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Do topical phosphodiesterase 4 inhibitors share the depression signal of apremilast? A route-based disproportionality analysis in the FDA Adverse Event Reporting System

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Abstract

Apremilast carries a label warning for depression, whereas the topical phosphodiesterase 4 (PDE4) inhibitors roflumilast and crisaborole do not. Whether psychiatric adverse events of this class depend on the route of administration has not been examined. We analysed FDA Adverse Event Reporting System reports from 2023 Q1 to 2026 Q3 (5,269,853 after deduplication). Primary-suspect reports for oral apremilast, topical roflumilast and topical crisaborole, and for two systemically absorbed PDE4 inhibitors used in respiratory disease (oral roflumilast and inhaled ensifentrine), were compared with all other reports for the same indication and with non-PDE4 drugs for that indication, using reporting odds ratios (ROR) with Mantel–Haenszel adjustment. Gastrointestinal events, headache and application-site reactions were control outcomes. Depression/suicidality was disproportionately reported for apremilast (323 cases; ROR 3.17, 95% CI 2.81–3.58), oral roflumilast (6 cases; 13.33, 5.68–31.27) and ensifentrine (40 cases; 9.15, 6.43–13.03), but not for topical roflumilast (2 cases; 0.71, 0.18–2.83) or crisaborole (2 cases; 0.83, 0.21–3.34). Compared with apremilast, adjusted reporting was lower for topical roflumilast (0.04, 0.01–0.33) and crisaborole (0.11, 0.03–0.46). Topical roflumilast nevertheless showed disproportionate insomnia (8.48, 5.50–13.08), headache and gastrointestinal reports, in line with its label, whereas crisaborole showed only application-site reactions. In spontaneous reports, the depression and suicidality signal of PDE4 inhibitors accompanied systemic administration and was not seen with topical use. Estimates for the topical agents rest on few cases and need confirmation in controlled data.

1. INTRODUCTION

Phosphodiesterase 4 (PDE4) inhibitors have become an established part of dermatological treatment. Oral apremilast is used for psoriasis, psoriatic arthritis and oral ulcers of Behçet disease, and two topical agents, roflumilast cream or foam and crisaborole ointment, are used for psoriasis, seborrhoeic dermatitis and atopic dermatitis [1, 2, 3, 4]. The class is valued for the absence of laboratory monitoring and of the immunosuppression associated with other systemic treatments.

One safety concern has accompanied the class from the start. PDE4 is widely expressed in the brain, and the prototype inhibitor rolipram was first developed as an antidepressant [5]; yet the labels of both oral PDE4 inhibitors warn in the opposite direction. The apremilast label carries a warning for depression, and the label of oral roflumilast, used in chronic obstructive pulmonary disease (COPD), warns of psychiatric events including suicidality. Both warnings are based on small excesses over placebo in controlled trials [6, 7, 8]. The inhaled PDE3/PDE4 inhibitor ensifentrine, approved for COPD in 2024, carries a similar warning [9, 10].

The topical agents carry no psychiatric warning. Their labels nevertheless document measurable plasma concentrations after application, and the roflumilast cream label lists insomnia, headache, diarrhoea and nausea among adverse reactions [11, 12]. Dermatologists who prescribe a topical PDE4 inhibitor to a patient with a history of depression, or who switch a patient from apremilast because of mood symptoms, therefore have little evidence on whether the psychiatric warning of the oral drug is relevant. Psychiatric

events were too rare in the topical trial programmes to answer this question, and psoriasis and atopic dermatitis are themselves associated with depression [13].

Spontaneous reports offer a complementary source. Disproportionality analyses of the FDA Adverse Event Reporting System (FAERS) have described psychiatric signals for roflumilast [14, 15] and have compared apremilast, crisaborole and roflumilast with a focus on sex differences [16]. One of these studies included an oral versus topical subgroup analysis of roflumilast [15]. None compared psychiatric outcomes across routes of administration within the class, and all used the whole database as the reference. That reference is problematic here, because a comparison with all other drugs cannot separate the effect of a drug from the effect of the disease it treats [17, 18]; depression is also more common in people with COPD [19].

We therefore compared psychiatric adverse event reporting for the three PDE4 inhibitors used in dermatology, one oral and two topical, using backgrounds matched on indication, active non-PDE4 comparators and control outcomes with known route dependence. Oral roflumilast and inhaled ensifentrine were included as further systemically absorbed members of the class. Our hypothesis was that depression and suicidality reporting would be disproportionate for systemically administered agents and not for topical agents.

2. MATERIALS AND METHODS

2.1 Study design and data source

This was a retrospective disproportionality analysis of individual case safety reports, reported in line with the READUS-PV statement [20] (Table S7). We used the FAERS quarterly ASCII files for 2023 Q1 to 2026 Q3, downloaded in October 2026 [21]. The period was chosen so that all five agents were marketed for most or all of it and so that reporting practices were comparable across agents. Reports listed in the FDA deletion files were removed, and the most recent version of each case was retained (by case identifier, FDA receipt date and primary identifier). Of 6,151,833 report versions, 5,269,853 unique reports remained.

2.2 Agents and classification of route

Drugs were identified by whole-word matching of generic and brand names in the drug name and active ingredient fields. Only reports in which the agent was the primary suspect were analysed. Apremilast (oral), ensifentrine (inhaled) and crisaborole (topical) are each marketed for a single route. Roflumilast is marketed as tablets and as cream or foam, so each roflumilast record was classified as topical if the brand name was Zoryve, if the route or dose form field indicated cutaneous use, or if the indication recorded for that drug was a dermatological one, and otherwise as oral if the brand name was Daliresp or Daxas, if the route or dose form indicated oral use, or if the indication was COPD. Records that could not be classified (30 reports) were excluded. Agents were ranked by expected systemic exposure as oral, inhaled and topical.

2.3 Outcomes

Adverse events are coded in FAERS with Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA) [22]. The primary outcome was a predefined depression/suicidality group of 14 Preferred Terms (depression, depressed mood, major depression, depressive symptom, persistent depressive disorder, suicidal ideation, suicide attempt, completed suicide, suicidal behaviour, suicide threat, intentional self-injury, self-injurious ideation, intentional overdose and hopelessness). Secondary outcomes were predefined groups for anxiety, sleep disturbance and psychosis, any psychiatric term, and the single terms depression, suicidal ideation and insomnia. The term lists are given in Table S1.

Three control outcomes were defined before the analysis. Gastrointestinal events (diarrhoea, nausea, vomiting, decreased appetite, weight decreased) and headache are established class effects of systemic PDE4 inhibition and were expected to follow systemic exposure. Application-site reactions were expected only for topical agents. These outcomes test whether the method reproduces known route-dependent effects.

2.4 Comparisons

Three comparisons were made. First, each agent was compared with all other reports in the database, as in previous studies. Second, in the primary analysis, each agent was compared with a disease-matched background. Reports were assigned to an indication family from the indication text: COPD (including emphysema and chronic bronchitis), psoriasis (including psoriatic arthritis), atopic dermatitis or eczema, and a combined dermatological family (psoriasis, atopic dermatitis, eczema and seborrhoeic dermatitis) for topical roflumilast, which is approved for several of these conditions. The analysis was restricted to reports with the relevant indication, and the agent was compared with all other such reports.

Third, each agent was compared directly with a pooled group of non-PDE4 drugs used for the same indication and by a comparable route, again restricted to reports with that indication: inhaled long-acting bronchodilators for COPD (tiotropium, umeclidinium, revefenacin and aclidinium, alone or in fixed combinations), other systemic psoriasis drugs (secukinumab, ixekizumab, guselkumab, risankizumab, adalimumab, ustekinumab and deucravacitinib) and non-PDE4 topical drugs (pimecrolimus, tacrolimus, ruxolitinib and tapinarof). Three within-class comparisons were also made: ensifentrine against oral roflumilast, and each topical agent against apremilast.

2.5 Statistical analysis

For each agent–outcome pair we calculated the reporting odds ratio (ROR) with its 95% confidence interval (CI), the proportional reporting ratio (PRR) with Yates-corrected χ^2, and the information component (IC) with the lower limit of its 95% credibility interval (IC025) [23, 24, 25, 26]. A signal of disproportionate reporting required at least three cases, a lower CI limit of the ROR above 1, PRR ≥ 2 with $\chi^2 \geq 4$, and IC025 > 0. A continuity correction of 0.5 was applied when a cell was zero. P values were adjusted by the Benjamini–Hochberg false discovery rate procedure.

Direct comparisons were additionally adjusted with the Mantel–Haenszel method, stratified by sex, age band (under 18, 18–44, 45–64, 65 years or over, unknown), reporter type (healthcare professional, consumer or unknown) and region (United States or other), with the Robins–Breslow–Greenland variance

[27]. Time to onset was calculated from therapy start to event date where both were available. Because roflumilast records with a dermatological indication but no brand, route or dose form could represent off-label oral use, a sensitivity analysis classified roflumilast only by brand name, route or dose form and ignored the indication. Analyses were run in Python 3.15 with pandas 3.1.0, NumPy 2.5.4 and SciPy 1.18.1.

2.6 Ethics

The study used anonymised, publicly available data and did not require ethics committee approval or informed consent.

3. RESULTS

3.1 Reports

The five agents accounted for 16,111 primary-suspect reports (Table 1). Apremilast contributed most (12,900), followed by ensifentrine (1,308), crisaborole (1,001), topical roflumilast (582) and oral roflumilast (320). The relevant indication was recorded in 49% to 72% of reports for four agents but in only 63 of 320 reports for oral roflumilast. The disease-matched backgrounds comprised 25,845 reports for COPD, 152,106 for psoriasis, 216,154 for atopic dermatitis and 368,195 for the combined dermatological family.

Table 1
Agents, routes and report counts

Agent	Route	Target	First US approval	Psychiatric warning in US label	Primary-suspect reports	With matched indication	Matched background (reports)
Apremilast	Oral	PDE4	2014	Yes (depression)	12,900	9,300	Psoriasis (152,106)
Roflumilast	Oral	PDE4	2011	Yes (psychiatric events including suicidality)	320	63	COPD (25,845)
Ensifentrine	Inhaled	PDE3 and PDE4	2024	Yes (psychiatric events including suicidality)	1,308	690	COPD (25,845)
Roflumilast	Topical	PDE4	2022	No	582	348	Psoriasis, atopic dermatitis, eczema, seborrhoeic dermatitis (368,195)
Crisaborole	Topical	PDE4	2016	No	1,001	488	Atopic dermatitis, eczema (216,154)

The matched background is all reports with an indication in the same family. Thirty roflumilast reports could not be classified by formulation and were excluded. COPD chronic obstructive pulmonary disease, PDE phosphodiesterase.

3.2 Depression and suicidality

Against the disease-matched background, depression/suicidality was disproportionately reported for all three systemically administered agents and for neither topical agent (Table 2, Fig. 1). The ROR was 3.17 (95% CI 2.81–3.58; 323 cases) for apremilast, 13.33 (5.68–31.27; 6 cases) for oral roflumilast and 9.15 (6.43–13.03; 40 cases) for ensifentrine. For topical roflumilast and crisaborole it was 0.71 (0.18–2.83) and 0.83 (0.21–3.34), with two cases each. The three systemic agents met all signal criteria.

At the level of single terms, depression showed the same pattern (apremilast 3.63, 3.15–4.17; oral roflumilast 10.43, 3.23–33.71; ensifentrine 7.05, 4.35–11.45). Suicidal ideation was disproportionately reported for apremilast (2.30, 1.68–3.15; 45 cases) and, with a much larger estimate, for ensifentrine (54.76, 26.93–111.35; 19 cases). Each of the other three agents had a single report of suicidal ideation.

Against the whole database the picture was less clear. Depression/suicidality remained a signal for apremilast (2.20, 2.02–2.40) and ensifentrine (2.59, 2.02–3.32), but not for oral roflumilast (1.09, 0.52–

2.31; 7 cases among 320 reports), and reporting was lower than expected for topical roflumilast (0.34, 0.13–0.90) and crisaborole (0.29, 0.13–0.66) (Table S2).

Table 2
Reporting odds ratios against disease-matched backgrounds

Outcome	Apremilast (oral)	Roflumilast (oral)	Ensifentrine (inhaled)	Roflumilast (topical)	Crisaborole (topical)
Depression/suicidality	323; 3.17 (2.81–3.58)*	6; 13.33 (5.68–31.27)*	40; 9.15 (6.43–13.03)*	2; 0.71 (0.18–2.83)	2; 0.83 (0.21–3.34)
Suicidal ideation (PT)	45; 2.30 (1.68–3.15)*	1; 13.40 (1.80–99.68)	19; 54.76 (26.93–111.35)*	1; 2.30 (0.32–16.39)	1; 3.95 (0.55–28.36)
Anxiety	167; 1.01 (0.86–1.18)	4; 4.39 (1.59–12.15)	26; 2.62 (1.75–3.93)*	2; 0.38 (0.10–1.54)	12; 1.96 (1.11–3.49)
Sleep	112; 1.16 (0.96–1.41)	7; 9.82 (4.44–21.71)*	28; 3.47 (2.34–5.15)*	28; 4.26 (2.90–6.28)*	9; 0.68 (0.35–1.31)
Insomnia (PT)	68; 1.07 (0.84–1.37)	7; 15.67 (7.06–34.80)*	21; 4.12 (2.61–6.52)*	22; 8.48 (5.50–13.08)*	7; 1.66 (0.79–3.51)
Psychosis	18; 1.55 (0.96–2.52)	0; 2.16 (0.13–35.23)	19; 9.60 (5.76–15.98)*	2; 7.38 (1.83–29.76)	0; 2.31 (0.14–37.26)
Any psychiatric	610; 1.62 (1.48–1.76)	13; 6.38 (3.45–11.78)*	94; 4.11 (3.28–5.16)*	35; 2.33 (1.65–3.31)*	23; 0.99 (0.65–1.50)
Gastrointestinal events (control)	2204; 6.91 (6.54–7.29)*	11; 4.69 (2.44–9.01)*	69; 2.54 (1.96–3.28)*	38; 3.28 (2.34–4.60)*	2; 0.18 (0.04–0.70)
Headache (control)	811; 4.01 (3.71–4.35)*	5; 3.85 (1.54–9.65)	25; 1.70 (1.13–2.56)	46; 7.51 (5.50–10.25)*	1; 0.14 (0.02–0.96)
Application-site reactions (control)	2; 0.24 (0.06–0.95)	0; 135.34 (5.46–3353.93)	0; 12.14 (0.49–298.37)	15; 62.72 (36.87–106.69)*	15; 58.93 (34.16–101.66)*

Cells show number of cases; ROR (95% CI). * Signal of disproportionate reporting: at least three cases, lower CI limit of the ROR above 1, PRR ≥ 2 with $\chi^2 \geq 4$, and IC025 > 0. When no case was reported, the estimate reflects the continuity correction only and is not interpretable. CI confidence interval, IC information component, PRR proportional reporting ratio, PT Preferred Term, ROR reporting odds ratio.

3.3 Other psychiatric outcomes

Insomnia did not follow the same pattern as depression. It was disproportionately reported for oral roflumilast (15.67, 7.06–34.80), ensifentrine (4.12, 2.61–6.52) and topical roflumilast (8.48, 5.50–13.08; 22 cases), but not for apremilast (1.07, 0.84–1.37) or crisaborole (1.66, 0.79–3.51). Anxiety met signal criteria only for ensifentrine (2.62, 1.75–3.93).

Psychosis-related terms met signal criteria only for ensifentrine (9.60, 5.76–15.98; 19 cases). Hallucination was the most frequent term (13 cases; 12.37, 6.57–23.27). Ensifentrine also showed signals for the aggression/irritability group (8.79, 4.39–17.60; 10 cases) and for mood lability (10.71, 5.08–22.58; 9 cases). Two psychosis-related reports were recorded for topical roflumilast and none for oral roflumilast or crisaborole.

3.4 Control outcomes

Application-site reactions behaved as expected. They were strongly disproportionate for topical roflumilast (62.72, 36.87–106.69) and crisaborole (58.93, 34.16–101.66) and were not reported for oral roflumilast or ensifentrine (Table 2).

Gastrointestinal events were disproportionately reported for apremilast (6.91, 6.54–7.29), oral roflumilast (4.69, 2.44–9.01) and ensifentrine (2.54, 1.96–3.28), and also for topical roflumilast (3.28, 2.34–4.60). For crisaborole they were reported less often than expected (0.18, 0.04–0.70). Headache met signal criteria for apremilast (4.01, 3.71–4.35) and topical roflumilast (7.51, 5.50–10.25). The two topical agents therefore differed: topical roflumilast showed the systemic class effects that are listed in its label, and crisaborole showed none.

3.5 Comparison with non-PDE4 drugs

Direct comparison with non-PDE4 drugs for the same indication gave the same pattern after adjustment (Table 3). The Mantel–Haenszel ROR for depression/suicidality was 6.05 (5.04–7.25) for apremilast against other systemic psoriasis drugs, 11.84 (4.27–32.80) for oral roflumilast and 13.93 (7.89–24.60) for ensifentrine against inhaled bronchodilators. For the topical agents against non-PDE4 topical drugs it was 2.22 (0.43–11.46) for roflumilast and 0.31 (0.05–1.95) for crisaborole.

Ensifentrine also exceeded inhaled bronchodilators for psychosis-related terms (27.26, 10.32–72.04), insomnia (4.59, 2.61–8.06) and gastrointestinal events (4.89, 3.54–6.77). Topical roflumilast exceeded non-PDE4 topical drugs for insomnia (13.08, 5.48–31.24), gastrointestinal events (5.82, 3.47–9.77) and headache (4.62, 2.89–7.37), but not for application-site reactions (0.60, 0.33–1.08).

Table 3
Direct comparisons with non-PDE4 drugs for the same indication and within the class

Agent	Comparator	Outcome	Cases (agent / comparator)	Crude ROR (95% CI)	Adjusted ROR (95% CI)
Apremilast (oral)	Other systemic psoriasis drugs	Depression/suicidality	323 / 859	3.65 (3.21–4.16)	6.05 (5.04–7.25)
		Insomnia (PT)	68 / 605	1.06 (0.83–1.37)	1.74 (1.28–2.35)
		Gastrointestinal events	2204 / 3791	6.90 (6.51–7.31)	9.19 (8.45–10.00)
		Headache	811 / 1935	4.25 (3.90–4.63)	5.54 (4.91–6.26)
Roflumilast (oral)	Inhaled bronchodilators	Depression/suicidality	6 / 40	20.37 (8.31–49.93)	11.84 (4.27–32.80)
		Insomnia (PT)	7 / 53	18.22 (7.94–41.83)	11.12 (3.98–31.07)
		Gastrointestinal events	11 / 168	9.58 (4.91–18.69)	5.47 (2.60–11.50)
		Headache	5 / 134	4.92 (1.94–12.46)	4.40 (1.62–11.99)
Ensifentrine (inhaled)	Inhaled bronchodilators	Depression/suicidality	40 / 40	11.91 (7.63–18.59)	13.93 (7.89–24.60)
		Insomnia (PT)	21 / 53	4.58 (2.74–7.63)	4.59 (2.61–8.06)
		Psychosis	19 / 11	20.00 (9.48–42.19)	27.26 (10.32–72.04)
		Gastrointestinal events	69 / 168	5.03 (3.76–6.74)	4.89 (3.54–6.77)
		Headache	25 / 134	2.14 (1.39–3.31)	1.94 (1.22–3.07)

Agent	Comparator	Outcome	Cases (agent / comparator)	Crude ROR (95% CI)	Adjusted ROR (95% CI)
Roflumilast (topical)	Non-PDE4 topical drugs	Depression/suicidality	2 / 9	1.34 (0.29–6.22)	2.22 (0.43–11.46)
		Insomnia (PT)	22 / 26	5.37 (3.00–9.58)	13.08 (5.48–31.24)
		Gastrointestinal events	38 / 61	4.08 (2.68–6.23)	5.82 (3.47–9.77)
		Headache	46 / 81	3.78 (2.58–5.54)	4.62 (2.89–7.37)
Crisaborole (topical)	Non-PDE4 topical drugs	Depression/suicidality	2 / 9	0.95 (0.21–4.42)	0.31 (0.05–1.95)
		Insomnia (PT)	7 / 26	1.16 (0.50–2.68)	0.90 (0.30–2.71)
		Gastrointestinal events	2 / 61	0.14 (0.03–0.56)	0.09 (0.02–0.35)
		Headache	1 / 81	0.05 (0.01–0.37)	0.02 (0.00–0.15)
Ensifentrine (inhaled)	Roflumilast (oral)	Depression/suicidality	40 / 6	0.58 (0.24–1.44)	0.18 (0.05–0.63)
		Insomnia (PT)	21 / 7	0.25 (0.10–0.62)	0.17 (0.04–0.65)
		Psychosis	19 / 0	3.69 (0.22–61.81)	Not estimable
		Gastrointestinal events	69 / 11	0.53 (0.26–1.05)	0.27 (0.10–0.73)
Roflumilast (topical)	Apremilast (oral)	Depression/suicidality	2 / 323	0.16 (0.04–0.65)	0.04 (0.01–0.33)
		Insomnia (PT)	22 / 68	9.16 (5.59–15.00)	14.71 (4.92–43.97)

Agent	Comparator	Outcome	Cases (agent / comparator)	Crude ROR (95% CI)	Adjusted ROR (95% CI)
		Gastrointestinal events	38 / 2204	0.39 (0.28–0.55)	0.41 (0.28–0.62)
		Headache	46 / 811	1.59 (1.16–2.19)	1.57 (1.03–2.39)
Crisaborole (topical)	Apremilast (oral)	Depression/suicidality	2 / 323	0.11 (0.03–0.46)	0.11 (0.03–0.46)
		Insomnia (PT)	7 / 68	1.98 (0.90–4.32)	1.49 (0.63–3.51)
		Gastrointestinal events	2 / 2204	0.01 (0.00–0.05)	0.01 (0.00–0.04)
		Headache	1 / 811	0.02 (0.00–0.15)	0.01 (0.00–0.11)

Both groups were restricted to reports with the relevant indication. Adjusted estimates are Mantel–Haenszel RORs stratified by sex, age band, reporter type and region. Comparators: inhaled bronchodilators (tiotropium, umeclidinium, revefenacin, aclidinium and their fixed combinations); other systemic psoriasis drugs (secukinumab, ixekizumab, guselkumab, risankizumab, adalimumab, ustekinumab, deucravacitinib); non-PDE4 topical drugs (pimecrolimus, tacrolimus, ruxolitinib, tapinarof). CI confidence interval, ROR reporting odds ratio.

3.6 Comparisons within the class

Compared with oral roflumilast in COPD, ensifentrine had a crude ROR for depression/suicidality of 0.58 (0.24–1.44) and an adjusted ROR of 0.18 (0.05–0.63). Gastrointestinal events were lower to a similar degree (crude 0.53, 0.26–1.05; adjusted 0.27, 0.10–0.73). These estimates rest on six and 11 oral roflumilast cases. Compared with apremilast, depression/suicidality was reported much less often for topical roflumilast (adjusted 0.04, 0.01–0.33) and crisaborole (0.11, 0.03–0.46), whereas insomnia was reported more often for topical roflumilast (14.71, 4.92–43.97).

3.7 Case characteristics

Characteristics of all primary-suspect reports with a depression/suicidality term, regardless of recorded indication, are shown in Table 4. Ensifentrine cases were older than apremilast cases (median age 74 versus 53 years), were all reported from the United States, were more often serious (64% versus 37%) and were less often reported by healthcare professionals (41% versus 59%). Five ensifentrine cases and 21 apremilast cases had a fatal outcome recorded; a fatal outcome in a report is not necessarily a death by

suicide. Among cases with dates, the median time to onset was 18.5 days (interquartile range 3–68; n = 12) for ensifentrine and 22.5 days (2–152; n = 60) for apremilast, and more than half of cases began within 30 days of starting treatment.

Table 4
Characteristics of primary-suspect reports with a depression/suicidality term

Agent	Cases	Serious (%)	Fatal outcome (n)	Healthcare professional reporter (%)	Female (% of known)	Median age (years)	United States (%)	Median time to onset, days (IQR; n)
Apremilast (oral)	555	37	21	59	67	53	91	22.5 (2–152; 60)
Roflumilast (oral)	7	86	0	57	43	71.5	57	375.5 (349–402; 2)
Ensifentrine (inhaled)	66	64	5	41	46	74	100	18.5 (3–68; 12)
Roflumilast (topical)	4	75	0	25	100	77.5	50	No dated cases
Crisaborole (topical)	6	67	0	83	50	47.5	100	No dated cases

All primary-suspect reports regardless of recorded indication; counts therefore exceed those in Table 2. A fatal outcome recorded in a report is not necessarily a death by suicide. Time to onset was calculated among reports with complete therapy start and event dates. IQR interquartile range.

3.8. Sensitivity analysis

When roflumilast was classified only by brand name, route or dose form, 387 reports remained topical (224 with a dermatological indication), 305 remained oral (41 with a COPD indication) and 248 were unclassifiable (Table S8). The results did not change materially. For topical roflumilast, depression/suicidality was not disproportionately reported against the dermatological background (one case; ROR 0.55, 95% CI 0.08–3.90) and remained lower than for apremilast (adjusted 0.06, 0.01–0.47), whereas signals persisted for insomnia (17 cases; 10.30, 6.27–16.92), headache (7.90, 5.40–11.55), gastrointestinal events (3.51, 2.33–5.29) and application-site reactions (57.01, 28.95–112.24). For oral roflumilast, the depression/suicidality signal was stronger (six cases; 21.73, 9.04–52.23; adjusted ROR against inhaled bronchodilators 24.55, 8.35–72.21).

4. DISCUSSION

In this analysis of spontaneous reports, the depression and suicidality signal associated with PDE4 inhibitors was present for apremilast and for the two systemically absorbed respiratory agents and was absent for the two topical agents. The pattern was the same against disease-matched backgrounds and, after adjustment, against non-PDE4 drugs used for the same conditions. Control outcomes behaved as expected for local reactions, which supports the validity of the route classification.

4.1. Topical agents

For dermatological practice the central observation is that neither topical agent showed a depression or suicidality signal. Each had two such reports, reporting was lower than expected against the whole database, and after adjustment both were reported with these events far less often than apremilast. Their profiles nevertheless differed. Crisaborole showed local reactions only, with fewer gastrointestinal and headache reports than expected. Topical roflumilast showed insomnia, headache and gastrointestinal signals, the same reactions that occurred more often than with vehicle in its trials and are listed in its label [11, 3]. Roflumilast is a far more potent PDE4 inhibitor than crisaborole and has an active metabolite with a long half-life [1, 11], so some systemic pharmacological effect after application to large skin areas is plausible. The absence of a depression signal despite these systemic-type effects suggests either that exposure after topical use is below the level associated with mood effects, or that the number of reports is still too small to detect them. With two cases and upper confidence limits near 3, our data cannot exclude a moderate increase.

Misclassification of roflumilast formulation is unlikely to explain these findings. Oral roflumilast is sometimes used off-label for psoriasis, and in the main analysis records with a dermatological indication were classified as topical even when no brand or route was given. When classification was restricted to records with a brand name, route or dose form, the insomnia, headache and gastrointestinal signals for topical roflumilast persisted with similar estimates, and the depression/suicidality estimate remained below 1.

4.2. Apremilast and other systemically absorbed agents

Apremilast provided by far the largest number of cases, and its depression/suicidality signal was robust to the choice of reference: it was present against the whole database, against all other reports for psoriasis and, after adjustment, against biologics and deucravacitinib. This is consistent with the label warning [6]. The comparison with biologics needs care, because apremilast is generally used in less severe disease, in which a lower background rate of depression might be expected, and because effective biologic treatment may itself improve mood; both would act in opposite directions and we could not separate them.

The two respiratory agents support the interpretation that systemic exposure matters more than the organ treated. Oral roflumilast showed a signal among reports with a COPD indication, based on six cases. Ensifentrine is inhaled, but its label states that about 90% of the dose is absorbed from the lung [9]; it was reported with depression/suicidality nine times more often than other drugs for COPD and 14 times more often than inhaled bronchodilators after adjustment. Ensifentrine is, however, the only agent studied during its first two years on the market, when reporting is typically highest [28]; its label already contained a

psychiatric warning that may itself stimulate reports [29]; and all its cases came from the United States, most from non-professional reporters. Its estimates are therefore likely to be inflated relative to those of the older agents. The psychosis-related reports with ensifentrine, mainly hallucination in older patients with COPD, have many alternative explanations, including delirium during exacerbations, hypoxia and corticosteroids, and we did not review case narratives.

4.3 Mechanistic considerations

The association of PDE4 inhibition with depression is pharmacologically unexpected, since PDE4 inhibitors increase cyclic adenosine monophosphate signalling in pathways that antidepressants also enhance, and rolipram showed antidepressant activity in early trials [5]. Our study cannot explain this discrepancy. The route pattern is compatible with an effect that requires systemic exposure, whether central or mediated indirectly, for example through nausea, weight loss and sleep disturbance. The fact that insomnia and depression did not follow the same pattern across agents (apremilast showed depression without insomnia, and topical roflumilast insomnia without depression) argues against sleep disturbance as the only pathway.

4.4 Comparison with previous studies

Previous FAERS analyses of roflumilast reported signals for suicidal ideation, depression, insomnia and anxiety against the whole database over the full marketing period [14, 15]. In our more recent period, oral roflumilast was not disproportionately reported with depression/suicidality against the whole database, and the signal appeared only among reports with a COPD indication. This shows how much the choice of reference group matters for a drug used in a population with a high background rate of psychiatric reporting, and it is why we treated the disease-matched comparison as primary. The comparative study of apremilast, crisaborole and roflumilast attributed differences between agents to route in its discussion but did not test route formally and did not include an inhaled agent [16].

4.5 Strengths and limitations

The strengths of the study are the comparison within one pharmacological class across three routes, the use of disease-matched backgrounds and active comparators to reduce confounding by indication, adjustment for basic report characteristics, and prespecified control outcomes.

The limitations are substantial. Spontaneous reports lack denominators, are subject to under-reporting, duplicate and incomplete reporting, and do not allow incidence or causality to be estimated [17, 18]. The agents differ in indication, patient age, time on the market and prior warnings, and route cannot be separated from these differences; in particular, the only inhaled agent is also the only dual PDE3/PDE4 inhibitor and the only recently launched one. Estimates for oral roflumilast and for both topical agents rest on two to seven cases and have wide confidence intervals. Only 63 oral roflumilast reports had a COPD indication recorded, and restriction to reports with a recorded indication may select reports that are more complete. Indication matching reduces but does not remove confounding by disease severity; apremilast is used in less severe psoriasis than biologics, and patients given a new add-on COPD treatment may have more advanced disease. Psychiatric history, concomitant drugs and dose were not analysed, and area of

application was not available for the topical agents. Multiple outcomes were tested, and secondary findings are exploratory. Finally, the study period was limited to 2023–2026 and does not describe the first years of marketing of the older agents.

4.6 Implications

For dermatologists, the findings provide some reassurance that the depression warning attached to apremilast does not appear to extend to topical PDE4 inhibitors in routine use, including in patients for whom apremilast is considered unsuitable because of mood symptoms. They also indicate that insomnia may occur with topical roflumilast and is worth asking about. For apremilast, they support continued attention to mood, particularly in the first weeks of treatment, when more than half of the dated cases began. For research, cohort studies in health-care databases comparing topical and oral PDE4 inhibitors with other treatments for the same disease, with adjustment for psychiatric history and disease severity, would be the appropriate next step.

5. CONCLUSIONS

Among PDE4 inhibitors, disproportionate reporting of depression and suicidality accompanied systemic administration, most robustly for apremilast, and was not seen with topical roflumilast or crisaborole. Topical roflumilast showed insomnia and other systemic-type effects without a depression signal, and crisaborole showed local reactions only. These are signals from spontaneous reports, those for the topical agents based on small numbers, and they require confirmation in studies with denominators and adjustment for psychiatric history.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

Not applicable. The study used anonymised, publicly available data.

Use of artificial intelligence

During the preparation of this work, the tool Claude AI was used to enhance the readability of the text. Following the use of this tool, the content was reviewed and necessary adjustments were made; full responsibility for the final version of the work is assumed.

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Author Contribution

Yeşim Olğun: conceptualisation, methodology, software, data curation, formal analysis, visualisation, writing – original draft, writing – review and editing. Nesrin Dilbaz: supervision, writing – review and editing. Both authors approved the final version.

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None.

Data Availability

The data analysed in this study are publicly available from the FDA Adverse Event Reporting System (FAERS) Quarterly Data Extract Files at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. All derived result tables are provided in the Supplementary Information (Tables S1–S6 and S8). The analysis code is available from the corresponding author on reasonable request.

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Figures

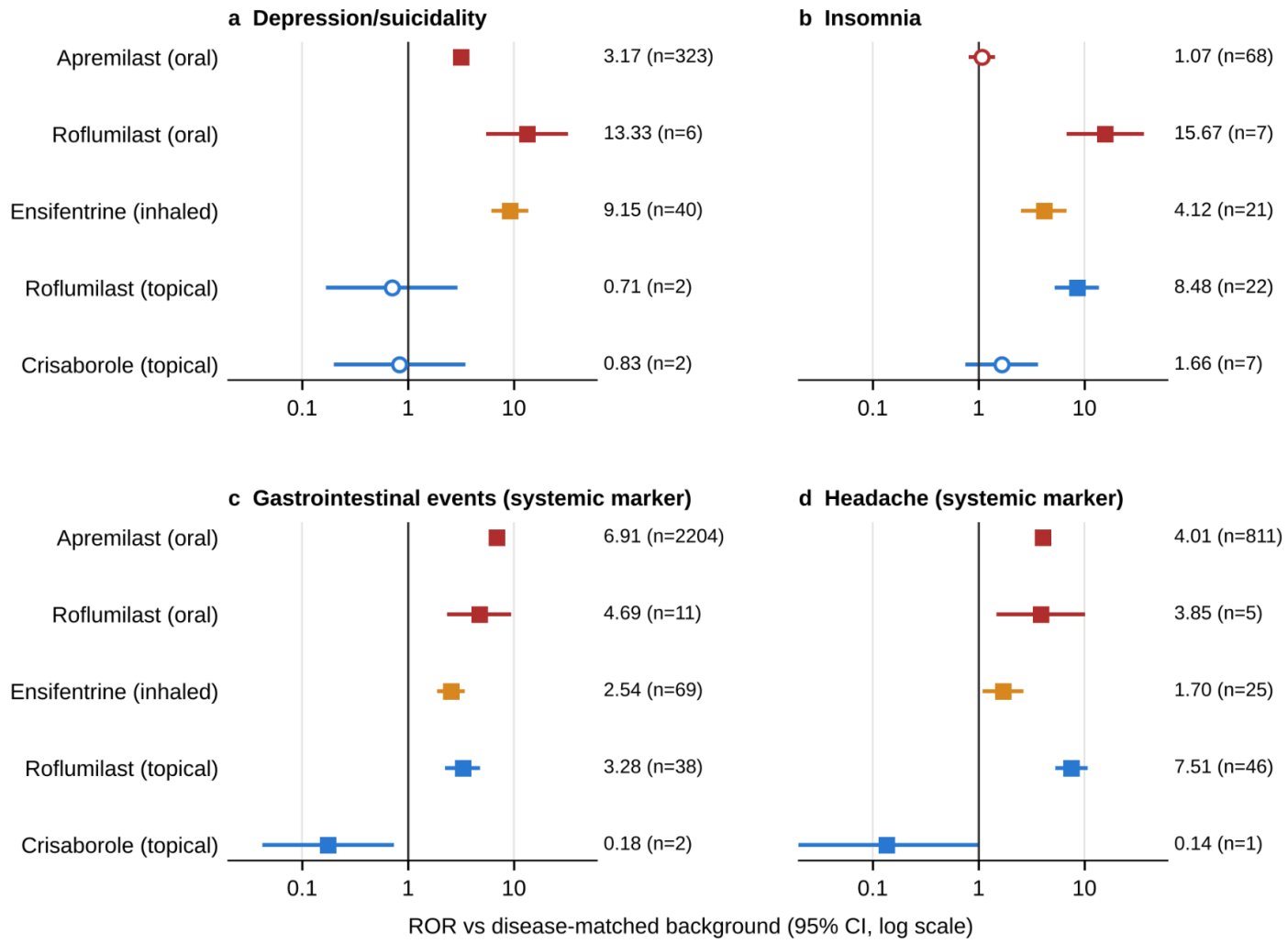

Figure 1

Reporting odds ratios against disease-matched backgrounds for depression/suicidality, insomnia, gastrointestinal events and headache, by agent. Agents are ordered by expected systemic exposure (oral, inhaled, topical). Points are RORs and bars are 95% confidence intervals on a logarithmic scale. ROR reporting odds ratio

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS7READUSPV.docx
- TableS8sensitivityroflumilast.xlsx
- TablesS1S6.xlsx