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ORIGINAL RESEARCH

Survey of Drugs Induced Skin Pigmentation (Hyper and Hypo Pigmentation)

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Background: Drug-induced skin pigmentary changes are an underrecognized yet clinically significant type of adverse event (AE). Despite growing awareness, labeling for many implicated drugs remains incomplete.

Objective: To conduct a comprehensive pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database (2010–2024) to identify drugs associated with skin hyperpigmentation, hypopigmentation, or both, and to explore their clinical implications and repurposing potential.

Methods: The study analyzed case reports from the FAERS database using the OpenVigil 2.1 platform. Pigmentary AEs were identified based on the MedDRA Preferred Terms "skin hyperpigmentation" and "skin hypopigmentation." To ensure consistency, all drug names were standardized to their generic forms using the DrugBank database before inclusion in the analysis. Disproportionality analysis was performed using the Reporting Odds Ratio (ROR) to detect significant associations between drugs and pigmentary AEs.

Results: A spectrum of agents demonstrated strong associations with pigmentary changes. Minocycline (ROR 115.66) and setmelanotide (ROR 1506.82) showed high RORs for hyperpigmentation, while triamcinolone (ROR 37.20) and ribociclib (ROR 60.20) were strongly linked to hypopigmentation. Several drugs, including dupilumab, tretinoin, and clobetasol, exhibited bidirectional pigmentary modulation. Notably, a substantial proportion of implicated drugs lacked labeling for these effects.

Conclusion: This study identifies notable pigmentary AE signals associated with several commonly prescribed drugs. These findings emphasize the importance of early recognition and dermatologic monitoring during prolonged therapy. Considering the odds ratio and analysis results, the drugs found to be associated with hyperpigmentation or hypopigmentation warrant further investigation.

Keywords: drug-induced pigmentation, hyperpigmentation, hypopigmentation, pharmacovigilance, drug repurposing

Key Messages

What is already known on this topic

Drug-induced pigmentary changes are increasingly recognized but remain poorly characterized in large-scale surveillance studies. Previous literature has focused primarily on case reports or small series, and labeling for many implicated drugs is incomplete.

What this study adds

This FAERS-based pharmacovigilance analysis identified strong disproportionality signals linking numerous widely used drugs to skin hyperpigmentation and hypopigmentation. Several high-signal agents, including ribociclib and amlodipine, lack pigmentary warnings in their product labeling.

How this study might affect research, practice or policy

The findings support the need for enhanced dermatologic monitoring for high-risk drugs with pigmentary safety signals. Drug-induced pigmentary changes may indicate therapeutic repurposing potential in pigmentary skin disorders, warranting further translational research.

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Introduction

Adverse drug reactions (ADRs), though increasingly prevalent and clinically impactful, remain underrecognized when presenting as skin pigmentary disorders, despite their visible manifestations and psychosocial consequences.[1,2] Drug-induced pigmentary changes account for approximately 20% of all cases of acquired pigmentation.[3] The clinical heterogeneity and overlap of these pigmentary changes with common dermatoses-such as post-inflammatory pigmentation, melasma, or vitiligo-pose diagnostic challenges, often leading to misdiagnosis or delayed recognition. Drug-related hyperpigmentation and hypopigmentation are best managed by discontinuation or substitution of the culprit medication.[4] Additional measures include rigorous photoprotection and topical agents such as hydroquinone for hyperpigmentation, whereas hypopigmentation may respond to topical corticosteroids or calcineurin inhibitors, phototherapy, or surgical techniques (eg, grafting techniques). Timely recognition of these manifestations is critical for mitigating drug-induced pigmentary sequelae.[5]

Drugs can induce pigmentary disorders via distinct pathways, resulting in either hyperpigmentation or hypopigmentation.[6] Common drugs that lead to pigmentary changes include alkylating/cytotoxic agents, analgesics, antiarrhythmics, and anticoagulants.[3] Drug-induced cutaneous hyperpigmentation is typically non–immune-mediated and arises through mechanisms such as melanin accumulation, drug deposition, novel pigment formation, and iron deposition. Melanin increase may result from melanocyte stimulation, drug-melanin complex formation, or inflammation, while vascular injury may lead to iron or pigment granule deposition within dermal macrophages.[3] In contrast, drug-induced hypopigmentation is more often associated with immune-mediated or cytotoxic mechanisms that impair melanocyte function or viability. The principal pathways include decreased melanocyte density, inhibition of melanogenesis, and disruption of melanosome transport. Topical or intralesional corticosteroids may also cause localized hypopigmentation by suppressing melanocyte activity, typically near the site of application or injection, and often with partial reversibility.[7]

This study leverages the FDA Adverse Event Reporting System (FAERS)-the largest global pharmacovigilance database-to systematically identify drugs associated with skin pigmentary changes.[8] Through an in-depth analysis of drug-related adverse event (AE) data from the FAERS database, this study aims to enhance clinicians' vigilance and diagnostic awareness regarding drug-induced pigmentary disorders, thereby facilitating timely recognition and intervention in routine dermatologic practice. Moreover, identifying specific agents associated with pigmentary changes may offer novel insights for drug repurposing and optimization of therapeutic strategies in clinical pharmacology.

Methods

Data Source

This study was conducted between April and June 2025, with three investigators involved in the analysis of the FAERS dataset. This pharmacovigilance study was conducted based on data extracted from the FAERS, a publicly available database designed to support post-marketing safety surveillance for drugs and biologics. The FAERS database contains spontaneous reports of AEs voluntarily submitted by healthcare professionals, pharmacists, consumers, and other reporters. These reports provide detailed information on patient demographics, suspected medications, therapeutic indications, AEs, clinical outcomes, and other relevant clinical data. We utilized OpenVigil 2.1, a validated pharmacovigilance analytics platform (http://h2876314.stratoserver.net:8080/OV2/search/), to access and analyze the FAERS dataset. OpenVigil 2.1 performs data import, cleaning, and statistical processing directly on FAERS data and provides disproportionality analysis outputs, including the Reporting Odds Ratio (ROR). The version of OpenVigil used in this study contains AE reports from the first quarter of 2010 to the fourth quarter of 2024.[9]

Drug Identification

AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0), using the Preferred Term (PT) level. We retrieved reports associated with two PTs: "skin hyperpigmentation" and "skin hypopigmentation". To identify the suspect drugs related to these pigmentary changes, we extracted all reports containing these two PT terms in the AE. For consistency in drug naming, we standardized all drug entries to their generic names. Brand

names were mapped to generics using the DrugBank database (https://go.drugbank.com). Reports with unidentified or ambiguous drug names were excluded after manual review.

Statistical Analysis

We conducted descriptive statistical analyses to characterize reports related to pigmentary disorders, including reporting year, patient age group, sex, country of origin, and the top five associated indications. The primary analytical method employed was disproportionality analysis–a widely accepted pharmacovigilance approach for detecting potential drug safety signals. Common disproportionality metrics include the ROR, Proportional Reporting Ratio, Information Component, and Empirical Bayes Geometric Mean, each based on distinct statistical assumptions and detection thresholds. In this study, we applied the ROR, a well-established and interpretable metric. ROR compares the odds of reporting a specific AE with a drug of interest to the odds of reporting the same AE with all other drugs in the database. A drug–AE pair was considered to yield a statistically significant signal if the lower bound of the 95% confidence interval (CI) for the ROR exceeded 1 and the number of reports was ≥3. Data processing, summarization, and visualization were performed using Microsoft Excel 2019 and R software (version 4.5.0).

Results

Demographic Characteristics

A total of 9594 hyperpigmentation-related AE reports were identified (see Table 1), with the majority from the United States (62.6%). The most common indications were psoriasis (5.9%) and magnetic resonance imaging (4.4%). The age

Table 1 Clinical Characteristics of Reported Skin Hyperpigmentation

Characteristics	Total	%
	9594	
Age		
≤18	487	5.07 (7.7)
19–40	1364	14.2 (21.7)
41–64	2839	29.6 (45.1)
≥65	1603	16.7 (25.5)
Unknown	3301	34.4
Gender		
Male	3068	32.0 (35.4)
Female	5590	58.3 (64.6)
Unknown	936	9.8
Indication (top 5)		
Psoriasis	566	5.9
Nuclear magnetic resonance imaging	424	4.4
Growth of eyelashes	394	4.1
Rheumatoid arthritis	385	4.0
Acne	245	2.6

(*Continued*)

Table 1 (Continued).

Characteristics	Total	%
Reporting country (top 5)		
United States	6010	62.6
United Kingdom	471	4.9
India	289	3.0
Netherlands	111	1.2
China	62	0.6

Notes: Percentages in parentheses represent the proportion of patients within each group after excluding cases with unknown data.

distribution showed that most cases were in individuals aged 41–64 years. Hyperpigmentation-related AE reports peaked in 2023, as shown in Figure 1. A total of 2,397 hypopigmentation-related AE reports were identified (Table 2). Most cases involved individuals aged 41–64 years and ≥65 years. The top indications were malignant melanoma (13.8%) and hypertension (12.9%). The majority of reports came from the United States (46.5%), followed by Germany (13.3%). Reports steadily increased from 64 in 2010 to a peak of 352 in 2023, with a slight decline to 249 in 2024 (Figure 1).

Disproportionality Signals

A total of 5,329 hyperpigmentation signals were identified based on the ROR threshold. The top 50 drugs with the highest signal strength are summarized in Table 3. Gadolinium-based contrast agents, notably gadodiamide (ROR 83.42),

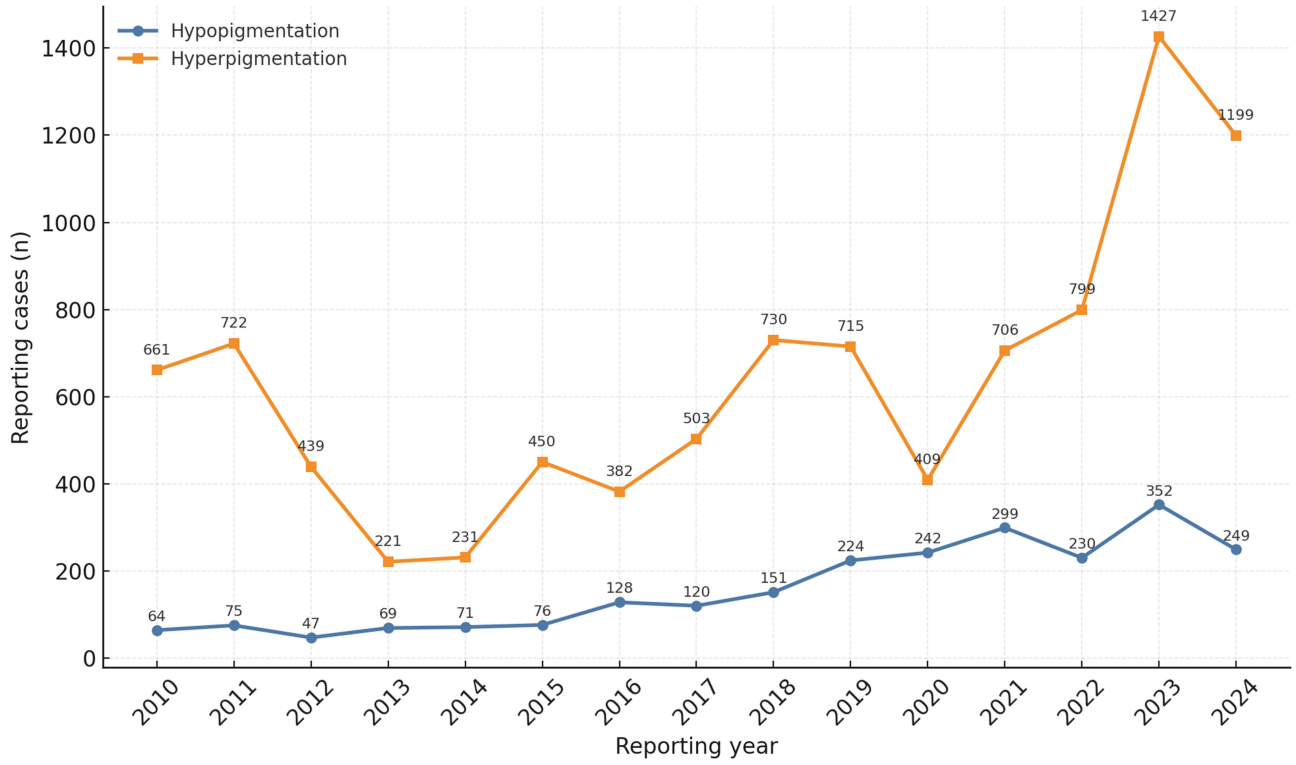

Figure 1 Annual reporting trends of drug-induced skin pigmentation disorders in FAERS, 2010–2024. The Orange line represents annual reports of hyperpigmentation, while the blue line denotes hypopigmentation. Hyperpigmentation cases were consistently more frequent and exhibited substantial year-to-year variation. In contrast, hypopigmentation reports were fewer and showed a steadier trend over time.

Table 2 Clinical Characteristics of Reported Skin Hypopigmentation

Characteristics	Total	%
	2397	
Age		
≤18	211	8.8 (13.7)
19–40	214	8.9 (13.9)
41–64	582	24.3 (37.8)
≥65	532	22.2 (34.6)
Unknown	858	35.8
Gender		
Male	1017	42.4 (48.9)
Female	1064	44.4 (51.1)
Unknown	316	13.2
Indication (top 5)		
Malignant melanoma	330	13.8
Hypertension	309	12.9
Vascular graft	252	10.5
Psoriasis	113	4.7
Breast cancer	110	4.6
Reporting country (top 5)		
United States	1114	46.5
Germany	319	13.3
India	92	3.8
Japan	58	2.4
China	13	0.5

Notes: Percentages in parentheses represent the proportion of patients within each group after excluding cases with unknown data.

Table 3 Top 50 Drugs for Signal Strength of Skin Hyperpigmentation

Drug Name	Number of Skin Hyperpigmentation Reports	ROR (95% CI)	Package Insert Suggests Risk for Skin Hyperpigmentation
Bimatoprost	567	105.36 (96.01–115.62)	Y
Dupilumab	210	1.84 (1.6–2.11)	N
Minocycline	199	115.66 (99.96–133.82)	Y
Secukinumab	131	3.01 (2.53–3.59)	Y

(*Continued*)

Table 3 (Continued).

Drug Name	Number of Skin Hyperpigmentation Reports	ROR (95% CI)	Package Insert Suggests Risk for Skin Hyperpigmentation
Methotrexate	123	2.17 (1.81–2.6)	N
Capecitabine	119	8.32 (6.92–9.99)	N
Hydroxychloroquine	98	5.1 (4.17–6.24)	Y
Adapalene	90	20.25 (16.41–25.0)	Y
Prednisone	90	1.74 (1.41–2.15)	N
Lenalidomide	88	1.47 (1.19–1.82)	N
Amlodipine	71	1.38 (1.09–1.75)	N
Botulinum toxin type a	65	2.51 (1.96–3.2)	N
Prednisolone	63	2.8 (2.18–3.6)	N
Cholecalciferol	56	1.79 (1.37–2.33)	N
Ibuprofen	55	1.61 (1.23–2.1)	N
Cyclosporine	50	2.98 (2.25–3.94)	N
Tacrolimus	50	2.22 (1.68–2.93)	Y
Triamcinolone	48	6.53 (4.91–8.68)	N
Gadopentetate dimeglumine	47	49.61 (37.12–66.29)	Y
Levofloxacin	47	3.71 (2.78–4.95)	Y
Ruxolitinib	47	2.75 (2.06–3.66)	Y
Fluorouracil	45	4.58 (3.41–6.15)	N
Simvastatin	43	1.74 (1.29–2.35)	N
Mechlorethamine	41	65.99 (48.37–90.03)	Y
Clofazimine	41	53.3 (39.09–72.69)	Y
Benzoyl peroxide	41	39.23 (28.78–53.47)	Y
Clobetasol	40	14.63 (10.7–20.0)	Y
Fluocinolone acetonide	39	49.63 (36.12–68.2)	Y
Cyclophosphamide	39	1.64 (1.19–2.24)	Y
Mycophenolate mofetil	38	2.18 (1.58–3.0)	N
Hydrocortisone	36	4.43 (3.19–6.15)	Y
Doxycycline	35	4.74 (3.4–6.62)	Y
Azathioprine	35	3.99 (2.86–5.57)	N
Leflunomide	35	3.41 (2.45–4.77)	N
Trastuzumab	35	2.81 (2.01–3.92)	N
Bevacizumab	35	1.73 (1.24–2.41)	N

(*Continued*)

Table 3 (Continued).

Drug Name	Number of Skin Hyperpigmentation Reports	ROR (95% CI)	Package Insert Suggests Risk for Skin Hyperpigmentation
Fluconazole	33	5.71 (4.05–8.05)	N
trimethoprim	33	2.22 (1.57–3.13)	N
Calcium	33	1.44 (1.02–2.03)	N
Gadobenate dimeglumine	32	61.13 (43.04–86.82)	N
Tretinoin	32	10.76 (7.59–15.26)	Y
Dolutegravir	32	6.13 (4.33–8.69)	N
Sulfamethoxazole	32	2.3 (1.62–3.26)	N
Gadodiamide	31	83.42 (58.35–119.24)	Y
Daxibotulinumtoxina	30	2.41 (1.68–3.46)	N
Ondansetron	30	1.5 (1.05–2.15)	N
Setmelanotide	29	1506.82 (986.31–2302.02)	Y
Methylprednisolone	29	1.96 (1.36–2.82)	Y
Doxorubicin	29	1.91 (1.32–2.75)	Y
Lamotrigine	29	1.71 (1.18–2.46)	Y

Abbreviations: ROR, reporting odds ratio; CI, confidence interval; Y, yes; N, not.

antibiotics such as minocycline (ROR 115.66) and clofazimine (ROR 53.30), topical agents including bimatoprost (ROR 105.36) and adapalene (ROR 20.25), pigmentation axis modulators represented by setmelanotide (ROR 1506.82), antimetabolites like mechlorethamine (ROR 65.99), and targeted therapies such as ribociclib (ROR 60.20) demonstrated the strongest disproportionality signals. Notably, certain drugs, including dupilumab and capecitabine, lack labeling for hyperpigmentation risks in their package inserts.

A total of 1,054 hypopigmentation signals were identified based on the criteria of ROR. The top 50 drugs with high signal strength are listed in Table 4. These drugs were categorized into four major pharmacological classes: anticancer

Table 4 Top 50 Drugs for Signal Strength of Skin Hypopigmentation

Drug Name	Number of Skin Hypopigmentation Reports	ROR (95% CI)	Package Insert Suggests Risk for Skin Hypopigmentation
Dupilumab	84	3.46 (2.75–4.35)	N
Letrozole	61	37.05 (28.43–48.29)	N
Ribociclib	60	60.20 (46.09–78.63)	N
Triamcinolone	60	37.20 (28.52–48.52)	Y
Pazopanib	43	27.67 (20.30–37.72)	Y
Secukinumab	33	3.47 (2.44–4.93)	N
Imatinib	28	10.02 (6.86–14.64)	Y

(*Continued*)

Table 4 (Continued).

Drug Name	Number of Skin Hypopigmentation Reports	ROR (95% CI)	Package Insert Suggests Risk for Skin Hypopigmentation
Salbutamol	25	2.45 (1.64–3.66)	N
Cabozantinib	24	8.98 (5.97–13.51)	N
Prednisone	20	1.80 (1.15–2.81)	N
Nivolumab	19	7.84 (4.97–12.39)	N
Adapalene	18	18.69 (11.69–29.89)	N
Clobetasol	16	27.46 (16.70–45.13)	N
Cyclophosphamide	16	3.16 (1.92–5.19)	N
Cholecalciferol	15	2.23 (1.34–3.73)	N
Trastuzumab	14	7.08 (4.17–12.04)	N
Docetaxel	14	6.03 (3.55–10.24)	N
Tamoxifen	13	25.11 (14.49–43.52)	N
Epirubicin	13	21.89 (12.63–37.93)	N
Folic acid	13	2.65 (1.53–4.59)	N
Crisaborole	12	30.66 (17.30–54.31)	N
Iron	12	8.97 (5.06–15.88)	N
Ruxolitinib	12	4.76 (2.69–8.44)	N
Levetiracetam	12	3.33 (1.88–5.90)	N
Cyclosporine	11	3.01 (1.66–5.46)	N
Ustekinumab	11	2.44 (1.34–4.43)	N
Ipilimumab	10	8.45 (4.52–15.79)	N
Dasatinib	10	5.04 (2.70–9.42)	N
Hydroxychloroquine	10	2.98 (1.59–5.57)	N
Tacrolimus	10	2.34 (1.25–4.38)	Y
Losartan	10	2.21 (1.18–4.13)	N
Clobetasol propionate	9	31.91 (16.51–61.66)	Y
Allopurinol	9	2.95 (1.53–5.70)	N
Palbociclib	9	2.55 (1.32–4.92)	N
Mycophenolate mofetil	9	2.40 (1.24–4.63)	N
Dimenhydrinate	8	44.55 (22.16–89.57)	N
Vemurafenib	8	18.96 (9.43–38.10)	N
Bimatoprost	8	6.33 (3.15–12.71)	N
Lacosamide	8	5.86 (2.92–11.77)	N

(*Continued*)

Table 4 (Continued).

Drug Name	Number of Skin Hypopigmentation Reports	ROR (95% CI)	Package Insert Suggests Risk for Skin Hypopigmentation
Epinephrine	8	5.33 (2.65–10.71)	N
Sulfamethoxazole	8	2.67 (1.33–5.37)	N
Ramipril	8	2.52 (1.25–5.05)	N
Trimethoprim	8	2.50 (1.24–5.02)	N
Hydroxyurea	7	12.75 (6.05–26.87)	N
Trametinib	7	4.53 (2.15–9.54)	N
Lamivudine	7	4.15 (1.97–8.74)	N
Methylprednisolone	7	2.20 (1.04–4.63)	N
Sunitinib	7	4.99 (2.37–10.52)	N
Cobimetinib	6	46.01 (20.57–102.92)	N
Tretinoin	6	9.34 (4.18–20.87)	Y

Abbreviations: ROR, reporting odds ratio; CI, confidence interval; Y, yes; N, not.

and targeted therapies, such as ribociclib (ROR 60.20), which exhibited one of the highest signal strengths; topical corticosteroids and dermatologics, including triamcinolone (ROR 37.20); immunomodulators and biologics, represented by dupilumab (ROR 3.46) and secukinumab (ROR 3.47); miscellaneous systemic drugs, such as dimenhydrinate (ROR 44.55). Notably, the majority of these drugs do not include skin hypopigmentation as a documented ADR in their package inserts.

Among hyperpigmentation-related events, the most frequently reported agents were bimatoprost (n = 567) and dupilumab (n = 210) (Figure 2). For hypopigmentation, dupilumab (n = 84) and letrozole (n = 61) accounted for the highest number of reports (Figure 2). Notably, several agents appeared in both hyperpigmentation and hypopigmentation datasets, including dupilumab, secukinumab, triamcinolone, cholecalciferol, clobetasol, hydroxychloroquine, and prednisone.

Discussion

While prior research on drug-induced pigmentary disorders has primarily relied on systematic reviews or isolated case reports, our analysis fills a crucial gap by utilizing large-scale pharmacovigilance data. Our findings reveal that reports of drug-induced hyperpigmentation were significantly more frequent than those of hypopigmentation. This discrepancy may stem from intrinsic mechanistic differences—hyperpigmentation often arises through more direct and common biological pathways,[3] whereas hypopigmentation tends to involve rarer and more complex mechanisms—as well as from external reporting biases, such as variations in clinical visibility and diagnostic attention.[7] Furthermore, inappropriate or excessive use of certain drugs, particularly those associated with long-term or high-dose exposure, may further widen the disparity between hyperpigmentation and hypopigmentation reports. The observed temporal pattern differences may partly reflect baseline reporting effects, with hyperpigmentation showing greater variability and hypopigmentation appearing relatively stable due to its lower baseline reporting frequency.

Among hyperpigmentation cases, females were disproportionately represented compared to males, whereas hypopigmentation exhibited no significant gender difference. This observation aligns with previous literature indicating a female predominance in drug-induced hyperpigmentary disorders, potentially attributable to estrogen's stimulatory effects on melanogenesis in human melanocytes and the synergistic interactions of elevated α-melanocyte-stimulating hormone levels with estrogen.[10] Both hyperpigmentation and hypopigmentation were predominantly reported in middle-

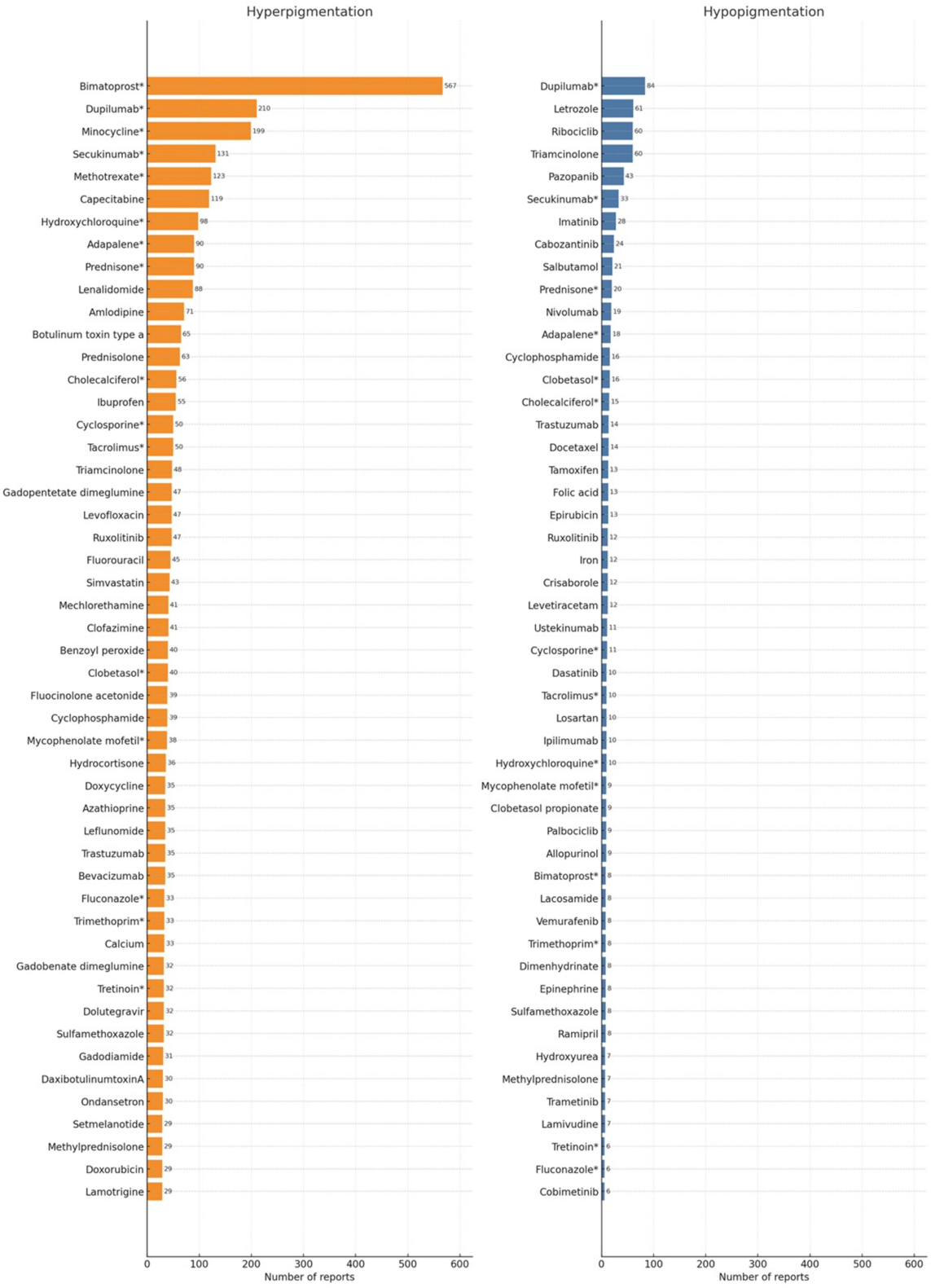

Figure 2 Comparative frequency of drugs associated with skin hyperpigmentation (left) and hypopigmentation (right) in FAERS, 2010–2024. Orange and blue bars represent the number of reports for drug-induced hyperpigmentation and hypopigmentation, respectively. Drug names are ranked by report frequency within each category; numeric values indicate absolute counts. An asterisk (*) denotes drugs reported in both pigmentation directions.

aged and elderly patients, likely due to pre-existing imbalances in melanin metabolism associated with chronological skin aging and cumulative photodamage. This age distribution is consistent with previous clinical studies, such as the series by Giménez García and Carrasco Molina, which reported a mean patient age of 63 years (SD = 16; range, 34–86 years), with half of the affected individuals being over 60 years old.[11]

Among drugs associated with skin hyperpigmentation, minocycline, bimatoprost, and setmelanotide warrant particular attention based on their robust signal strength. Minocycline, a tetracycline derivative widely used for acne and other inflammatory dermatoses, showed a notably high signal for hyperpigmentation in our study (ROR = 115.66; n = 199). Previous studies have suggested that approximately 3–15% of patients receiving long-term, high-dose minocycline therapy (defined as >1.5 years and cumulative doses >70–100 g) may develop cutaneous hyperpigmentation. This occurs due to the dermal deposition of melanin–iron–minocycline complexes.[12] Four distinct clinical patterns have been reported, often mimicking sunspots or age-related hyperpigmentation, leading to underrecognition.[13] Therefore, regular dermatologic monitoring is advisable in patients receiving minocycline treatment. Early recognition can help prevent progression, and clinicians should inform patients of this potential risk prior to long-term use.

Bimatoprost is a synthetic prostaglandin F2α analog commonly used in the treatment of glaucoma and eyelash hypotrichosis.[14] In our analysis, bimatoprost was associated with a remarkably strong hyperpigmentation signal (ROR = 105.36; 95% CI: 96.01–115.62). Consistent with this finding, multiple clinical studies have reported periorbital and eyelid hyperpigmentation following long-term ocular administration of bimatoprost, typically emerging within 4–6 weeks of treatment.[14–16] Mechanistically, bimatoprost has been shown to stimulate melanogenesis by upregulating tyrosinase activity via activation of prostanoid FP receptors, leading to increased melanin synthesis and deposition, particularly in periorbital regions. This pigmentary effect is typically reversible upon drug discontinuation. Interestingly, this pharmacologic property has also prompted its off-label use in repigmentation therapy for localized vitiligo and hypopigmented scars, suggesting a potential role in pigmentary disorders beyond its approved indications.[17]

Setmelanotide exhibited the strongest signal for hyperpigmentation in our FAERS-based analysis (ROR: 1506.82), which aligns with published clinical data showing up to 61% of users developing visible skin hyperpigmentation.[18,19] Unlike post-inflammatory pigmentation, this effect appears to be a direct consequence of melanocortin receptor activation, especially MC1R (melanocortin 1 receptor),[20,21] offering a unique perspective on drug-induced pigmentation and highlighting a pathway potentially exploitable for therapeutic repurposing in pigmentary disorders.

In our disproportionality analysis, ribociclib emerged as one of the top-ranking agents associated with hypopigmentation (ROR = 60.20), despite the absence of any pigmentation-related AEs in its product labeling. Ribociclib is a selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor approved for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer.[22] The pathogenesis of ribociclib-induced hypopigmentation remains uncertain. Although it does not directly target immune pathways, inhibition of the p16 INK4a/Cyclin D1–CDK4/6–retinoblastoma protein axis may disrupt melanocyte homeostasis. The absence of autoimmune history in reported cases suggests a mechanism distinct from classical vitiligo, though a noncanonical immune contribution cannot be excluded.[23]

Our findings are consistent with prior clinical observations.[22,24,25] For example, Alexander et al reported vitiligo-like lesions in patients receiving CDK4/6 inhibitors, particularly ribociclib.[22] Vitiligo-like lesions associated with ribociclib are typically resistant to conventional skin-directed therapies, with only mild repigmentation observed in isolated cases treated with ruxolitinib cream.[26] The poor treatment response of ribociclib-induced vitiligo-like lesions warrants deeper exploration of their mechanisms and clinical relevance.[27] This association raises important questions regarding the underlying mechanisms, including whether it involves immune modulation or melanocyte-targeted cytotoxicity. Further research is needed to elucidate these pathways and potentially inform therapeutic strategies for pigmentary disorders.

In contrast, triamcinolone, a mid-potency corticosteroid, also demonstrated a strong hypopigmentation signal (ROR = 37.20), which is consistent with known effects documented in the prescribing information. Corticosteroids are well-established inhibitors of melanogenesis, acting through suppression of tyrosinase activity, downregulation of microphthalmia-associated transcription factor, and reduced dendritic transport of melanosomes. Chronic use may also induce local skin atrophy and structural disruption, further exacerbating pigmentary loss. In a comparative study, intralesional triamcinolone was associated with hypopigmentation in 80% of patients and skin atrophy in 73.3%, supporting these

mechanistic insights.[28] The concordance between FAERS data and clinical labeling in triamcinolone underscores the reliability of pharmacovigilance signal detection in capturing expected AEs.

Certain agents, including dupilumab, tretinoin, and clobetasol, exhibit bidirectional pigmentary modulation, manifesting as both hyperpigmentation and hypopigmentation. This observation highlights the complexity of drug-induced pigmentary changes, which are not always unidirectional and may involve intricate immunological, inflammatory, and melanocytic mechanisms—especially in the case of biologics that act through immune pathways. Moreover, factors such as patient ethnicity, underlying dermatologic conditions, and individual immune history may further influence the pigmentary response. Given this complexity, clinicians should be aware of the potential for both pigmentary outcomes when prescribing these agents, and patients should be appropriately counseled regarding these possible effects.

These findings highlight the need to strengthen post-marketing surveillance for agents with high disproportionality signals in the FAERS database, particularly those not currently reflecting pigmentary AEs in their prescribing information. Notable examples include ribociclib and amlodipine, which exhibited significant associations with hyper- or hypopigmentation but lack corresponding label warnings. Furthermore, for drugs frequently prescribed in chronic disease contexts, it is advisable to establish standardized protocols for routine dermatologic monitoring of long-term users, with a focus on early detection and documentation of pigmentary changes. This study also provides a foundation for future large-scale cohort studies or clinical trials to validate the causal relationship between drugs and pigmentary changes. Moreover, the identified agents may offer novel opportunities for drug repurposing, such as utilizing hyperpigmentation-inducing drugs in treating hypopigmentary disorders (eg, vitiligo).

Several limitations of this study should be acknowledged. First, FAERS data are subject to underreporting, reporting bias, and incomplete information, likely leading to an underestimation of actual AE incidence. Second, disproportionality analysis can reveal associations but not establish causality. Third, the absence of detailed clinical information—such as lesion morphology, outcome, or histopathology—limits mechanistic interpretation. Fourth, confounding factors such as polypharmacy and comorbidities may influence the observed signals. For instance, concurrent use of minocycline with photosensitizing agents may intensify hyperpigmentation, while hepatic, endocrine, or chronic inflammatory disorders can independently cause pigmentary changes. Finally, the exclusion of non-cutaneous pigmentary events (eg, ocular or nail involvement) may underestimate the overall pigmentary burden.

Conclusion

This pharmacovigilance analysis of the FAERS database from 2010 to 2024 identified a spectrum of drugs associated with hyperpigmentation, hypopigmentation, or both, some of which are not currently labeled for such risks. Disproportionality signals were particularly strong for some agents, including minocycline, ribociclib, and setmelanotide, underscoring the need for strengthened dermatologic monitoring, especially in long-term therapy. Drugs with bidirectional pigmentary effects—such as dupilumab, hydroxychloroquine, and clobetasol—were also identified in our analysis. Considering the odds ratios and analytical findings, the drugs implicated in either hyperpigmentation or hypopigmentation warrant further investigation to better elucidate their underlying mechanisms and clinical relevance.

Abbreviations

AE, Adverse Event; ADR, Adverse Drug Reaction; CDK4/6, Cyclin Dependent Kinase 4 and 6; CI, Confidence Interval; FAERS, FDA Adverse Event Reporting System; MC1R, Melanocortin-1 Receptor; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; ROR, Reporting Odds Ratio.

Data Sharing Statement

The data used in this study were obtained from the publicly accessible FDA Adverse Event Reporting System (FAERS), available at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers. All data were fully de-identified by the original data provider. The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Considerations

This study is exempt from ethics approval according to Items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, February 18, 2023). These provisions stipulate that research may be exempt from ethics review when: (1) it uses legally obtained public data or observational data of public behavior without interfering with such behavior; and (2) it uses anonymized information data that does not contain identifiable personal information. As this study analyzed publicly available, de-identified data from the FAERS database, it meets both conditions above and therefore qualifies for exemption from institutional ethics review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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