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Giovanni DAMIANI, Alessia PACIFICO, Sherman CHU, Young Dermatologists Italian Network (YDIN), Ching-Chi CHI

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Frequency Of Phototherapy For Treating Psoriasis: A Systematic Review

Giovanni Damiani[1,2,3], Alessia Pacifico[4], Sherman Chu[3], Young Dermatologists Italian Network (YDIN), Ching-Chi Chi[5,6] *

[1] Clinical Dermatology, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy

[2] Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

[3] Department of Dermatology, Case Western Reserve University, Cleveland, USA

[4] San Gallicano Dermatological Institute, IRCCS, Rome, Italy

[5] Department of Dermatology, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan

[6] College of Medicine, Chang Gung University, Taoyuan, Taiwan

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Correspondence:

Ching-Chi CHI

chingchichi@gmail.com

ABSTRACT

INTRODUCTION:

Narrow band ultraviolet B (NB-UVB) and psoralen-ultraviolet A (PUVA) remain inexpensive and effective anti-psoriatic therapies adopted worldwide with different frequency protocols. We aimed to systematically assess the evidence on the effects of different frequency protocols of phototherapy in treating psoriasis.

EVIDENCE ACQUISITION:

We used the following terms, namely "photochemotherapy", "phototherapy", "psoriasis", "UVB", "UVA" and "ultraviolet therapy", to search the Cochrane Controlled Register of Trials, MEDLINE and Embase databases on August 1, 2019. We organized results using a PRISM diagram and analyzed bias risks with RoB-2 tool.

EVIDENCE SYNTHESIS

We included five randomized controlled trials (RCTs) on oral PUVA and three RCTs on NB-UVB. The five studies on PUVA included a total of 1452 patients with plaque psoriasis and did not find any significant difference in efficacy comparing two- vs. three- vs. four times weekly protocols. The three studies on NB-UVB included a total of 248 patients with plaque psoriasis. No differences in efficacy were reported in comparing different frequencies in delivering NB-UVB, namely twice vs. thrice weekly, twice vs. four times weekly, and thrice- vs. five times weekly protocols. Although protocols with higher treatments frequency per week achieved clearance faster than lower frequency ones, but they did not differ in terms of efficacy.

CONCLUSIONS

PUVA and NB-UVB remain an effective anti-psoriatic treatment; however further studies are needed to elucidate which protocol may be more effective in different skin phototypes.

Key words: phototherapy; psoriasis; narrow band-ultraviolet B (NB-UVB), psoralen-ultraviolet A (PUVA), frequency.

INTRODUCTION

Phototherapy revolutionized anti-psoriatic treatment from the middle 1980s and continues to be valuable today. Narrow-band ultraviolet B (NB-UVB) and psoralen-ultraviolet A (PUVA) are the most widely adopted phototherapeutic treatments to treat psoriasis. PUVA utilizes a topical (bath PUVA) or oral psoralen to potentiate the effect of UVA irradiation; conversely NB-UVB does not use psoralens. In contrast to PUVA, NB-UVB is characterized by low photo-aging effects and no photo-carcinogenesis and is recommended as the first line treatment for moderate to severe psoriasis (Psoriasis Area Severity Index (PASI) score > 10) in the psoriasis guidelines worldwide [1-3]. In the biologic era, phototherapy still has a place in the dermatologic armamentarium as demonstrated recently in different registries worldwide [4-6]. Compared with biologics and small molecules, both NB-UVB and PUVA are more time consuming, slower to clear plaques, but inexpensive and NB-UVB is not related to photo-carcinogenesis [4].

In order to optimize these treatments that started as monotherapy, dermatologists started to couple NB-UVB with biologics or small molecules in order to achieve higher effectiveness [7,8]. Furthermore, NB-UVB can also be used at home by physician-trained patients that purchase or lease the phototherapeutic machines [9].

Despite the great advantages and versatility displayed, phototherapy is time-consuming not because the treatment time is long, as the average application ranges from 30 seconds to 3 minutes,

but because patients should attend the phototherapeutic center at least twice weekly. Although both are not suitable for maintenance, PUVA have a lifetime cumulative limit of 200 applications, but no limits have been set for NB-UVB [10].

Remarkably, PUVA and NB-UVB are delivered with different frequency protocols. NB-UVB regimens vary from 2-3 times/week in Canadian and British guidelines to 3-5 times/week in the US ones, while PUVA regimens vary from 2-3 times/week in US guidelines to 4 times/week in Canadian ones [3]. Due to the present disagreement in phototherapy frequency delivering, we decided to systematically evaluate the evidence regarding the effects of various frequency protocols of phototherapy for treating psoriasis.

METHODS

We performed a systematic review examining the effects of various frequencies of NB-UVB and PUVA phototherapy for treating psoriasis. The protocol for this systematic review has been registered with PROSPERO (CRD42018104687) [11].

By using key words, namely “photochemotherapy”, “phototherapy”, “psoriasis”, “UVB”, “UVA” and “ultraviolet therapy”, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase databases on August 1, 2019. The search strategy was modified according to the controlled vocabulary for each database. We also checked the references of included articles and relevant reviews. We included articles in English, Italian, Spanish, French, and German. Gray literature and conference abstracts were discarded.

We decided to include only randomized controlled trials (RCTs). Patients included had their plaque psoriasis diagnosed by a dermatologist and underwent NB-UVB or PUVA as monotherapy with different regimens of frequencies compared with quantitative outcome measures such as PASI or Physician’s Global Assessment (PGA). No limitations on participants’ age, Fitzpatrick’s skin phototype, and location were imposed.

After discarding duplicated articles, two authors (GD and AP) selected studies according the the aforementioned criteria independently. A third author (CC) was available for arbitrating any disagreement. The following data were extracted from the included studies: first author's name, year of publication, country of origin, journal, types of phototherapy treatment, frequency protocols compared, and the number of participants. The risk of bias of the included studies were evaluated independently by GD and AP using the revised Cochrane risk of bias tool for randomized trials (RoB-2) tool [12].

RESULTS

As shown in Figure 1, we manually screened 552 articles after removing duplicates. The full text of 21 articles were further evaluated with 13 excluded. We finally included 8 RCTs, with 5 on PUVA [13-17] and 3 on NB-UVB [18-20] (Table I). Due to the specific intervention, blinding of participants was not possible. However, 7 out of the 8 included RCTs applied blinding of outcome assessors, with 4 on PUVA [13,15-17] and 3 on NB-UVB [18-20], respectively. Two RCTs on PUVA used split-body design, i.e. splitting the patient body surface in two symmetric parts and treating them with two different protocols [13,14].

PUVA studies

The five studies on PUVA included a total of 1452 patients with plaque psoriasis, with Melski *et al.* contributing 1308 patients [17]. The inclusion criteria of participants such as age and disease severity were similar across the included RCTs; however, Melski *et al.* did not report participants' severity and age. Additionally, the age range of participants reported by Melski *et al.* was between 5 and 85 years, in contrast with the other included RCTs that globally excluded participants under 16 years old [17]. The included RCTs enrolled participants with various skin phototypes. As shown in Table II, 3 out of the 5 included RCTs were rated with high risk of bias [14, 16,17] and 2 with some concerns of bias [13,15].

Four included RCTs evaluated twice vs. thrice weekly protocol [13, 15-17], while one RCT compared two- vs. four times weekly protocol with differing minimal phototoxic doses (MPDs) [14]. Valbuena *et al.* and El-Mofty *et al.* compared two- vs. three times weekly therapy and found no difference in PASI decrease with different frequency protocols (92.9% vs. 94.8% PASI decrease and 5.16 ± 6.88 vs. 5.88 ± 5.24 final PASI score, respectively) [13, 16]. Additionally, Legat *et al.* reported no differences in the final PASI score comparing 0.5 MPD four times weekly protocol vs. 1 MPD twice weekly protocol [14]. Three RCTs reported a significantly lower number of sessions required for clearance using twice weekly protocol (15 vs. 22 sessions; 18.7 ± 5.6 vs. 35.3 ± 2.0 sessions; 18.3 vs. 20.3 sessions, respectively) [13, 16, 17]. Additionally, these same studies reported a significantly lower mean total dosage required for clearance with the use of twice weekly protocol (142.5 vs. 241.4 J/cm^2; 54.57 ± 20.42 J/cm^2 vs. 99.20 ± 19.48 J/cm^2; 173 vs. 201 J/cm^2, respectively [13, 16, 17]. However, Buckley *et al.* reported no significant differences in the cumulative dosage and number of treatments required for clearance between twice- and thrice weekly protocols (66.5 vs. 78.5J/cm^2, 17 vs. 15 sessions, respectively) [15]. Furthermore, one RCT reported the twice weekly protocol required a longer time required for clearance (9.7 vs. 7.6 weeks, respectively) [17].

NB-UVB studies

The four RCTs on NB-UVB included a total of 179 participants with plaque psoriasis, divided in 109 males and 70 females. Participants were enrolled globally if aged over 16 years, with only Hallaji *et al.* utilizing a different inclusion criterion (age > 10 years) [20]. Two RCTs included only participants with skin phototypes I, II, and III [18,19] and one RCTs included only phototypes II, III, and IV [20]. Two RCTs did not employ severity inclusion criteria and both evaluated efficacy outcome using a scaling, erythema, induration (SEI) score [18,19]. One RCT used body surface area > 10% as the severity inclusion criteria and used PASI score to measure the efficacy [20]. The risk of bias analysis evaluated that only one RCT had a low risk of bias [19], one with a high risk of bias [20], and one with some concerns of bias [18] (Table II).

A RCT performed by Cameron *et al.* compared the use of twice to thrice weekly NB-UVB treatment protocol and found that three-times weekly protocol cleared psoriasis significantly faster than twice weekly protocol (mean of 88 days vs. 24.4 days, respectively) [19]. However, this RCT did not detect differences in total dose, number of treatments required for clearance, and change from baseline SEI score (125 (range 17-923) vs. 95 (36-357) MEDs, 24.4 (11-41) vs. 23.0 (14-38) sessions [19]. Additionally, Dawe *et al.* compared three-times and five-times weekly treatment protocols and did not find a significant difference between the two in psoriasis severity using SEI scores (4 (range 0-18) vs. 3 (range 0-13), respectively) [18].

Two RCTs compared the effects of three times weekly vs. five times weekly protocols [18, 20]. Hallaji *et al.* reported that thrice weekly protocol required a significantly longer treatment period (14.7 weeks vs. 8.9 weeks, respectively), but there was no differences in the number of treatments, cumulative NB-UVB dose, and disease clearance in participants compared to five-times weekly protocol (43.0 vs. 46.3J/cm^2, 37.6 vs. 37.8 sessions, and 78% vs. 68% clearance, respectively) [20]. However, participants' mean PASI score was significantly lower at the end of the treatment period with the use of three-times weekly protocol (1.9 vs. 4.9, respectively) [20].

DISCUSSION

In the biologic era, PUVA is less and less employed in treating moderate to severe psoriasis [1-3]. The optimal administered protocol of PUVA phototherapy is controversial; from this systematic review, we did not find any significant difference in the reduction of PASI score between twice and thrice weekly regimens. Melski *et al.* presented that twice-weekly protocol was superior in lighter skin phototypes in comparison to a thrice-weekly protocol [17]. However, one RCT reported that lighter skin phototypes (I and II) required a significantly higher UVA dose for clearance [15]. Several studies reported a significantly lower number of sessions and mean total dosage required for clearance using twice weekly protocol compared to thrice weekly protocol [13, 16, 17]. However, another RCT found no significant differences in the cumulative dosage and number of

sessions required for clearance between the two protocols [15]. Additionally, one study reported twice weekly protocol required a longer time for clearance [17]. Regardless, twice weekly protocol is more convenient for patients, enhances adherence to therapy, and reduces the costs of treatments. Thus, due to its accumulated carcinogenetic potential, we conclude that twice weekly protocol is preferred.

NB-UVB phototherapy has been proved to be safe and effective for treating mild to moderate psoriasis. Although considered a relatively safe treatment, the optimal weekly frequency to treat psoriasis has not been clarified [22,23]. Current literature presents that the weekly frequency varies from two to five times per week [23]. Our reviewed literature compared twice to thrice weekly protocol and thrice to five times weekly protocols [18-20]. Only one out of the four RCTs that compared thrice to five times weekly protocol found a difference in the mean PASI score at the end of treatment [20]. Twice weekly NB-UVB therapy was found to take significantly longer to clear in comparison to thrice-weekly therapy [19]. However, there were no differences in treatment efficacy, number of treatments required for clearance, and total UVB dose required [19]. On the other hand, thrice weekly protocol required a significantly longer treatment period compared to five times weekly protocol, but no differences in the cumulative dosage, number of treatments, or efficacy in patient clearance was found [20].

Parrish *et al.* showed that when irradiating the same lesion with a fixed dose of NB-UVB corresponding to a slightly higher dose than the effective one, the cumulative dose was lower due to less treatments being required to obtain clearance [23].

To our knowledge, a standardized phototherapeutic protocol does not currently exist for treating psoriasis. Moreover, the carcinogenic risk of NB-UVB, which is a small selected portion of the entire UVB wavelength, is still under debate since the carcinogenic potential of the entire UVB has been widely demonstrated in the late 1990s. *In vivo* and *in vitro* experiments performed in humans and animals have demonstrated NB-UVB irradiation might induce the development of skin tumors [24, 25].

Taking all these observations into account, it is safe to consider a protocol using lower amounts of the cumulative UV exposure to be effective for patients. Several studies have highlighted that there are no significant differences between twice weekly and thrice weekly protocols. For this reason, we prefer to consider a three-weekly sessions treatment protocol because psoriasis therapy should be aggressive and the thrice weekly protocol allows a patient to rapidly reach the effective dose of treatment. This dose progression will allow faster clearing in a shorter period of time, thus limiting the potential adverse effects following UVB exposure.

Giovanni Damiani[1,2,3*], Alessia Pacifico[4], Sherman Chu[3], Young Dermatologists Italian Network (YDIN), Ching-Chi Chi[5,6]

Authors' contribution: Conceptualization: G.D. and C.C.C.; Methodology: G.D. and C.C.C.; Software: G.D.; Validation:. A.P. and S.C.; Formal analysis: G.D.; Investigation: G.D., A.P., and S.C.; Resources: C.C.C.; Data curation: G.D.; Writing – Original Draft: G.D., A.P. and C.C.C.; Writing –Review & Editing: G.D., A.P., S.C. and C.C.C.; Visualization: G.D.; Supervision:C.C.C.; Project Administration: G.D.

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Table I. Characteristics of the included studies

	Participants	Study type	Outcomes	Country
Oral PUVA				
Valbuena *et al.*	*Age*: 41.9 ± 15.1 years.	Randomized, controlled,	No significant difference between median percentage	Colombia

	Included only >18 years *M/F*: 18/5 *Skin phototypes*: II= 6 III-IV=17 *Sample*: 23 patients *Severity inclusion criteria*: BSA > 20%	single blinded, half-side *Protocol*: two- vs three times/week	of PASI decrease: 92.9% for twice-weekly vs 94.8% for thrice-weekly. Significant difference in median number of sessions needed for clearance and median cumulative dose: 15 vs 22 sessions and 142.5 vs 241.4 J/cm^2, respectively	
Legat *et al.*	*Age*: 39.4 ± 3.6 years Included only >16 years *M/F*: 14/4 *Skin phototypes*: Not reported *Sample*: 18 patients *Severity inclusion criteria*: PASI>10	Randomized, controlled, half-side trial *Protocol*: two- vs four times /week with different MDPs fractions	No differences in final PASI between 0.5 MPD 4 times/week and 1 MPD twice/week therapy.	Austria
Melski *et al.*	*Age*: 44 [5-85] years *M/F*: 65%/35% *Skin phototypes*: I= 48 II=214 III=571 IV=126 V=17 VI=16 *Sample*: 1308 patients	Randomized, controlled, single blinded trial N.B. patients with phototypes V and VI were not randomized and arbitrary treated three times/week	Twice a week presented significantly lower mean total dosage and mean number of treatments, but significantly higher mean number of weeks for clearance compared to thrice a week: 173 vs 201 J/cm^2, 18.3 vs 20.3 sessions, and 9.7 vs 7.6 weeks, respectively.	USA

	Severity inclusion criteria: BSA>30%	*Protocol*: two- vs three times/week	Twice a week regimen was superior in patients with lighter phototypes	
El-Mofty *et al.*	*Age*: 42.0 ± 14.2 years Included only >16 years *M/F*: 9/11 *Skin phototypes*: III= 6 IV= 12 V=2 *Sample*: 20 patients *Severity inclusion criteria*: 30%<BSA<70%	Randomized, controlled, single blinded trial *Protocol*: two- vs three times/week	Twice a week therapy presented significantly lower UVA dose at final response and total number of sessions compared to thrice a week therapy: 54.57 ± 20.42 J/cm^2 vs 99.20 ± 19.48 J/cm^2, 18.70 ± 5.61 vs 35.33 ± 2.00 sessions, respectively. Final PASI not significantly different between twice and thrice weekly therapy: 5.16 ± 6.88 vs 5.88 ± 5.24, respectively.	Egypt
Buckley *et al.*	*Age*: 39.4 ± 3.6 years Included only >18 years *M/F*: 51/24 *Skin phototypes*: I= 15 II=35 III=25 *Sample*: 83 patients *Severity inclusion criteria*: PASI>10	Randomized controlled, single blinded trial *Protocol*: twice-weekly MPD-PUVA vs three times-weekly skin typing-PUVA	Twice weekly clearing dosage and number of days to clear was significantly lower than three times weekly treatment: 6 (3.5-7.0) vs 8.5 J/cm^2 (5.5-8.5), 41 (36-50) vs 50 days (43-66), respectively. Cumulative dose and number of treatments did not differ significantly between two- and three-times weekly therapy: 66.5 (44.0-90.0) vs 78.5J/cm^2 (59.5-113.0), 17 (14-19) vs 15 (11-	Ireland and UK

			18) sessions, respectively).	
NB-UVB				
Cameron *et al.*	*Age*: 41 [17-80] years. Included only >16 years *M/F*: 70/43 *Skin phototypes*: included I, II, III but not reported absolute numbers. *Sample*: 113 patients *Severity inclusion criteria*: not reported	Randomized, controlled, single blinded trial *Protocol*: two- vs three times/week	Days to clearance between twice weekly therapy was significantly higher compared to three-times weekly: 88 (48-150) vs 58 (32-112) days, respectively. Total dose in MED and number of treatments for clearance was not significantly different in twice- and three-times weekly therapy: 125 (17-923) vs 95 (36-357) MEDs, 24.4 (11-41) vs 23.0 (14-38) sessions, respectively. Scaling, erythema, induration (SEI score) change: Twice weekly 11.1 ± 4.2 vs three times weekly 11.9 ± 3.6; not statistically significant.	UK
Dawe *et al.*	*Age*: 43 ± 13.6 years. Included only >18 years *M/F*: 13/8 *Skin phototypes*: I=2 II=14 III=5 *Sample*: 21 patients *Severity inclusion*	Randomized, controlled, single blinded, half-side *Protocol*: three- vs five times/week	Three times a week presented a non-significant increase in scaling, erythema, induration psoriasis severity scores (SEI) compared to five times a week therapy: 4 (0-18 range) vs 3 (0-13 range), respectively.	UK

	criteria: not reported			
Hallaji *et al.*	*Age*: 32.6 [13-75] vs 36.1 [20-58] years[B]. Included only >10 *M/F*: 26/19 *Skin phototypes*: II=9 III=29 IV=7 *Sample*: 45 patients *Severity inclusion criteria*: BSA>10	Randomized, controlled, single blinded trial. *Protocol*: three- vs five times/week	18/23 (78%) cleared in three times weekly group vs 15/22 (68%) in five times weekly group, difference was not statistically significant. Mean PASI significantly lower in three-times weekly group: 1.9 vs 4.9. Mean length of treatment significantly shorter in five times weekly group compared to three: 8.9 vs 14.7 weeks, respectively. Cumulative UVB dose and number of treatments were not significantly different between three- and five-times weekly treatment: 43.0 vs 46.3J/cm^2, 37.6 vs 37.8 sessions, respectively.	Iran

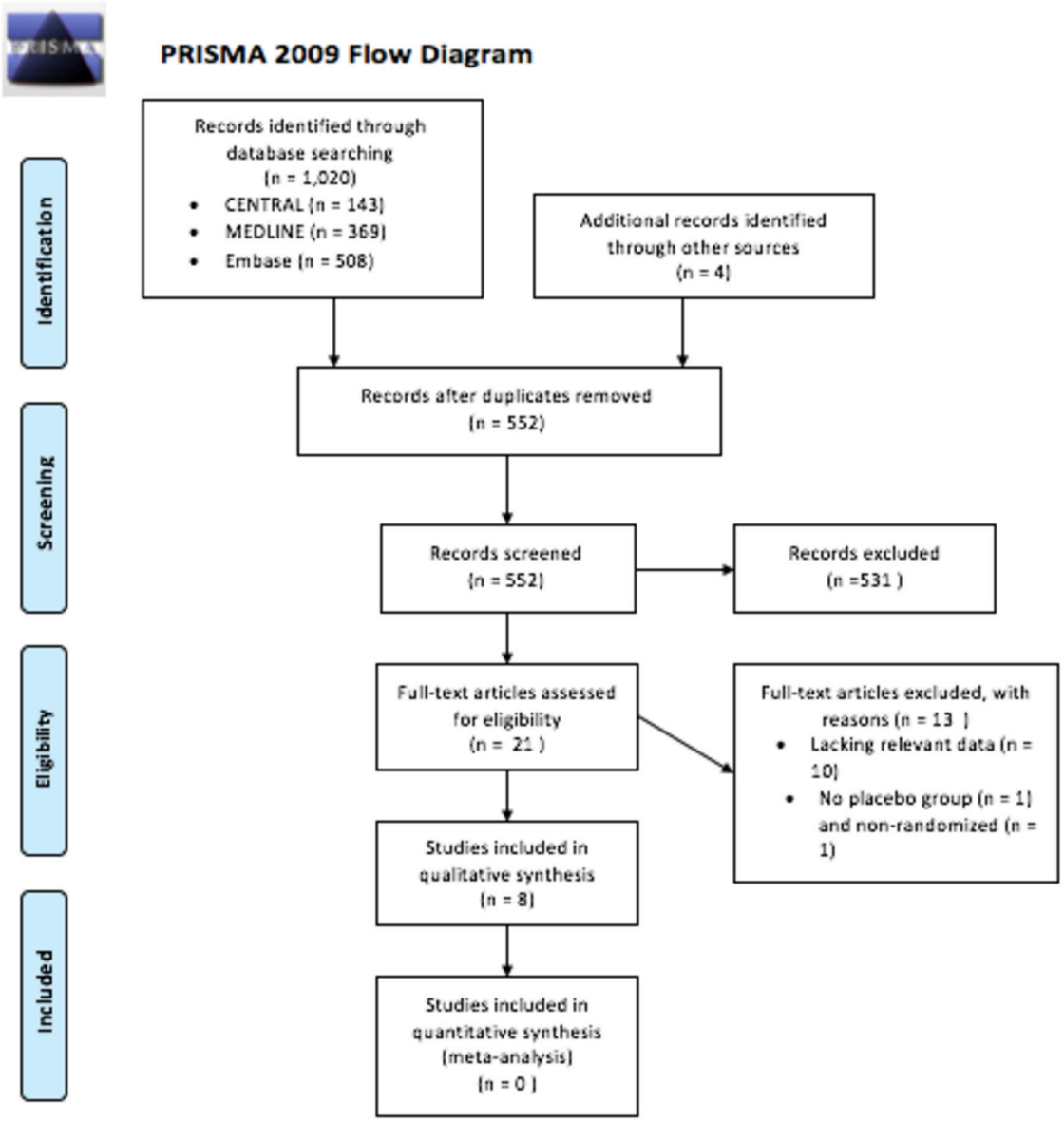
MPD: minimal phototoxic dose
MED: minimal erythema dose

[A]: included also erythrodermic, guttate, pustular psoriasis
[B]: reported only group related average age

Table II. Risk of bias evaluation for the included studies

	Randomization process	Effect of assignment to intervention	Effect of adhering to an intervention	Missing outcome data	Measurement the outcome	Selection of the reported results	Overall evaluation
Oral PUVA							
Valbuena *et al.*	+	+	+/-	+	+	+	+/-
Legat *et al.*	+/-	+	+/-	+	+	+	-
Melski *et al.*	-	-	-	-	+	+	-
El-Mofty *et al.*	+	+/-	+/-	+	+	+	-
Buckley *et al.*	+	+	+/-	+	+	+	+/-
NB-UVB							
Cameron *et al.*	+	+	+	+	+	+	+
Dawe *et al.*	+	+	+/-	+	+	+	+/-
Hallaji *et al.*	+/-	+/-	+/-	+	+	+	-

-: High risk of bias. The study have at least one domain of high risk or multiple evaluated with some concerns.
+/-: Some concerns in at least one domain but not to be at high risk of bias for any domain.
+: Low risk of bias



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