
	NB-UVB	42					
2010	BB-UVB	24	22	3	24	17	0
	Sunshine	20	17	0	20	4	0
	Total	183	134	10	161	94	6

Note: *N* = number of patients.

Significant increases in serum 25(OH)D concentrations post-treatment were also reported in each clinical trial, with many greater than 50 ng/mL, and several greater than 100 ng/mL. Peak serum 25(OH)D concentrations of 90, 98, 112, 118, 123, and 159 ng/mL were reported following treatment with UVB phototherapy, with a peak of 60 ng/mL reported following treatment with sunshine. This data is also shown in Table 5. The mean and range of serum 25(OH)D concentrations appear to be lower pre and post-treatment in patients treated with sunshine compared to those treated with UVB phototherapy. Reasons for this are discussed in the Supplementary Materials.

Table 5 shows the distribution of serum 25(OH)D concentrations greater than 20 ng/mL, 50 ng/mL and 100 ng/mL at baseline and post-treatment in each phototherapy clinical trial.

As seen in the table, 87% (134/154) of treated patients with active plaque psoriasis had pre-treatment serum 25(OH)D concentrations greater than 20 ng/mL, 10 of whom were also greater than 50 ng/mL. Following improvement of their psoriasis after treatment with UVB phototherapy or sunshine, 100% had serum 25(OH)D concentrations greater than 20 ng/mL, 61% (94/154) were greater than 50 ng/mL, with at least 6 greater than 100 ng/mL.

4. Summary and Discussion of Key Findings in the Reviewed Reports

The following summarizes the main points highlighted in this paper thus far:

(1) Four different oral forms of vitamin D are safe and effective treatments for plaque psoriasis
(2) Normal serum 25(OH)D concentrations (>20 ng/mL) were common pretreatment but insufficient to improve psoriatic lesions
(3) High serum 25(OH)D concentrations (>100 ng/mL) were often reported with safe control of psoriasis
(4) Changes in serum 25(OH)D concentrations after treatment vary significantly with the treatment used
(5) A therapeutic dose response of psoriasis to vitamin D appears to be present
(6) Calcitriol formation is the common endpoint after treatment with vitamin D, sunshine and UVB phototherapy
(7) Psoriasis can recur with cessation of treatment with vitamin D, sunshine or UVB phototherapy
(8) Psoriasis can improve again with resumption of treatment with vitamin D, sunshine or UVB phototherapy
(9) Post treatment serum 25(OH)D concentrations are higher after UVB phototherapy compared to sunshine
(10) A paucity of adverse reactions was observed with vitamin D supplementation in the reviewed studies
(11) Clinical efficacy and safety of oral and topical vitamin D treatments are comparable to UVB phototherapy and sunshine treatments
(12) All authors reviewed stated unequivocal support for the safety and efficacy of vitamin D in treating psoriasis
(13) Estimates of vitamin D production in the 1970s are significantly lower than doses used clinically in treating diseases in the 1930s and 1940s— but significantly higher than the doses recommended for use today.

4.1. Four Different Oral Forms of Vitamin D Are Safe and Effective Treatments for Plaque Psoriasis

Since 1985 four different oral forms of vitamin D, specifically vitamin D_2, vitamin D_3, 1-hydroxyvitaminD_3 (1(OH)D_3), and 1,25-dihydroxyvitaminD_3 (calcitriol) and several topical formulations of vitamin D including calcitriol [13–28,81–109] have been reported safe and effective treatments for psoriasis—as has UVB phototherapy and sunshine [40–44,61–64,115–131]. This is consistent with findings first reported by Krafka in 1936 [12].

4.2. Normal Serum 25(OH)D Concentrations (>20 ng/mL) Are Often Insufficient for Disease Control in Psoriasis Patients

The serum 25(OH)D concentrations reported in 10 of the 12 clinical trials reviewed (no data in 2 reports) consistently show a high percentage of pre-treatment serum 25(OH)D concentrations > 20 ng/mL, ranging up to 88 ng/mL, in patients with active plaque psoriasis [14,19,22,25,26,28,61–64]. These pre-treatment concentrations are within what is currently considered the normal range of serum 25(OH)D concentrations as defined by the IOM (20 to 50 ng/mL) [55] and Endocrine Society (30 to 100 ng/mL) [56] in 2011. However, the significant clinical improvement observed in many of these patients after treatment with the four different forms of oral vitamin D is evidence that the range of serum 25(OH)D concentrations currently classified as normal are not sufficient for disease control in patients suffering from active plaque psoriasis.

4.3. High Serum 25(OH)D Concentrations (>100 ng/mL) Were often Reported with Safe Control of Psoriasis

Post-treatment serum 25(OH)D concentrations > 100 ng/mL were observed in plaque psoriasis patients treated with UVB phototherapy [61–63], oral vitamin D_2 at a dose of 50,000 IU/day for over 2 years [28], and oral vitamin D_3 at a dose of 35,000 IU/day for

6 months [26], while none were observed in patients treated with sunshine [64], oral or topical calcitriol [14,19,22], or oral 1(OH)D_3 [14]. Serum 25(OH)D concentrations > 100 ng/mL are currently considered to be above the normal range of serum 25(OH)D concentrations by the Endocrine Society [56], while serum 25(OH)D concentrations > 50 ng/mL are considered high by the IOM [55]. However, no significant clinical toxicity was observed in any plaque psoriasis patient who achieved these serum 25(OH)D concentrations, as indicated by the significant clinical improvement observed in their skin after each treatment without the observation of any adverse events.

4.4. Changes in Serum 25(OH)D Concentrations after Treatment Vary Significantly with the Treatment Used

There were no changes in serum 25(OH)D concentrations in patients treated with either oral 1(OH)D_3 [14], oral calcitriol [14,19,22], or topical calcitriol [14,19], as neither 1(OH)D_3 or calcitriol is metabolized into 25(OH)D_3. There were significant increases in serum 25(OH)D concentrations in patients treated with oral vitamin D_2, [28], oral vitamin D_3, [26], UVB phototherapy [61–64] and sunshine [64], as described in Section 4.3.

The highest serum 25(OH)D concentration observed after 6 months of 35,000 IU/day of vitamin D_3 was 202 ng/mL [26]. The highest serum 25(OH)D concentration observed after more than 2 years on 50,000 IU/day of vitamin D_2 was 308 ng/mL [28]. The highest post-treatment serum 25(OH)D concentration observed after 8 weeks of UVB phototherapy was 159 ng/mL reported in 1996 [61]. Current definitions of normal serum vitamin D concentrations need to be reconsidered in light of this data.

4.5. A Therapeutic Dose Response to Vitamin D Appears to Be Present

A dose response was noted by Huckins et al. in 1990 in the treatment of psoriatic arthritis with calcitriol in doses ranging from 0.5 µg to 2 µg/day, as improvement reportedly never occurred at a dosage < 1.5 ug/day [21]. Similarly, when calcitriol was titrated from 0.5 to 4 µg/day in a 3 year study of plaque psoriasis by Perez et al. in 1996, mean calcitriol doses of 2.1 µg/day at 24 months, and 2.4 µg/day at 36 months were obtained, suggesting a dose response was also observed, although this was not stated by the authors [22]. This needs further clarification for each of the four forms of oral vitamin D shown to be effective treatments for psoriasis in this review.

4.6. Calcitirol Formation Is the Common Endpoint after Treatment with Vitamin D, UVB Phototherapy and Sunshine

Vitamin D_3, vitamin D_2, and 1(OH)D_3 are all metabolized into calcitriol, the active hormone form of vitamin D. Sunshine and UVB phototherapy cause the formation of vitamin D_3 in the skin from the precursor molecule 7-dehydrocholesterol, which is then metabolized to 25(OH)D and subsequently into calcitriol. The formation of calcitriol appears to be the final common pathway for these six treatments. The primary function of calcitriol is regulation of gene transcription. Calcitriol regulates several thousand genes located in many different cells and tissues throughout the body [132–138], including keratinocytes [19,83,84,90,103–106,109,131] and cells of the innate and adaptive immune system [139–207]. See Figure 1 for an illustration of this process.

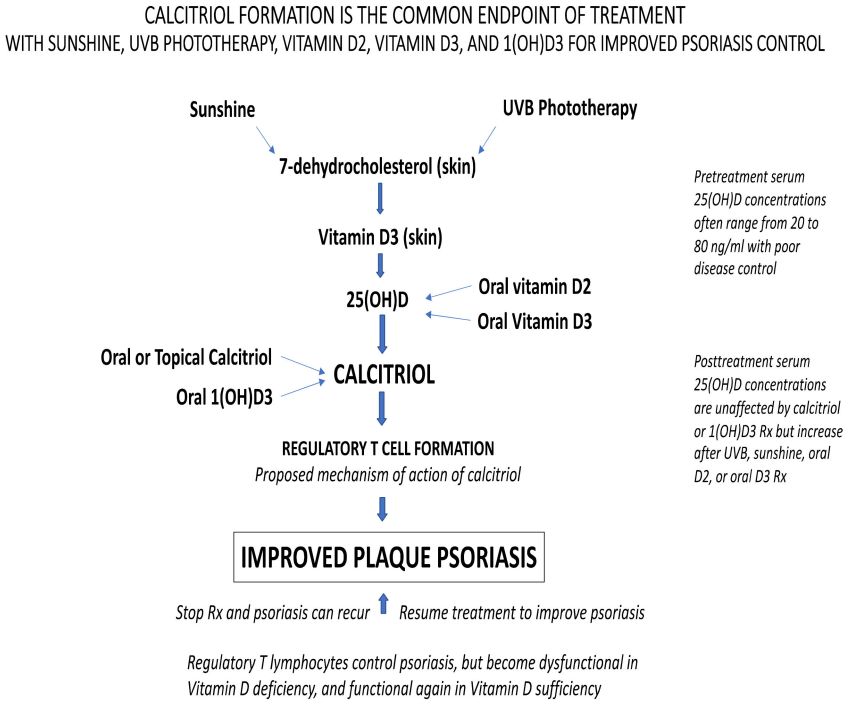

Figure 1. The metabolic pathway of calcitriol production from 7-dehydrocholesterol in the skin after interaction with UVB radiation present in sunshine or UVB phototherapy.

4.7. Psoriasis Can Recur with Cessation of Vitamin D or UVB Phototherapy

Psoriasis was observed to recur with cessation of oral calcitriol by Smith et al. in 1988 [19] and with cessation oral vitamin D_3 by McCullough et al. in 2012 [25]. Krafka noted in 1936 that psoriasis control improved with sunshine and worsened in the abcense of sunshine which was the motivation to use vitamin in the treatment of psoriasis [12]. The National Psoriasis Foundation and the American Academy of Dermatology have also reported that psoriasis will often recur after cessation of UVB phototherapy [8,119].

4.8. Psoriasis Can Improve Again with Resumption of Treatment with Vitamin D or UVB Phototherapy

Psoriasis was also noted to improve again after resuming oral calcitriol by Smith et al. in 1988 [19] and oral vitamin D_3 by McCullough et al. in 2012 [25]. Similarly, maintenance phototherapy is recommended by the National Psoriasis Foundation and the American Academy of Dermatology due to psoriasis plaques commonly reoccurring after cessation of treatment with UVB phototherapy [8,119].

The exact gene products regulated by calcitriol that cause the improvement in plaque psoriasis are currently unknown but may be related to the positive effect that topical vitamin D [153–158], oral vitamin D [159–207], sunshine [208–210] and UVB phototherapy [211–233] have been shown to have on the formation and functional status of regulatory T lymphocytes. Tregs have been shown to play an important role in suppression of autoimmune diseases [234–254]. Several mechanisms of action by which Tregs control psoriasis were proposed in 2013 [246].

Thus, psoriasis appears to be controlled but not cured by vitamin D and UVB phototherapy and requires maintenance therapy to maintain disease control. This is consistent with the observed dependency of regulatory T lymphocytes on vitamin D, sunshine and UVB phototherapy to maintain their functional status. Psoriasis appears to behave like an autosomal recessive disease that becomes dominant in a state of vitamin D deficiency when Tregs are dysfunctional, and recessive in a state of vitamin D sufficiency when Treg functional status is restored.

4.9. Post Treatment Serum 25(OH)D Concentrations Are Higher after UVB Phototherapy Compared to Sunshine

Treatment with UVB phototherapy consistently resulted in several patients achieving serum 25(OH)D concentrations > 100 ng/mL in the reports reviewed [61–63]. Treatment with sunshine resulted in smaller increases in serum 25(OH)D concentrations than observed with UVB or NB phototherapy, with none > 100 ng/mL, although several were > 50 ng/mL post treatment [64]. These results are consistent with reports of serum 25(OH)D concentrations observed in healthy individuals after prolonged sun exposure, where serum 25(OH)D concentrations > 100 ng/mL were also not observed, but serum concentrations > 50 ng/mL were commonly observed [255–257]. Three reports will be discussed.

In 1971 serum 25(OH)D concentrations in eight lifeguards measured four weeks after working at an outdoor pool were included in a report by Haddad and Chyu describing the first successful assay for measuring serum 25(OH)D concentrations [255]. The mean serum 25(OH)D concentration after four weeks of sun exposure was 64.4 ± 8.7 ng/mL, and all eight were >50 ng/mL (range 53 to 79 ng/mL).

In 2007, ninety-three individuals living in Hawaii with variable daily sun exposure ranging from total body exposure in surfers to only head, arms and hands in skateboarders, had serum 25(OH)D concentrations ranging from 11 to 71 ng/mL, of which seven (7.5%) were >50ng/mL [256].

In 2012, sixty traditionally living healthy dark-skinned individuals in East Africa were evaluated for serum 25(OH)D concentrations [257]. The mean serum 25(OH)D concentration was 46 ng/mL (range 23.2 to 68.4 ng/mL), with 13.3% between 20 to 32 ng/mL, 15% between 32.4 to 40 ng/mL, 28.3% between 40.4 to 48 ng/mL, 33.3% between 48.4 to 60 ng/mL, and 10% > 60.4 ng/mL, for a total of approximately 43% with serum concentrations > 50 ng/mL.

4.10. A Paucity of Adverse Reactions Was Observed in the Reviewed Studies

Very few adverse events were reported in the patients treated with vitamin D, sunshine or UVB phototherapy reviewed in this report. No cases of hypercalcemia, nephrolithiasis, or renal dysfunction were reported in any of the vitamin D studies reviewed. Six total cases of hypercalciuria were reported in three reports, four with calcitriol [19,21] and two with UVB phototherapy [61]. No cases of hypercalciuria were reported after 6 months of treatment in 25 patients with 35,000 IU/day of vitamin D_3 [26], and a very mild elevation was noted in an individual after 2 years of treatment with 50,000 IU/day of vitamin D_2 [28].

In 1988 Smith reported two cases of hypercalciuria with oral calcitriol [19]. Both patients withdrew from the study. There were no reports of renal insufficiency, nephrolithiasis or any other adverse events.

In 1996 Prystowsky reported hypercalcemia in 2 patients in the UVB phototherapy and calcitriol group, but neither had hypercalciuria [61]. The hypercalcemia resolved with reduction in their intake of calcitriol. Three patients in both the calcitriol and placebo groups developed hypercalciuria (values not provided). There were no reports of renal insufficiency, nephrolithiasis or any other adverse events related to the hypercalcemia or hypercalciuria reported.

In 1986 Morimoto did not report any adverse events related to treatment with vitamin D [14]. The authors reported "None of the patients in the three groups suffered from any topical or systemic complications or symptoms during these observation periods. Blood and urine analysis showed values within normal limits at all times. Hepatic and renal function, evaluated by measuring the serum levels of glutamic oxaloacetic transferase, glutamic pyruvic transferase, urea nitrogen and creatinine, were within normal ranges and did not change significantly during the observation periods". Morimoto did report a significant difference between baseline and 3-month calcium levels was noted in the 1(OH)D_3 and oral calcitriol groups, and for calcitriol in the 1-OHD_3 group, but all values were within the normal range.

In 1990 Huckins reported two patients were unable to receive therapeutic doses due to hypercalciuria but did not report any other adverse events related to treatment with oral calcitriol [21].

In 1996 Perez did not report any adverse events related to treatment with oral calcitriol [22]. Perez did report that the mean 24-h urine calcium concentrations (mg/24 h), calcium/creatinine ratios, and the serum calcium levels were significantly increased compared to baseline at 6, 12, 24 and 36 months, but remained within normal limits.

In 2009 and 2010 Osmancevic did not report any adverse events related to treatment with UVB phototherapy or sunshine [63,64]. In 2009 Osmancevic reported serum concentrations of calcium, creatinine, and 1,25-dihydroxyvitamin D3 were unchanged after UVB phototherapy, while iPTH concentrations decreased in the BB group.

In 2010 Ryan did not report any adverse events related to treatment with UVB phototherapy [62].

In 2012 and 2019 McCullough did not report any adverse events related to treatment with oral vitamin D_3 [25,28].

In 2013 Finamor did not report any adverse events related to treatment with oral vitamin D_3 [26]. The authors reported "Laboratory or clinical signs of toxicity (hypercalcemia, hypercalciuria or kidney dysfunction) were not observed in any of the 25 participants, including a patient with vitiligo who reached a serum concentration of $25OHD_3$ of 202 ng/mL.

The evidence in these studies show that the clinical efficacy and safety of oral and topical vitamin D are comparable to the clinical efficacy and safety of UVB phototherapy and sunshine in the treatment of plaque psoriasis. Several reports have addressed the potential for photo-carcinogenesis as an adverse effect of UVB phototherapy and have not found this to be a risk [115,119]. Several risks associated with UVB phototherapy identified by the American Academy of Dermatology include photoaging, a possible risk of genital tumors in men treated without genital shielding, and UVB-related cataract formation, which can be mitigated by the use of eye goggles, in addition to acute reactions such as erythema, itching, burning and stinging [119].

4.11. Sunshine and Topical Vitamin D Appear to Work More Quickly Than UVB Phototherapy and Oral Vitamin D

In comparing topical vs oral vitamin D, both Morimoto et al. in 1986 [14] and Smith et al. in 1988 [19] found topical calcitriol resulted in significant clearing of psoriasis plaques within a few weeks, versus a few months with oral 1(OH)D or oral calcitriol. Sunshine was also shown to clear psoriasis plaques within a few weeks compared to a few months for UVB/NB phototherapy by Osmancevic et al. in 2010 [64].

4.12. Authors Reported Views Support the Safety and Efficacy of Vitamin D for the Treatment of Psoriasis

Krafka 1936 [12]: "If the treatment were at all hazardous or difficult, we would not presume to lay it before the profession. But the treatment is so simple that it should be put to a trial test in the interest of every patient suffering from this obnoxious condition. Certainly, it is worth a fair trial. We leave our results to be tested on a more elaborate scale by the larger clinics".

Morimoto 1986 [14]: "These data suggest that exogenous active forms of vitamin D_3 are effective for the treatment of psoriasis, and that the endogenous 1,25-dihydroxyvitamin D level also may be involved in the development of this disease".

Smith 1988 [19]: "Topical or oral use of $1,25\text{-}(OH)_2D_3$ heralds a new mode of treatment that appears to be both safe and effective for the treatment of psoriasis".

Perez 1996 [22]: "Oral calcitriol is effective and safe for the treatment of psoriasis".

Prystowsky 1996 [61]: "Because phototherapy for psoriatic plaques produces changes in keratinocytes similar to those described for 1,25-(OH)2D3 (i.e., slowed proliferation and enhanced differentiation), this raises the possibility that one of the mechanisms of action of UVB may be through enhanced vitamin D metabolism".

Finamor 2013 [26]: "In summary, the present study suggests that, at least for patients with autoimmune disorders like vitiligo and psoriasis, a daily dose of 35,000 IU of vitamin D_3 is a safe and effective therapeutic approach for reducing disease activity".

McCullough previously reported on the long-term safety of daily supplementation of oral vitamin D_3 in doses ranging from 5000 IU to 60,000 IU/day and found no adverse events after treatment for up to 7 years [28,114]. Several thousand long-term hospitalized patients taking 5000 to 10,000 IU/day were included the review [28]. We recently measured 24 urine calcium and creatinine levels in 16 individuals after long-term supplementation with varying doses of vitamin D. This included measurements in 4 individuals after taking 5000 IU/day for 13 to 94 months, in 9 individuals after taking 10,000 IU/day for 7 to 105 months, in one individual after taking vitamin D_2 50,000 IU/day for 51 months reported earlier, in one individual after taking vitamin D_3 60,000 IU/day for 67 months, and in one individual after sunbathing periodically for 33 months. Normal 24 urinary calcium excretion was observed in all 16 individuals (unpublished data).

4.13. Estimates of Vitamin D Production in the 1970s Are Much Lower Than Doses Used in the 1930s and 1940s

The first estimates of the physiologic amounts of vitamin D produced in the skin after exposure to UVB radiation were not available until 1977 and were found to be greater than 10,000 IU/day [110]. This data was later confirmed by other investigators [56,111–113]. These researchers also noted that the upper limits of daily vitamin D production in the skin from UVB exposure appear to be in the range of 20,000 to 25,000 IU/day [56,111–113]. This range is much less than the 60,000 to 600,000 IU/day used successfully clinically in the 1930s and 1940s and is much higher than the upper limit of 4000 IU/day currently recommended by the IOM [55] but is within the upper limit of 10,000 IU/day recommended by the Endocrine Society [56].

These estimates of physiologic vitamin D production in the skin may explain why hypercalcemia was often observed as a side effect of treatment with vitamin D in the 1930s and 1940s but was not observed in the oral vitamin D_3 and oral vitamin D_2 studies reviewed in this report which used doses ranging from 35,000 to 50,000 IU/day for 6 months to over 2 years. The serum 25(OH)D concentrations associated with the clinical benefits reported in the 1930s and 1940s when supraphysiologic doses of vitamin D were used to cure both tuberculosis [33–39] and rickets [32,46], and to control asthma [29], psoriasis [12] and rheumatoid arthritis [30,31] are unknown as tests for measuring serum 25(OH)D concentrations were not available until 1971 [255]. The upper limit of daily vitamin D intake that that is clinically effective but does not result in adverse events in the treatment of psoriasis and other vitamin D deficiency linked diseases needs to be further investigated.

Figure 1 shows the metabolic pathway of calcitriol production from 7-dehydrocholesterol in the skin after exposure to either sunshine or UVB phototherapy. It also illustrates why supplementation with 1(OH)D and calcitriol have no effect on serum 25(OH)D concentrations, as opposed to the dose dependent increase observed after supplementation with oral vitamin D_2 and oral vitamin D_3.

UVB radiation in sunshine causes the transformation of 7-dehydrocholesterol in the skin into vitamin D_3 [18,53,56,111–113,258]. Vitamin D_3 then undergoes a hydroxylation reaction on the 25th carbon to form 25(OH)D, which has a circulating half-life of a few weeks, and is what is measured to determine vitamin D status [132,133,258]. A second hydroxylation reaction on the 1st carbon is required to form calcitriol, which can occur in the skin, kidneys and multiple other organs [18,83,132,133].

Both 25OHD and calcitriol circulate in serum in free and carrier protein (albumin and vitamin D binding protein (DBP)) bound forms [259]. The sum of the free and albumin bound forms are referred to bioavailable vitamin D, as both 25OHD and calcitriol dissociate more easily from albumin than from DBP. Vitamin D needs to be in the free form to pass through the lipophilic cell membrane, and it is thought that the free serum 25OHD concentration may reflect its biological actions better than the total serum 25OHD concentration [260]. A recent study in pregnant women found opposite correlations between

serum 25OHD and serum calcitriol concentrations with gestational age, bone and lipid biomarkers. Free and bioavailable 25OHD showed a better overall correlation than total 25OHD with these biomarkers, while total serum calcitriol showed a better correlation with the same biomarkers than free or bioavailable calcitriol [259]. This may explain the why "normal" total serum 25OHD concentrations correlate poorly with psoriasis control. However, at this time total serum 25OHD concentrations are usually reported, and more research will be needed to assess whether free or bioavailable 25OHD correlate better with psoriasis control than total serum 25OHD.

A primary action of calcitriol is regulation of gene transcription, which has been shown to be regulated by vitamin D in multiple different cell types and tissues throughout the body [132–138]. Close to three thousand binding sites for the VDR have been identified in a human cell line [134]. Many cells of the immune system have been shown to require vitamin D for normal cellular metabolism including regulatory T lymphocytes [143], which we hypothesize to be the target cells regulated by vitamin D that control psoriasis and other autoimmune diseases as previously discussed [153–254].

Figure 1 also illustrates why treatment with oral or topical calcitriol and 1(OH)D does not affect serum 25(OH)D concentrations, as neither are metabolized into 25(OH)D. In contrast, both oral vitamin D_2 and oral vitamin D_3 are metabolized into 25(OH)D and cause an increase in circulating serum 25(OH)D concentrations in a dose dependent manner [28,114,261–265].

5. Implications for the Treatment of Other Vitamin D Deficiency Related Diseases with Vitamin D or Phototherapy

These observations raise important questions about the adequacy of serum 25(OH)D concentrations falling between 20 to 100 ng/mL not only for patients suffering from plaque psoriasis, but for those suffering from other diseases that are also strongly linked to vitamin D deficiency. Such diseases are numerous and include asthma, atherosclerosis, autoimmune diseases, cancers, falls, fractures, infections, mortality, myopathies, muscle weakness, neurological disorders, osteomalacia, osteoporosis, and psychiatric disorders [12,29–39,46,53,65–80,258,261–264,266–319]. Of particular interest currently are adverse outcomes from viral infections such as influenza [65,264,281,289,294,303] and COVID-19 [65–80], both of which have shown a strong association with vitamin D deficiency.

Many clinical trials using oral vitamin D supplementation performed and reported in the past 30 years have used daily dosing ranging from 800 IU/day to 4000 IU/day, with few exceeding 4000 IU/day [258,261–264,266–319]. This is well below the range of 10,000 to 25,000 IU/day reported to be produced by sun exposure to the skin, and far below the clinically effective doses of vitamin D used in the 1930s and 1940s. While several clinical trials using daily dosing ranging from 800 IU/day to 4000 IU/day were effective, others showed mixed or negative results. Three such negative trials will be briefly reviewed. Several case reports and clinical trials showing clinical benefits with supplementation with vitamin D in doses > 4000 IU/day will also be reviewed.

5.1. Inadequacy of 4000 IU/Day of Vitamin D_3 in the Treatment of Asthma and of 2000 IU/Day in the Prevention of Cancer

Two recent clinical trials investigating the effects of daily intake of 4000 IU/day of vitamin D_3 versus placebo on asthma control in adults and children showed no significant clinical benefits [304,318]. The first clinical trial was a 28-week study published in 2014 involving 201 treated adults [304], and the second was a 48-week study published in 2020 involving 96 treated children [318]. Similarly, a 5-year clinical trial comparing the effect of daily intake of 2000 IU/day of vitamin D_3 versus placebo published in 2019 in preventing invasive cancer or cardiovascular events in 12,927 treated adults found no significant clinical benefit [317]. Mean baseline serum 25(OH)D concentrations in these three clinical trials were 18.8 ng/mL, 22.5 ng/mL and 30.8 ng/mL respectively. On treatment mean serum 25(OH)D concentrations averaged 42 ng/mL in the first study at 12, 20 and 28 weeks (range 6.3 to 97.3 ng/mL at week 12), and in the second study were 57.2, 53.8 and 49.4 ng/mL

at weeks 16, 32 and 48 (ranges not indicated). A subgroup of 1644 participants in the third clinical trial had a baseline mean serum 25(OH)D concentration of 29.8 ng/mL which increased to 41.8 ng/mL at one year (range not indicated). No changes were seen in mean serum 25(OH)D concentrations in the placebo groups over the time course of the studies.

The on-treatment data reported in these clinical trials are similar to the baseline serum 25(OH)D concentrations in the psoriasis reports reviewed in this report, which were insufficient for disease control in psoriasis. This suggests the possibility that daily intakes higher than 2000 to 4000 IU/day of vitamin D_3 may be needed for treating asthma and for preventing cancer and cardiovascular disease, which is consistent with the observations first reported in the 1930s and 1940s with asthma, psoriasis, rheumatoid arthritis, and tuberculosis, as well as with the psoriasis studies reviewed in this report. It is also consistent with several recent case reports and clinical trials of diseases showing clinical improvement with vitamin D intake > 4000 IU/day.

5.2. Case Reports and Clinical Trials of Diseases Showing Clinical Improvement with Vitamin D Intake > 4000 IU/Day

Several case reports and clinical trials published in the past few decades [80,114,272,296,297,303,308–310], in addition to the 3 discussed in this report [25,26,28], have shown significant clinical benefits without toxicity with vitamin D supplementation when using doses of vitamin D above 4000 IU/day, and ranging up to 50,000 IU/day for extended periods of time, thus providing further support for this recommendation. This includes significant clinical improvement in:

(1) A 1997 case report of chronic Parkinson's disease symptoms over the course of a year using 4000 IU/day of 25(OH)D [272], roughly equivalent to 20,000 IU/day of vitamin D_3 [110];
(2) Control of chronic pain in children suffering from sickle cell disease using 50,000 IU twice weekly of vitamin D_3 for 8 weeks, followed by once weekly for 32 months in a 2011 case report [296], and subsequently in a weight-based dosing study using 40,000 IU to 100,000 IU/ week for 6 weeks in 20 children in a 6 month placebo controlled trial published in 2012 [297];
(3) Chronic fatigue in a 2014 prospective study of 171 adult patients with low serum 25(OH)D concentrations (<30 ng/mL) using 50,000 IU of vitamin D_2 three times a week for 5 weeks [303], which averages out to 21,429 IU/day;
(4) Prevention of statin intolerance secondary to myalgia, myositis, myopathy or necrosis in 171 previously statin intolerant patients with low serum 25(OH)D concentrations (<32 ng/mL) using either 50,000 or 100,000 IU/week of vitamin D_2 for 24 months published in 2015 [308];
(5) 282 patients treated with these same doses in a prospective one-year clinical safety trial from this same group using vitamin D_3 instead of vitamin D_2, and again found to be safe in 2016 [309];
(6) Prevention of progression of a case of advanced pancreatic cancer using 50,000 IU/day of vitamin D_3 for 9 months reported in 2016 [310];
(7) Asthma control in a case of long-standing asthma using 20,000 to 25,000 IU/day of vitamin D_3 for several years reported in 2019 [28,114];
(8) A non-melanoma skin cancer in an individual taking 60,000 IU/day of vitamin D_3 for several years reported in 2019 [28,114];
(9) The need for ICU treatment in patients requiring hospitalization due to proven COVID-19 infections in 50 patients treated with 25(OH)D (532 μg (21,280 IU) on day 1; 266 μg (10,640 IU) on days 3 and 7, followed by 266 μg weekly until discharge) which resulted in one ICU admission (2%), versus a group of 26 untreated patients of which thirteen (50%) required admission for care in an ICU [80].

COVID-19 deaths have now passed 2.4 million worldwide [319]. In the United States, there have been over 28 million cases and over 510,000 deaths [319] with no signs of slowing down soon. A recent report analyzing over 190,000 patients infected with COVID-

19 in the United States showed a strong correlation with vitamin D deficiency and risk of infection, with a 53% lower SARS-CoV-2 positivity rate among patients with a serum 25(OH)D concentration > 55 ng/mL versus those < 20 ng/mL, and a 43% lower risk for contracting COVID-19 with an increase in serum 25(OH)D concentrations from 20 ng/mL to 55 ng/mL [75], providing further evidence of the urgency to conduct such clinical trials.

5.3. Need to Better Define the Therapeutic Index of Vitamin D

The serum 25(OH)D concentrations in psoriasis patients before and after treatment reviewed in this report suggest revision of current definitions of vitamin D deficiency, insufficiency, sufficiency and toxicity, as well as diseases currently recognized as being responsive or unresponsive to vitamin D supplementation. There is a dearth of clinical trial data examining the clinical utility and toxicity of oral vitamin D supplementation between the conventional dose ranges of 800 to 4000 IU/day and 60,000 to 600,000 IU/day. The supraphysiologic (by current standards) doses of vitamin D used in the 1930s and 1940s were proven clinically effective in treating asthma, rheumatoid arthritis and tuberculosis in addition to psoriasis, but were associated with reversible hypercalcemia and calcium crystal formation after prolonged daily intake [31,35,39,320,321]. Clinical trials in patients suffering from psoriasis and other diseases shown to be strongly linked to vitamin D deficiency using daily oral supplementation between these extremes, particularly dosing encompassing the range of 10,000 to 25,000 IU shown to be produced by adequate daily UVB exposure to the skin, need to be done to clarify the therapeutic index of vitamin D.

6. Conclusions and Future Directions

Psoriasis responds safely to treatment with 4 different forms of oral vitamin D: vitamin D_2, vitamin D_3, 1-alpha-hydroxyvitaminD_3, and 1,25-dihydroxyvitamin D_3 (calcitriol). Pre-treatment serum 25(OH)D_3 concentrations above 20 ng/mL, ranging up to 67 ng/mL, were common in patients with plaque psoriasis in the oral vitamin D dosing studies reviewed. However, patients showed significant dermatological improvement in their skin without toxicity after daily treatment with four different forms of oral vitamin D. This suggests that serum 25(OH)D_3 concentrations > 20 ng/mL are not adequate for many patients with plaque psoriasis, even though they are considered adequate for the majority of the population by the IOM [55] and the Endocrine Society [56], calling into question the definition of an adequate serum 25OHD concentration. Pre-treatment serum 25(OH)D_3 concentrations > 20 ng/mL, ranging up to 88 ng/mL, were also commonly observed in patients with plaque psoriasis in the UVB phototherapy studies reviewed, yet these patients still showed significant improvement in their skin after treatment with UVB phototherapy. This was associated with significantly increased serum 25(OH)D_3 concentrations post-treatment, with several patients > 100 ng/mL, and ranging up to 159 ng/mL without any adverse events.

Post-treatment serum 25(OH)D_3 concentrations > 100 ng/mL were also observed in patients with plaque psoriasis safely treated with 35,000 IU/day of vitamin D_3 for 6 months, and in a patient treated with 50,000 IU/day of vitamin D_2 for over 3 years, without any adverse events. This was associated with peak serum 25(OH)D_3 concentrations of 202 ng/mL and 308 ng/mL respectively. The fact that serum 25(OH)D_3 concentrations > 100 ng/mL have been obtained safely after disease control using UVB phototherapy, 35,000 IU/day of vitamin D_3, and 50,000 IU/day of vitamin D_2 calls into question the safe upper limit of serum 25(OH)D_3 concentrations. Currently, a serum 25(OH)D_3 concentration > 50 ng/mL is considered potentially dangerous for the majority of the population and is not recommended by the IOM [55] and a serum 25OHD concentration > 100 ng/mL is considered high by the Endocrine Society [56]. In contrast, several reviews [57–59] and case reports [60] on vitamin D toxicity have suggested that serum 25OHD concentrations > 100 ng/mL and ranging up to 400 ng/mL may be safe. This needs further clarification. A recent review on vitamin D safety suggests that "Vitamin D is not as toxic as was once thought" [307]

The exact range of total serum 25OHD concentrations needed to be achieved to improve psoriasis is currently unknown and is speculative at this time. Dose response studies need to be performed with all four forms of oral vitamin D to clarify the time response to treatment with varying doses and the therapeutic index. However, as mentioned elsewhere in this review, current "normal" levels for vitamin sufficiency are not likely to be effective in treating psoriasis. We suggest that total serum 25OHD concentrations closer to 100 ng/mL might be needed when oral vitamin D_2 or vitamin D_3 are used. However, because there will be no change in total serum 25OHD concentrations when either 1(OH)D or calcitriol are used, as total serum 25OHD concentrations are not affected when these agents are used (Figure S1, Table S2, Supplementary Materials), measurement of free and bioavailable serum 25OHD may prove to be better markers of disease control in psoriasis, as previously discussed [259,260]. In addition there may be differences in responses between males and females, as a correlation between vitamin D deficiency and insulin resistance was recently reported in females, but not in males [322].

Vitamin D toxicity was absent in the reviewed clinical reports. When it occurs, it is manifested by complications related to hypercalcemia, renal insufficiency, hypercalciuria, calcium crystal formation, and undetectable serum parathyroid hormone concentrations, which have been shown to be reversible by simply stopping the vitamin D and providing supportive care with no long-term sequelae. Several such complications induced by excessive vitamin D intake (hypercalcemia, renal insufficiency, hypercalciuria, and undetectable serum PTH) were shown to resolve when serum 25(OH)D_3 concentrations dropped below 400 ng/mL in 2 case reports in 2011 after accidental ingestion of massive amounts of vitamin D over a period of 1 to 2 months [60]. Due to labeling and manufacturing errors of over the counter supplements, one patient took 1,864,000 units (46,000 μg) of vitamin D_3 daily for 2 months and achieved a peak serum 25OHD concentration of 1220 ng/mL. The second took 970,000 units of vitamin D_3 a day for one month and achieved a peak serum 25OHD concentration of 645 ng/mL. Both recovered uneventfully after cessation of vitamin D intake. Our clinical experience is consistent with this, as we have not observed hypercalcemia, renal insufficiency, hypercalciuria, undetectable serum parathyroid hormone concentrations or any other toxicity in patients with serum 25(OH)D_3 concentrations ranging from 202 ng/mL to 384 ng/mL [28].

Vitamin D has a much safer toxicity profile than methotrexate, cyclosporine and biologics such as Humira and Enbrel, which are more commonly used for the treatment of psoriasis. Biologics are among the most frequently reported drugs for adverse events to the FDA, and many have FDA mandated black box warnings for risk of cancers such as lymphoma, serious infections such as tuberculosis and invasive fungal infections, and death [323–335]. In contrast, vitamin D was shown in the 1940s to safely cure tuberculosis infections as a single agent using daily oral intake of 100,000 to 150,000 units for 2 to 3 months [33–39], most likely by turning on genes that make antimicrobial peptides active against TB [39,282,289]. More recently, vitamin D has been shown to have anticancer properties [28,284,287,295,298,301,310], and appears to reduce the risk for developing cancer, and not increase it as biologics do. More clinical research utilizing a range of vitamin D intakes is needed to confirm these findings and to see if a dose response exists in cancer prevention, in light of the recent clinical trial reviewed earlier that showed no clinical benefit in cancer prevention after daily intake of 2000 units of vitamin D_3 over five years [318]. Vitamin D also appears to have a safer toxicity profile than sunshine, UVB phototherapy, and even acetaminophen, one of the most commonly used over the counter medications, and a leading cause of liver failure [336,337].

The fact that both oral and topical vitamin D were able to produce the same clinical outcomes as seen with sunshine and UVB phototherapy is compelling evidence that the effects of sunshine and UVB phototherapy in treating psoriasis is mediated by vitamin D production in the skin. The mechanism of action explaining how vitamin D works to clear psoriasis skin lesions is currently unknown but appears likely to be related to the documented effects vitamin D has on stimulating the production and maintenance of

regulatory T lymphocytes (Tregs), which have been characterized as master regulators of the immune system due to their ability to control autoimmune diseases [239]. This also needs further clarification. However, consistent with this notion, Tregs have been shown to be dysfunctional in a state of vitamin D deficiency, and can have their functional status restored by sunshine, phototherapy and oral or topical vitamin D [153–233]. Vitamin D causes the formation of Tregs to occur indirectly through direct effects on antigen presenting cells, which then cause naïve T cells to transform into Tregs [143].

Placebo controlled, blinded clinical trials using oral vitamin D_3 for the treatment of patients suffering from psoriasis are warranted based on the results of the studies reviewed in this paper. There is strong evidence that physiologic doses in the range of 10,000 to 25,000 IU/day, and ranging up to 50,000 IU/day, should be able to be administered safely in a clinical trial setting. Serum calcium and PTH concentrations, renal function and urine calcium concentrations can be easily monitored and readily corrected without long-term risk if they become abnormal by simply stopping vitamin D supplementation. The vitamin D could then be resumed again at a lower dose to monitor clinical efficacy and safety. There is potentially much to gain if these dose-response clinical trials are successful. Oral vitamin D is the most affordable treatment option for psoriasis by a wide margin, especially when compared to biologics. The potential cost savings to the health care system by the increased use of oral vitamin D in treating psoriasis is enormous, in the range of billions of dollars/year, with improved patient safety and satisfaction. It is not clear why the four forms of oral vitamin D discussed in this review are not currently being used to treat psoriasis, after being endorsed as safe and effective treatments by the authors of the clinical trials reviewed.

The failure of clinical trials that used sub-physiologic doses of vitamin D and achieved inadequate serum 25(OH)D concentrations has created doubt about the importance of vitamin D in the prevention and treatment of human disease. The fear of causing toxicity by using excessive amounts of vitamin D has led to the unintended consequence of causing needless suffering by perpetuating uncontrolled disease states that might otherwise be controlled by sufficient vitamin D intake or exposure to UVB radiation. Clinical trials examining the dose response of oral vitamin D_3 using 10,000 to 25,000 IU/day or higher may prove beneficial in controlling plaque psoriasis and other vitamin D related diseases without causing harm. It may have major promise in treating COVID-19 infections, where therapy with "higher than usual" doses probably need to be given only short term given the nature of the clinical course of COVID-19 infections. This was shown to be a successful treatment strategy for chronic tuberculosis infections in the 1940s. Current definitions of normal and excessive serum 25OHD concentrations need to be re-evaluated based on the clinical data reviewed in this manuscript. The therapeutic index of vitamin D in the treatment of human disease needs to be better defined.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13051511/s1, Table S1: Baseline and 3-month mean serum 25O(H)D3 (ng/ml), calcium (mg/dl) and calcitriol (pg/ml) concentrations in the 3 treatment groups. TableS2: Range and distribution of pre-treatment serum 25(OH)D3 concentrations in the combined group of 15 psoriasis patients treated with oral calcitriol (n = 13) and topical calcitriol (n = 2). Table S3. Mean serum 25(OH)D3, calcium, PTH, calcitriol, creatinine, and 24-hour urine calcium concentra-tions at 0, 6, 12, 24 and 36 months in 88 plaque psoriasis patients treated with oral calcitriol. Table S4. Distribution and mean serum concentrations of 25(OH)D3, PTH, calcium, urea and cre-atinine, and 24-hour urinary calcium in 9 patients with psoriasis and 16 patients with vitiligo pre-and 6 months' post-treatment with oral vitamin D3 at 35,000 IU/day. Figure S1. Improvement in psoriasis plaques after resuming 40,000 IU/day of vitamin D3 in pa-tient 2, whose disease recurred after stopping vitamin D3. Nearly complete clearing of the plaques occurred by 88 days. The yearly cost of treatment with oral vitamin D3 at a dose of 40,000 IU/day is around $104 per year, based on currently available over the counter pricing at $14/bottle for a USP verified bottle of 400 gel caps with 5000 IU/cap. Table S5. Changes in serum 25(OH)D2, iPTH and calcium concentrations over time in a patient with psoriasis completely cleared on 50,000 IU/day of vitamin D2 for > 42 months. Table S6. Mean,

range and distribution of serum 25(OH)D3 concentrations, and mean serum cal-cium and calcitriol concentrations before and after UVB phototherapy in 13 patients with plaque psoriasis also treated with placebo (n = 7) or calcitriol (n = 6). Table S7. Range, median and distribution of serum 25(OH)D3 concentrations pre-and post NB-UVB treatment in 29 psoriasis patients and 29 untreated controls. Table S8. Mean, range and distribution of serum 25(OH)D3 concentrations before and after BB-UVB (n = 26) and NB-UVB (n = 42) phototherapy in 68 patients with psoriasis. Table S9. Mean, range and distribution of serum 25(OH)D3 concentrations pre-and post 8-12 weeks of BB-UVB phototherapy (n = 24 postmenopausal women) or 15 days of whole-body sun-shine (n = 20) exposure in 44 patients with plaque psoriasis.

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