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Assessing the Adverse Events of Roflumilast and Tapinarof Use in Pediatric and Young Adult Patients with Atopic Dermatitis: A Systematic Review

Running Head: Adverse Events of Roflumilast and Tapinarof in Young Patients with Atopic Dermatitis

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Abstract:

Background: Atopic Dermatitis (AD), a chronic inflammatory skin disease characterized by intensely pruritic episodes and eczematous lesions. This disease is prevalent in up to 25% of children, with about half of these cases persisting into adulthood. This systemic review aims to examine two new topical AD therapies, roflumilast and tapinarof, and investigate the adverse effects associated with their use.

Methods: A systemic review following the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was performed to assess the adverse events experienced by pediatric and young adult patients receiving either roflumilast or tapinarof for AD (PROSPERO CRD420251066719). A search was performed in Scopus, Embase, PubMed, Cochrane Library, and Web of Science on June 2, 2025. Randomized controlled trials were included if they reported adverse event outcomes in pediatric patients with AD after either roflumilast or tapinarof treatment. Studies were excluded if they did not include treatment with roflumilast or tapinarof, pediatric patients with AD, and/or report any adverse event outcomes. The Cochrane Risk of Bias 2 tool was used to assess bias. Results were reported as the occurrence (n) and frequency (%) within the pooled studies for the roflumilast and tapinarof groups. Risk ratio (RR) and 95% confidence intervals for reported adverse events of treatment (roflumilast or tapinarof vs vehicle cream) were evaluated using the Mantel-Haenszel method with a fixed-effect analysis model and risk ratios as the effect measure.

Results: Seven studies with a total of 3,615 patients with AD using roflumilast (n=1,979), tapinarof (n=658), or vehicle control (n=978) were included in the final data extraction and analysis. Three studies assessed roflumilast use (1,979 patients, a mean age of 19.8 years) with 0.05% or 0.15% roflumilast cream once daily with follow-up of four, 24 or 52 weeks. Four studies assessed tapinarof use (658 patients, mean age of 8.15 years) with 0.5% or 1% topical tapinarof cream once daily with follow-up of two or eight weeks. Both therapies displayed significant changes in treatment-emergent adverse events (TEAE) (RR=1.46 [1.20-1.77] with p=0.0001 for roflumilast; RR = 1.49 [1.24-1.79], p<0.0001 for tapinarof) when compared to vehicle controls. Treatment-related TEAEs were significantly increased with roflumilast use (RR=1.92 [1.15-3.19], p=0.01), but not tapinarof use (RR=1.30 [0.89-1.91], p=0.17). Roflumilast had an increased association with non-dermatologic adverse events compared to the vehicle control. Tapinarof was found to have an association with dermatologic adverse events.

Discussion: Some limitations of this review include the lack of direct comparative studies, limited data in pediatric and young adult populations, studies with mixed pediatric and adult patients, and heterogeneity of reported adverse events. Despite this, understanding the adverse event profiles of roflumilast and tapinarof is crucial.

Key Points:

- Despite new systemic therapies being released, topical therapy continues to be the cornerstone therapy used for AD. Roflumilast and tapinarof are two relatively new topical therapies used for AD in pediatric populations. It is important that patients, parents/guardians, and providers consider the adverse event profiles when considering treatment.
- Both tapinarof and roflumilast have an association with non-dermatologic adverse events like headache, upper respiratory tract infection, nasopharyngitis, diarrhea, and vomiting compared to the vehicle control groups.
- Tapinarof was also found to have an association with dermatologic adverse events, such as folliculitis, and a higher occurrence of TEAEs compared to the control group.

1. Introduction

Atopic Dermatitis (AD) is a chronic inflammatory skin disease that is characterized by eczematous lesions and intensely pruritic episodes that can lead to a poor quality of life in those affected [1]. Studies estimate that about 200 million individuals globally are affected, with estimated prevalence of up to 25% of children [2]. From the 25% of children, about half of those with AD will go into remission by adolescence, while the other half will have AD into adulthood [2]. In addition, those who develop AD at a young age are at an increased risk of other atopic diseases like asthma, allergic rhinitis, and food allergies [2,3]. Those with more severe AD are at an increased risk for the other atopic diseases. The "atopic march" describes the development of AD, asthma, allergic rhinitis, and IgE-mediated food allergies, with AD typically developing first [3,4].

The pathophysiology of the "atopic march" is initiated by an impaired skin barrier that results in a dysregulated immune response and constant IgE sensitization leading to exaggerated allergic responses with re-exposure. In atopic conditions, filaggrin, a protein that serves an essential role in maintaining skin barrier function, is often mutated [3,5]. This mutation enables environmental triggers like dust mites and food allergens to cause an inflammatory response [3,5]. This inflammatory response leads to increased release of proinflammatory cytokines, causing the signs and symptoms seen in each individual disorder. Even though the diseases comprising the atopic march all have an overlap in the mechanism of development, differences in the disease pathways factor into the way each disease presents and necessitate distinct treatments for each disease. This study will focus on the developing pharmacologic treatments for AD.

Historically, topical and systemic agents (tacrolimus or corticosteroids) have been used as first-line treatment for AD [6]. However, use of these pharmacological agents is not without their own adverse effects. Tacrolimus, a topical calcineurin inhibitor, has been found to cause local burning and stinging sensations, especially during first days of use [7]. Meanwhile, chronic use of corticosteroids (including topical corticosteroids) has been shown to cause skin atrophy and adrenal suppression [8,9].

As the understanding of the underlining pathophysiology of AD becomes better elucidated, new agents targeting specific molecular mediators involved in the development of atopic disease are being developed. Two agents, roflumilast and tapinarof, have been shown to have comparable efficacy with improved safety and tolerability for long-term use [10,11]. Roflumilast is a selective phosphodiesterase-4 (PDE4) inhibitor that inhibits cyclic adenosine monophosphate phosphodiesterase activity and acts as an effective anti-inflammatory drug [11]. Tapinarof is a topical aryl hydrocarbon receptor (AhR) agonist that results in downregulation of Th2 and Th17 cytokines and allows for increased skin-barrier protection, which has been shown to be an effective treatment for AD [10]. While these drugs have been found to be effective, the adverse effects of these drugs have not been fully investigated [12]. This study aims to investigate the occurrence and risk ratios of the adverse effects associated with roflumilast and tapinarof.

2. Methods

2.1 Search Strategy

This review was conducted following the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered to PROSPERO (CRD420251066719). The completed PRISMA 2020 Checklist and PRISMA 2020 for Abstracts Checklist can be found in **Online Resource 1 and 2,** respectively. A thorough search was performed in the search engines Scopus (Elsevier; Amsterdam, Netherlands), Embase (Elsevier; Amsterdam, Netherlands), PubMed (National Institutes of Health; Bethesda, Maryland, United States of America), Cochrane Library (Cochrane; London, United Kingdom), and Web of Science (Clarivate; London, United Kingdom). The Boolean search phrase "((Roflumilast) OR (Zoryve) OR (Tapinarof) OR (Vtama)) AND ((eczema) OR (atopic dermatitis)) AND (pediatrics)" was used in each search engine. **Online Resource 3** details the search terms and results; **Online Resource 4** details the Population, Intervention, Comparator, Outcomes, Timing, and Study Design (PICOTS) framework.

2.2 Study Screening Criteria and Study Selection

Inclusion criteria were (1) patients receiving roflumilast or tapinarof, (2) patients with AD, (3) studies including pediatric patients ≤18 years of age, (4) studies reporting adverse events after drug treatment, and (5) randomized controlled trials. Exclusion criteria were (1) patients treated with agents other than roflumilast or tapinarof, (2) patients without AD, (3) studies including only patients >18 years of age, (4) studies without any form of adverse event reporting, (5) all studies that were not randomized controlled trials, (6) studies that did not have a full-length text available (i.e., conference abstracts, as these do not provide complete information for extraction and analysis), and (7) studies not published in English.

Covidence (Covidence; Melbourne, Australia) software was used for the title/abstract and full-text screening stages. Screening at these stages was independently conducted by two authors via a double-blinded dual-screening process. Any discrepancies were resolved via discussion between the two voting authors or consultation with a third reviewer. All included studies then underwent further reference review to search for additional studies to include; one study was included this way.

2.3 Data Extraction, Statistical Analysis, Quality Assessment, and Risk of Bias

Data extraction was performed by one independent reviewer using a standardized template including: level of evidence, number of patients, number of males and females, mean age (including confidence intervals or ranges or standard deviations), treatment (Roflumilast or Tapinarof), dosages, route of administration, mean follow-up time, and adverse events. The extracted data was cross-checked by two other reviewers. The full extraction can be found in **Online Resource 5.** The primary endpoints of this analysis were any adverse event outcomes and any variation of that such as treatment-emergent adverse event (TEAE) or a specific adverse event, like upper respiratory tract infection (URI). Descriptive statistics (mean, median, ranges, standard deviation) were reported if applicable and available. The extracted variables were compiled on Google Sheets (Google; Mountain View, California, United States of America).

A statistical analysis was initially planned for all primary endpoints; however this was not possible due to the available data and results across the pooled studies. Therefore, a statistical analysis was performed to evaluate the risk ratios of the TEAE, treatment-related TEAE, and/or TEAE on the application site for roflumilast or tapinarof. The statistical analysis was performed using only studies that compared roflumilast or tapinarof to a control group. The statistical method used was Mantel-Haenszel with a fixed-effect analysis model and risk ratios as the effect measure. Heterogeneity was assessed using the I-squared statistic. Forest plots were generated using Cochrane's Review Manager (RevMan, version 5.4, The Cochrane Collaboration; London, United Kingdom).

The Cochrane Risk of Bias (RoB 2) tool was used to evaluate study quality as all included studies were randomized controlled trials. Two independent reviewers completed this using the following six domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias due to measurement of outcomes, bias in selection of the reported result, and overall bias. Each domain is categorized as having a "high," "low," or "unclear" risk of bias. The full quality assessment and risk of bias can be found in **Online Resource 6.**

3. Results

3.1 Literature Selection

A total of 194 studies were screened in the title and abstract screening, as 35 of the initial 229 studies were identified as duplicates. Sixteen studies were screened in the full text screening stage, with nine of these being excluded for being an abstract only, having no access to a full-length peer-reviewed text, or presenting the wrong study design. A final seven studies were included in the final data extraction and analysis **(Figure 1).**

Of the initial 229 studies identified, only seven studies [10,11,13–17] included pediatric patients and were thus included in the final analysis. Of the seven included studies, five had a low risk of bias and two had an unclear risk of bias. A total of 3,615 patients with AD were analyzed in the present study; 2,637 of these patients were treated with either roflumilast or tapinarof and 978 were treated with a control. Three studies assessed roflumilast and included 1,979 patients who were treated with either 0.05% or 0.15% topical roflumilast cream once daily. These patients had a mean age of 19.8 years and were assessed for follow up durations of either four, 24, or 52

weeks. Simpson *et al.* 2024 presented the INTEGUMENT-1 and INTEGUMENT-2 trials, and Simpson *et al.* 2025 presented the INTEGUMENT-open label extension (OLE) trial, all of which included mixed pediatric and adult patients receiving roflumilast [11,17]. Four studies assessed tapinarof and included 658 patients who were treated with 0.5% or 1% once daily topical tapinarof cream. These patients had a mean age of 8.15 years and were followed for either two or eight weeks. Gold *et al.* 2025 and Silverberg *et al.* 2024 both report results from the ADORING 1 and ADORING 2 trials which included mixed pediatric and adult patients receiving tapinarof [10,14].

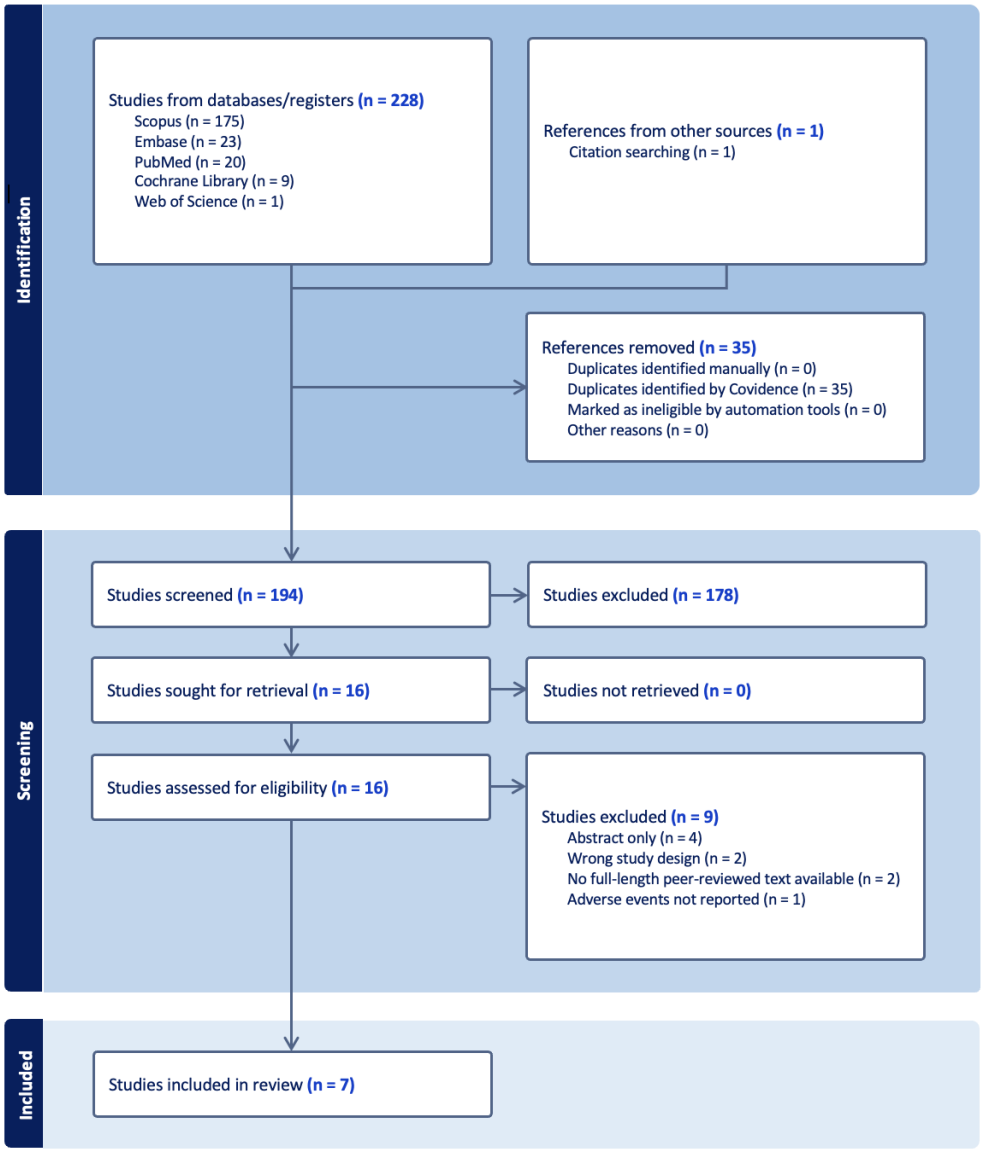

Figure 1. PRISMA flowchart depicting study selection and inclusion. Of the initial 229 studies identified, 194 were screened, and seven were included in the final analysis.

3.2 Roflumilast

Adverse events were presented in all three of the studies analyzing roflumilast [11,13,17]. A summary of the pooled adverse event occurrences and risk ratios with roflumilast treatment can be found in **Table 1** and **Table 2.** Of the 1,979 patients that were treated with roflumilast, treatment-emergent adverse events (TEAE) were found in 565 (28.5%) patients. Compared to the vehicle cream, the risk ratio of experiencing a TEAE was significantly increased in patients treated with roflumilast; the risk ratio (RR) was 1.46 with a 95% confidence interval (95% CI) of 1.20 to 1.77 and p-value of 0.0001 (**Online Resource 7**). Ninety-nine (5.00%) patients experienced a treatment-

related TEAE. Patients treated with roflumilast had a significantly increased risk of experiencing a treatment-related TEAE compared to patients treated with the vehicle cream (RR = 1.92, 95% CI = 1.15 to 3.19, and p-value = 0.01) (**Online Resource 8**). TEAE on the application site (application site pain) was observed in 29 (1.47%) of the patients treated with roflumilast cream. The risk ratio of a TEAE on the application site was not significantly different between patients treated with roflumilast cream compared to the vehicle cream (RR = 1.12, 95% CI = 0.63 to 1.99, p-value = 0.70) (**Online Resource 9**).

Specific adverse events were also observed in patients treated with roflumilast. Upper respiratory tract infections (URI) were reported in 44 (2.22%) patients across all three studies analyzing roflumilast [11,13,17]. Nasopharyngitis was reported in 28 (1.41%) patients across two studies with patients receiving 0.15% roflumilast [11,17]. The frequency of headache was similar to that of upper respiratory tract infections, as headache was observed in 44 (2.22%) patients. Eichenfield *et al.* 2025 and Simpson *et al.* 2024 both reported diarrhea, and vomiting [11,13]. Diarrhea and vomiting were observed in 24 (1.21%) and 22 (1.11%) of the patients treated with roflumilast, respectively. Diarrhea and vomiting were slightly increased in patients treated with 0.05% roflumilast compared to patients 0.15% roflumilast.

Interestingly, a total of seven (0.35%) patients who received roflumilast were reported to have a progression of AD after treatment. Eichenfield *et al.* 2025 reported progression of AD in two (0.5%) of the 437 patients that received 0.5% roflumilast cream, compared to five (2.3%) of the 215 patients that received the vehicle cream [13].

Table 1. Pooled occurrence of adverse events after roflumilast treatment

	Roflumilast* (N = 1,979)
Treatment Emergent Adverse Events	565 (28.5%)
Treatment-Related Treatment Emergent Adverse Events	99 (5.00%)
Treatment Emergent Adverse Events on Application Site	29 (1.47%)
Upper Respiratory Tract Infection	44 (2.22%)
Nasopharyngitis	28 (1.41%)
Headache	44 (2.22%)
Diarrhea	24 (1.21%)
Vomiting	22 (1.11%)
Progression of Atopic Dermatitis	7 (0.35%)

*The values are reported as number of events and percentage of the total population experiencing the event: n (%)

Table 2. Risk ratios for selected adverse events across roflumilast treatment. The reported risk ratios were calculated using roflumilast vs vehicle control. A p-value of less than 0.05 indicates statistical significance, *p-value < 0.05. I^2 refers to heterogeneity.

	Risk Ratio (95% Confidence Interval)	**I^2 (%)**	**p-value**
Treatment Emergent Adverse Events	1.46 (1.20-1.77)	0	0.0001*
Treatment-Related	1.92 (1.15-3.19)	10	0.01*

Treatment Emergent Adverse Events			
Treatment Emergent Adverse Events on Application Site	1.12 (0.63-1.99)	16	0.70

3.3 Tapinarof

All four of the studies evaluating tapinarof reported adverse events [10,14–16]. A summary of the pooled adverse events and risk ratios with tapinarof treatment can be found in **Table 3** and **Table 4.** Three of these articles presented adverse events as TEAE, treatment-related TEAE, and/or specific adverse events [10,15,16]. Of the 658 patients treated with tapinarof, 269 (40.9%) experienced a TEAE. There was a significantly increased risk of experiencing a TEAE when treated with tapinarof compared to the vehicle cream (RR = 1.49, 95% CI = 1.24 to 1.79, p-value < 0.0001) (**Online Resource 10**). Eighty (12.2%) of the patients reported treatment-related TEAEs, although there was no significant difference in risk of experiencing this compared to the vehicle cream (RR = 1.30, 95% CI = 0.89 to 1.91, p-value = 0.17) (**Online Resource 11**). Application site adverse events were only reported in five (0.76%) patients. Only Igarashi *et al.* 2025 reported application site irritation; they found that two (5.00%) of the 40 patients treated with 0.5% tapinarof cream and three (7.32%) of the 41 patients treated with 1% tapinarof experienced application side irritation [15].

Between the studies evaluating tapinarof, there was less overlap between the specific adverse events compared to the three studies evaluating roflumilast. Only one study reported URI as an adverse event in three (7.31%) of the 41 patients that were treated with 1% tapinarof cream [15]. Therefore, URI was only reported in three (0.46%) of the patients treated with tapinarof that are analyzed in the present study. Nasopharyngitis was reported in 22 (3.34%) patients treated with 1% tapinarof across two studies [9,14]. Headache was reported in 29 patients (4.41%). Igarashi *et al.* 2025 reported headache in one of 40 patients (2.5%) treated with 0.5% tapinarof and in two of 41 patients (4.9%) treated with 1% tapinarof [15]. Silverberg *et al.* 2024 reported headache in a higher proportion of patients treated with 1% tapinarof in the ADORING 1 trial, as compared to patients treated with 1% tapinarof in the ADORING 2 trial, as headache was reported in 7.0% and 1.5% of patients, respectively [10]. None of the studies reported diarrhea. Vomiting was only reported in two (0.30%) of the 658 patients treated with tapinarof. Paller *et al.* 2025 reported vomiting in one patient aged between two to six years old and in another patient aged between seven to 11 years old [16].

Dermatologic related adverse events were more noticeably reported in the studies regarding tapinarof compared to the studies regarding roflumilast. Folliculitis was reported in two studies, with 45 (6.84%) patients experiencing this as an adverse event [10,16]. Paller *et al.* 2025 reported one patient aged between 7 to 11 years old treated with 1% tapinarof cream that experienced folliculitis [16]. Silverberg *et al.* 2024 reported 44 patients treated with 1% tapinarof cream that experienced folliculitis [10]. Similarly, Silverberg *et al.* 2024 reported follicular events in 51 patients [10]. Contact dermatitis was reported in a total of eight patients who were treated with 1% tapinarof [10,15].

Gold *et al.* 2025 reported safety data from Silverberg *et al.* 2024, and made special note that none of the trial discontinuations in patients treated with 1% tapinarof were due to burning/stinging or itching [10,14]. Gold *et al.* 2025 also reported that the patient or parent/caregiver scores of burning/stinging and itching decreased throughout the eight-week trial and that score reduction was greater in the patients treated with 1% tapinarof compared to the vehicle cream [14].

Table 3. Pooled occurrence of adverse events after tapinarof treatment

	Tapinarof* (N = 658)
Treatment Emergent Adverse Events	269 (40.9%)

Treatment-Related Treatment Emergent Adverse Events	80 (12.2%)
Treatment Emergent Adverse Events on Application Site	5 (0.76%)
Upper Respiratory Tract Infection	3 (0.46%)
Nasopharyngitis	22 (3.34%)
Headache	29 (4.41%)
Diarrhea	0 (0.00%)
Vomiting	2 (0.30%)
Folliculitis	45 (6.84%)
Follicular events	51 (7.75%)
Contact dermatitis	8 (1.22%)

*The values are reported as number of events and percentage of the total population experiencing the event: n (%)

Table 4. Risk Ratios for selected adverse events across tapinarof treatment. The reported risk ratios were calculated using tapinarof vs vehicle control. A p-value of less than 0.05 indicates statistical significance, *p-value < 0.05. I^2 refers to heterogeneity.

	Risk Ratio (95% Confidence Interval)	**I^2 (%)**	**p-value**
Treatment Emergent Adverse Events	1.49 (1.24-1.79)	73	<0.0001*
Treatment-Related Treatment Emergent Adverse Events	1.30 (0.89-1.91)	56	0.17

4. Discussion

4.1 Roflumilast and Tapinarof

Roflumilast and tapinarof have quickly emerged as effective and safer alternatives to the traditional steroidal approach for AD, which had previously complicated the management of AD in pediatric populations due to extensive adverse effects with long-term use. However, due to the novelty of these agents and recent FDA-approval in the pediatric population for AD, it is essential to continue assessing for safety with use of roflumilast and tapinarof.

The INTEGUMENT 1 and 2 trials from Simpson *et. al* 2024 served as an extensive analysis of the efficacy and safety of roflumilast for AD in both pediatric and adult patient populations (mean age of 27.7 years old) [11]. TEAE rates were found to be 21.8% (any TEAE) and 6.1% (treatment-related TEAE) for roflumilast cream 0.15% compared to vehicle cream, the most common AEs being headache (2.3%), nausea (1.8%), and nasopharyngitis (1.8%).

Our analysis of the three studies examining roflumilast yielded similar findings, with a TEAE occurrence of 28.5% and treatment-related TEAEs occurrence of 5%. The most common adverse events were headache and URI, both occurring in 2.22% of patients, followed by nasopharyngitis in 1.41%.

The ADORING 1 and 2 trials from Silverberg *et. al* 2024 provided comprehensive insight into the efficacy of tapinarof for AD in both children and adults (mean age 15.6 years old), with TEAE rates up to 45.6% (any TEAE) and 12.6% (treatment-related TEAE) for tapinarof cream 0.15% compared to vehicle cream, the most common being folliculitis (8.1%), headache (7%), and nasopharyngitis (4.8%) [10]. Similarly, our findings for the four studies evaluating tapinarof observed TEAE rates up to 40.9% and treatment-related TEAEs up to 12.2% for tapinarof 1% once daily cream compared to vehicle cream, with the most common adverse events being folliculitis (6.84%), headache (4.41%), nasopharyngitis (3.34%), and contact dermatitis (1.22%).

Overall, the acute safety data for occurrence of TEAEs found in this review for a primarily pediatric population (mean age between 8.15 to 19.8 years old) aligns with the large-scale study data for these agents for both adults and children alike, with slightly higher occurrence of TEAEs in tapinarof compared to roflumilast, the most common being headaches, nasopharyngitis, and folliculitis. The large difference in mean age between the two studied drugs can be attributed to the included age of the pediatric patient population being wider for tapinarof as compared to roflumilast. The efficacy of tapinarof was assessed in patients down to 2 years of age in ADORING 1 and 2 trials, compared to roflumilast, which was only assessed in patients down to 6 years of age in INTEGUMENT 1 and 2 trials. This is important to be aware of when analyzing these results, as the patient population for which these results apply will differ as tapinarof results can be applied to pediatric patients aged 2 and up while roflumilast results analyzed will only apply to ages 6 and up. Mean follow-up time also greatly differed between tapinarof (2 to 8 weeks follow-up) as compared to roflumilast (4 to 52 weeks), which indicates slightly greater accuracy of analyzed long-term effects for roflumilast compared to tapinarof.

Subsequent meta-analysis of the roflumilast studies found statistically significant increased risk for TEAEs (RR:1.46; CI: [1.20-1.77]) and treatment-related TEAEs (RR: 1.92; CI: [1.15-3.19]) compared to a vehicle cream, with low heterogeneity (between 0% and 10%) within this statistical analysis. These studies also found a <1% occurrence of AD progression with roflumilast (0.35%), with most of the adverse events observed being non-dermatologic (headache, URI, nasopharyngitis, diarrhea, vomiting). This is a contrast to topical steroid use for children with AD, which are associated almost exclusively with dermatologic adverse events such as skin irritation, folliculitis, skin infections, striae, acne, skin atrophy, and telangiectasias [18]. Furthermore, while our study did not examine efficacy rates, the aforementioned INTEGUMENT trials demonstrated statistically significant improvements in AD clinical progression at multiple end points, which points to the efficacy of roflumilast for this condition [11,17]. These findings, along with the high efficacy of roflumilast seen in the INTEGUMENT trials, further emphasize the advantage of roflumilast use for AD, especially in pediatric populations that may experience more severe complications with chronic steroid use for this disease process.

Subsequent meta-analysis of the tapinarof studies found statistically significant increased risk for TEAEs (RR:1.49; CI: [1.24-1.79]), but no statistical significance for treatment-related TEAEs (RR: 1.30; CI: [0.89-1.91]) compared to a vehicle cream, with high heterogeneity (between 56% to 73%) within this statistical analysis. The high heterogeneity could be due to variation in sample size between the four included studies, as two of the studies included had a sample size less than 100 patients while the other two studies had a sample size greater than 400 patients. Sensitivity analysis was performed and revealed that the high heterogeneity lies in the inclusion of study data from Igarashi *et al.* 2025, which included sample sizes less than 100 [15]. With exclusion of this study, there is found to be a stronger risk of TEAEs (RR:1.77; CI: [1.39-2.25]) and of treatment-related TEAEs (RR:1.86; CI: [1.13-3.06]), with a heterogeneity of 0%. Further subgroup analysis was not possible due to the limited quantity of included studies. Efficacy of tapinarof was established by the ADORING trials, which found a statistically significant clinical improvement of AD from baseline with tapinarof 1% cream compared to vehicle cream.

The most common adverse events we found for tapinarof were dermatologic in nature, with folliculitis/follicular events being most common (6.84%), followed by headache, nasopharyngitis, and contact dermatitis. This aligns with the findings of the ADORING trials, where folliculitis was the most common adverse event reported (8.1%) [10]. In comparison with topical steroids, folliculitis was only reported in 0.6% of pediatric patients with AD, but these agents are associated with significantly increased risk of skin thinning (RR:4.86; CI: [1.06 to 22.28]) [19]. Thus, while tapinarof can be used as an efficacious, non-steroidal agent for AD, it does have a

greater association with dermatologic adverse events, such as folliculitis, and a higher frequency of TEAEs compared to control groups.

When comparing the occurrence of TEAEs in patients treated with tapinarof vs patients treated with roflumilast, tapinarof has a higher occurrence of TEAEs (40.6% vs 28.5%) and treatment-related TEAEs (12.2% vs 5.00%). This is also supported by the risk ratio for TEAEs with tapinarof being slightly higher than that of roflumilast (RR: 1.49 vs RR:1.46).

Tapinarof was also found to have a greater association with specific dermatologic adverse events (6.84% of patients experiencing folliculitis and 1.22% experiencing contact dermatitis) when compared to roflumilast, which was only found to have a 0.35% occurrence of progressive AD. On the other hand, roflumilast had a greater frequency of application site reactions (1.47%) compared to tapinarof (0.76%). However, the risk ratios for these application-site TEAEs were not statistically significant. One possible explanation for the increased occurrence of dermatologic adverse events in tapinarof compared to roflumilast may lie in the pharmacokinetic differences of the treatments. Tapinarof is an AhR agonist and AhR is expressed at high levels in skin [20,21]. Tapinarof has shown little-to-no systemic absorption, which may help to explain its association with dermatologic-related adverse events [10]. Roflumilast is a PDE4 inhibitor, with PDE4 being widely expressed in the central nervous system, smooth muscle, immune system, and skin barrier [22]. Roflumilast is converted to its active metabolite of roflumilast N-oxide; while systemic absorption with topical roflumilast is less than that of oral roflumilast, systemic exposure of both roflumilast and roflumilast N-oxide has been observed with topical administration in pediatric and adult patients [23,24]. This observed systemic absorption coupled with the expression pattern for PDE4 can provide a potential explanation for why dermatologic-related adverse events were not as common with roflumilast.

Based on these comparisons of adverse event occurrence alone, it seems that roflumilast may be a safer option dermatologically for pediatric patients with AD compared to tapinarof. However, no definitive conclusions can be made about the relative safety of these two agents against one another without a more in-depth meta-analysis comparing the specific adverse events in these two agents, which would require a greater quantity of included studies.

4.2 Limitations

There were many limitations to the scope of this research, with the primary one being lack of sufficient quantity of data on these agents in pediatric populations. With these two agents only recently being approved for use in children with AD, the number of studies performed with these agents in this specific patient population is lacking, which greatly limited the depth of the meta-analyses performed. Further, studies directly comparing these two agents should be performed, as there were no direct comparative studies available at the time of this review. Subgroup analyses (based on sample size, dosing, comorbidities, etc.) were unable to be performed due lack of sufficient quantity of included studies; subsequent research should expand upon this analysis with more included studies to increase the power of the conclusions drawn. Furthermore, the adverse events reported in different studies were inconsistent. Thus, this study only included meta-analysis on general TEAEs and treatment-related TEAEs. The specific AEs were compared via occurrence percentages. Subsequent analyses should include studies with uniformity of reported adverse events to perform specific meta-analyses for each adverse event reported. Another limitation for this study is the age of the included patient population. While three of the seven studies were exclusively pediatric patients with AD, two of the roflumilast studies (Simpson *et al.* 2024 and Simpson *et al.* 2025) and two of the tapinarof studies (Gold *et al.* 2025 and Silverberg *et al.* 2024) included a mix of adult and pediatric patients with AD [10,11,14,17]. This may have contributed to heterogeneity in the meta-analysis results, but the heterogeneity was low enough (0% to 10%) that including these studies did not significantly skew the data. Even with these included studies, the mean age of the patient population for all tapinarof and roflumilast studies ranged from 8.15 years old to 19.8 years old, which is still considered late adolescence, and many pediatricians will see their patients up to age 21. Another limitation mentioned previously is the high heterogeneity for the tapinarof meta-analyses, which is likely due to variations in sample size, but we cannot do a subgroup analysis to find out if this is the case due to the limited number of studies. The final limitation for this research is due to the timing of every included study being 2024-2025, due to roflumilast being FDA approved for AD in ages 6 and older in July 2024

and tapinarof being approved for ages 2 and older in December 2024 [25,26]. This indicates that the adverse events reported in these studies are more likely acute in nature, and longitudinal adverse events with these agents have yet to be observed and reported.

4.3 Future Directions

As the use of these agents becomes more widespread in practice and more data on safety and tolerability becomes available, analysis of the long-term outcomes for roflumilast and tapinarof should be performed. Additionally, future analyses should be performed to directly compare the two agents against one another, to hopefully provide a definitive conclusion for which treatment is more beneficial. This information can help guide clinical decision-making in management of AD as physicians can determine whether the long-term efficacy and safety of these agents is comparable or superior to that of traditional management options. As more patients utilize these agents and more safety data is collected, this research can be refined to categorize risks of adverse events by age groups (younger children versus older children) rather than grouping all pediatric patients together because post-pubertal changes can greatly affect how the body responds to stimuli. This will further inform pediatricians on what recommendations are most suited for their patient based on age and comorbidities.

5. Conclusion

Both roflumilast and tapinarof are newly developed and efficacious agents in the treatment of pediatric AD. In the short-term, both agents have a significant increase in treatment-emergent adverse events. However, the long-term adverse event profiles have yet to be assessed. Ultimately, these agents provide a promising new avenue for treating the complex, chronic condition that is AD, a disease that often starts in childhood and can hopefully be controlled early on by keeping patients, their parents, and pediatricians alike informed and aware of their management options.

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