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Psychiatric Adverse Events Associated With Lebrikizumab: An FDA Adverse Event Reporting System (FAERS) Disproportionality Analysis With an Indication-Matched Active Comparator

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Abstract

Introduction: Lebrikizumab, an anti-interleukin-13 antibody approved for moderate-to-severe atopic dermatitis, has not been evaluated for psychiatric adverse event reporting, although dupilumab and tralokinumab, which act on the same pathway, have generated postmarketing psychiatric signals, most consistently for sleep disturbance.

Methods: We performed a disproportionality analysis of FDA Adverse Event Reporting System (FAERS) reports accessed through the FDA Health Informatics initiative, openFDA (data through July 30, 2026), reported according to the READUS-PV (REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance) guideline. All exposure arms and the whole-database reference were restricted to reports received from September 2024, when lebrikizumab was approved in the United States, through June 2026. Reporting odds ratios (RORs) with 95% confidence intervals (CIs) compared lebrikizumab with an indication-matched active comparator (dupilumab and tralokinumab) and, contextually, with the entire database, for a composite of psychiatric MedDRA (Medical Dictionary for Regulatory Activities) preferred terms from which any term showing a comparator-specific signal against the whole database was removed by a prespecified rule.

Results: The analysis included 1,743 lebrikizumab, 142,906 dupilumab, and 3,315 tralokinumab reports. Of 51 psychiatric terms identified, five were excluded for comparator-specific signals. For the 46-term composite, 38 lebrikizumab reports (2.2%) and 2,716 pooled comparator reports (1.9%) qualified; the ROR was 1.18 (95% CI, 0.85 to 1.63) against the pooled comparator, 1.17 (95% CI, 0.85 to 1.62) against dupilumab, 1.37 (95% CI, 0.90 to 2.09) against tralokinumab, and 0.42 (95% CI, 0.31 to 0.58) against the whole database. The full 51-term composite gave RORs of 0.44 to 0.77, the difference attributable to the excluded terms. A composite without sleep-wake terms gave 1.40 (95% CI, 0.94 to 2.06) against the pooled comparator and 2.08 (95% CI, 1.19 to 3.63) against tralokinumab. Nervousness and anxiety were nominally elevated against dupilumab and the pooled comparator; no term remained significant after Benjamini-Hochberg correction.

Conclusions: Within a common reporting period, psychiatric adverse events were not reported disproportionately for lebrikizumab relative to dupilumab or to the pooled indication-matched comparator. The higher estimates against tralokinumab alone rest on small numbers and warrant replication. These findings characterize reporting, not risk.

Categories: Therapeutics, Pharmacology, Dermatology
Keywords: active comparator bias, atopic dermatitis, disproportionality analysis, faers, lebrikizumab, pharmacovigilance, psychiatric adverse events, reporting odds ratio

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease with a substantial psychiatric burden. Adults with AD have a two- to threefold higher risk of depression and anxiety than the general population, attributable to itch, sleep disruption, unpredictable flares, and stigma, and largely independent of treatment [1]. Mendelian randomization data suggest that AD may causally increase the risk of anxiety, and shared neuroinflammatory mechanisms, including microglial activation, IL (interleukin)-4 and IL-13 signaling, and altered serotonergic transmission, plausibly link skin and mood disorders in both directions [2,3]. Any assessment of psychiatric adverse events in AD therapy must therefore be read against this

disease-related background rather than against a psychiatrically healthy reference population.

Lebrikizumab is a high-affinity monoclonal antibody against IL-13, approved for moderate-to-severe AD on the basis of the ADvocate1 and ADvocate2 trials [4] and the ADhere combination trial [5]. An Investigator Global Assessment response was achieved by 43.1% and 33.2% of patients in ADvocate1 and ADvocate2, as compared with 12.7% and 10.8% with placebo, and the safety profile was dominated by conjunctivitis, injection-site reactions, and herpes infections [4]. An integrated analysis of eight trials (1,720 patients; 1,637 patient-years) found no psychiatric safety signal [6], and neither did the 104-week ADjoin extension [7] or an adolescent subgroup analysis [8]. A post hoc analysis of the pivotal trials found that lebrikizumab improved patient-reported anxiety and depression scores (PROMIS) over 16 weeks, together with quality of life [9]. Phase 3 trials, however, are underpowered for uncommon adverse events; psychiatric outcomes are seldom prespecified safety endpoints in dermatologic trials, and favorable patient-reported outcomes in trials do not exclude rarer psychiatric events that emerge only with wider postmarketing exposure.

The one published FDA Adverse Event Reporting System (FAERS) analysis of lebrikizumab, covering its first year on the market (fourth quarter of 2024 through third quarter of 2025; 791 reports), identified conjunctivitis, eyelid irritation, and injection-site reactions as the leading signals and a serious-report proportion of 15.68%, but did not examine psychiatric outcomes [10]. This gap matters because dupilumab and tralokinumab, the two other biologics approved for AD that act on the IL-4 and IL-13 axis, have each generated postmarketing psychiatric signals in FAERS and VigiBase, the World Health Organization global database of individual case safety reports for medicines and vaccines, most consistently for sleep-related disorders [11-13]. Whether lebrikizumab shares that signal has not been tested.

Such a comparison faces a methodologic problem. A conventional disproportionality analysis against the entire FAERS database (case/non-case design) is vulnerable to confounding by therapeutic area: a biologic prescribed for a chronic skin disease may be reported with psychiatric events less often than the database average for reasons unrelated to the drug [14,15]. Restricting the comparison to an indication-matched active comparator removes that confounding but creates a second hazard. If the comparator carries its own psychiatric signal, a null or sub-unity ROR against it shows only that the index drug is no worse than a comparator that may itself be unsafe. We refer to this as the active-comparator interpretation trap.

Our objective was to evaluate, by disproportionality analysis of FAERS reports, whether psychiatric adverse events are reported in excess for lebrikizumab. The primary analysis compared a composite of psychiatric preferred terms between lebrikizumab and an indication-matched active comparator (dupilumab and tralokinumab), after an algorithmic check that removed from the composite any term for which a comparator itself showed excess reporting. Two further sets of results are reported with lower inferential weight: a contextual comparison against the entire FAERS database, included to make the confounding by therapeutic area visible rather than to answer the safety question, and prespecified sensitivity analyses (the full term domain without exclusions, serious reports, deduplicated reports, health care professional reporters, and symmetric indication restriction) that test the robustness of the primary estimate.

Materials And Methods

Study design and data source

We performed a retrospective disproportionality (case/non-case) analysis of individual case safety reports in FAERS. The study is reported according to the READUS-PV (REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance) guideline [16,17] and follows current recommendations for the conduct and interpretation of disproportionality analyses of spontaneous reports [15]. FAERS is maintained by the FDA and contains spontaneous and mandatory reports of adverse events submitted by healthcare professionals, consumers, and manufacturers, predominantly from the United States. Data were accessed through the openFDA drug adverse event application programming interface [18,19]. openFDA republishes the FAERS public quarterly releases with harmonized drug fields; the endpoint exposes a single last_updated field for the whole dataset and does not identify the quarterly release of each report; it returns one record per safetyreportid, the most recent version of each case. Adverse events in FAERS are coded with the Medical Dictionary for Regulatory Activities (MedDRA); at the time of extraction, the current release was MedDRA version 29.0 (March 2026) [20], and terms were matched on the exact preferred term string.

All three exposure arms and the whole-database reference were restricted to reports received by the FDA from September 1, 2024, the month in which lebrikizumab was approved in the United States, through July 31, 2026; the release available at extraction contained reports received through June 30, 2026. For each study drug, all reports containing a drug entry whose generic_name or medicinalproduct field matched the generic or brand name (case-insensitive substring match: lebrikizumab or Ebglyss; dupilumab or Dupixent; tralokinumab, Adtralza, or Adbry) were downloaded in pages through the application programming interface (API), month by month of receipt date, in any drug role, and stored locally as one JavaScript Object Notation (JSON) record per report with its safetyreportid, report version, receipt date, manufacturer control number, reporter qualification, seriousness, age, sex, country of occurrence, drug list, and reaction list. The total number of reports in the database and the number containing a given preferred term were obtained from the

API count endpoint with the same receipt-date restriction and an exact-string match on the preferred term. Data were extracted on October 6, 2026; database content was current as of July 30, 2026, according to the endpoint's last_updated field.

Records were downloaded and analyzed with Python 3.14 (Python Software Foundation, Wilmington, Delaware, United States) using the standard library only (json, urllib, math, csv); no external statistical package was used. The download and analysis scripts, the downloaded records as analyzed, and the unrounded outputs are deposited in a public repository [21]. No case-by-case review of individual reports was performed. The two analytic layers, the comparator check, the composite endpoints, and the sensitivity analyses were specified before the data were examined; the plan was not registered in a public repository.

The analysis had two prespecified layers. Analysis 1 compared lebrikizumab with the entire FAERS database using the reporting odds ratio (ROR) with a 95% confidence interval (CI). Because this comparison is subject to confounding by therapeutic area, it was designated contextual and was not used to answer the safety question. The whole-database reference group excluded the lebrikizumab reports themselves (non-cases were all other FAERS reports). Analysis 2, the primary analysis, compared lebrikizumab with an indication-matched active comparator composed of dupilumab and tralokinumab, biologics approved for the same indication that act on the same IL-4 and IL-13 pathway. Because dupilumab is approved for several indications, its reports were restricted to those in which the recorded indication contained an atopic dermatitis or eczema term or in which no indication was recorded; reports with a clearly non-AD indication were excluded. The openFDA placeholder value “Product used for unknown indication” was treated as no recorded indication. Indication is often missing in FAERS, and requiring a positive match would have introduced differential missingness. Tralokinumab, approved for a single indication, required no restriction. Results are presented for each comparator drug and for the pooled comparator.

Before any Analysis 2 result was interpreted, each comparator drug was assessed for its own disproportionality signal against the entire FAERS database for every psychiatric term under study (step 1). Any term for which a comparator showed excess reporting, defined by the same signal threshold used throughout the study (at least 3 comparator reports and a lower 95% confidence limit above 1), was removed from the primary composite. The criterion was deliberately one-sided. The interpretation trap arises when a comparator over-reports a term, which inflates the comparator denominator and biases the index-versus-comparator ROR toward a falsely reassuring null. Underreporting by a comparator would bias the same ROR upward, against reassurance, and is in any case the nonspecific pattern shared by most psychiatric terms for all three drugs, reflecting therapeutic-area confounding rather than a comparator-specific hazard. The rule was applied algorithmically to the entire outcome domain, not by naming individual terms, so that any contaminated term, anticipated or not, would be excluded consistently (step 2).

Exposure definition

Lebrikizumab (Ebglyss), dupilumab (Dupixent), and tralokinumab (Adtralza/Adbry) were identified from the generic_name and medicinalproduct fields of each drug entry (openFDA generic names may carry a suffix, such as tralokinumab-ldrm, which the substring match accommodates) and restricted to reports in which the matching drug entry itself carried drugcharacterization=1 (suspect drug). This restriction addresses a limitation of the public openFDA API: because the nested drug array is flattened for indexing, a query that combines drug name and drug characterization can match fields belonging to different drugs within the same report. Raw records were therefore downloaded and filtered locally so that drug identity and suspect role were verified within the same object.

Outcome definition

The psychiatric outcome domain was defined in two steps. First, every distinct MedDRA preferred term (PT) recorded in any report of the three exposure arms was screened by case-insensitive substring match against a fixed list of 17 keyword stems (depress, suicid, anxi, insomnia, sleep, panic, mood, agitation, irritab, nervous, emotional, psychiatric, self-injurious, self harm, hallucinat, confusional, aggress); the suicidality stems cover the core terms of the MedDRA Suicide/self-injury query. Second, terms that matched a keyword but do not belong to the MedDRA Psychiatric disorders system organ class were removed as textual false positives. The domain was built from all three arms rather than from lebrikizumab reports alone, because a domain built from the index drug alone would undercount comparator events and bias composite estimates upward. Each PT was counted once per report.

Primary composite and exclusion rule

The primary composite endpoint was the set of PTs remaining after step 1 exclusions. The full domain was analyzed as a prespecified sensitivity composite to quantify the contribution of comparator-contaminated terms to any composite deviation. The sequence (step 1 check before composite definition) was fixed before execution. The exclusion rule was therefore prespecified even though the PTs it removed were identified only during execution.

Statistical analysis

The estimand of every comparison is the ratio of the odds of a report containing the outcome among lebrikizumab reports to the same odds among reference reports, a measure of differential reporting within FAERS; it is not an incidence, a relative risk, or a causal effect. The ROR was calculated from the 2 by 2 table of reports with and without the outcome in the index and reference groups, with the 95% CI obtained on the logarithmic scale by the method of Katz et al. [22]; when any cell was zero, 0.5 was added to all four cells (Haldane-Anscombe correction) [23,24]; the correction was applied only in that case. Formulas are given in Appendices.

Reference counts used exact MedDRA field matching to avoid overcounting from partial text matches. A single signal threshold, at least three reports and a lower 95% confidence limit above 1, was applied wherever an individual PT was assessed for a signal [25,26]: at step 1, and descriptively for lebrikizumab against each comparator and against the whole database. Because every PT in the domain was examined without adjustment for multiplicity in the original analysis plan, individual PT results are descriptive, and the composite endpoint is the sole inferential comparison. As an additional, exploratory check, the Benjamini-Hochberg false discovery rate procedure (q=0.05) [27] was applied post hoc across the PT-level comparisons separately for each comparator, with two-sided Wald P values derived from each PT's log ROR and its standard error.

Prespecified sensitivity analyses were heuristic case deduplication, motivated by documented extreme duplication in FAERS [28], in which reports sharing the same manufacturer control number (companynumb) were collapsed to one and, for reports without a control number, reports with identical age, sex, and reaction set were collapsed to one; restriction to serious reports (death or hospitalization); restriction to reports from healthcare professionals (exploratory, without the signal threshold, given reduced power); application of the indication restriction to all three arms, which also tests the decision to retain dupilumab reports with no recorded indication; and, as an alternative outcome definition, the primary composite without sleep-wake PTs (every PT containing the stem sleep or insomnia), which tests the influence of the broad sleep terms on the composite. The non-deduplicated data set served as the primary analysis because the heuristic cannot separate true duplicates from distinct reports with identical features and would remove distinct reports preferentially from the larger arms. Age, sex, seriousness, reporter qualification, country of occurrence, recorded indication, and year of receipt were tabulated by arm to describe the comparability of the exposure groups.

Ethics

The study used publicly available, de-identified data released by the FDA through openFDA. It did not involve human subjects research, and institutional review board approval and informed consent were not required.

Results

The openFDA queries retrieved 2,088 records for lebrikizumab, 217,288 for dupilumab, and 3,707 for tralokinumab (Table *1*). After exclusion of records in which the drug was not recorded as a suspect drug (345, 2,285, and 392, respectively) and, for dupilumab, of 72,097 reports with a recorded indication other than atopic dermatitis or eczema, 1,743 lebrikizumab reports, 142,906 dupilumab reports, and 3,315 tralokinumab reports remained (pooled comparator, 146,221). Among the 215,003 dupilumab suspect reports, 125,969 recorded atopic dermatitis or eczema, 72,097 recorded another indication, and 16,937 recorded no indication and were retained. Only two product strings matched each drug (EBGLYSS and LEBRIKIZUMAB, the openFDA generic_name field being unpopulated for Ebglyss records; DUPIXENT and DUPILUMAB; ADBRY, with the generic name TRALOKINUMAB-LDRM, and TRALOKINUMAB), and each safetyreportid appeared once in each arm. The database contained 2,421,231 reports received in the study window, of 20,692,690 in total.

Exposure arm	Records retrieved	Excluded: drug not recorded as suspect	Excluded: recorded indication other than atopic dermatitis or eczema	Reports analyzed
Lebrikizumab	2,088	345	Not applied	1,743
Dupilumab	217,288	2,285	72,097	142,906
Tralokinumab	3,707	392	Not applied	3,315

TABLE 1: Report-selection flow by exposure arm

Records retrieved are all FAERS reports received from September 1, 2024, through July 31, 2026, returned by the openFDA query for the drug name in any role. Reports were excluded when the drug was not recorded as a suspect drug within the same drug object, and, for dupilumab only, when a recorded indication was other than atopic dermatitis or eczema; dupilumab reports with no recorded indication, including the openFDA placeholder for an unknown indication, were retained. The indication restriction was not applied to lebrikizumab or tralokinumab in the main analysis.

FAERS, FDA Adverse Event Reporting System

Fifty-one psychiatric PTs were reported in at least one exposure arm after removal of 13 keyword matches outside the Psychiatric disorders system organ class ("Autonomic nervous system imbalance," "Central nervous system infection," "Central nervous system inflammation," "Central nervous system lesion," "Depressed level of consciousness," "Irritable bowel syndrome," "Metastases to central nervous system," "Nervous system disorder," "Obstructive sleep apnoea syndrome," "Sleep apnoea syndrome," "Sleep paralysis," "Sudden onset of sleep," and "Tympanic membrane perforation," the last matched by the stem panic). Five met the step 1 exclusion criterion. Against the whole database, Sleep disorder was reported in excess for dupilumab (ROR, 2.31; 95% CI, 2.17 to 2.45) and for tralokinumab (ROR, 2.83; 95% CI, 2.03 to 3.95), Initial insomnia for dupilumab (ROR, 2.38; 95% CI, 2.03 to 2.80) and for tralokinumab (ROR, 6.05; 95% CI, 3.24 to 11.29), Mood altered for dupilumab (ROR, 1.25; 95% CI, 1.08 to 1.44) and for tralokinumab (ROR, 10.65; 95% CI, 7.78 to 14.58), and Sleep disorder due to a general medical condition (ROR, 12.27; 95% CI, 11.79 to 12.77) and Mood disorder due to a general medical condition (ROR, 15.35; 95% CI, 11.03 to 21.36) for dupilumab. No other PT met the criterion for either comparator. The primary composite therefore comprised 46 PTs.

In the primary analysis, 38 of 1,743 lebrikizumab reports (2.2%) and 2,716 of 146,221 pooled comparator reports (1.9%) contained at least one composite PT (Table *2*). The ROR was 1.18 (95% CI, 0.85 to 1.63) against the pooled comparator, 1.17 (95% CI, 0.85 to 1.62) against dupilumab, and 1.37 (95% CI, 0.90 to 2.09) against tralokinumab. Against the entire database, the same composite gave an ROR of 0.42 (95% CI, 0.31 to 0.58); including the lebrikizumab reports in the reference group changed this estimate by less than 0.01.

Composite	Comparator	Lebrikizumab reports with at least one composite PT	Comparator reports with at least one composite PT	Lebrikizumab reports without composite PT	Comparator reports without composite PT	ROR	95% CI
46 PTs (primary)	vs dupilumab	38	1,705	2,663	140,243	1.17	0.85 to 1.62
46 PTs (primary)	vs tralokinumab	38	1,705	53	3,262	1.37	0.90 to 2.09
46 PTs (primary)	vs pooled comparator	38	1,705	2,716	143,505	1.18	0.85 to 1.63
46 PTs (primary)	vs whole FAERS	38	1,705	121,437	2,298,051	0.42	0.31 to 0.58
51 PTs (sensitivity)	vs dupilumab	45	1,698	8,094	134,812	0.44	0.33 to 0.59
51 PTs (sensitivity)	vs tralokinumab	45	1,698	110	3,205	0.77	0.54 to 1.10
51 PTs (sensitivity)	vs pooled comparator	45	1,698	8,204	138,017	0.45	0.33 to 0.60
51 PTs (sensitivity)	vs whole FAERS	45	1,698	134,440	2,285,048	0.45	0.34 to 0.61

TABLE 2: Reporting odds ratios for the composite psychiatric adverse-event end point: primary (46-PT) and full-domain sensitivity (51-PT) analyses

The primary composite (46 PTs) excludes the five PTs for which a comparator met the signal threshold against the whole database at step 1; the sensitivity composite includes all 51 PTs. The whole-FAERS reference comprises all other FAERS reports received in the study window and excludes the lebrikizumab reports. Comparators are dupilumab, tralokinumab, the pooled comparator (dupilumab plus tralokinumab), and the entire FAERS database (Analysis 1).

PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; FAERS, FDA Adverse Event Reporting System

In the 51-PT sensitivity composite, 45 lebrikizumab reports (2.6%) and 8,204 pooled comparator reports (5.6%) qualified. The ROR was 0.45 (95% CI, 0.33 to 0.60) against the pooled comparator, 0.44 (95% CI, 0.33 to 0.59) against dupilumab, and 0.77 (95% CI, 0.54 to 1.10) against tralokinumab (Table *2*). The seven additional lebrikizumab reports and 5,488 additional comparator reports were contributed by the five excluded PTs, chiefly Sleep disorder and Sleep disorder due to a general medical condition in the dupilumab arm.

Lebrikizumab counts for individual PTs were low (Table *3*). Of the 51 PTs, 36 had no lebrikizumab report, 10 had one or two, and five reached the minimum of three reports required by the signal threshold: Anxiety and Insomnia (12 each), Depression (n=6), Sleep disorder (n=5), and Nervousness (n=4). Against the entire database, no PT met the signal threshold for lebrikizumab. One PT, Confusional state, showed lower reporting disproportionality (ROR, 0.19; 95% CI, 0.05 to 0.74), a descriptive finding; for Anxiety (ROR, 0.70; 95% CI, 0.40 to 1.24), Insomnia (ROR, 0.73; 95% CI, 0.41 to 1.29), and Depression (ROR, 0.51; 95% CI, 0.23 to 1.13) the confidence intervals included 1. For PTs with no lebrikizumab reports and very few reports in the reference, the continuity correction produces large and unstable estimates (for example, Adjustment disorder with anxiety, with four reports in the whole database during the study window); these do not meet the signal threshold and are not interpreted. The continuity correction was required in 148 of the 204 PT-level comparisons and in none of the composite comparisons. Completed suicide and Suicide attempt had no lebrikizumab reports; Suicidal ideation had one. RORs against each comparator for every PT are given in Table *4*.

Preferred term	Lebrikizumab reports	ROR vs whole FAERS	95% CI	Excluded at step 1
Adjustment disorder with anxiety	0	154.19	8.30 to 2865.11	No
Aggression	0	0.18	0.01 to 2.90	No
Agitation	2	0.49	0.12 to 1.96	No
Anxiety	12	0.70	0.40 to 1.24	No
Anxiety disorder	0	2.58	0.16 to 41.44	No
Completed suicide	0	0.11	0.01 to 1.75	No
Confusional state	2	0.19	0.05 to 0.74	No
Depressed mood	1	0.23	0.03 to 1.64	No
Depression	6	0.51	0.23 to 1.13	No
Depressive symptom	0	1.48	0.09 to 23.77	No
Disruptive mood dysregulation disorder	0	51.40	3.05 to 864.96	No
Emotional disorder	0	0.24	0.01 to 3.77	No
Emotional distress	1	0.27	0.04 to 1.94	No
Euphoric mood	0	0.95	0.06 to 15.24	No
Generalised anxiety disorder	0	4.87	0.30 to 78.26	No
Hallucination	0	0.07	0.00 to 1.10	No
Hallucination, auditory	0	0.43	0.03 to 6.88	No
Hallucination, visual	0	0.24	0.02 to 3.90	No
Increased need for sleep	0	5.32	0.33 to 85.49	No
Infant irritability	0	27.21	1.66 to 447.14	No
Initial insomnia	0	0.57	0.04 to 9.17	Yes
Insomnia	12	0.73	0.41 to 1.29	No
Irregular sleep phase	0	28.32	1.72 to 465.90	No
Irritability	1	0.30	0.04 to 2.14	No
Major depression	0	1.01	0.06 to 16.15	No
Middle insomnia	1	0.70	0.10 to 5.01	No
Mood altered	1	0.50	0.07 to 3.56	Yes
Mood disorder due to a general medical condition	0	9.31	0.58 to 150.35	Yes
Mood swings	0	0.29	0.02 to 4.65	No
Nervousness	4	1.83	0.69 to 4.88	No
Panic attack	0	0.20	0.01 to 3.27	No
Panic disorder	0	2.28	0.14 to 36.53	No
Panic reaction	0	1.10	0.07 to 17.62	No
Perinatal depression	0	7.42	0.46 to 119.57	No

Poor quality sleep	1		0.56	0.08 to 4.00	No
Procedural anxiety	0		7.27	0.45 to 117.05	No
Psychiatric symptom	0		1.10	0.07 to 17.62	No
Rapid eye movements sleep abnormal	0		22.75	1.39 to 372.19	No
Self-injurious ideation	0		1.57	0.10 to 25.12	No
Sleep deficit	0		1.29	0.08 to 20.63	No
Sleep disorder	5		0.76	0.32 to 1.83	Yes
Sleep disorder due to a general medical condition	1		0.23	0.03 to 1.66	Yes
Sleep disorder due to general medical condition, insomnia type	0		0.44	0.03 to 7.08	No
Sleep talking	0		4.22	0.26 to 67.75	No
Sleep terror	0		1.40	0.09 to 22.47	No
Social anxiety disorder	0		8.41	0.52 to 135.65	No
Suicidal behaviour	0		2.41	0.15 to 38.69	No
Suicidal ideation	1		0.16	0.02 to 1.16	No
Suicide attempt	0		0.12	0.01 to 1.96	No
Suicide threat	0		9.44	0.58 to 152.42	No
Terminal insomnia	0		2.23	0.14 to 35.70	No

TABLE 3: Reporting odds ratios for individual psychiatric preferred terms, lebrikizumab versus whole FAERS (51-PT domain)

Lebrikizumab reports are the number of the 1,743 lebrikizumab reports containing the PT. The ROR compares lebrikizumab with all other FAERS reports received in the study window (Analysis 1). Exclusion at step 1 indicates that dupilumab, tralokinumab, or both met the signal threshold (at least three reports and a lower 95% confidence limit above 1) against the whole database for that PT, leading to exclusion from the primary composite. Individual-PT results are descriptive.

PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; FAERS, FDA Adverse Event Reporting System.

Preferred term	Lebrikizumab	Dupilumab	Tralokinumab	FAERS	ROR vs dupilumab	95% CI	ROR vs tralokinumab	95% CI	ROR vs pooled	95% CI	ROR vs FAERS	95% CI
Adjustment disorder with anxiety	0	2	0	4	16.39	0.79 to 341.60	1.90	0.04 to 95.88	16.77	0.80 to 349.52	154.19	8.30 to 2865.11
Aggression	0	24	0	3,826	1.67	0.10 to 27.51	1.90	0.04 to 95.88	1.71	0.10 to 28.15	0.18	0.01 to 2.90
Agitation	2	31	1	5,676	5.29	1.27 to 22.14	3.81	0.34 to 42.02	5.25	1.26 to 21.92	0.49	0.12 to 1.96
Anxiety	12	535	5	23,686	1.84	1.04 to 3.28	4.59	1.61 to 13.05	1.87	1.05 to 3.32	0.70	0.40 to 1.24
Anxiety disorder	0	4	1	268	9.11	0.49 to 169.22	0.63	0.03 to 15.56	7.62	0.42 to 137.94	2.58	0.16 to 41.44
Completed suicide	0	1	0	6,322	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	0.11	0.01 to 1.75

Confusional state	2	82	1	14,860	2.00	0.49 to 8.14	3.81	0.34 to 42.02	2.02	0.50 to 8.23	0.19	0.05 to 0.74
Depressed mood	1	113	0	6,006	0.73	0.10 to 5.20	5.71	0.23 to 140.20	0.74	0.10 to 5.32	0.23	0.03 to 1.64
Depression	6	324	4	16,317	1.52	0.68 to 3.41	2.86	0.81 to 10.15	1.54	0.68 to 3.45	0.51	0.23 to 1.13
Depressive symptom	0	1	0	467	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	1.48	0.09 to 23.77
Disruptive mood dysregulation disorder	0	1	0	13	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	51.40	3.05 to 864.96
Emotional disorder	0	97	1	2,940	0.42	0.03 to 6.77	0.63	0.03 to 15.56	0.43	0.03 to 6.85	0.24	0.01 to 3.77
Emotional distress	1	76	2	5,076	1.08	0.15 to 7.76	0.95	0.09 to 10.49	1.08	0.15 to 7.74	0.27	0.04 to 1.94
Euphoric mood	0	5	0	728	7.45	0.41 to 134.81	1.90	0.04 to 95.88	7.62	0.42 to 137.94	0.95	0.06 to 15.24
Generalised anxiety disorder	0	4	0	142	9.11	0.49 to 169.22	1.90	0.04 to 95.88	9.32	0.50 to 173.15	4.87	0.30 to 78.26
Hallucination	0	34	0	10,017	1.19	0.07 to 19.38	1.90	0.04 to 95.88	1.22	0.07 to 19.83	0.07	0.00 to 1.10
Hallucination, auditory	0	2	0	1,613	16.39	0.79 to 341.60	1.90	0.04 to 95.88	16.77	0.80 to 349.52	0.43	0.03 to 6.88
Hallucination, visual	0	5	1	2,842	7.45	0.41 to 134.81	0.63	0.03 to 15.56	6.45	0.36 to 114.56	0.24	0.02 to 3.90
Increased need for sleep	0	8	0	130	4.82	0.28 to 83.57	1.90	0.04 to 95.88	4.93	0.28 to 85.50	5.32	0.33 to 85.49
Infant irritability	0	1	0	25	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	27.21	1.66 to 447.14
Initial insomnia	0	170	10	1,210	0.24	0.01 to 3.86	0.09	0.01 to 1.54	0.23	0.01 to 3.73	0.57	0.04 to 9.17
Insomnia	12	1,019	29	22,752	0.97	0.55 to 1.71	0.79	0.40 to 1.54	0.96	0.54 to 1.70	0.73	0.41 to 1.29
Irregular sleep phase	0	2	0	24	16.39	0.79 to 341.60	1.90	0.04 to 95.88	16.77	0.80 to 349.52	28.32	1.72 to 465.90
Irritability	1	116	2	4,602	0.71	0.10 to 5.06	0.95	0.09 to 10.49	0.71	0.10 to 5.09	0.30	0.04 to 2.14
Major depression	0	5	1	687	7.45	0.41 to 134.81	0.63	0.03 to 15.56	6.45	0.36 to 114.56	1.01	0.06 to 16.15
Middle insomnia	1	71	0	1,970	1.15	0.16 to 8.32	5.71	0.23 to 140.20	1.18	0.16 to 8.51	0.70	0.10 to 5.01
Mood altered	1	204	40	2,773	0.40	0.06 to 2.87	0.05	0.01 to 0.34	0.34	0.05 to 2.45	0.50	0.07 to 3.56
Mood disorder due to a general medical condition	0	67	1	74	0.61	0.04 to 9.81	0.63	0.03 to 15.56	0.61	0.04 to 9.89	9.31	0.58 to 150.35
Mood swings	0	56	3	2,386	0.73	0.04 to 11.74	0.27	0.01 to 5.26	0.70	0.04 to 11.40	0.29	0.02 to 4.65
Nervousness	4	75	0	3,043	4.38	1.60 to 11.99	17.15	0.92 to 318.81	4.48	1.64 to 12.27	1.83	0.69 to 4.88
Panic attack	0	67	3	3,389	0.61	0.04 to 9.81	0.27	0.01 to 5.26	0.59	0.04 to 9.60	0.20	0.01 to 3.27

Panic disorder	0	6	1	304	6.30	0.36 to 111.96	0.63	0.03 to 15.56	5.59	0.32 to 97.93	2.28	0.14 to 36.53
Panic reaction	0	13	0	630	3.04	0.18 to 51.08	1.90	0.04 to 95.88	3.11	0.18 to 52.27	1.10	0.07 to 17.62
Perinatal depression	0	1	0	93	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	7.42	0.46 to 119.57
Poor quality sleep	1	34	2	2,469	2.41	0.33 to 17.63	0.95	0.09 to 10.49	2.33	0.32 to 17.01	0.56	0.08 to 4.00
Procedural anxiety	0	1	0	95	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	7.27	0.45 to 117.05
Psychiatric symptom	0	21	0	630	1.91	0.12 to 31.48	1.90	0.04 to 95.88	1.95	0.12 to 32.21	1.10	0.07 to 17.62
Rapid eye movements sleep abnormal	0	1	0	30	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	22.75	1.39 to 372.19
Self-injurious ideation	0	6	0	442	6.30	0.36 to 111.96	1.90	0.04 to 95.88	6.45	0.36 to 114.56	1.57	0.10 to 25.12
Sleep deficit	0	5	1	538	7.45	0.41 to 134.81	0.63	0.03 to 15.56	6.45	0.36 to 114.56	1.29	0.08 to 20.63
Sleep disorder	5	1,234	35	9,103	0.33	0.14 to 0.80	0.27	0.11 to 0.69	0.33	0.14 to 0.79	0.76	0.32 to 1.83
Sleep disorder due to a general medical condition	1	4,175	2	5,926	0.02	0.00 to 0.14	0.95	0.09 to 10.49	0.02	0.00 to 0.14	0.23	0.03 to 1.66
Sleep disorder due to general medical condition, insomnia type	0	79	0	1,567	0.52	0.03 to 8.31	1.90	0.04 to 95.88	0.53	0.03 to 8.51	0.44	0.03 to 7.08
Sleep talking	0	3	0	164	11.71	0.60 to 226.78	1.90	0.04 to 95.88	11.98	0.62 to 232.04	4.22	0.26 to 67.75
Sleep terror	0	6	0	494	6.30	0.36 to 111.96	1.90	0.04 to 95.88	6.45	0.36 to 114.56	1.40	0.09 to 22.47
Social anxiety disorder	0	1	0	82	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	8.41	0.52 to 135.65
Suicidal behaviour	0	2	0	287	16.39	0.79 to 341.60	1.90	0.04 to 95.88	16.77	0.80 to 349.52	2.41	0.15 to 38.69
Suicidal ideation	1	27	0	8,511	3.04	0.41 to 22.37	5.71	0.23 to 140.20	3.11	0.42 to 22.89	0.16	0.02 to 1.16
Suicide attempt	0	8	0	5,659	4.82	0.28 to 83.57	1.90	0.04 to 95.88	4.93	0.28 to 85.50	0.12	0.01 to 1.96
Suicide threat	0	1	0	73	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	9.44	0.58 to 152.42
Terminal insomnia	0	1	0	311	27.32	1.11 to 670.95	1.90	0.04 to 95.88	27.96	1.14 to 686.51	2.23	0.14 to 35.70

TABLE 4: Reporting odds ratios for each psychiatric preferred term against each comparator (51 PTs)

The lebrikizumab, dupilumab, tralokinumab, and FAERS columns give the number of reports containing the PT in each arm and in the whole database during the study window (September 1, 2024, to July 31, 2026). Each ROR compares lebrikizumab with the named comparator (dupilumab, tralokinumab, the pooled comparator, or the whole database); the whole-FAERS reference excludes lebrikizumab reports. Values are rounded to two decimal places.

PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; FAERS, FDA Adverse Event Reporting System.

When the signal threshold was applied to lebrikizumab against each comparator, two PTs met it.

Nervousness (four reports) had an ROR of 4.38 (95% CI, 1.60 to 11.99) against dupilumab and 4.48 (95% CI, 1.64 to 12.27) against the pooled comparator; against tralokinumab, which had no Nervousness reports, the ROR was 17.15 (95% CI, 0.92 to 318.81), and against the entire database it was 1.83 (95% CI, 0.69 to 4.88). Anxiety (12 reports) had an ROR of 1.84 (95% CI, 1.04 to 3.28) against dupilumab, 4.59 (95% CI, 1.61 to 13.05) against tralokinumab, 1.87 (95% CI, 1.05 to 3.32) against the pooled comparator, and 0.70 (95% CI, 0.40 to 1.24) against the entire database. After Benjamini-Hochberg correction across the 51 comparisons against the pooled comparator, the nominal P values for Nervousness (0.0035; rank 2 of 51) and Anxiety (0.0325; rank 5) exceeded their critical values (0.0020 and 0.0049). The only PT that met the corrected threshold against the pooled comparator and against dupilumab was Sleep disorder due to a general medical condition, a term excluded from the primary composite at step 1, in the direction of less frequent reporting for lebrikizumab (ROR against the pooled comparator, 0.02; 95% CI, 0.00 to 0.14). No PT met the corrected threshold against tralokinumab. Against the entire database, the only PT that did was Adjustment disorder with anxiety, which had no lebrikizumab report.

Results of the sensitivity analyses are shown in Table *5*. Deduplication removed 0.2% of lebrikizumab, 0.1% of dupilumab, and 0.6% of tralokinumab reports; the ROR for the primary composite against the pooled comparator was 1.18 (95% CI, 0.85 to 1.63). Among serious reports, two of 271 lebrikizumab reports and 435 of 11,499 pooled comparator reports contained a composite PT (ROR, 0.19; 95% CI, 0.05 to 0.76). Among reports from healthcare professionals, the corresponding numbers were two of 449 and 1,700 of 95,855 (ROR, 0.25; 95% CI, 0.06 to 0.99). With the indication restriction applied to all three arms, the lebrikizumab cohort fell from 1,743 to 1,724 reports; 38 of 1,724 lebrikizumab reports and 2,715 of 146,156 pooled comparator reports contained a composite PT (ROR, 1.19; 95% CI, 0.86 to 1.65). The proportion of serious reports in the lebrikizumab cohort was 15.5% (271 of 1,743). Without the 11 sleep-wake PTs, the composite comprised 35 PTs; 26 of 1,743 lebrikizumab reports and 1,570 of 146,221 pooled comparator reports contained one of them (ROR, 1.40; 95% CI, 0.94 to 2.06); the ROR was 1.38 (95% CI, 0.94 to 2.05) against dupilumab and 2.08 (95% CI, 1.19 to 3.63) against tralokinumab, which had 24 such reports.

Analysis	Comparator	Lebrikizumab reports with at least one composite PT	Comparator reports with at least one composite PT	Lebrikizumab reports without composite PT	Comparator reports without composite PT	ROR	95% CI
Serious reports only	vs dupilumab	2	269	426	10,569	0.18	0.05 to 0.74
Serious reports only	vs tralokinumab	2	269	9	495	0.41	0.09 to 1.91
Serious reports only	vs pooled comparator	2	269	435	11,064	0.19	0.05 to 0.76
After deduplication	vs dupilumab	38	1,702	2,661	140,157	1.18	0.85 to 1.63
After deduplication	vs tralokinumab	38	1,702	53	3,243	1.37	0.90 to 2.08
After deduplication	vs pooled comparator	38	1,702	2,714	143,400	1.18	0.85 to 1.63
Health care professional reporters only	vs dupilumab	2	447	1,661	91,831	0.25	0.06 to 0.99
Health care professional reporters only	vs tralokinumab	2	447	39	2,324	0.27	0.06 to 1.11
Health care professional reporters only	vs pooled comparator	2	447	1,700	94,155	0.25	0.06 to 0.99
Indication restriction applied	vs dupilumab	38	1,686	2,663	140,243	1.19	0.86 to

to all three arms							1.64
Indication restriction applied to all three arms	vs tralokinumab	38	1,686	52	3,198	1.39	0.91 to 2.11
Indication restriction applied to all three arms	vs pooled comparator	38	1,686	2,715	143,441	1.19	0.86 to 1.65
Primary composite without sleep-wake PTs	vs dupilumab	26	1,717	1,546	141,360	1.38	0.94 to 2.05
Primary composite without sleep-wake PTs	vs tralokinumab	26	1,717	24	3,291	2.08	1.19 to 3.63
Primary composite without sleep-wake PTs	vs pooled comparator	26	1,717	1,570	144,651	1.40	0.94 to 2.06

TABLE 5: Sensitivity analyses of the primary composite end point (46 preferred terms)

Serious reports are those recording death or hospitalization in both arms. Deduplication collapsed reports with the same manufacturer control number and, when that field was missing, reports with identical age, sex, and reaction set; it removed 0.2% of lebrikizumab, 0.1% of dupilumab, and 0.6% of tralokinumab reports. Health care professional reporters were restricted in both arms (exploratory; the signal threshold was not applied). Indication restriction to atopic dermatitis or eczema was applied to all three arms, with the openFDA placeholder for an unknown indication treated as no recorded indication. The composite without sleep-wake PTs excludes every primary-composite PT containing the stem sleep or insomnia.

ROR, reporting odds ratio; CI, confidence interval

Characteristics of the analyzed reports are compared in Table 6. Lebrikizumab reports were more often submitted by consumers (73.6%, as compared with 34.5% of dupilumab and 27.1% of tralokinumab reports), more often serious (15.5%, as compared with 7.7% and 15.2%), and less often accompanied by a recorded indication (50.4%, as compared with 88.1% and 86.6%); age and sex were also missing more often in lebrikizumab reports. Where recorded, the median age was 52 years (interquartile range, 29-67) for lebrikizumab, 44 years (21-63) for dupilumab, and 51 years (31-64) for tralokinumab, and women accounted for 59%, 61%, and 63% of reports of lebrikizumab, dupilumab, and tralokinumab, respectively, with recorded sex.

Characteristic	Lebrikizumab (n=1743), n (%)	Dupilumab (n=142,906), n (%)	Tralokinumab (n=3,315), n (%)
Reports analyzed	1,743	142,906	3,315
Age recorded	942 (54.0)	107,487 (75.2)	3,097 (93.4)
Female	800 (45.9)	84,792 (59.3)	2,073 (62.5)
Male	564 (32.4)	55,012 (38.5)	1,199 (36.2)
Sex not recorded	379 (21.7)	3,102 (2.2)	43 (1.3)
Serious	271 (15.5)	10,995 (7.7)	504 (15.2)
Reporter: physician	127 (7.3)	29,896 (20.9)	173 (5.2)
Reporter: pharmacist	31 (1.8)	1,750 (1.2)	1,886 (56.9)
Reporter: other health care professional	291 (16.7)	61,846 (43.3)	304 (9.2)
Reporter: consumer	1,283 (73.6)	49,269 (34.5)	899 (27.1)
Reporter: other or not recorded	11 (0.6)	145 (0.1)	53 (1.6)
Country of occurrence: United States	1,512 (86.7)	140,003 (98.0)	2,908 (87.7)
Country of occurrence: other	138 (7.9)	2,255 (1.6)	201 (6.1)
Country of occurrence: not recorded	93 (5.3)	648 (0.5)	206 (6.2)
Indication for the study drug recorded	878 (50.4)	125,969 (88.1)	2,870 (86.6)
Received in 2024	67 (3.8)	24,887 (17.4)	712 (21.5)
Received in 2025	988 (56.7)	75,650 (52.9)	1,718 (51.8)
Received in 2026	688 (39.5)	42,369 (29.6)	885 (26.7)

TABLE 6: Characteristics of the analyzed reports by exposure arm

Percentages are of all reports analyzed in the arm. Serious reports are those recording death or hospitalization. Reporter qualification follows the openFDA primarysource.qualification field; other or not recorded combines lawyer and missing values. Indication recorded means that an indication other than the openFDA placeholder for an unknown indication was entered for the study drug. Year of receipt is the year in which the FDA received the report; the study window ran from September 1, 2024, through June 30, 2026, the last receipt date in the release used.

Discussion

In this two-tier disproportionality analysis, restricted to a common reporting period, lebrikizumab showed no differential psychiatric reporting relative to an indication-matched active comparator. The 46-PT primary composite yielded RORs of 1.17 to 1.37 against dupilumab, tralokinumab, and the pooled comparator, with confidence intervals that included 1, and the result was essentially unchanged after deduplication. Against the entire FAERS database over the same period, the same composite gave an ROR of 0.42. This discordance is consistent with confounding by therapeutic area, a form of indication bias in spontaneous reporting [14,15]: a biologic prescribed for a chronic skin disease is reported with psychiatric events less often than the average drug in FAERS for reasons unrelated to its own psychiatric safety. The whole-database estimate should not be read as evidence of a protective psychiatric effect: it is vulnerable to confounding by therapeutic area and to differences in reporter population, prescribing, and reporting behavior that the analysis cannot separate, and it is presented only as context. Had it been used as the primary analysis, it would have suggested a protective effect that the active-comparator analysis does not support. The present findings extend the only previous FAERS study of lebrikizumab, which characterized the overall adverse-event profile but did not examine psychiatric outcomes [10], and are consistent with the improvement in patient-reported anxiety and depression observed in the pivotal trials [9].

The only departure from the null in the composite analyses, in the 51-PT sensitivity composite (RORs, 0.44 to 0.77), was accounted for by the five sleep and mood terms for which dupilumab, tralokinumab, or both showed excess reporting against the whole database, chiefly Sleep disorder and Sleep disorder due to a general medical condition in the dupilumab arm and Mood altered in the tralokinumab arm. This accords with previous FAERS and VigiBase analyses of dupilumab, including an analysis of more than 37,000

VigiBase reports in which sleep deficit was the strongest signal identified (OR, 15.67; 95% credible interval, 8.61 to 28.51) [11,12], and with a more recent report for tralokinumab [13]. The very large number of dupilumab reports coded as Sleep disorder due to a general medical condition (n=4,175, or 2.9% of all dupilumab reports) most likely reflects a product-specific convention for coding sleep disturbance attributed to the underlying disease rather than a drug effect, and it illustrates why comparator-specific terms must be identified before an active-comparator comparison is interpreted. The ROR for lebrikizumab itself was null for Sleep disorder against the whole database (ROR, 0.76; 95% CI, 0.32 to 1.83) and below 1 against the pooled comparator (ROR, 0.33; 95% CI, 0.14 to 0.79), which is consistent with the sleep signal not being a class effect of IL-4 and IL-13 blockade, although lebrikizumab has a much shorter reporting history than its comparators and this inference should be regarded as provisional. The tralokinumab signal for Mood altered (40 reports) has not, to our knowledge, been reported previously; it may reflect coding practice as much as a drug effect, and it requires replication.

These results illustrate the interpretation trap that the design was built to address. An unadjusted comparison of the 51-PT composite against dupilumab and tralokinumab would have produced a sub-unity ROR driven by the comparators' own sleep signal. Checking each comparator against the whole database before defining the composite reduces, although it cannot eliminate, both the confounding of a whole-database comparison and the contamination of an unadjusted active-comparator comparison. Because the exclusion could in principle remove a signal that lebrikizumab shared, the full 51-PT composite is reported alongside the primary one, and lebrikizumab's own estimates for the five excluded terms were compatible with no excess (Table *3*).

The three drugs also differ in time on the market, and therefore in the maturity of their reporting, even within a common reporting period. Dupilumab was approved for AD in March 2017, tralokinumab in December 2021, and lebrikizumab in September 2024 [29]; the study window covers the first 22 months of lebrikizumab reporting but a mature phase for both comparators. An early postapproval peak in reporting, described as the Weber effect, could in principle distort comparisons across drugs of different tenure. Analyses of modern FAERS data indicate that most drugs no longer follow the classic Weber pattern; reporting rises over roughly the first three quarters after approval and then stabilizes [30], and the monthly lebrikizumab counts in our extraction followed that pattern. We therefore do not assume a Weber-type curve for lebrikizumab, but differences in cumulative reporting volume and stability remain plausible. The design mitigates this in part. Restricting all arms and the reference to the same receipt window removes secular differences in reporting and coding; the composite compares within-cohort proportions (a/b versus c/d, where a=Lebrikizumab reports with at least one composite PT, b=Comparator reports with at least one composite PT, c=Lebrikizumab reports without composite PT, d=Comparator reports without composite PT), which are less sensitive to absolute reporting volume than raw counts, and the step 1 check compares each comparator with the whole database and is unaffected by lebrikizumab's shorter market history. Differences in the stage of the product life cycle, and in the composition of reporters that accompanies it (Table *6*), may nonetheless contribute to the differences between individual comparators in Table *2* and should be kept in mind when interpreting comparator-specific rather than composite results.

Two PTs, Nervousness and Anxiety, met the signal threshold for lebrikizumab against dupilumab and the pooled comparator but not against the whole database, on the basis of four and 12 reports. A signal present against some referents and absent against others, resting on a small numerator, is characteristic of the instability of disproportionality measures at very low counts rather than of a drug effect [26]; for Anxiety, the lower confidence limit against dupilumab barely exceeded 1. After Benjamini-Hochberg correction across the 51 PT-level comparisons, neither PT met the corrected threshold, and the only PT that did against the active comparators was in the direction of less frequent reporting for lebrikizumab. We report them because all individual-PT results were prespecified as descriptive, but they do not alter the composite conclusion. The step 1 rule screens only for comparator-side excess and applies no symmetric check on the lebrikizumab side. A symmetric rule would risk removing the very outcomes the study was designed to evaluate, and in this data set the two PTs that might have triggered it did not survive correction for multiplicity.

Two sensitivity analyses require caution. The serious-report analysis gave RORs of 0.18 to 0.41 and the healthcare professional analysis RORs of 0.25 to 0.27, but each rests on two lebrikizumab reports and should not be read as evidence of a protective effect. Both also compare subsets whose composition differs markedly between arms: 15.5% of lebrikizumab reports were serious as compared with 7.7% of dupilumab reports, and 26% came from healthcare professionals as compared with 65% (Table *6*). The indication restriction applied to all arms removed 1% of lebrikizumab reports and gave an estimate that matched the primary analysis. The composite without sleep-wake PTs moved the estimates upward, to 1.40 against the pooled comparator and 2.08 (95% CI, 1.19 to 3.63) against tralokinumab. The estimates against tralokinumab were above 1 in every composite analysis, and this is the one in which the lower confidence limit exceeded 1. It rests on 26 lebrikizumab and 24 tralokinumab reports, in a comparator arm of 3,315 reports, of which 56.9% came from pharmacists (Table *6*), a reporter group that may record psychiatric terms less often than consumers; it is consistent with the nominal Anxiety signal against the same comparator, and it is reported as a hypothesis for replication, not as a signal.

These findings should be read against the psychiatric burden of AD itself, which is independent of treatment

[1-3]. The improvement in patient-reported anxiety and depression over 16 weeks in the pivotal trials points in the same direction as our null finding, although it most likely reflects improvement in disease severity rather than a direct psychiatric effect and was not a primary endpoint [9]. A null pharmacovigilance signal for lebrikizumab does not lessen the need to screen patients with AD for depression and anxiety, whichever biologic is prescribed [1].

Limitations

This study has the limitations of spontaneous reporting: confounding by indication and therapeutic area, which the active comparator reduces but cannot remove; reporting bias, including notoriety and stimulated reporting that favor the more established comparators; no exposure denominator and no information on exposure duration; no temporal information and hence no basis for causal inference; unverified reports; and residual duplication, since our heuristic could not identify duplicates filed under different manufacturer control numbers or lacking age or sex [15,17,28]. The common receipt window controls calendar time but not product life-cycle stage, and the arms differ in reporter type, seriousness, and completeness of indication, age, and sex (Table 6), a pattern that follows reporter composition rather than chance and for which disproportionality analysis offers no adjustment; indication was unrecorded for half of the lebrikizumab reports. Reporter country was not adjusted for, and FAERS was used alone; replication in VigiBase or EudraVigilance, as has been done for the dupilumab sleep signal [12], would strengthen both the null composite finding and the estimates against tralokinumab.

The primary composite was constructed in a data-adaptive way. Although the exclusion rule and the sequence of steps were fixed before execution and the rule uses no lebrikizumab result, the terms removed were determined by the data, the confidence intervals do not account for this selection, and the 46-term composite should be read as the composite remaining after a comparator-driven exclusion rather than as an independently specified endpoint. The outcome domain was built by keyword search within the Psychiatric disorders system organ class rather than from a Standardised MedDRA Query; it can omit psychiatric terms that contain none of the stems and admit broad sleep and mood terms that describe disease symptoms, and the composite without sleep-wake terms addresses only the second of these. Multiplicity across the PT-level comparisons was not part of the original plan, and the Benjamini-Hochberg correction was added afterward. Between an intermediate and the final version of the analysis code, the step 1 threshold was aligned with the signal threshold, 13 keyword matches outside the system organ class were removed, the openFDA placeholder for an unknown indication was treated as missing, and all arms and the reference were restricted to a common receipt window; because the rule operates on the whole domain rather than on named terms, none of these revisions could target a particular result.

The number of events was small. The primary composite rests on 38 lebrikizumab reports, so the upper confidence limit against the pooled comparator (1.63) cannot exclude an excess of about 60%; 46 of 51 terms had two or fewer lebrikizumab reports, and the serious-report and healthcare professional analyses each rest on two. These estimates are reported for completeness and should not be interpreted on their own.

Conclusions

In this FAERS disproportionality analysis, restricted to a common reporting period and designed to identify and exclude comparator-specific signals before any comparison was made, psychiatric adverse events were not reported disproportionately for lebrikizumab relative to dupilumab or to the pooled indication-matched comparator. Estimates against tralokinumab alone were higher and, without sleep-wake terms, nominally significant; they rest on small numbers and require replication in an independent database. The two individual terms that met the nominal signal threshold did not survive correction for multiplicity. These findings characterize differential reporting within a spontaneous-reporting system; they establish neither equivalence nor the absence of psychiatric risk.

Appendices

Formulas
Reporting odds ratio (ROR) = $\frac{\frac{a}{b}}{\frac{c}{d}} = \frac{a \times d}{b \times c}$
95% confidence interval [21]: \(\exp\left[\ln(\mathrm{ROR}) \pm 1.96 \times \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right]\)
Haldane-Anscombe correction [22,23]: when any of a, b, c, or d was zero, 0.5 was added to all four cells before the ROR and its confidence interval were calculated.
Signal threshold [24,25]: a ≥ 3 and lower 95% confidence limit of the ROR > 1.
Benjamini-Hochberg procedure [26]: for each comparator, the two-sided Wald P values of the 51 PT-level comparisons, \(P = 2 \times \left[1 - \Phi\left(\frac{|\ln(\mathrm{ROR})|}{SE}\right)\right]\) with \(SE = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\) were ordered from smallest to largest, P(1) ≤ … ≤ P(m), m = 51; the largest k such that P(k) ≤ (k/m) × 0.05 was identified, and the comparisons with rank ≤ k were declared significant at a false discovery rate of 5%. The comparisons that met this criterion are reported in the Results.

TABLE 7: Statistical formulas

For each comparison, a is the number of index-drug reports containing the outcome, b the number of index-drug reports without the outcome, c the number of reference-group reports containing the outcome, and d the number of reference-group reports without the outcome.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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corresponding editor.

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