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ORIGINAL RESEARCH ARTICLE

Active-Comparator Disproportionality of Akathisia Reports for Cariprazine and Brexpiprazole versus Aripiprazole in FAERS

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ABSTRACT

Background. Akathisia is a distressing antipsychotic-associated syndrome that can be mistaken for psychiatric agitation. Comparative spontaneous-report analyses may identify reporting patterns, but they cannot estimate clinical incidence.

Objective. To estimate crude and year-adjusted reporting disproportionality of akathisia for cariprazine and brexpiprazole versus aripiprazole, to assess variation across report-receipt years, and to evaluate robustness to alternative cohort definitions.

Methods. This retrospective case-non-case study used the openFDA endpoint of the FDA Adverse Event Reporting System (FAERS). The primary cohort held mutually exclusive reports naming cariprazine, brexpiprazole, or aripiprazole, received from 1 January 2015 through 30 March 2026. Cases contained the exact Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) Akathisia. We calculated reporting proportions, reporting odds ratios (RORs), proportional reporting ratios (PRRs), year-stratified Mantel–Haenszel RORs (MH-RORs), Tarone-adjusted Breslow–Day tests, and pairwise binomial models adjusted for year. Two cohort-definition sensitivity analyses were performed.

Results. Among 113,653 reports, 3,079 contained exact-PT akathisia: 374/8,901 cariprazine, 691/14,411 brexpiprazole, and 2,014/90,341 aripiprazole reports. Crude RORs versus aripiprazole were 1.92 (95% CI 1.72–2.15) for cariprazine and 2.21 (2.02–2.41) for brexpiprazole. Corresponding MH-RORs were 1.77 (1.58–1.99) and 2.21 (2.02–2.42). The cariprazine-brexpiprazole contrast moved from a crude ROR of 0.87 (0.77–0.99) to an MH-ROR of 1.06 (0.92–1.21). Heterogeneity across years was present in all comparisons.

Conclusion. Cariprazine and brexpiprazole showed higher akathisia reporting disproportionality than aripiprazole in this FAERS snapshot. The data did not support a stable ranking between the two. These are pharmacovigilance signals. They are not estimates of patient-level risk.

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1. Introduction

Akathisia is a neuropsychiatric syndrome. Its core is a compelling subjective need to move, often accompanied by visible pacing, rocking, weight shifting, or repetitive leg movement. The subjective component decides the diagnosis in practice: a patient may describe inner tension, an inability to stay seated, or intolerable unease even when motor signs are modest; the Barnes Akathisia Rating Scale formalized the assessment of objective movement, subjective awareness, distress, and global severity, and it remains a widely recognized clinical framework.[1] Accurate identification matters. Akathisia can resemble anxiety, restless legs syndrome, psychotic agitation, manic activation, medication withdrawal, or other extrapyramidal syndromes. Management begins with systematic assessment. It then considers dose reduction, simplification of antipsychotic polypharmacy, switching, or selected adjunctive treatment, according to the individual clinical context.[2] Cariprazine, brexpiprazole, and aripiprazole are commonly described as dopamine D_2/D_3 receptor partial agonists; the shared class label does not imply interchangeable pharmacology or tolerability. Receptor affinity, intrinsic activity, active-metabolite exposure, half-life, dose range, formulation, and approved clinical context all differ. A recent treatment-program analysis of aripiprazole examined

treatment-emergent akathisia and its association with propranolol use; it showed that active monitoring and management can affect how events are documented[3]. A phase 3 adjunctive cariprazine trial in major depression similarly identified a treatment-emergent adverse-event profile that must be read within its antidepressant-background setting.[4] Pooled randomized bipolar data later demonstrated efficacy across manic and depressive symptom spectra.[5] Post hoc analyses of irritability, hostility, agitation, and early response showed that the treated symptom phenotype can alter how activation or restlessness is recognized.[6,7]

The breadth of contemporary cariprazine research shows why a single adverse-event percentage cannot represent all use. A maintenance trial evaluated prevention of mood episodes over a longer treatment horizon than acute studies.[8] An adjunctive major-depression analysis examined anhedonia.[9] A pediatric pharmacokinetic and tolerability study covered a very different population,[10] and a randomized-trial post hoc analysis examined anxiety symptoms during adjunctive treatment.[11] A recent FAERS study of atypical antipsychotics used for major-depression augmentation showed how indication-specific reporting backgrounds shape comparative adverse-event patterns.[12] Taken together, these empirical studies establish clinical credibility for akathisia. They also show that indication, duration, age, co-treatment, and reporting context differ materially across programs. Brexpiprazole evidence is likewise heterogeneous in population and design. Randomized studies of agitation associated with Alzheimer dementia extended evaluation beyond schizophrenia and major depressive disorder.[13,14] A phase 3 randomized study paired brexpiprazole with sertraline for posttraumatic stress disorder;[15] an adolescent schizophrenia trial used both placebo and an active reference.[16] Pooled safety analyses and clinically defined subgroup analyses in dementia examined tolerability across multiple trials and extensions.[17,18] Randomized and extension studies in borderline personality disorder and dementia added other titration, background-risk, and observation settings.[19,20] A long-term adjunctive study in Japanese patients with major depressive disorder[21] and pooled analyses of anxiety symptoms in schizophrenia[22] show again that treatment-emergent restlessness occurs in many diagnostic and therapeutic contexts. Aripiprazole has a longer and broader evidence base, yet recent studies keep showing that context and formulation matter; in treatment-resistant geriatric depression, aripiprazole augmentation was evaluated against alternative next-step strategies.[23] Studies of two-month long-acting injectable aripiprazole characterized pharmacokinetics and tolerability under structured follow-up.[24] The ASCERTAIN-TRD randomized trial compared augmentation with alternative strategies for resistant depression.[25] A target-trial emulation in first-episode psychosis addressed comparative effectiveness with observational data,[26] while secondary analyses of a two-month injectable formulation and a randomized study of a novel microsphere formulation evaluated distinct delivery systems.[27,28] Quality-of-life outcomes from ASCERTAIN-TRD and a dose-response study in schizophrenia add evidence that population, endpoint, and dose affect how treatment is interpreted.[29,30]

Recent real-world research also documents clinically meaningful differences in who receives these partial agonists and how outcomes are measured. A retrospective cohort of patients with schizophrenia-spectrum disorders and cannabis use disorder compared oral or long-acting aripiprazole, brexpiprazole, and other treatment patterns.[31] Claims-based studies evaluated disability and healthcare-resource outcomes among patients receiving adjunctive cariprazine, brexpiprazole, aripiprazole, or other atypical antipsychotics for major depressive disorder.[32,33] Medicare data compared new use of brexpiprazole and aripiprazole among persons with dementia.[34] None of these analyses estimates comparative akathisia risk directly. They do show channeling across diagnoses, formulations, comorbidity profiles, and healthcare settings, and that channeling can influence both event occurrence and reporting. Spontaneous-report research offers a different perspective. A pharmacovigilance-pharmacodynamic analysis of impulse-control disorders examined aripiprazole, brexpiprazole, and cariprazine in the FDA Adverse Event Reporting System (FAERS).[35] A brexpiprazole-specific FAERS study detected multiple neurologic and psychiatric reporting signals;[36] other contemporary analyses assessed QT-prolongation reporting across antipsychotics,[37] hospitalization signals among atypical antipsychotics,[38] obsessive-compulsive symptoms,[39] and drug-induced liver injury.[40] These studies show the range of questions that disproportionality methods can address. They also show that results depend on event definition, comparator, suspect-role restriction, product normalization, calendar window, and database composition. Meta-research found wide variation in the strategies used to validate and contextualize published disproportionality signals.[41] An empirical active-comparator analysis showed that masking can shift signal estimates a great deal when external events alter reporting within the reference set.[42]

FAERS, accessed here through the openFDA drug adverse-event endpoint, contains spontaneous and mandatory reports from manufacturers, health professionals, consumers, and other sources; its breadth supports signal detection for uncommon, delayed, or context-dependent events. A report can nevertheless contain multiple products and reactions without a validated link between a particular drug and event. Reports are not a census of treated patients. There is no denominator of exposed persons or person-time. Disproportionality therefore asks whether an event occupies a larger share of selected reports for one drug than for a comparator; it does not estimate whether the event occurs more often per treated patient. An active comparator can make the reporting background more clinically similar than an all-database comparator would; it cannot eliminate confounding by indication, channeling, product age, formulation, utilization, or selective reporting. Calendar time matters

especially. Aripiprazole has a longer reporting history, whereas cariprazine and brexpiprazole entered use later and followed different indication, uptake, and reporting trajectories. Pooling unlike years can obscure or reverse within-year patterns. Temporal heterogeneity therefore deserves direct analysis and not treatment as a secondary graphical detail.

The unresolved question is not whether any of these agents can be associated with akathisia. Contemporary clinical and pharmacovigilance evidence already establishes that possibility. The gap is whether exact-PT akathisia has different report-level prominence among the three agents within a shared reporting era, how calendar composition affects those contrasts, and whether the two newer agents can be ranked after temporal control; the novelty of this study is a mutually exclusive, within-class active-comparator analysis that brings together exact outcome coding, calendar-year stratification, multivariable year adjustment, formal temporal-heterogeneity testing, and cohort-definition sensitivities in one reconciled framework. We aimed to estimate crude and year-adjusted akathisia reporting disproportionality for cariprazine versus aripiprazole, brexpiprazole versus aripiprazole, and cariprazine versus brexpiprazole. We also aimed to assess variation across report-receipt years and to evaluate robustness to alternative cohort definitions and observation periods.

2. Methods

2.1. Study design and setting

Study design and reporting framework. We conducted a retrospective observational case-non-case disproportionality study using public aggregate results from the openFDA drug adverse-event application programming interface (API); the unit of analysis was a safety report returned by the endpoint, not a patient, prescription, treatment episode, or adverse-event episode. Reporting was organized with reference to the Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV) statement and applicable principles of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline[43]. The analytic objective was signal characterization within an active-comparator cohort, not causal estimation.

Data source and snapshot. The openFDA drug adverse-event endpoint serves publicly releasable records collected through FAERS and represents records in JSON format with openFDA annotations; one report may contain several products and reactions, and the public data do not establish drug-reaction causality. The API updates periodically and can revise historical records; therefore, every result is specific to a data snapshot. All queries used in this study returned meta.last_updated = 2026-03-30.

We refer to the analyzed source as openFDA/FAERS and identify the precise endpoint, query fields, extraction date, and snapshot throughout the reproducibility materials; public report counts alone cannot compare patient-level safety or calculate incidence because exposure denominators and clinically adjudicated drug-event relationships are unavailable. These limitations were incorporated into the design and interpretation.

Study period and calendar strata. The primary shared era extended from 1 January 2015 through 30 March 2026; the starting date was chosen to place the three drug groups within a common contemporary period and to avoid allowing the much longer pre-2015 aripiprazole reporting history to dominate the primary comparison. Report receipt year defined the calendar strata. Years 2015 through 2025 were complete annual strata; 2026 was a partial stratum ending on 30 March and was explicitly identified as such in the analysis and figures.

2.2. Participants

Drug exposure groups. Reports were assigned to one of three medicinal-product groups using the reported medicinal product field; the cariprazine group matched cariprazine or Vraylar; the brexpiprazole group matched brexpiprazole or Rexulti; and the aripiprazole group matched aripiprazole, Abilify, or Aristada. The inclusion of brand and generic terms was intended to improve retrieval across heterogeneous product-name reporting. Aristada was included in the aripiprazole group because its active moiety is aripiprazole, while recognizing that this choice combines oral and long-acting formulation contexts.

The primary cohort was mutually exclusive. A report assigned to one target group was excluded if it also contained an alias for either of the other target groups. This restriction prevented the same report from appearing in both sides of a pairwise 2 × 2 table and reduced direct overlap among the target products; it did not establish that the retained target drug caused the event. All reported drug-characterization roles were eligible because the primary estimand concerned report-level co-occurrence. The proportion of exact-PT akathisia reports in which a target product was coded as primary suspect was not used to redefine the main cohort because reporter-assigned role is not independently validated.

2.3. Variables and instruments

Outcome definition. The primary case definition was the exact MedDRA Preferred Term Akathisia, queried through patient.reaction.reactionmeddrapt.exact; although MedDRA standardizes terminology, coding remains dependent on submitted information and term selection. Exact matching was chosen to maximize specificity and reproducibility. Reports with the target drug group and exact-PT Akathisia were cases; all other reports in the same target drug cohort were non-cases.

The exact-field implementation was verified separately from a tokenized search of the non-exact reaction field; the tokenized search returned nine additional reports across brexpiprazole and aripiprazole groups. Because the clinical outcome of interest was the exact PT, the exact-field counts control all final primary and adjusted

analyses. No broader standardized MedDRA query or collection of related restlessness terms was used, so the study should not be interpreted as measuring the full clinical spectrum of possible akathisia-like presentations.

2.4. Data collection procedure

Aggregate extraction and reproducibility. For each drug group, outcome status, and calendar stratum, we constructed an explicit openFDA query and recorded the aggregate total returned in meta.results.total; only aggregate totals were retained; no report payload, safety-report identifier, narrative, or exact receipt date was stored in the final analysis dataset. The primary dataset therefore contained 36 drug-year rows: three drug groups across 12 receipt-year strata, with counts of akathisia cases and non-cases.

Query provenance, URLs, extraction time, and snapshot date were saved in a machine-readable JSON file. A Python script using the standard library executed the API calls with bounded retry logic. An R script reconstructed cohort totals, calculated all estimates, fitted the grouped-binomial models, and generated the figures; the scripts and derived aggregate CSV files are included with the analysis package. This approach permits exact reproduction of the reported counts while avoiding retention of individual report records.

The complete analytic construction—from the openFDA/FAERS snapshot through mutually exclusive drug groups and pairwise analyses—is summarized in Figure 1.

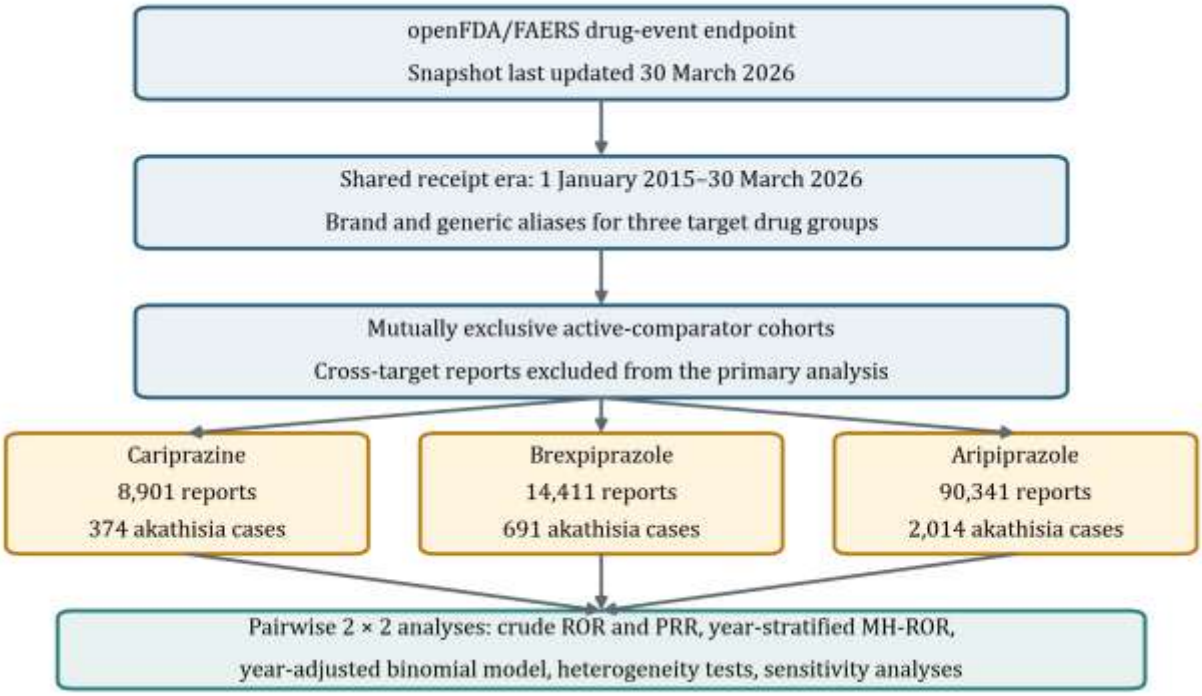


Figure 1. Analytic construction of the mutually exclusive active-comparator cohort. Counts are selected safety reports and exact-PT akathisia cases, not exposed patients. MH-ROR, Mantel–Haenszel reporting odds ratio; PRR, proportional reporting ratio; ROR, reporting odds ratio.

2.5. Statistical analysis

Descriptive analysis. We summarized total reports, exact-PT akathisia reports, and non-case reports for each target drug; reporting proportions were expressed per 1,000 reports, with Wilson 95% confidence intervals. These quantities describe the composition of the selected report cohorts. They are not incidence rates because the denominator is the number of reports containing the drug alias rather than the number of exposed patients, prescriptions, or treatment-years; annual all-report and exact-PT case counts were retained as the auditable basis for the annual table and figures presented in the Results.

Crude pairwise disproportionality. For each pairwise comparison, the 2 × 2 table contained a, index-drug reports with exact-PT akathisia; b, index-drug reports without exact-PT akathisia; c, comparator reports with exact-PT akathisia; and d, comparator reports without exact-PT akathisia. The estimators were calculated as follows:

$$ROR = (a \times d)/(b \times c)$$

$$PRR = [a/(a + b)]/[c/(c + d)]$$

$$SE[\ln(ROR)] = \sqrt{(1/a + 1/b + 1/c + 1/d)}$$

The 95% confidence interval was obtained by exponentiating $\ln(ROR) \pm 1.96 \times SE[\ln(ROR)]$. A two-sided Fisher exact test evaluated independence. PRR was retained as a complementary reporting measure; neither estimator solves the exposure-denominator or confounding limitations of spontaneous reporting. Statistical significance was not used as the sole interpretive criterion. Magnitude, precision, temporal stability, sensitivity, and clinical context were considered together.

Year-stratified and multivariable analyses. To address calendar composition, we formed a 2 × 2 table for each pairwise contrast within each report-receipt year. A

Mantel–Haenszel common reporting odds ratio and 95% confidence interval summarized the within-year association. The Tarone-adjusted Breslow–Day test evaluated homogeneity of the odds ratios across the 12 yearly strata. A significant result was treated as evidence that the common estimate should not be interpreted as a constant association across time.

We complemented the stratified analysis with pairwise grouped-binomial logistic models. For each drug pair, the dependent data were the case and non-case counts in each drug-year cell. The model included drug group and categorical receipt year as fixed effects, yielding a year-adjusted odds ratio for the drug contrast; the model is multivariable (one binary outcome, with drug and year indicators as predictors) and not multivariate. Reports were treated as independent within drug-year cells.

For each pair, a second model included drug-by-year interaction terms. We compared the main-effects and interaction models using a likelihood-ratio test. The interaction analysis was a diagnostic of temporal non-uniformity rather than an attempt to select favorable years or create a causal time trend; given only aggregate annual cells and one partial year, we did not fit splines, change-point models, or a linear trend that would imply a stable temporal mechanism.

Because disproportionality estimates are sensitive to database composition, reporting practice, and model specification, we present crude, stratified, model-adjusted, interaction, and sensitivity findings together; for the descriptive annual-ROR heatmap only, a Haldane–Anscombe correction of 0.5 was added to all four cells when a yearly 2 × 2 table contained a zero. The correction affected the 2015 cariprazine comparisons and was not used for the pooled inferential estimates.

Sensitivity analyses. Two cohort-definition sensitivity analyses were performed. First, a shared-era non-exclusive analysis retained reports naming more than one target drug. This tested whether cross-target exclusion materially determined the direction of the two contrasts against aripiprazole. Second, an all-era exclusive analysis expanded the observation window to the earliest openFDA drug-event coverage date used by the endpoint through 30 March 2026, while maintaining cross-target exclusion. This sensitivity primarily added earlier aripiprazole reports and examined the influence of calendar composition.

The direct cariprazine-brexpiprazole comparison was treated as exploratory because both drugs have shorter and different reporting histories and because the crude result was particularly vulnerable to differences in annual composition; we did not correct the three pairwise tests for multiplicity as if they formed a confirmatory clinical trial family. Instead, we reported exact confidence intervals, identified the direct comparison as exploratory, and avoided treating nominal significance as a treatment ranking.

Software and quality control. API extraction used Python 3.12.13. Statistical analysis and graphics used R 4.5.3 with base statistical functions and ggplot2. Independent checks included reconciliation of annual cells to drug-level totals, confirmation that case plus non-case counts equaled all reports in every cell, verification of the API snapshot across calls, and comparison of Mantel–Haenszel and year-fixed-effect estimates; all numeric values in the abstract, text, tables, and figures were generated from the same exact-outcome analysis files.

2.6. Ethical approval

Ethics and privacy. The study used public, de-identified, secondary report data and involved no recruitment, intervention, direct contact, or access to protected patient identifiers; Ethical approval was granted by the CMHC Research Center Ethics Committee Indonesia (No. 2026/0225). Only aggregate query totals were retained in the final analytic dataset.

3. Results

3.1. Primary cohort

The mutually exclusive shared-era cohort contained 113,653 reports: 8,901 in the cariprazine group, 14,411 in the brexpiprazole group, and 90,341 in the aripiprazole group. Exact-PT akathisia was present in 3,079 reports. The corresponding case counts were 374 for cariprazine, 691 for brexpiprazole, and 2,014 for aripiprazole; the three drug denominators reconciled exactly to the total cohort, and annual strata reconciled exactly to each drug total. Cohort composition, non-case counts, and Wilson intervals are detailed in Table 1.

The reporting proportion was 42.0 per 1,000 cariprazine reports (95% CI 38.0–46.4), 47.9 per 1,000 brexpiprazole reports (44.6–51.6), and 22.3 per 1,000 aripiprazole reports (21.4–23.3). Thus, exact-PT akathisia occupied a larger share of reports in each newer-drug group than in the aripiprazole group. These proportions describe report composition only and do not provide treated-patient denominators.

Table 1. Primary mutually exclusive active-comparator cohort, 2015–30 March 2026.

Drug group	All reports	Akathisia	Non-cases	Per 1,000 reports (95% CI)
Cariprazine	8,901	374	8,527	42.0 (38.0–46.4)
Brexpiprazole	14,411	691	13,720	47.9 (44.6–51.6)
Aripiprazole	90,341	2,014	88,327	22.3 (21.4–23.3)

Notes: CI, confidence interval. The denominator is selected safety reports, not exposed patients. The 2026 stratum is partial through 30 March. PT, Preferred Term; cases are reports containing the exact-PT Akathisia.

The annual source cells are detailed in Table 2. Summing the 12 rows within each drug reproduced the pooled values exactly: 8,901 reports and 374 cases for cariprazine, 14,411 and 691 for brexpiprazole, and 90,341 and 2,014 for aripiprazole. The 2026 row is partial through 30 March and is displayed separately rather than annualized.

Table 2. Annual selected reports and exact-PT akathisia cases in the primary cohort.

Year	Cariprazine reports	Cariprazine cases	Brexpiprazole reports	Brexpiprazole cases	Aripiprazole reports	Aripiprazole cases
2015	1	0	167	7	8,032	183
2016	140	4	1,852	154	7,444	97
2017	319	28	1,341	96	12,994	262
2018	392	19	1,203	59	10,477	177
2019	881	36	1,501	62	7,075	148
2020	1,036	37	1,242	70	7,088	182
2021	862	51	1,204	60	8,141	213
2022	819	34	1,145	47	6,333	168
2023	1,211	44	1,231	52	6,663	217
2024	1,206	58	1,614	53	6,745	154
2025	1,412	42	1,249	19	5,979	149
2026*	622	21	662	12	3,370	64

Notes: *2026 is partial through 30 March. Annual cells sum exactly to the drug-level totals in Table 1. Cases are reports containing the exact MedDRA PT Akathisia.

3.2. Crude pairwise disproportionality

Cariprazine had a crude ROR of 1.92 versus aripiprazole (95% CI 1.72–2.15) and a PRR of 1.88 (1.69–2.10); brexpiprazole had a crude ROR of 2.21 versus aripiprazole (2.02–2.41) and a PRR of 2.15 (1.98–2.34). Both confidence intervals were entirely above 1, and Fisher exact p values were less than 0.001. The exact crude estimates and two-sided Fisher tests are detailed in Table 3.

The crude direct comparison produced an ROR of 0.87 for cariprazine versus brexpiprazole (95% CI 0.77–0.99) and a PRR of 0.88 (0.77–0.99); considered alone, this result suggested a slightly lower share of akathisia reports for cariprazine. However, the estimate combined years with materially different product histories and annual report distributions; its stability was therefore evaluated in the calendar-adjusted analyses.

Table 3. Crude pairwise disproportionality for exact-PT akathisia.

Index drug vs reference	ROR (95% CI)	PRR (95% CI)	Fisher p
Cariprazine vs Aripiprazole	1.92 (1.72–2.15)	1.88 (1.69–2.10)	<0.001
Brexpiprazole vs Aripiprazole	2.21 (2.02–2.41)	2.15 (1.98–2.34)	<0.001
Cariprazine vs Brexpiprazole	0.87 (0.77–0.99)	0.88 (0.77–0.99)	0.036

Notes: CI, confidence interval; PRR, proportional reporting ratio; ROR, reporting odds ratio. Fisher exact tests are two-sided. PT, Preferred Term.

The crude, Mantel–Haenszel, and year-adjusted estimates are displayed together in Figure 2; the visual agreement between the two adjusted estimators and the crude-to-adjusted movement of the cariprazine–brexpiprazole contrast make the calendar effect directly apparent.

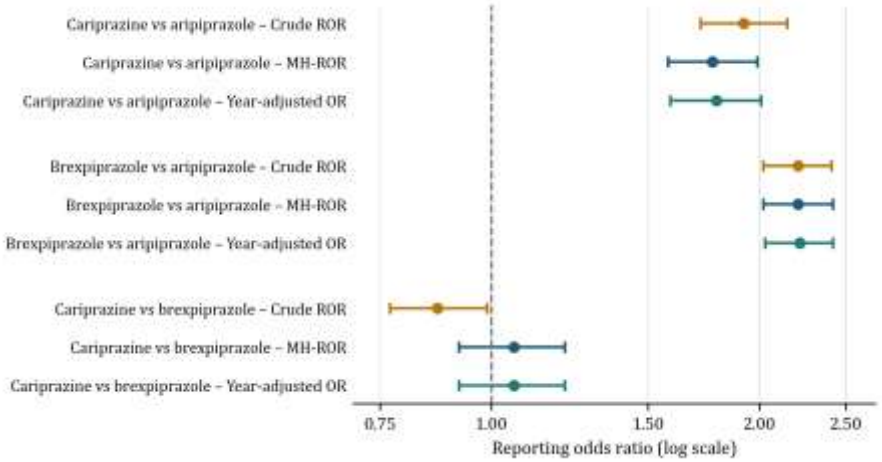


Figure 2. Crude and calendar-adjusted reporting odds ratios. Points are estimates and horizontal bars are 95% confidence intervals. The vertical dashed line is the null value of 1. MH-ROR, Mantel–Haenszel reporting odds ratio; OR, odds ratio; ROR, reporting odds ratio.

3.3. Calendar adjustment and temporal heterogeneity

After stratification by receipt year, the cariprazine-aripiprazole MH-ROR was 1.77 (95% CI 1.58–1.99); the pairwise binomial model adjusted for categorical year produced a similar odds ratio of 1.79 (1.59–2.01). For brexpiprazole versus aripiprazole, the MH-ROR was 2.21 (2.02–2.42), and the year-adjusted binomial estimate was 2.22 (2.03–2.42). The concordance between the two adjustment approaches supported the persistence of report-level signals relative to aripiprazole within the shared era; full adjusted estimates, χ^2 statistics, degrees of freedom, and interaction tests are detailed in Table 4.

The direct cariprazine-brexpiprazole comparison changed materially after calendar control. Its MH-ROR was 1.06 (95% CI 0.92–1.21), and the year-adjusted binomial odds ratio was 1.06 (0.92–1.21). Both estimates were near the null, with confidence intervals spanning 1; the contrast between the crude ROR of 0.87 and the adjusted estimates near 1 is consistent with an influence of annual report composition and does not support a stable ordering of the two newer drugs.

Tarone-adjusted Breslow–Day tests indicated heterogeneity across years for cariprazine versus aripiprazole (χ^2 47.66, 11 df; $p < 0.001$), brexpiprazole versus aripiprazole (χ^2 166.08, 11 df; $p < 0.001$), and cariprazine versus brexpiprazole (χ^2 25.85, 11 df; $p = 0.007$). Drug-by-year interaction likelihood-ratio tests also supported temporal non-uniformity for all three pairs. Accordingly, the pooled estimates are summaries across variable yearly associations rather than time-invariant effects.

Table 4. Calendar-adjusted estimates and temporal heterogeneity.

Comparison	MH-ROR (95% CI)	Year-adjusted OR (95% CI)	Tarone-adjusted Breslow–Day	Drug × year LRT
Cariprazine vs Aripiprazole	1.77 (1.58–1.99)	1.79 (1.59–2.01)	$\chi^2 = 47.66$; df = 11; $p < 0.001$	$\chi^2 = 41.72$; df = 11; $p < 0.001$
Brexpiprazole vs Aripiprazole	2.21 (2.02–2.42)	2.22 (2.03–2.42)	$\chi^2 = 166.08$; df = 11; $p < 0.001$	$\chi^2 = 167.74$; df = 11; $p < 0.001$
Cariprazine vs Brexpiprazole	1.06 (0.92–1.21)	1.06 (0.92–1.21)	$\chi^2 = 25.85$; df = 11; $p = 0.007$	$\chi^2 = 27.90$; df = 11; $p = 0.003$

Notes: CI, confidence interval; LRT, likelihood-ratio test; MH-ROR, Mantel–Haenszel reporting odds ratio; OR, odds ratio. Receipt year was categorical; 2026 was partial through 30 March. Breslow–Day tests are Tarone-adjusted (11 df); LRT, drug-by-year interaction versus main-effects model (11 df).

3.4. Annual reporting pattern

Annual reporting proportions varied appreciably, as shown in Figure 3. The cariprazine series was particularly unstable in its earliest year because only one report entered the exclusive cohort in 2015 and none contained exact-PT akathisia. Proportions increased as report volume accumulated, then fluctuated across later years; brexpiprazole likewise showed higher early proportions followed by variation over time. Aripiprazole proportions were generally lower but were not constant.

The 2026 points represent reports received only through 30 March and should not be compared with full years as if follow-up were complete. Figure 4 separates annual all-report volume from annual exact-PT case counts, showing that a change in the numerator can coexist with a different change in report volume. The annual displays are descriptive: changes can reflect utilization, indication expansion, reporter mix, product maturity, publicity, coding, or manufacturer submissions rather than changes in pharmacologic risk.

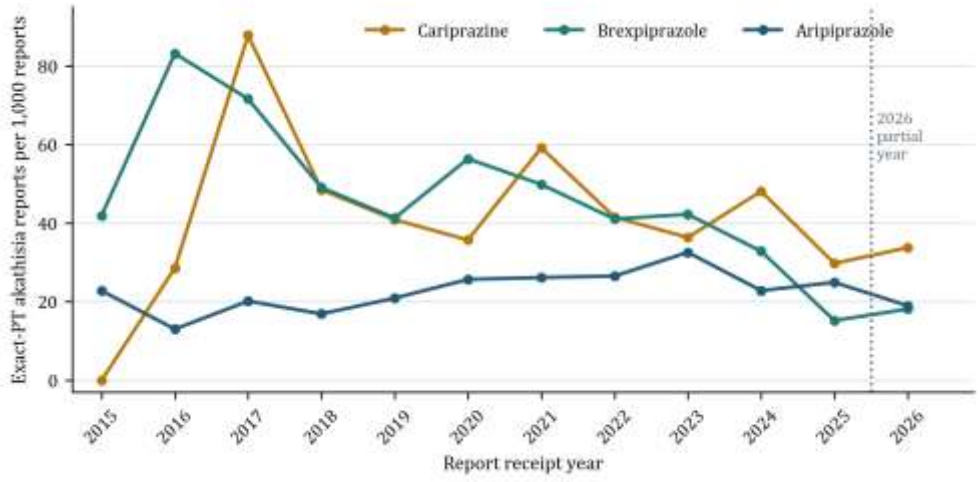


Figure 3. Annual exact-PT akathisia reporting proportions within selected drug-report cohorts. The dotted boundary identifies 2026, which is partial through 30 March. Values are report proportions, not incidence rates.

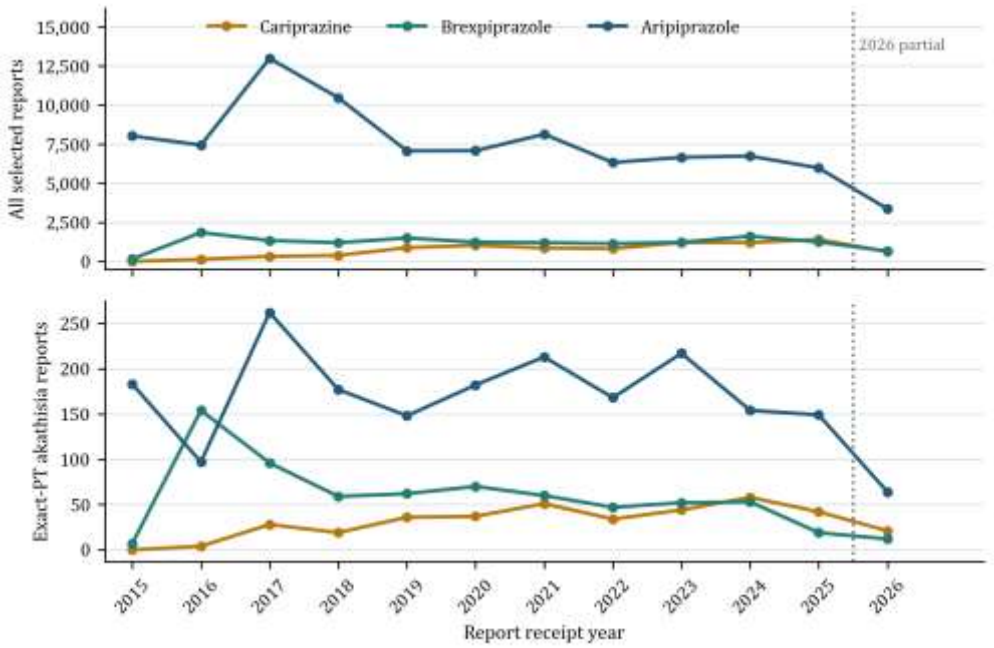


Figure 4. Annual selected report volume and exact-PT akathisia counts. The upper panel shows all selected reports; the lower panel shows exact-PT cases. The dotted boundary identifies partial-year 2026 through 30 March.

Year-specific RORs are presented as a $\log_2$-scaled heatmap in Figure 5; values above 1 are shaded toward red and values below 1 toward blue. The 2015 cariprazine comparisons are marked with an asterisk because a 0.5 continuity correction was required for the zero-case cell. The dispersion of values across columns complements the formal heterogeneity tests and shows why no pooled ratio should be treated as constant over time.



Figure 5. Year-specific pairwise reporting odds ratios. Cell labels are annual RORs; color represents $\log_2$(ROR), with red above and blue below the null. Asterisks mark 2015 cariprazine comparisons calculated with a 0.5 Haldane–Anscombe correction because the cariprazine case cell was zero. The heatmap is descriptive; pooled inference is reported in Tables 3 and 4.

3.5. Sensitivity analyses

Allowing reports that named more than one target drug did not change the direction of either contrast against aripiprazole; in the shared-era non-exclusive cohort, the cariprazine-aripiprazole ROR was 1.93 (95% CI 1.74–2.14), and the brexpiprazole-aripiprazole ROR was 2.27 (2.09–2.46). These estimates were close to the exclusive-cohort results and are detailed in Table 5.

Expanding to the all-era exclusive cohort reduced both contrasts modestly. The cariprazine-aripiprazole ROR was 1.83 (95% CI 1.64–2.05), and the brexpiprazole-aripiprazole ROR was 2.10 (1.93–2.29). The attenuation is compatible with the influence of earlier aripiprazole report composition; the persistence of direction across these definitions supports robustness as a report-level signal but does not address unmeasured indication, dose, utilization, or reporting differences.

Table 5. Cohort-definition sensitivity analyses.

Cohort definition	Comparison	Crude ROR (95% CI)	PRR (95% CI)
Shared era, non-exclusive	Cariprazine vs Aripiprazole	1.93 (1.74–2.14)	1.89 (1.71–2.09)
Shared era, non-exclusive	Brexpiprazole vs Aripiprazole	2.27 (2.09–2.46)	2.20 (2.04–2.38)
All era, exclusive	Cariprazine vs Aripiprazole	1.83 (1.64–2.05)	1.80 (1.62–2.00)
All era, exclusive	Brexpiprazole vs Aripiprazole	2.10 (1.93–2.29)	2.05 (1.89–2.22)

Notes: CI, confidence interval; PRR, proportional reporting ratio; ROR, reporting odds ratio. Shared era: 1 January 2015–30 March 2026.

4. Discussion

4.1. Principal findings

This active-comparator analysis produced three linked findings. First, exact-PT akathisia took up a larger share of cariprazine and brexpiprazole reports than of aripiprazole reports in the mutually exclusive 2015–2026 cohort. Both contrasts against aripiprazole stayed above the null after stratification by year and in pairwise binomial models adjusted for categorical year. Second, the crude direct comparison between cariprazine and brexpiprazole was unstable. A crude ROR below 1 turned into an adjusted estimate near 1 once calendar time was controlled, which indicates that the apparent difference appeared to arise mainly from how the two sets of reports were spread across years. Third, every pairwise association varied across annual strata. No pooled estimate should therefore be read as a constant property of the drugs over the study period.

These findings answer the study aim at the level the data can support; they describe the relative prominence of akathisia within selected report cohorts, and they show that calendar composition changes the comparative picture. They do not show that cariprazine or brexpiprazole causes akathisia more often per patient than aripiprazole. Nor do they show that cariprazine and brexpiprazole carry equal clinical risk. After adjustment the direct comparison sits near the null. Under the stated cohort and adjustment, this reporting system gives no stable basis for ranking the two drugs.

4.2. Comparison with the existing literature

Relation to controlled and clinical evidence. These signals fit what is known about akathisia, which is recognized across dopamine partial-agonist treatment programs; recent aripiprazole work directly evaluated treatment-emergent akathisia and propranolol use.[3] Contemporary cariprazine randomized and post hoc studies broadened the clinical context to adjunctive major depression, bipolar symptom spectra, irritability and agitation, early response, maintenance treatment, anhedonia, pediatric exposure, and anxiety symptoms.[4–11] A recent FAERS analysis of atypical augmentation in major depression adds an indication-specific postmarketing comparison.[12] Together these studies support the clinical sense of the signal. They do not supply a single incidence that transfers to the heterogeneous postmarketing population.

Brexpiprazole evidence reaches similarly diverse clinical settings. Randomized dementia-agitation studies, a posttraumatic-stress-disorder trial, and an adolescent schizophrenia trial enrolled populations that differed in baseline behavior, concomitant therapy, and the way adverse events were captured.[13–16] Pooled safety, subgroup, extension, long-term major-depression, and schizophrenia-anxiety analyses widened the observation windows and the case mix;[17–22] the present report-level signal therefore cannot be mapped onto one brexpiprazole trial percentage. Its meaning lies in how prominent the exact coded term is within the selected FAERS report cohort.

The aripiprazole evidence also argues against simple cross-program comparison. Recent randomized and comparative-effectiveness research spans geriatric treatment-resistant depression, first-episode psychosis, and several long-acting injectable settings.[23–28] Quality-of-life analysis and dose-response research show that outcomes depend on treatment strategy and exposure intensity;[29,30] structured trials and target-trial emulations beat spontaneous reports for their own comparative questions. Even so, they address defined populations, not the entire postmarketing reporting environment.

Real-world cohorts show further channeling. Partial agonists are used in schizophrenia with substance-use comorbidity, in adjunctive major depression, and in dementia, and the comparator groups differ in illness, formulation, prior treatment, and utilization.[31–34] Our aggregate annual cells contain none of those measured differences. The active-comparator restriction improves clinical similarity. It cannot make the report cohorts exchangeable.

Existing pharmacovigilance studies of partial agonists and atypical antipsychotics have identified signals for impulse-control disorders, neurologic and psychiatric events, QT prolongation, hospitalization, obsessive-compulsive symptoms, and hepatic injury.[35–40] Two points follow. A report signal is specific to its event and comparator, and method choices can change its magnitude considerably; our adjusted direct cariprazine-brexpiprazole result therefore does not contradict clinical trial findings. It shows that spontaneous-report disproportionality answers a different question, one about report composition.

4.3. Interpretation and mechanism

Why the active comparator helps, and what it cannot solve. Using aripiprazole as an active comparator narrows the comparison to agents with related therapeutic roles and partial-agonist pharmacology; an all-drug background is more crowded with products from unrelated specialties, dissimilar indications, or very different adverse-event profiles. Mutual exclusivity adds a second gain: it stops cross-target reports from

appearing on both sides of the same 2 × 2 table. Both are meaningful design improvements for signal characterization.

Active comparators do not make spontaneous reports exchangeable. Aripiprazole has broader and older indications, several formulations, longer market exposure, and a different prescriber history. Cariprazine and brexpiprazole have their own indication expansions and uptake trajectories; even within schizophrenia, the patients receiving each product may differ in prior treatment, symptom profile, metabolic concerns, adherence, or clinician preference. In depression, the drugs may be used adjunctively at different doses, in patients whose underlying symptoms include anxiety or restlessness. Such factors shape the probability of akathisia. They also shape the probability that it is recognized and reported.

The aripiprazole alias set included Aristada, a long-acting formulation. Formulation can alter dose delivery, adherence, clinical monitoring, and the timing between exposure and symptoms. Combining oral and long-acting aripiprazole makes the comparator more inclusive but less specific to formulation. Excluding Aristada would answer a narrower question. Keeping it preserves the active-moiety grouping of the source design. The result should therefore be read for the stated alias group and not generalized to each aripiprazole formulation separately.

Calendar composition and the reversal of the direct comparison. The direct cariprazine-brexpiprazole result is the most instructive methodological finding of the study; the crude table pooled all reports across the shared era and gave a modest ROR below 1. The year-stratified MH estimate and the year-fixed-effect model both moved to about 1.06, with confidence intervals spanning the null. This pattern points to confounding by calendar composition. The drug groups contributed different proportions of their reports in years that had different baseline akathisia-reporting environments.

Such a reversal needs no data error. A pooled association can differ from within-stratum associations whenever observations are unevenly distributed across strata and outcome prevalence varies by stratum. In pharmacovigilance, product launch, indication approval, risk communication, reporting requirements, and publicity can all alter that distribution; the lesson is not that adjustment always reveals a true causal effect. It is that a crude pooled disproportionality can be a poor summary when the calendar structure of two products differs sharply.

The significant Breslow–Day and interaction tests add a second caution. Even after grouping by year, the pairwise odds ratios were not homogeneous. The MH-ROR works as a weighted summary, but it should not be described as a timeless product characteristic; for cariprazine versus aripiprazole, the pooled signal persisted while annual magnitudes varied. For brexpiprazole versus aripiprazole, the heterogeneity was stronger. For the two newer drugs, the adjusted summary stayed near the null while annual contrasts still varied; the annual figure therefore belongs beside the pooled estimates and not in a decorative supplement.

Reporting mechanisms that may explain temporal heterogeneity. Several non-exclusive mechanisms could generate the annual variation. Utilization changes alter the number and kind of exposed patients, even though FAERS shows no exposure denominators. Early adopters may differ from later users. New indications can shift the diagnostic mix and the background therapies. Dose recommendations and titration practice may change as clinicians gain experience. Manufacturer-sponsored programs, patient support systems, and reporting channels can shift the source distribution of reports.

Notoriety, stimulated reporting, and comparator masking also matter. Safety communications, publications, label changes, or media attention can change the relative reporting of index and comparator products without any change in clinical incidence. A retrospective FAERS analysis showed that masking can weigh heavily in active-comparator designs when external safety concerns alter reporting in the reference set.[42] We did not identify and model every product-specific communication date. Year adjustment therefore remains a coarse control and not a full explanation.

Database evolution is another mechanism. Coding practices, harmonization, duplicate handling, and report-source composition can change over time. openFDA serves the most recent version visible at the endpoint. Separate reporters may still submit clinically related reports, and public records lack some fields available to FDA reviewers; exact PT matching improves reproducibility but does not guarantee clinical adjudication. A report coded as akathisia may still lack the narrative detail needed to confirm onset, severity, alternative explanations, or the implicated product.

Interpretation of ROR, PRR, and adjusted estimates. ROR and PRR measure relative reporting. They do not measure incidence or prevalence. A crude ROR of 2.21 for brexpiprazole versus aripiprazole means that the odds of exact-PT akathisia, relative to another event, in a selected brexpiprazole report were about twice the corresponding odds in a selected aripiprazole report. It does not mean that a brexpiprazole-treated patient has twice the clinical risk of akathisia. The unknown numbers of treated patients, prescriptions, doses, and person-time block that inference.

The distinction matters because disproportionality measures address report composition, whereas randomized trials, target-trial emulations, and claims cohorts address other estimands with other denominators;[23–34] missing exposure denominators, selective reporting, and confounding prevent any conversion of an ROR into a patient-level comparative-risk estimate. Active comparators, calendar stratification, and sensitivity analyses improve the characterization of this signal. They leave its estimand unchanged.

The grouped-binomial year-adjusted models deserve the same restraint. They give a multivariable adjustment for categorical calendar year and closely corroborate the pairwise MH estimates. They do not adjust for indication, age, sex, dose, concomitant medication, reporter type, country, formulation, or utilization; significant drug-by-year interactions also show that a common coefficient averages over non-uniform annual associations. Model sophistication cannot make up for variables that are absent from the data.

4.4. Implications for practice and policy

Clinical implications. The practical implication is heightened attention to akathisia across all three drugs; it is not an instruction to select or avoid one agent on the basis of FAERS. Clinicians should ask directly about inner restlessness, inability to remain still, worsening tension, and distress after treatment initiation or dose changes. Observation should cover pacing, shifting posture, rocking, and repetitive leg movement; structured assessment with the Barnes scale can separate the subjective and objective components and document change over time.[1]

Differential diagnosis should stay broad. Akathisia may resemble anxious distress, agitation from psychosis or mania, antidepressant activation, withdrawal, restless legs syndrome, substance effects, or other movement disorders. The temporal relationship to medication initiation or titration helps but does not settle the question; the underlying illness can change during the same period, and more than one cause may coexist. Misclassification has consequences: raising an antipsychotic dose in response to presumed psychiatric agitation can intensify medication-induced restlessness.

When clinically significant akathisia is identified, management should be individualized. Evidence-informed options include reducing the antipsychotic dose when feasible, simplifying polypharmacy, switching to an alternative with a different tolerability profile, or adding selected adjunctive treatment after contraindications and risks are reviewed.[2] The current study compares no management strategies and should not be used to prescribe a specific intervention; what it supports is systematic monitoring and serious attention to patient descriptions of restlessness.

The results also argue against presenting small differences in pooled reporting estimates as clinically decisive; the direct comparison between cariprazine and brexpiprazole changed with year adjustment, and all pairs showed temporal heterogeneity. Treatment selection should draw on the individual patient's diagnosis, prior response, symptom targets, metabolic and neurologic vulnerabilities, formulation needs, co-medications, and preferences. A spontaneous-report signal is one input to that assessment. It cannot replace the assessment.

Implications for pharmacovigilance research. This analysis illustrates several practices that can strengthen comparative disproportionality studies. First, investigators should state whether a MedDRA outcome is an exact PT, a set of PTs, or a standardized query, and implement that definition explicitly. A textual claim of exact matching is insufficient when the executable query uses a tokenized field. Second, product aliases and cross-product exclusions should be reproducible. Third, the database version and cutoff date should be reported, since dynamic endpoints can change historical totals.

Fourth, calendar structure deserves routine attention when products differ in age; at minimum, investigators should display annual counts or proportions, run stratified analyses, and test heterogeneity where cell sizes permit. Fifth, active-comparator analyses should say what is gained and what remains uncontrolled. Sixth, sensitivity analyses should probe reasonable design decisions, such as exclusivity and study era, and not produce a large set of unmotivated models.

The READUS-PV statement offers a detailed framework for transparent reporting of disproportionality analyses of individual case safety reports.[43] Meta-research has shown wide variation in how published studies validate and contextualize signals. Statistical adjustment, case-by-case assessment, other data sources, and explicit comparison with accumulated evidence are applied inconsistently;[41] our design addresses several of these domains through active comparators, temporal adjustment, exact definitions, and clinical contextualization. It cannot perform case adjudication, because narratives and case-level data for the exact cohort were not retained.

Restriction choices can reduce bias and can also introduce it. Mutual exclusion removes overlapping target-drug reports, but it conditions on a feature related to polypharmacy. Active-comparator restriction increases clinical similarity, yet it changes the reporting background and may condition on treatment selection; the real-world studies of partial agonists show how much measured channeling can exist before unmeasured reporting processes are even considered.[31–34] These tradeoffs should be stated openly. No single restriction removes confounding universally.

Future research. The next step is not simply a larger pooled FAERS analysis. A more informative pharmacovigilance study would use quarterly FAERS extract files with documented case-version handling, rigorous product normalization, explicit reporter and country variables, and primary- or secondary-suspect restrictions as sensitivity analyses. Calendar adjustment could use quarter instead of year if cell counts permit, with product-specific approval and safety-communication dates mapped prospectively.

Indication-stratified analyses would help separate schizophrenia, bipolar disorder, adjunctive depression, and other contexts. Dose and formulation should be included where reasonably complete. A broader akathisia case definition could be prespecified using relevant MedDRA terms or a validated standardized query, with exact PT kept as a high-specificity analysis. Negative-control outcomes and alternative active comparators could test whether the observed patterns

are specific to akathisia or reflect broader reporting differences.

Patient-level causal questions require sources with exposure denominators and measured confounders. A new-user active-comparator cohort in claims or electronic health records could estimate incidence and relative risk, provided akathisia can be identified with a validated algorithm or chart review. Propensity-score methods, high-dimensional adjustment, dose and titration information, and sensitivity analyses for unmeasured confounding would suit such a design; prospective studies could apply Barnes ratings at baseline and during titration to capture symptoms that never generate a spontaneous report.

Head-to-head randomized evidence would remain the most direct route to comparative incidence, but large trials powered for an adverse event may be hard to run; pragmatic studies, registry-based trials, or harmonized individual-participant analyses across existing trials may offer alternatives. Whatever the design, the key is to keep three things apart: a coded report signal, a clinically adjudicated event, and the risk experienced by treated patients.

4.5. Strengths and limitations

Strengths. The study has several strengths. The comparator drugs share partial-agonist pharmacology and overlapping psychiatric uses, which makes the contrast more clinically similar than an all-drug comparison would be. The primary period was shared across products. Cross-target exclusion kept the same report from populating both sides of a pairwise table. The outcome was implemented as an exact MedDRA PT, and every primary count was independently reproduced from explicit API queries.

The analysis went beyond a single crude statistic. Reporting proportions, RORs, PRRs, Fisher tests, year-stratified MH estimates, Tarone-adjusted Breslow–Day tests, pairwise year-fixed-effect models, interaction diagnostics, and two cohort sensitivities were reconciled with one another. Agreement between MH and binomial estimates increased confidence in the arithmetic; it also showed that the persistence of signals against aripiprazole was not an artifact of one estimator. Showing the crude-to-adjusted shift for the direct comparison kept an unstable hierarchy from being overstated.

Reproducibility is another strength. The API snapshot, date range, aliases, exact outcome field, exclusions, aggregate query provenance, derived data, statistical code, and software information were preserved. Only aggregate totals were retained, which reduced privacy exposure. Tables and figures came from the same analysis outputs as the manuscript text, so transcription inconsistency was minimized.

Finally, the interpretation is placed against controlled trials, product information, and pharmacovigilance methodology. A disproportionality estimate gains meaning only within the broader evidence landscape. The manuscript separates clinical credibility from comparative causal inference, and it separates signal prominence from incidence.

Limitations. The principal limitation is the absence of exposure denominators. FAERS does not record the number of patients treated, prescriptions dispensed, doses administered, or person-time at risk. Reporting proportions, RORs, PRRs, MH-RORs, and binomial odds ratios therefore cannot estimate incidence, prevalence, absolute risk, or risk differences; differences in utilization could change report counts and reporting composition independently of adverse-event risk.

Under-reporting, selective reporting, stimulated reporting, and notoriety bias all affect spontaneous reports; the probability that akathisia is recognized and reported may differ by drug, year, indication, reporter, and severity. Newer products may attract more intensive surveillance. Familiar events with older products may be less likely to prompt a report; manufacturer submissions and consumer reports may also differ in completeness and coding.

A report can contain multiple drugs and reactions without validated drug-reaction linkage; mutual exclusivity removed reports naming another target drug, but retained reports could still carry many concomitant medications able to cause or modify restlessness. Reporter-assigned primary-suspect status was not used as proof of causality. Confounding by indication, disease severity, previous treatment, titration speed, dose, co-medication, comorbidity, and formulation was not controlled.

The medicinal-product alias strategy may misclassify reports. Product names can be misspelled, truncated, or recorded under formulations that the chosen terms do not capture. openFDA harmonization is useful but incomplete. Including Aristada in the aripiprazole group combines formulation contexts, and leaving out less common aliases may reduce sensitivity; because only aggregate API totals were retained, the study used no RxNorm mapping and no manual product normalization.

The exact PT outcome improves specificity but may lower clinical sensitivity. Reports coded under restlessness, psychomotor hyperactivity, agitation, extrapyramidal disorder, or related terms were not counted unless exact-PT akathisia was also present. Conversely, an exact coded term was not clinically adjudicated. The study therefore evaluates a reproducible coding signal. It does not apply a validated case definition based on narrative, timing, examination, or Barnes scores.

Calendar adjustment was limited to receipt year. Year is a coarse proxy that cannot separate indication expansion, utilization, safety communications, reporting-source changes, or database-process changes. Significant heterogeneity and interaction tests indicate that pooled estimates average non-uniform associations; the 2026 stratum was incomplete through 30 March, and its reporting composition may differ from that of a full year.

The direct cariprazine-brexpiprazole comparison was exploratory, and three pairwise contrasts were evaluated; we applied no formal multiplicity correction, because the study was not a confirmatory trial. Nominal confidence intervals should still not be used to declare a definitive hierarchy. The crude direct interval narrowly excluded 1 and then crossed 1 after adjustment. That pattern underlines the uncertainty instead of resolving it.

Patient-level subgroup analyses were not possible in the exact primary cohort; the source material held broader token-query summaries of age, sex, seriousness, and co-reactions, but these were not imported into the final exact-outcome analysis. We therefore could not assess effect modification by age, sex, indication, country, reporter type, dose, or treatment role. Time-to-onset, dechallenge, rechallenge, and validated outcome severity were also unavailable.

Finally, no external validation was performed in another spontaneous-report database, claims source, electronic health record, or prospective cohort. A signal that persists across cohort definitions within FAERS may still reflect reporting-system processes. Replication and triangulation are needed before any clinical comparative conclusion is drawn.

5. Conclusion

In this mutually exclusive openFDA/FAERS cohort from 2015 through 30 March 2026, exact-PT akathisia was disproportionately represented in reports naming cariprazine and brexpiprazole relative to reports naming aripiprazole; the contrasts persisted after calendar-year control, with MH-RORs of 1.77 for cariprazine versus aripiprazole and 2.21 for brexpiprazole versus aripiprazole. The crude cariprazine-brexpiprazole association, by contrast, became a near-null estimate after year adjustment. All three comparisons showed temporal heterogeneity.

The defensible reading is a set of report-level pharmacovigilance signals. They support careful clinical monitoring and targeted follow-up research. They do not estimate incidence, prove causality, or justify a patient-level safety ranking; comparative treatment decisions should rest on direct clinical assessment, controlled evidence, patient characteristics, dose and indication, and the full benefit-risk profile.

Declarations

Use of Generative Artificial Intelligence. None.

Author Contributions. R.H.: conceptualization, methodology, software, formal analysis, investigation, data curation, visualization, writing – original draft, supervision. A.M.: validation, writing – review & editing.

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Conflict of Interest. The authors declare that they have no competing interests.

Ethical Approval. Ethical approval was granted by the CMHC Research Center Ethics Committee Indonesia (No. 2026/0225).

Informed Consent. Individual informed consent was not applicable because the study analyzed public, de-identified secondary report data.

Data Availability. The source data are publicly available through the openFDA drug adverse-event endpoint. Aggregate query provenance, derived drug-year counts, statistical code, and machine-readable outputs supporting this manuscript are included in the accompanying analysis package. No individual report payloads or identifiers are distributed.

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