Overlapping network meta-analyses on psoriasis systemic treatments, an overview: quantity does not make quality

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Abstract

Background Network meta-analyses (NMAs) have become successful in addressing gaps in the comparative effectiveness of systemic treatments in moderate-to-severe psoriasis. However, their increasing number carries both a risk of overlap and reproducibility issues that can hamper clinical decision-making.

Objectives In this overview, we aimed to assess redundancy across these NMAs and to describe their characteristics.

Materials and methods We considered all systematic reviews with NMAs of randomized controlled trials that included adult patients with moderate-to-severe psoriasis and that evaluated the efficacy and/or safety of systemic treatments compared with placebo or with an active comparator. PubMed/MEDLINE, Epistemonikos, PROSPERO and the Evidence update of the Centre of Evidence-Based Dermatology of the University of Nottingham were searched up to 25 February 2021. Our main outcome was the number per year of redundant NMAs and the extent of their overlap. We also described their features, especially, the confidence in the results of the reviews, the funding of the studies and the presence of spin (a description that overstates efficacy and/or understates harm), reporting issues and methodological characteristics.

Results In total, 47 redundant NMAs were included. Only two of 47 (4%) included all available treatments. Both efficacy and safety were evaluated in 14 of 47 (30%) NMAs and both short- and long-term evaluations were assessed in five of 47 (11%). Confidence in the results was critically low for 39 of 47 (83%) NMAs and only 10 of 47 (21.3%) registered a protocol. Twenty-six of 47 NMAs (55%) received pharmaceutical funding. Contract research organizations were involved in 19 of 47 (40%) NMAs. Reporting was poor across most of the NMA abstracts and spin was present in all of the abstracts. Almost half of the NMAs failed to consider important limitations such as heterogeneity (considered in 32%) or consistency (considered in 66%).

Conclusions In addition to a duplication of efforts, our overview showed heterogeneous methods and poor confidence in the results in a majority of the included NMAs, further distorted by reporting issues and spin. Clinicians need to interpret NMAs with caution when looking for the most reliable and comprehensive evidence.
Psoriasis is a chronic inflammatory skin disease that affects 1–8% of the general population. Considering that since 2015, eight new molecules, including seven biological treatments and one small molecule, have been made available to treat moderate-to-severe psoriasis, physicians need complete and up-to-date synthesis of the evidence available in order to highlight their therapeutic choices. However, most biological treatments have been compared with placebo, and head-to-head comparisons of biologicals vs. conventional or between them are rare. Network meta-analysis (NMA) allows, after a systematic review (SR), the evaluation of several treatments in a single analysis by combining both direct and indirect evidence. This method also allows an estimation of the ranking of the interventions and has become a successful tool in addressing gaps in comparative effectiveness research, especially when numerous treatments are available. However, in some areas, there is a dramatic growing number of redundant NMAs. Such redundancy carries both a risk of overlap and reproducibility issues with differences in results that may be due to different methodological choices and to the exclusions of some of the available interventions. This observation is also true for psoriasis. Many NMAs have been published, hence the value in assessing their methodological quality as well as their comprehensiveness and agreement. The objective of our study was to assess the number per year of redundant NMAs evaluating the efficacy or safety of systemic treatments in moderate-to-severe plaque psoriasis, to describe their characteristics, and compare their differences.

Eligibility criteria
We considered all SRs with NMAs of randomized controlled trials (RCTs) that included adults with moderate-to-severe psoriasis and that evaluated the efficacy or safety of systemic treatments compared with placebo or with an active comparator. Systemic treatments included nonbiologic systemic treatments (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, BMS-986165) and biologic treatments (antitumour necrosis factor-α: etanercept, infliximab, adalimumab, certolizumab; anti-interleukin (IL) 12/23: ustekinumab; anti-IL17: secukinumab, ixekizumab, brodalumab, bimekizumab; anti-IL23: guselkumab, tildrakizumab, risankizumab, mirikizumab).

Study identification
We aimed to identify all relevant SRs with NMAs, regardless of language. We searched PubMed/MEDLINE, Epistemonikos and PROSPERO, as well as the Evidence update of the Centre of Evidence-Based Dermatology of the University of Nottingham from inception up to 25 February 2021. We checked the reference lists of the included and excluded publications to identify additional NMAs. The detailed search strategy is provided in Table S2 (see Supporting Information).

The selection process was conducted by two authors (R.G., L.L.C.) independently through Covidence (http://covidence.org). After exclusion of the duplicates, these two authors screened each title and abstract to exclude irrelevant studies and then examined the remaining full texts for eligibility. The two authors discussed any disagreement to reach consensus and, if necessary, were helped by a third author (E.S.). Two authors independently extracted the data in duplicate using a standardized form previously piloted; all eight authors

Materials and methods
This research was based on a protocol registered prior to data collection on the Open Science Framework on 10 February 2021 (osf.io/sjrk5). Reporting was performed according to the PRISMA 2020 checklist (Table S1; see Supporting Information).
We assessed Table S3 (see Supporting Information). Two authors independently assessed (see Supporting Information). We also assessed overlaps between NMAs for the studied population, the included treatments, the considered outcomes and the timing of evaluation, defined either as short term (between 2 and 28 weeks after randomization) or long term (after 28 weeks), and the methodological choices used for the NMA. A treatment was considered available for inclusion if at least one phase II or above trial evaluating that treatment had been published before the date of last search of the considered NMA.

Our secondary outcomes aimed to describe and compare the general characteristics of the included NMA. Hence, we:

• assessed the confidence in the results of the reviews according to AMSTAR 2 and the study’s funding and its effect on the reporting of efficacy in the abstract. AMSTAR 2 is a 16-item instrument designed to critically appraise SRs of RCTs or nonrandomized studies of healthcare intervention with or without meta-analysis.14 Two authors independently assessed the methodological quality as ‘high’, ‘moderate’, ‘low’ or ‘critically low’ according to AMSTAR 2 rules (Table S4; see Supporting Information), using the same process as outlined above in ‘Study identification’.

• checked for the presence of spin and reporting issues in the abstract according to the classification of Yavchitz et al., and the 2013 PRISMA checklist for abstracts (see Table S5 and Figure S1; see Supporting Information).15,16 The detection and description of spin in the abstracts was done by two authors (R.G., L.L.C.) independently following the classification from Yavchitz et al.,15 blinded to the funding status of each article. To fit to NMA specificities items 10, 11 and 12, related to the ‘misleading interpretation’ category, were summarized as one item: ‘Selective reporting of or overemphasis on the ranking of interventions without considering its uncertainty’.

• evaluated the agreement between the conclusions of the NMAs published at similar periods by comparing the treatments reported as having the best short-term efficacy.

Data extraction

The main characteristics of the NMAs were extracted, such as the name of the first author, date of publication, inclusion and exclusion criteria of the primary studies, studied population, included interventions in the network and considered outcomes with their timeframe of evaluation. We also extracted information regarding the registration of a protocol, the use of reporting guidelines, the number of studies included in the SR and the NMA and the methodological choices used for the NMA. Additionally, we extracted the list of previously cited NMAs on the same topic, authors’ affiliations, study funding, declaration of efficacy in the abstracts, conflicts of interest among authors, and assistance of a contract research organization (CRO).17 See Table S6 (see Supporting Information) for further details.

Statistical analyses

Descriptive analyses were conducted and categorical variables were presented as percentages. Medians were presented with their interquartile range (IQR). The effect of funding was analysed according to the following categories: academic funding, industry funding, none, not reported. As an exploratory analysis, the assessments of significant difference were based on the $\chi^2$ or Fisher’s exact test for categorical data as appropriate. The statistical significance threshold was set at 0.05.

Deviation from the protocol

Descriptions of the methodological characteristics of the included NMAs were added to provide additional details of the included studies. We also assessed the agreement between the studies’ conclusions regarding the treatments reported as having the best short-term efficacy in the abstracts.

Results

Included studies

Of the 1176 citations of potentially eligible studies, 47 were included (Figure 1).

Redundant network meta-analyses and overlaps

We included 47 NMAs assessing systemic treatments in moderate-to-severe psoriasis.18–64 The publication rate grew from one published per year in 2006 to a maximum of 12 per year in 2020 (Figure 2). The main characteristics of the included NMAs are summarized in Table 1 and detailed in Table S7 (see Supporting Information).

All NMAs included adult patients with moderate-to-severe plaque psoriasis and three also included children and young adults.12,41,58 Most NMAs included only some of the available treatments. A majority (39 of 47; 83%) of the NMAs evaluated exclusively the licensed dosage of the included interventions. Biological treatments were evaluated in all NMAs but all available biological treatments were considered in six of 47 (12.8%) NMAs. Included interventions in each NMA are summarized in Figure 3. Disregarding other interventions, biological treatments were the only treatment category evaluated in 28 of 47 (59.6%) NMAs. Five NMAs
NMAs evaluated all treatment categories. All available nonbiological treatments were included in 14 of 47 (29.8%) and two of 47 (4.3%) included all available small molecules. In the end, two NMAs included all available biological treatments, nonbiological treatments and small molecules.11,48

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. Forty-seven studies are included in our review; several were referenced twice. NMAs, network meta-analyses; RCT, randomized controlled trial.

Figure 2 Cumulative number of published network meta-analyses (NMAs) over time.

(10.6%) NMAs evaluated all treatment categories. All available nonbiological treatments were included in 14 of 47 (29.8%) and two of 47 (4.3%) included all available small molecules. In the end, two NMAs included all available biological treatments, nonbiological treatments and small molecules.11,48
| Included NMA                  | Number of studies in SR | Number of studies in NMA | Included interventions | Number of included interventions | Studied outcomes | Duration of evaluation | Source of funding | CRO |
|------------------------------|-------------------------|--------------------------|------------------------|---------------------------------|------------------|------------------------|-------------------|-----|
| Woolacott 2006               | 18                      | 39                       | Some Biol, some Conv   | 6                               | Efficacy         | ST                     | Academic          | No  |
| Reich 2008                   | 18                      | 39                       | Some Biol              | 4                               | Efficacy and QoL | ST                     | Industry          | Yes |
| Bansback 2009                | 18                      | 39                       | All Biol, some Conv    | 7                               | Efficacy         | ST                     | Industry          | No  |
| Reich 2012                   | 20                      | 40                       | Some Biol              | 5                               | Efficacy         | ST                     | Industry          | Yes |
| Lin 2012                     | 17                      | 34                       | All Biol               | 5                               | Efficacy         | ST                     | Academic          | No  |
| Baker 2012                   | 31                      | 60                       | Some Biol              | 4                               | Efficacy         | ST                     | Industry          | No  |
| Galván-Banqueri 2013         | 14                      | 28                       | Some Biol              | 4                               | Efficacy         | ST                     | NR               | No  |
| Igarashi 2013                | NR                      | NR                       | Some Biol              | 5                               | Efficacy         | ST                     | Industry          | Yes |
| Schmitt 2014                 | 48                      | 96                       | Some Biol, some Conv   | 8                               | Efficacy         | ST                     | None             | No  |
| Gupta 2014                   | 21                      | 42                       | Some Biol, some Conv   | 6                               | Efficacy         | ST                     | None             | Yes |
| Signorovitch 2015            | 15                      | 30                       | Some Biol              | 4                               | Efficacy         | ST                     | Industry          | Yes |
| Messori 2015                 | 13                      | 26                       | Some Biol              | 3                               | SAEs, infection  | ST                     | None             | No  |
| Fan 2015                     | 6                       | 12                       | Some Biol              | 2                               | Efficacy         | ST                     | Industry          | No  |
| Shibian 2017                 | 109                     | 170                      | All Biol, all Conv, all SmMol | 19                             | Efficacy, safety and QoL | ST | Academic | No |
| Jabbar-Lopez 2017            | 41                      | 82                       | Some Biol, some Conv   | 7                               | Efficacy, safety and QoL | ST | Academic | No |
| Gómez-García 2017            | 27                      | 54                       | Some Biol              | 5                               | Efficacy and safety | ST | Academic | No |
| Al Sawah 2017                | 24                      | 48                       | Some Biol              | 5                               | Efficacy         | ST                     | Industry          | No  |
| Loos 2018                    | 34                      | 68                       | Some Biol, some SmMol  | 8                               | Efficacy         | ST                     | Academic          | No  |
| Sawyer 2018                  | 67                      | 134                      | Some Biol, some Conv, some SmMol | 10                             | Efficacy         | ST | Industry | Yes |
| Imafuku 2018                 | 4                       | 8                        | Some Biol              | 4                               | Efficacy         | ST                     | Industry          | Yes |
| Geng 2018                    | 33                      | 66                       | Some Biol, some Conv   | 7                               | Efficacy         | NR                     | NR               | No  |
| Warren 2018                  | 6                       | 12                       | Some Biol              | 4                               | Efficacy, QoL    | ST                     | Industry          | No  |
| Lv 2018                      | 75                      | 150                      | Some Biol, some Conv, alfacept, efalizumab | NR                             | Efficacy, safety and QoL | NR | Academic | No |
| Armstrong 2018               | 20                      | 40                       | Some Biol, some SmMol  | 7                               | Efficacy         | ST and LT              | Industry          | Yes |
| Cameron 2019                 | 45                      | 90                       | Some Biol, some SmMol  | 10                              | Efficacy, safety and QoL | ST | Industry | Yes |
| Sawyer 2019                  | 83                      | 166                      | Some Biol, some Conv, some SmMol | 15                             | Efficacy         | ST | Industry | Yes |
| Bai 2019                     | 28                      | 56                       | Some Biol              | 7                               | Efficacy and safety | ST | None | No |
| Sawyer 2019                  | 98                      | 196                      | Some Biol, some SmMol  | 8                               | Efficacy         | LT                     | Industry          | Yes |
| Xu 2019                      | 54                      | 108                      | Some Biol              | 13                              | Efficacy, safety and QoL | ST | None | No |
| Xu 2019                      | 13                      | 26                       | Some Biol              | 5                               | Efficacy and safety | ST | Academic | No |
| Shibian 2020                 | 140                     | 280                      | All Biol, all Conv, all SmMol | 19                             | Efficacy, safety and QoL | ST and LT | Academic | No |
| Armstrong 2020               | 160                     | 320                      | Some Biol, all Conv, some SmMol | 16                             | Efficacy         | ST and LT              | Industry          | Yes |
| Warren 2020                  | 33                      | 66                       | Some Biol              | 11                              | Efficacy and QoL  | ST | Industry | Yes |
| Warren 2020                  | 60                      | 120                      | Some Biol              | 9                               | Efficacy         | ST | Industry | Yes |
| Yasmeen 2020                 | 88                      | 176                      | Some Biol, some SmMol  | 11                              | Efficacy         | LT | Industry | Yes |

(continued)
The majority of the NMAs evaluated the short-term efficacy of the included interventions. Efficacy outcomes alone were evaluated in 32 of 47 (68.1%) NMAs and 39 of 47 (83%) of NMAs evaluated only short-term outcomes (Figure S2; see Supporting Information). Both efficacy and safety outcomes were evaluated in 14 of 47 (29.8%) NMAs. The outcome quality of life was evaluated in 12 of 47 (25.5%) NMAs (Figure S3; see Supporting Information). Both short- and long-term outcomes were studied in five of 47 (10.6%) NMAs.

**Overlaps in the methodological choices for the network meta-analyses**

Regarding the methodological characteristics, most NMAs used a Bayesian approach for their analysis and the majority of the results were obtained using a random-effects model. The methodological characteristics of the NMAs are summarized in Table 2.

The definitions of the nodes in the NMAs differed between NMAs, which led to different network shapes. Most NMAs, 37 of 47 (78.7%), performed a dose-level analysis, nine of 47 (19.1%) performed a drug-level analysis and six of 47 (12.8%) a class-level analysis. Four performed both a drug- and class-level analysis, and one performed both a dose- and class-level analysis.

Similarity between studies and population baseline characteristics were evaluated and addressed in 17 of 47 (36.2%) NMAs. Heterogeneity in the classical meta-analysis was evaluated in 32 of 47 (68.1%) studies and 15 (of 47, 31.9%) also evaluated the heterogeneity in the NMA.

**Updates and citation of previous network meta-analyses**

Among the 47 NMAs, four (8.5%) were updates of previous NMAs and stated as such in their manuscript. Almost all studies (89.1%) cited previously published NMAs but the median percentage of NMAs cited in relation to the number of NMAs already published was 19% (IQR = 7.8–36.9%) (Figure S4; see Supporting Information).

**Assessment of the methodological quality**

In all, 21 of 47 reviews (44.7%) stated using reporting guidelines. Among the 11 (23.4%) NMAs that stated a written
| NMA                        | DLS          | Interventions |
|---------------------------|--------------|---------------|
| Woolacott 2006 [18]       | 01/04/2004   |               |
| Reich 2008 [19]           | 01/12/2006   |               |
| Bansback 2009 [20]        | 01/01/2007   |               |
| Reich 2012 [21]           | 31/10/2008   |               |
| Baker 2012 [23]           | 01/05/2009   |               |
| Igarashi 2013 [25]        | end-2010     |               |
| Fan 2015 [30]             | 05/04/2011   |               |
| Lin 2012 [22]             | 01/02/2012   |               |
| Galvan Banqueri 2013 [24] | 01/08/2012   |               |
| Schmitt 2014 [26]         | 18/10/2012   |               |
| Gupta 2014 [27]           | 15/10/2013   |               |
| Signorovitch 2015 [28]    | ?            |               |
| Messor 2015 [29]          | ?            |               |
| Geng 2018 [39]            | 01/02/2015   |               |
| Gomez Garcia 2017 [33]    | 01/09/2015   |               |
| AlSawah 2017 [34]         | 01/11/2015   |               |
| Loos 2018 [35]            | 28/06/2016   |               |
| Sawyer 2018 [37]          | 31/08/2016   |               |
| Sawyer 2019 [45]          | 31/08/2016   |               |
| Jabbar Lopez 2017 [32]    | 17/10/2016   |               |
| Sbidian 2017 [31]         | 15/12/2016   |               |
| Imafuku 2018 [38]         | ?            |               |
| Warren 2018 [40]          | 01/03/2017   |               |
| Cameron 2019 [36]         | 01/08/2017   |               |
| Xue 2020 [59]             | 24/10/2017   |               |
| Lv 2018 [41]              | ?            |               |
| Armstrong 2018 [42]       | ?            |               |
| Xu 2019 [47]              | 08/08/2018   |               |
| Bai 2019 [44]             | 01/08/2018   |               |
| Armstrong 2020 [49]       | 17/09/2018   |               |
| Mahil 2020 [58]           | 07/09/2018   |               |
| Mrowietz 2021 [64]        | 01/10/2018   |               |
| Sawyer 2019 [43]          | 22/11/2018   |               |
| Xu 2019 [46]              | 20/11/2018   |               |
| Dulardin 2020 [54]        | 20/11/2018   |               |
| Warren 2020 [51]          | 15/11/2018   |               |
| Warren 2020 [50]          | 12/12/2018   |               |
| Sbidian 2020 [48]         | 31/01/2019   |               |
| Xu 2021 [57]              | 13/03/2019   |               |
| Diaz Acedo 2020 [60]      | 01/06/2019   |               |
| Shi 2020 [53]             | 2019         |               |
| Tada 2020 [55]            | 31/08/2019   |               |
| Yasmeen 2020 [52]         | 23/09/2019   |               |
| Blauvelt 2021 [62]        | ?            |               |
| Song 2021 [61]            | 01/05/2020   |               |
| Shear 2021 [63]           | 01/07/2020   |               |
| Torres 2020 [56]          | 01/07/2020   |               |
for 39 of 47 (83.0%) NMAs, low for six of 47 (12.8%) and moderate for two of 47 (4.3%) (Figure S5; see Supporting Information). Some of the failed critical domains were the absence of registered protocol for 39 NMAs, the absence of adequate literature search for 37 NMAs or the absence of evaluation of the risk of bias of the included studies for 16 NMAs (Figure S6; see Supporting Information).

Funding and conflicts of interest

Among the 47 included NMAs, 12 (25.5%) received academic funding, 26 (55.3%) pharmaceutical funding, six (12.8%) NMAs reported an absence of funding and three (6.4%) did not report whether they were funded or not (Table S8; see Supporting Information). Authors’ conflicts of interest were declared in 43 of 47 (91.5%) NMAs and 33 of these 43 (76.7%) had at least one author with declared conflicts of interests with pharmaceutical companies. CROs were involved in 19 of 47 (40.4%) of the NMAs, 18 of those funded by pharmaceutical companies. We found employees of pharmaceutical companies among the authors of 24 of 47 (51.0%) NMAs and employees of CROs in 16 of 47 (34.0%) NMAs.

Ranking of treatments, reporting in the abstracts and spin evaluation

In all, 23 of 47 (48.9%) NMAs reported a statistical method to assess the ranking of the included interventions, and some used more than one method. Among the 47 NMAs, 16 (34.0%) used the SUCRA (surface under the cumulative ranking curve), three (6.4%) used the probability of being best, five (10.6%) used the ranking probabilities and four (8.5%) used the mean rank.

Regarding the reporting evaluation of the NMA abstracts, we found that 70% of them scored 3 or less out of the 11-item PRISMA checklist (Table S9; see Supporting Information). In addition, the number of treatments, as well as the molecules cited as best, varied between the NMAs. For the short-term efficacy, 17 NMAs stated one treatment as being best, 16 cited two or three treatments as being best and nine cited more than three treatments. For industry-funded NMAs, the funding company’s treatment was systematically cited among the best treatments. Even though industry-funded NMAs tended to be more likely to cite only one treatment as best, there was no statistically significant association between the funding status and the number of treatments cited as best in the abstracts (P = 0.084) (Table S10; see Supporting Information). Furthermore, even NMAs published in the same year had several discrepancies regarding the treatments reported as having the best short-term efficacy (Figure 4). In 2020 for example, ustekinumab was cited among the best treatments by Mahil et al.18 but not by Armstrong et al.19 nor by Sbidian et al.48

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Table 2 Methodological characteristics of the included network meta-analyses, total n = 47 (unless otherwise noted below)

| NMA approach                        | n (%)     |
|-------------------------------------|-----------|
| Bayesian                            | 32 (68.1) |
| Frequentist                         | 7 (14.9)  |
| Bayesian and frequentist            | 2 (4.3)   |
| Bucher method                       | 4 (8.5)   |
| NR                                  | 2 (4.3)   |
| **NMA model**                       |           |
| Fixed effects                       | 8 (17.0)  |
| Random effects                      | 26 (55.3) |
| Fixed and random effects            | 7 (14.9)  |
| NR                                  | 6 (12.8)  |
| Adjustment for placebo-arm response| 11 (23.4) |
| Graphical representation of the network | 29 (61.7) |
| Level of base case analysis*        |           |
| Dose level                          | 37/47 (78.7) |
| Drug level                          | 9/47 (19.1) |
| Class level                         | 6/47 (12.8) |
| Results reported of the classical meta-analysis | 18/47 (38.3) |
| Results reported for all prespecified outcomes of interest | 41/47 (87.2) |
| Results reported for all relative comparisons available | 30/47 (63.8) |
| Adequate treatment ranking          | 23 (48.9) |
| SUCRA                               | 16 (34.0) |
| Probability of being best           | 3 (6.4)   |
| Ranking probabilities               | 5 (10.6)  |
| Mean rank                           | 4 (8.5)   |
| Evaluation of heterogeneity         | 28/47 (59.6) |
| Study of baseline characteristics   | 17/47 (36.2) |
| Model fit                           | 8/47 (17.0) |
| Statistical tests or measure (χ², Q test, I², τ²) | 16/47 (34.0) |
| Evaluation of heterogeneity in the network | 15/47 (31.9) |
| Presence of heterogeneity           |           |
| Yes                                 | 8 (17.0)  |
| No                                  | 12 (25.5) |
| Unclear                             | 2 (4.2)   |
| NR                                  | 25 (53.2) |
| Exploration of heterogeneity        | 15/47 (31.9) |
| Meta-regression                     | 6/47 (12.8) |
| Subgroup analysis                   | 1/47 (2.1) |
| Sensitivity analysis                | 5/47 (10.6) |
| None or NRb                         | 33/47 (70.2) |
| Exploration of heterogeneity when present | 4/8 (50.0) |
| Evaluation of consistency when possiblec | 27/41 (65.9) |
| Presence of inconsistencyc          |           |
| Yes                                 | 9/41 (22.0) |
| No                                  | 14/41 (34.1) |
| NR                                  | 18/41 (43.9) |

*aCategory overlap is described in the text. bSome of the 15 studies that evaluated heterogeneity did not report how they did it and are included in "None or NR" also. cNot available for six (n = 41). NR, not recorded; SUCRA, surface under the cumulative ranking curve.

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protocol had been followed, 10 were registered and accessible on PROSPERO but one of these could not be retrieved. The confidence in the results, using AMSTAR 2, was critically low.
Finally, at least one type of spin was found in all NMA abstracts with the median instances of spin being 3 (IQR: 2–4) (Table S11; see Supporting Information). A type of spin found in 30 of 47 (63/8%) abstracts was the selective reporting of or overemphasis on efficacy outcomes. The effect of the type of funding (Table S12; see Supporting Information) on the number of instances of spin per NMA was not significant ($P$ = 0.67).

**Discussion**

Our overview included 47 NMAs evaluating the efficacy and safety of systemic treatments in moderate-to-severe psoriasis with an acceleration of publication from one NMA published in 2006 to 12 published in 2020. As well as the redundancy of the included NMAs, our overview showed, for a majority of them, their incompleteness and a low methodological quality of the SR as well as the NMA. Furthermore, aside from reporting issues, there were some discrepancies between the NMAs’ conclusions regarding the number of treatments declared as best in each abstract. Some declared one treatment as being the best, others a cluster of treatments, and the molecules cited as best varied between studies. These differences were found even between NMAs published in the same year, with a systematic declaration of efficacy for the supporting pharmaceutical company’s treatment when industry funding was present.

From a clinical perspective, all interventions with therapeutic indication in moderate-to-severe psoriasis should always be included in the SR and, if possible, in the network of evidence. For some clinicians, it can be relevant to consider only the biological treatments. However, all available treatments should be considered, even if not of direct interest, as it increases the amount of data for the comparisons of interest and thus provides more precise estimates. In our overview, most NMAs included only some of the available treatments. Only six included all available biological treatments and only two evaluated all available systemic treatments. Moreover, both efficacy and safety must be assessed. Nevertheless, efficacy was the only outcome of focus for two-thirds of the NMAs, and safety was evaluated in only one-third. Both short- and long-term endpoints were studied in only 10% of the NMAs.

Beyond the redundancy, confidence in the results was low or critically low for 96% of the NMAs according to AMSTAR 2. Among the critical domains that hindered the confidence in

| NMA | ACI | CIC | FUM | MTX | ITD | EFA | BRA | TYK2 | APR | TOF | BRO | CERTO | ADA | ETA | UST | GUS | INF | IXE | RIS | SEC | TIL | BIME | GOL | MIRI |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Acitretin 2006 [48] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [49] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [50] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [51] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [52] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [53] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [54] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [55] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [56] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [57] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [58] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [59] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [60] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [61] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [62] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [63] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [64] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [65] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [66] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [67] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [68] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [69] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [70] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [71] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [72] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [73] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [74] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [75] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [76] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [77] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [78] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [79] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [80] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [81] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [82] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [83] | X | X | X | | | | | | | | | | | | | | | | | | | | | |
| Acitretin 2006 [84] | X | X | X | | | | | | | | | | | | | | | | | | | | | |

**Figure 4** Treatments cited as best in the abstract in relation to the included treatments for each NMA. X, included treatments; green squares, treatments cited as best; red outlines, treatment of the funding pharmaceutical company. ACI, acitretin; CIC, ciclosporin; FUM, fumaric acid esters; MTX, methotrexate; ITO, itolizumab; EFA, efalizumab; ALE, alefacept; BRA, briakinumab; TYK2, tyrosine kinase 2 inhibitor; APR, apremilast; TOF, tofacitinib; BRO, brodalumab; CERTO, certolizumab; ADA, adalimumab; ETA, etanercept; UST, ustekinumab; GUS, guselkumab; INF, infliximab; IXE, ixekizumab; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; BIME, bimekizumab; GOL, golimumab; MIRI, mirikizumab.
the results of most of the NMAs, 39 NMAs did not register a protocol and 16 did not assess the risk of bias of the included studies. Additionally, NMA requires that some assumptions are verified, for example transitivity, to ensure the validity of the results.\textsuperscript{67} Our results show that at least two-thirds of the included NMAs did not explicitly report checking for those assumptions.

The incompleteness of the NMAs and the methodological differences identified might explain, to some extent, the differences in the results. As Mills et al. showed, excluding some studies from NMAs can have an important impact on the results.\textsuperscript{12} On the same note, Palpacuer et al. demonstrated using the ‘vibration of effects’ framework, i.e. the extent to which an effect might change under multiple distinct analyses, that different inclusion and exclusion criteria can lead to opposite results.\textsuperscript{13}

Adding to those previous points, several abstracts were impaired with poor reporting and included a varied number of instances of spin. The second most frequent type of spin was related to the ranking of treatments. In 24 of 47 NMAs, the included treatments were ranked in decreasing size of relative treatment effect without taking into consideration the uncertainty of the estimates or the overlap between confidence intervals. When adequate ranking methods were used, some authors still failed to take into consideration the uncertainty when interpreting the ranking of the interventions.\textsuperscript{67} As for the reporting, some NMAs reported a single treatment as being the best, while others reported several.

Pharmaceutical companies supported more than half of the included NMAs. When short-term efficacy was discussed in the abstract, the funding pharmaceutical company’s treatment was systematically mentioned as the best or one of the best. This observation, added to the lack of registered protocol across the NMAs and the malleability of the methodological choices, leads us to asks whether the industry-funded NMAs are prone to publication bias by submitting NMAs where only the treatment of the pharmaceutical company shows the best result possible.

This proliferation of redundant NMAs is troubling. Journals ought to be aware of this issue and not prioritize publications of redundant reviews. Authors of a new NMA should plan their study with a registered protocol to clearly lay out what is unique and contributory about theirs, as well as to allow other authors to identify ongoing NMAs and avoid unnecessary duplication. Academic and clinical authors should be wary of collaborating with industry when starting new NMAs.

To our knowledge, there is only one similar overview, published in 2021 and funded by LEO Pharma. In this article, Wright et al. addressed the same issue as this overview.\textsuperscript{68} Our overview included 47 NMA compared with the 25 they included. Wright et al. concluded that analyses published within a similar time period were similar in their results and conclusions despite different methodological choices and funding sources, but nonetheless highlighted that consideration should be given to the NMAs that include all relevant trials and interventions and rely on valid methodology. Our conclusion differed from theirs as we included more NMAs and focused our attention on the reporting of the efficacy of the interventions in the abstracts rather than the actual ranking reported in the articles. In contrast to Wright et al.,\textsuperscript{68} our review also assessed the methodological quality of the studies using AMSTAR 2 as well as the reporting of the results and the presence of spin.

Our overview has limitations. The date of the last search of this overview was 25 February 2021, and it is likely that additional NMAs have been published between then and the time of publication. However, we believe that conducting an updated search would certainly change the number of redundant NMAs identified but would not change our overall conclusion. Furthermore, as there is currently no validated tool to assess the methodological quality of the NMAs, we chose to use AMSTAR 2, which is used for SRs with classical meta-analysis. This was also true for the description of spin given by Yavchitz et al.,\textsuperscript{15} which led us to adapt their classification for the needs of this overview. Another limitation was the impossibility to assess outcome reporting bias because few NMAs registered a protocol.

In conclusion, a proliferation in the number of NMAs has led to the increase in the number of redundant and overlapping studies. Our overview found important differences in methodological choices. Most NMAs included a fraction of the available treatments and ignored safety outcomes. Some authors seemed to focus on the conduct of NMAs, but disregarded mandatory steps of systematic review prior to the quantitative synthesis such as protocol registration or appropriate search strategy. Consequently, many NMAs provided results of low confidence, further distorted by reporting issues and spin. As the studies’ conclusions diverged, clinicians need to interpret them with caution when looking for the most reliable and comprehensive evidence. Improving the quality of publications using this method requires joint efforts to disseminate these good practices. These efforts concern the authors, the experts in the methods used and the reviewers of scientific journals. In combination, an international effort led by scientific societies should aim to raise awareness among authors and reviewers in relation to the thoroughness of systematic review and meta-analysis methods.

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Table S12 Instances of spin identified among each group of funding status.

Figure S1 2013 PRISMA checklist for abstract.

Figure S2 Timeframe of evaluation in weeks of the outcome of interest for each NMA.

Figure S3 Outcomes reported in each NMA.

Figure S4 Graphical representation of the citation of previously published NMAs for each study.

Figure S5 Study-level data for AMSTAR 2 checklist.

Figure S6 Methodological quality assessment for all items across NMAs.