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# Neuropsychiatric Adverse-Event Reporting With Brexpiprazole Across Approved Indications: A Disproportionality Analysis Using the FDA Adverse Event Reporting System (FAERS)

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## Abstract

# Background

Brexpiprazole is an atypical antipsychotic approved for major depressive disorder, schizophrenia, and, most recently (May 2023), agitation associated with Alzheimer's disease. This expanded indication introduces an older, cognitively impaired population with potentially different safety risks. However, real-world neuropsychiatric adverse event data across these populations remain limited.

# Methods

We analyzed spontaneous adverse event reports from the FDA Adverse Event Reporting System (FAERS) between Q3 2015 and Q4 2025. Reports were classified by indication into three groups: Alzheimer's disease (Group A), MDD and related depressive disorders (Group B), and schizophrenia and related psychotic disorders (Group C). Reporting Odds Ratios (ROR) with 95% confidence intervals were calculated for 25 predefined neuropsychiatric adverse events with Bonferroni correction applied ($p < 0.002$). Three primary comparisons were performed (A vs B, A vs C, A vs B + C combined) alongside five pre-planned sensitivity analyses: primary suspect reports only, restriction to patients aged ≥ 65 years, collapsed MedDRA terms, a quetiapine active comparator analysis, and serious versus non-serious adverse event proportions.

# Results

After deduplication, 9,113 brexpiprazole reports were identified: 682 Alzheimer's disease, 6,858 MDD, and 1,573 schizophrenia cases. Alzheimer's patients were substantially older than both comparison groups (median age 83 vs 52 vs 43 years). Compared to MDD patients, Alzheimer's patients had higher reporting of delirium (ROR 32.91, 95% CI 12.26–88.33), falls (ROR 8.06, 95% CI 5.43–11.94), hallucination (ROR 10.01, 95% CI 6.73–14.90), neuroleptic malignant syndrome (ROR 11.47, 95% CI 3.62–36.36), and agitation (ROR 5.09, 95% CI 3.44–7.52; noting potential indication-outcome overlap). Akathisia and tardive dyskinesia were reported significantly less frequently. The overall pattern of findings was supported by multiple sensitivity analyses, including restriction to patients aged ≥ 65 years, where the hallucination signal strengthened further (ROR 30.59, 95% CI 12.34–75.87). Falls were not significantly disproportionate versus quetiapine users with Alzheimer's disease (ROR 1.02), supporting the possibility of an antipsychotic class effect. Serious adverse events were documented in 50.3% of Alzheimer's cases compared to 12.1% in MDD ($p < 0.001$) and 32.1% in schizophrenia ($p < 0.001$). Alzheimer's indication reports surpassed MDD reports in FAERS report volume by 2025.

# Conclusion

Brexpiprazole was associated with a distinct neuropsychiatric adverse-event reporting pattern in Alzheimer's disease compared with psychiatric indications, with the most consistent signals observed for delirium, falls, and agitation. Hallucination and neuroleptic malignant syndrome were disproportionately reported compared with MDD but not schizophrenia. The agitation signal should be interpreted cautiously given potential indication-outcome overlap. These findings provide clinically relevant hypothesis-generating evidence to inform prescriber vigilance and future pharmacovigilance priorities for the first FDA-approved pharmacological treatment for Alzheimer's-associated agitation.

# 1. INTRODUCTION

Brexpiprazole (Rexulti®) is an atypical antipsychotic that acts as a serotonin-dopamine activity modulator, with partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at 5-HT2A receptors [8]. Since its initial FDA approval in 2015 for schizophrenia and as adjunctive therapy for major depressive disorder (MDD), brexpiprazole has become established in psychiatric practice. In May 2023, brexpiprazole received a landmark FDA approval for agitation associated with Alzheimer's disease — becoming the first drug ever approved specifically for this indication. This approval was clinically significant because agitation affects up to 76% of patients with Alzheimer's disease, representing one of the most distressing behavioral symptoms of dementia and a leading driver of caregiver burden, institutionalization, and increased healthcare costs [1, 2].

Despite its expanding clinical use, the real-world neuropsychiatric safety profile of brexpiprazole across its three approved indications remains poorly characterized. The population approved for Alzheimer's-associated agitation differs fundamentally from those studied in the pivotal MDD and schizophrenia trials — they are older, cognitively impaired, and frequently polymedicated, with pharmacokinetic and pharmacodynamic profiles that may amplify susceptibility to neuropsychiatric adverse effects. Dementia patients in general, and those with Alzheimer's disease in particular, represent a uniquely vulnerable population in whom the balance between symptomatic benefit and adverse drug effects requires careful consideration. Antipsychotics as a class carry an FDA boxed warning for increased mortality in older patients with dementia-related psychosis, underscoring the need for rigorous post-marketing safety surveillance in this group. While pivotal randomized controlled trials demonstrated the efficacy of brexpiprazole for Alzheimer's-associated agitation [9], these trials enrolled a carefully selected patient population that may not fully represent the complexity and comorbidity burden of real-world dementia patients. While previous pharmacovigilance studies have characterized brexpiprazole adverse events using FAERS data — including analyses of MDD augmentation and general safety signal detection — no published study has directly compared neuropsychiatric adverse event profiles across all three FDA-approved indications, including the recently approved Alzheimer's disease indication [3, 4].

Post-marketing surveillance offers a critical complement to pre-approval trial data, particularly for older patients with dementia — a population characterized by polypharmacy, reduced renal clearance, and blood-brain barrier alterations that collectively increase susceptibility to centrally-acting drug effects. The FDA Adverse Event Reporting System (FAERS) captures real-world adverse event reports across diverse

clinical settings, providing a unique opportunity to examine safety signals that may not emerge until a drug reaches broader clinical use. With brexpiprazole's Alzheimer's indication approved only in May 2023 and real-world prescribing in this population now underway, a comparative analysis of neuropsychiatric adverse event reporting across its three approved indications is both timely and clinically warranted. Therefore, using FAERS data from Q3 2015 through Q4 2025, we compared neuropsychiatric adverse event reporting patterns between brexpiprazole users with Alzheimer's disease and those receiving brexpiprazole for major depressive disorder or schizophrenia, using disproportionality analysis with the Reporting Odds Ratio as the primary measure.

# 2. METHODS

## 2.1 Data Source

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting database maintained by the US Food and Drug Administration, containing post-marketing adverse event reports submitted by healthcare professionals, consumers, and pharmaceutical manufacturers worldwide. Quarterly ASCII data files — containing structured drug, adverse event, patient demographic, and outcome information — were downloaded from the FDA FAERS Quarterly Data Files repository [5]. Files covering Q3 2015 through Q4 2025 were included, representing the complete post-marketing surveillance period for brexpiprazole from its initial FDA approval in July 2015 through the most recently available data release at the time of download (March 2026). A total of 42 quarterly files were included in the analysis. This study used only publicly available, de-identified data and was therefore exempt from institutional review board approval in accordance with the HHS Common Rule (45 CFR 46.104). No patient consent was required as all data are publicly available and fully de-identified.

## 2.2 Drug Identification

All FAERS DRUG files were searched for brexpiprazole by querying the drugname and prod_ai fields for the generic name ("brexpiprazole") or brand name ("Rexulti") using case-insensitive string matching in R (version 4.5.2). Brexpiprazole is marketed under a single brand name (Rexulti) in the United States; no generic equivalents were available at the time of analysis. This search identified 25,524 unique case reports containing brexpiprazole across all role codes. Reports were subsequently filtered by role code to retain only those where brexpiprazole was designated as a primary suspect (PS) or secondary suspect (SS) drug, indicating clinical suspicion of a causal relationship between brexpiprazole and the reported adverse event. Reports where brexpiprazole appeared solely as a concomitant (C) or interacting (I) medication were excluded from the primary analysis dataset. As a pre-planned sensitivity analysis, a dataset restricted to primary suspect reports only (PS) was constructed and analyzed in parallel to assess the robustness of primary findings to this inclusion criterion.

## 2.3 Indication Classification

Indication data were extracted from the FAERS INDI files, which contain MedDRA-coded indication preferred terms (indi_pt field) linked to each drug report via a unique case identifier (primaryid). Each brexpiprazole report was classified into one of three mutually exclusive indication groups using a hierarchical keyword matching algorithm applied to the indi_pt field in R (version 4.5.2). Reports with missing, ambiguous, or unclassifiable indications (n = 73,085 rows) were excluded from the primary analysis. The complete keyword list and matching logic are provided in Supplementary Table S1.

Group A — Alzheimer's disease: Reports coded as "Dementia Alzheimer's type" (n = 480, 70.4%) were classified directly into Group A. Reports coded with the unspecified preferred term "Dementia" (n = 202, 29.6%) were additionally included under a prespecified temporal assumption: 189 of 202 (93.6%) were submitted after the May 2023 FDA approval of brexpiprazole for Alzheimer's-associated agitation, compared with 13 before approval. Brexpiprazole is not approved for other dementia subtypes; the inclusion of unspecified dementia cases is acknowledged as a potential source of misclassification.

Group B — MDD and related depressive disorders: Reports where the indi_pt field contained any of the following MedDRA preferred terms: "depression," "depressive," "adjuvant," "antidepressant," "mdd," "postpartum," or "perinatal." At the unique case level, the majority of Group B reports were coded as "Major depression" (n = 3,350, 48.8%) or "Depression" (n = 2,284, 33.3%), with "Adjuvant therapy" accounting for 17.0% (n = 1,169) — reflecting brexpiprazole's use as an augmentation agent for MDD. All terms were confirmed as actual MedDRA indi_pt values present in the dataset, and no non-depressive indications were identified under these terms during validation.

Group C — Schizophrenia and related psychotic disorders: Reports where the indi_pt field contained the terms "schizophrenia" or "schizoaffective." Non-specific psychotic terms ("psychotic disorder," "psychotic symptom," "psychotic behaviour") were intentionally excluded and classified as unclassifiable, as they could not be reliably assigned to a specific approved indication.

The classification algorithm was applied hierarchically — Group A first, Group C second, Group B third. This ordering was implemented to prevent misclassification of "Schizoaffective disorder depressive type" into Group B — a misclassification identified and corrected during initial validation. All unique indication terms within each final group were reviewed to confirm classification accuracy. Non-Alzheimer's dementia subtypes identified in the unclassifiable pool included vascular dementia, frontotemporal dementia, and Lewy body dementia; these were excluded to maintain diagnostic specificity aligned with the FDA-approved indication.

# 2.4 Deduplication

FAERS is known to contain duplicate reports, arising when the same adverse event case is submitted independently by multiple reporters. To address this, deduplication was performed following FDA-recommended methodology: for reports sharing the same case identifier (caseid), only the most recent version was retained, identified by the highest case sequence number. This process yielded a final

primary analysis dataset of 9,113 unique deduplicated cases: 682 in Group A, 6,858 in Group B, and 1,573 in Group C.

## 2.5 Adverse Event Extraction

Adverse event data were extracted from the FAERS REAC files, which contain MedDRA preferred terms (pt field) representing each reported adverse event, linked to case reports via the primaryid field. REAC files were filtered during loading to retain only records matching brexpiprazole case identifiers prior to merging, reducing computational burden. Records were subsequently linked to indication groups via the primaryid field.

Neuropsychiatric adverse events were identified using a predefined list of 25 MedDRA preferred terms, selected based on the brexpiprazole prescribing information, known antipsychotic class effects, and clinical relevance to the study population. Terms were organized into eight clinical domains: movement disorders (akathisia, tardive dyskinesia, extrapyramidal disorder, tremor, dyskinesia, parkinsonism); suicidality (suicidal ideation, suicide attempt); cognitive and neurological effects (delirium, confusional state, memory impairment, seizure); behavioral symptoms (agitation, aggression, hallucination, restlessness, mania); mood and psychiatric symptoms (anxiety, depression, insomnia); sedation-related effects (somnolence, sedation, fatigue); serious idiosyncratic reactions (neuroleptic malignant syndrome); and geriatric safety (falls), pre-specified given the established association between antipsychotic use and fall risk in older patients with dementia [6]. The complete predefined term list is provided in Supplementary Table S2.

As a pre-planned sensitivity analysis, related MedDRA preferred terms were collapsed into broader clinical groupings to address potential coding inconsistency across reporter types: delirium and confusional state were combined as “Delirium/Confusional State”; all hallucination subtypes as “Hallucination (any)”; akathisia and restlessness as “Akathisia/Restlessness”; tardive dyskinesia, dyskinesia, extrapyramidal disorder, and parkinsonism as “Movement Disorders (any)”; and suicidal ideation and suicide attempt as “Suicidality (any).”

## 2.6 Statistical Analysis

Primary analysis: Disproportionality was quantified using the Reporting Odds Ratio (ROR) with 95% confidence intervals, calculated using the standard 2×2 contingency table method [10]. For each adverse event term, the ROR compares the odds of that adverse event being reported with brexpiprazole in one indication group versus a reference group, relative to all other adverse events. A disproportionality signal was defined as an ROR greater than 1.0 with a lower bound of the 95% confidence interval greater than 1.0, and a minimum of 3 reports; statistical significance after multiplicity adjustment was defined as $p < 0.002$. The Proportional Reporting Ratio (PRR) was calculated as a confirmatory measure; PRR results are provided in Supplementary Table S3. Three primary comparisons were performed: Group A versus Group B (primary comparison), Group A versus Group C, and Group A versus Groups B and C combined.

To account for multiple comparisons across 25 predefined adverse event terms, Bonferroni correction was applied with an adjusted significance threshold of $p < 0.002$ (0.05/25). Multiplicity correction was applied separately within each prespecified group comparison across the 25 adverse-event terms, rather than jointly across all three comparisons. Standard errors were calculated as the square root of the sum of reciprocals of the four contingency table cells. P-values were derived from the standard normal distribution applied to the log-transformed ROR. Findings surviving this threshold are reported as Bonferroni-significant disproportionality; findings not surviving Bonferroni correction are reported as nominally significant exploratory observations.

Serious adverse events were defined as reports documenting at least one of the following outcomes in the FAERS OUTC file: death (DE), hospitalization (HO), life-threatening event (LT), or disability (DS), consistent with FDA outcome classification criteria for serious adverse event reporting [7]. The 'other serious outcome' category (OT) was analyzed separately and not included in the composite serious AE definition, as this category encompasses heterogeneous and inconsistently coded outcomes that may not reflect equivalent clinical severity across indication groups.

Five pre-planned sensitivity analyses were conducted: (1) restriction to primary suspect (PS) reports only; (2) restriction to patients aged ≥ 65 years, to minimize age-related confounding given the substantially older demographic of Group A; (3) collapsed MedDRA terminology groupings, to address potential coding inconsistency across reporter types; (4) active comparator analysis using quetiapine reports in Alzheimer's disease and dementia patients, to explore whether observed signals might be brexpiprazole-specific or shared with another antipsychotic; and (5) serious versus non-serious adverse event proportion analysis using chi-square testing with Yates' continuity correction.

Temporal analysis: Annual reporting trends were examined by extracting submission year from the FDA date field (fda_dt) in the FAERS DEMO files. Report counts per indication group per year were tabulated to characterize changes in reporting patterns before and after the May 2023 FDA approval of brexpiprazole for Alzheimer's-associated agitation.

Comedication analysis: Concomitant medications reported alongside brexpiprazole in Group A were extracted from the FAERS DRUG files (role code C) and tabulated descriptively to characterize the comedication burden in the Alzheimer's disease group.

All analyses were performed in R version 4.5.2 using the dplyr, readr, and stringr packages. AI assistance (Claude, Anthropic) was used for R programming guidance. All clinical decisions, data interpretation, and final manuscript content were reviewed and approved by the authors.

# 3. RESULTS

# 3.1 Study Population

A total of 25,524 brexpiprazole reports were identified in FAERS between Q3 2015 and Q4 2025 across all role codes. After excluding concomitant and interacting role codes, reports were linked to indication data from the FAERS INDI files. Following hierarchical indication classification, 9,113 unique deduplicated cases were assigned to one of three indication groups: Group A (Alzheimer's disease) n = 682, Group B (MDD and related depressive disorders) n = 6,858, and Group C (Schizophrenia and related psychotic disorders) n = 1,573. Reports with missing or unclassifiable indications were excluded from the primary analysis. The complete participant flow is presented in Fig. 1.

# 3.2 Baseline Characteristics

Baseline characteristics of the three indication groups are presented in Table 1. Alzheimer's disease patients (Group A) were substantially older than both comparison groups, with a median age of 83 years (mean 81.7) compared to 52 years (mean 51.2) in the MDD group and 43 years (mean 45.3) in the schizophrenia group. Age data were missing for 52.9%, 62.5%, and 53.0% of reports in Groups A, B, and C respectively.

Table 1
Baseline Characteristics of Brexpiprazole Reports by Indication Group

| Characteristic | Group A Alzheimer's Disease (n = 682) | Group B MDD & Related (n = 6,858) | Group C Schizophrenia & Related (n = 1,573) |
|---|---|---|---|
| Age (years) | | | |
| Median | 83 | 52 | 43 |
| Mean | 81.7 | 51.2 | 45.3 |
| Missing, n (%) | 361 (52.9%) | 4,283 (62.5%) | 833 (53.0%) |
| Sex, n (%) | | | |
| Female | 331 (55.4%) | 4,718 (73.8%) | 729 (50.5%) |
| Male | 267 (44.6%) | 1,675 (26.2%) | 715 (49.5%) |
| Missing | 84 | 465 | 129 |
| Reporter type, n (%) | | | |
| Physician (MD) | 316 (49.6%) | 1,257 (19.7%) | 671 (46.1%) |
| Consumer/Patient (CN) | 131 (20.6%) | 3,874 (60.6%) | 537 (36.9%) |
| Health professional (HP) | 141 (22.1%) | 1,163 (18.2%) | 163 (11.2%) |
| Pharmacist (PH) | 49 (7.7%) | 98 (1.5%) | 86 (5.9%) |
| Outcomes, n (%) | | | |
| Death | 219 (32.1%) | 188 (2.7%) | 135 (8.6%) |
| Hospitalization | 130 (19.1%) | 570 (8.3%) | 353 (22.4%) |
| Life-threatening | 6 (0.9%) | 50 (0.7%) | 24 (1.5%) |
| Serious AEs□, n (%) | 343 (50.3%) | 827 (12.1%) | 505 (32.1%) |

□ *Serious AEs defined as reports documenting death, hospitalization, life-threatening events, or disability (DE + HO+LT + DS) per FDA outcome classification criteria. Chi-square with Yates' correction: Group A vs B $\chi^2=688.8$, $p < 0.001$; Group A vs C $\chi^2=66.3$, $p < 0.001$.*

□ *Reporter type percentages are calculated among cases with known reporter type (Group A: n = 637; Group B: n = 6,392; Group C: n = 1,457). Cases with missing or other reporter type (Group A: n = 45; Group B: n = 466; Group C: n = 116) were excluded from percentage denominators.*

□ *Sex percentages are calculated among cases with known sex (Group A: n = 598; Group B: n = 6,393; Group C: n = 1,444); missing sex is shown separately.*

*MDD = major depressive disorder; AE = adverse event; MD = medical doctor; CN = consumer/patient; HP = healthcare professional; PH = pharmacist.*

Female patients predominated in Group B (73.8%) compared to a more balanced sex distribution in Groups A (55.4% female) and C (50.5% female). Physician-initiated reports were most frequent in Group A (49.6%) compared with Group B (19.7%) and Group C (46.1%), with consumer and patient reports predominating in Group B (60.6%). This pattern may partly reflect cognitive impairment limiting self-reporting in some patients with Alzheimer's disease, resulting in higher rates of clinically-initiated reporting in this group.

Death was reported as an outcome in 32.1% of Group A cases compared to 2.7% in Group B and 8.6% in Group C. This marked difference in mortality reporting may reflect advanced age, underlying disease severity, differential reporting, and other population-level differences rather than a drug-specific effect. Hospitalization was reported in 19.1% of Group A cases, 8.3% of Group B, and 22.4% of Group C, reflecting the acute care needs of the Alzheimer's and schizophrenia populations respectively. Serious adverse events overall were reported in 50.3% of Group A cases, significantly higher than both Group B (12.1%, $\chi^2$=688.8, $p < 0.001$) and Group C (32.1%, $\chi^2$=66.3, $p < 0.001$).

# 3.3 Primary Disproportionality Analysis

**Group A versus Group B (Alzheimer's disease vs MDD)**

Compared to MDD patients, Alzheimer's disease patients showed significantly higher reporting of multiple neuropsychiatric adverse events after Bonferroni correction ($p < 0.002$). The strongest signal was observed for delirium (ROR 32.91, 95% CI 12.26–88.33, $p = 4.03\times10^{-12}$), followed by neuroleptic malignant syndrome (ROR 11.47, 95% CI 3.62–36.36, $p = 3.40\times10^{-5}$), hallucination (ROR 10.01, 95% CI 6.73–14.90, $p = 6.47\times10^{-30}$), falls (ROR 8.06, 95% CI 5.43–11.94, $p = 2.75\times10^{-25}$), agitation (ROR 5.09, 95% CI 3.44–7.52, $p = 3.72\times10^{-16}$), aggression (ROR 4.84, 95% CI 2.58–9.09, $p = 9.38\times10^{-7}$), and sedation (ROR 4.46, 95% CI 2.61–7.60, $p = 4.11\times10^{-8}$). Akathisia (ROR 0.28, 95% CI 0.14–0.54, $p = 1.97\times10^{-4}$), tardive dyskinesia (ROR 0.20, 95% CI 0.08–0.50, $p = 3.96\times10^{-4}$), and dyskinesia (ROR 0.30, 95% CI 0.16–0.57, $p = 2.14\times10^{-4}$) were reported significantly less frequently in Alzheimer's patients after Bonferroni correction. Somnolence (ROR 2.01), fatigue (ROR 0.31), and parkinsonism (ROR 2.23) showed nominally significant associations that did not survive Bonferroni correction and are considered exploratory findings.

The agitation signal should be interpreted with caution, as agitation represents both the approved indication for Group A and a reported adverse event in FAERS, and may reflect indication overlap, therapeutic failure, or disease progression rather than a drug-specific adverse effect.

**Group A versus Group C (Alzheimer's disease vs Schizophrenia)**

Compared to schizophrenia patients, Alzheimer's disease patients showed significantly higher reporting of delirium (ROR 9.72, 95% CI 3.62–26.11, $p = 6.47\times10^{-6}$), agitation (ROR 5.68, 95% CI 3.48–9.27, $p = 3.93\times10^{-12}$), and falls (ROR 3.08, 95% CI 2.03–4.65, $p = 9.91\times10^{-8}$) after Bonferroni correction. Hallucination was not significantly disproportionate in this comparison (ROR 1.08, 95% CI 0.75–1.55, $p = 0.676$), reflecting the high baseline hallucination reporting in the schizophrenia group. Similarly,

neuroleptic malignant syndrome showed no significant disproportionality versus schizophrenia (ROR 0.66, 95% CI 0.26–1.71, p = 0.389), consistent with its established association with antipsychotic use in all indications. Akathisia (ROR 0.36), parkinsonism (ROR 3.31), and aggression (ROR 2.15) showed nominally significant associations that did not survive Bonferroni correction.

**Group A versus Groups B + C combined**

In the combined psychiatric reference group analysis, nine adverse events survived Bonferroni correction. Alzheimer's patients showed significantly higher reporting of delirium (ROR 21.32, 95% CI 9.49–47.87, $p = 1.23\times10^{-13}$), falls (ROR 5.92, 95% CI 4.09–8.56, $p = 3.64\times10^{-21}$), agitation (ROR 5.21, 95% CI 3.55–7.64, $p = 2.89\times10^{-17}$), hallucination (ROR 3.69, 95% CI 2.60–5.23, $p = 2.35\times10^{-13}$), aggression (ROR 3.77, 95% CI 2.07–6.88, $p = 1.55\times10^{-5}$), and sedation (ROR 3.08, 95% CI 1.85–5.12, $p = 1.45\times10^{-5}$). Akathisia (ROR 0.29, $p = 2.86\times10^{-4}$), dyskinesia (ROR 0.34, $p = 8.92\times10^{-4}$), and tardive dyskinesia (ROR 0.24, $p = 1.67\times10^{-3}$) were reported significantly less frequently. Somnolence (ROR 1.87), parkinsonism (ROR 2.41), and fatigue (ROR 0.33) showed nominally significant associations that did not survive Bonferroni correction in this comparison.

Three adverse events — delirium, falls, and agitation — demonstrated consistent statistically significant signals across all three primary comparisons after Bonferroni correction, representing the most robust findings of this study. Full results are presented in Table 2 and Fig. 2. The ten most frequently reported neuropsychiatric adverse events by indication group are shown in Fig. 3.

Table 2
Primary Disproportionality Analysis: Reporting Odds Ratios for Neuropsychiatric Adverse Events in Alzheimer's Disease vs Comparison Groups

| Adverse Event | A vs B ROR | A vs B 95% CI | A vs C ROR | A vs C 95% CI | A vs B + C ROR | A vs B + C 95% CI |
|---|---|---|---|---|---|---|
| Delirium□ | 32.91* | 12.26–88.33 | 9.72* | 3.62–26.11 | 21.32* | 9.49–47.87 |
| Hallucination | 10.01* | 6.73–14.90 | 1.08 | 0.75–1.55 | 3.69* | 2.60–5.23 |
| NMS | 11.47* | 3.62–36.36 | 0.66 | 0.26–1.71 | 2.46 | 0.97–6.28 |
| Falls□ | 8.06* | 5.43–11.94 | 3.08* | 2.03–4.65 | 5.92* | 4.09–8.56 |
| Agitation□□ | 5.09* | 3.44–7.52 | 5.68* | 3.48–9.27 | 5.21* | 3.55–7.64 |
| Aggression | 4.84* | 2.58–9.09 | 2.15□ | 1.10–4.19 | 3.77* | 2.07–6.88 |
| Sedation | 4.46* | 2.61–7.60 | 1.48 | 0.86–2.56 | 3.08* | 1.85–5.12 |
| Somnolence | 2.01□ | 1.21–3.33 | 1.51 | 0.88–2.61 | 1.87□ | 1.14–3.07 |
| Parkinsonism | 2.23□ | 1.10–4.52 | 3.31□ | 1.40–7.82 | 2.41□ | 1.20–4.85 |
| Akathisia | 0.28* | 0.14–0.54 | 0.36□ | 0.18–0.72 | 0.29* | 0.15–0.57 |
| Tardive dyskinesia | 0.20* | 0.08–0.50 | 0.47 | 0.19–1.19 | 0.24* | 0.10–0.57 |
| Dyskinesia | 0.30* | 0.16–0.57 | 0.56 | 0.29–1.10 | 0.34* | 0.18–0.64 |
| Fatigue | 0.31□ | 0.11–0.83 | 0.43 | 0.15–1.20 | 0.33□ | 0.12–0.89 |

** Significant after Bonferroni correction (p < 0.002). □ Nominally significant (p < 0.05), did not survive Bonferroni correction.*

*□ Three adverse events showing consistent significant signals across all three primary comparisons after Bonferroni correction.*

*□ Agitation signal should be interpreted with caution given potential indication-outcome overlap.*

*ROR = reporting odds ratio; CI = confidence interval; NMS = neuroleptic malignant syndrome; A = Group A (Alzheimer's disease); B = Group B (MDD); C = Group C (Schizophrenia).*

# 3.4 Sensitivity Analyses

**Primary suspect reports only (PS)**

Restriction to primary suspect reports yielded consistent findings with the primary analysis. Delirium (ROR 71.65, 95% CI 24.24–211.80), hallucination (ROR 11.63, 95% CI 8.21–16.49), falls (ROR 6.73, 95% CI 4.72–9.61), agitation (ROR 3.23, 95% CI 2.17–4.80), and neuroleptic malignant syndrome (ROR 12.74, 95% CI 4.59–35.34) remained significantly elevated in Alzheimer's patients versus MDD after Bonferroni correction. The delirium signal was stronger in PS-only reports, indicating that the finding was not attenuated when analysis was restricted to reports in which brexpiprazole was designated as the primary suspect drug.

**Age restriction (≥ 65 years)**

After restricting to patients aged ≥ 65 years, available age data yielded 315 Group A cases, 644 Group B cases, and 135 Group C cases. Given the reduced sample sizes following age restriction, confidence intervals in this analysis are correspondingly wider. Falls (ROR 2.70, 95% CI 1.36–5.35), agitation (ROR 7.66, 95% CI 2.61–22.47), aggression (ROR 11.53, 95% CI 3.42–38.87), delirium (ROR 11.20, 95% CI 2.03–61.78), and sedation (ROR 6.56, 95% CI 2.34–18.42) remained significantly elevated in Alzheimer's patients versus MDD. Hallucination showed a strengthened signal in the age-restricted analysis (ROR 30.59, 95% CI 12.34–75.87), suggesting this signal is particularly pronounced in older patients. Akathisia and tardive dyskinesia were no longer significant in the age-restricted analysis, likely reflecting lower baseline movement disorder reporting in older patients across all indications.

**Collapsed MedDRA terminology**

Analysis using collapsed MedDRA groupings yielded results consistent with the primary analysis. Delirium/Confusional State (ROR 3.62, 95% CI 2.04–6.41), Hallucination any (ROR 10.01, 95% CI 6.73–14.90), Fall any (ROR 8.06, 95% CI 5.43–11.94), Agitation (ROR 5.09, 95% CI 3.44–7.52), and Akathisia/Restlessness (ROR 0.47, 95% CI 0.30–0.73) all remained significant. ROR estimates for hallucination and falls were unchanged from the primary analysis, as no additional MedDRA terms were collapsed into these groupings. The delirium signal attenuated substantially from ROR 32.91 to 3.62 when confusional state was included, reflecting coding heterogeneity between these two clinically overlapping terms across reporter types.

**Quetiapine active comparator**

Compared to quetiapine users with Alzheimer's disease or dementia (n = 1,459), brexpiprazole Alzheimer's patients showed significantly higher reporting of tardive dyskinesia (ROR 6.69, 95% CI 1.79–25.07), agitation (ROR 2.16, 95% CI 1.44–3.24), hallucination (ROR 1.63, 95% CI 1.13–2.35), insomnia (ROR 2.98, 95% CI 1.75–5.08), and restlessness (ROR 2.71, 95% CI 1.38–5.34). Falls were not significantly different between brexpiprazole and quetiapine Alzheimer's patients (ROR 1.02, 95% CI

0.71–1.46, p = 0.92), suggesting that the falls signal observed in primary analyses may reflect a class effect across antipsychotics in older dementia patients rather than a brexpiprazole-specific risk. Conversely, confusional state (ROR 0.16, 95% CI 0.05–0.52), neuroleptic malignant syndrome (ROR 0.23, 95% CI 0.09–0.57), aggression (ROR 0.55, 95% CI 0.31–0.99), and fatigue (ROR 0.28, 95% CI 0.10–0.78) were reported significantly less frequently with brexpiprazole than quetiapine. The lower NMS reporting with brexpiprazole relative to quetiapine suggests that the signal may not be specific to brexpiprazole, although comparative risk cannot be inferred from spontaneous reporting data.

**Serious adverse event analysis**

Serious adverse events were reported in 50.3% of Group A cases, significantly higher than Group B (12.1%, $\chi^2$=688.8, p < 0.001) and Group C (32.1%, $\chi^2$=66.3, p < 0.001), with Yates' continuity correction applied. This difference may reflect underlying disease severity, age, differential reporting, and other population-level characteristics rather than a drug-specific effect.

# 3.5 Additional Analyses

**Temporal trends**

Annual reporting trends are presented in Fig. 4. Prior to the May 2023 FDA approval of brexpiprazole for Alzheimer's-associated agitation, Group A reports were negligible, ranging from 0 to 12 cases per year between 2015 and 2022. Following approval, Group A reports increased markedly from 19 cases in 2023 to 233 in 2024 and 408 in 2025, representing a 21-fold increase over two years. By 2025, Alzheimer's indication reports exceeded MDD reports (408 vs 354 respectively). This crossover suggests that Alzheimer's-associated agitation became the most frequently represented indication among brexpiprazole FAERS reports within two years of approval, with implications for post-marketing safety surveillance priorities; FAERS report volume reflects reporting patterns and is not a direct measure of prescribing volume. Group B and Group C reporting volumes remained relatively stable throughout the study period, with Group B showing a gradual decline from a peak of 1,099 reports in 2016 to 354 in 2025, a pattern compatible with the Weber effect.

This temporal pattern has two important implications for interpretation. First, the marked surge in Group A reporting following approval likely reflects a combination of increasing clinical use and stimulated reporting due to heightened clinical and regulatory awareness. Second, the ROR measures disproportionality relative to all other reported events and is therefore less susceptible to volume-driven bias than absolute case counts, though it remains subject to differential reporting intensity across indications.

**Comedication analysis**

Concomitant medication data were available for 184 of 682 Group A cases (27.0%). The most frequently co-reported medications were memantine (n = 50), quetiapine (n = 37), donepezil (n = 29), amlodipine (n = 15), lemborexant (n = 12), sertraline (n = 12), galantamine (n = 11), lorazepam (n = 11), and escitalopram

(n = 10). The concurrent use of quetiapine in 37 cases (5.4% of Group A) represents dual antipsychotic prescribing, which may have contributed to the observed delirium and movement disorder signals through additive antidopaminergic effects. Both lorazepam (n = 11, 1.6%) and lemborexant (n = 12, 1.8%) are CNS depressants that introduce independent risk factors for falls and sedation in this older population. The presence of acetylcholinesterase inhibitors — donepezil (n = 29) and galantamine (n = 11) — is expected in Alzheimer's disease management and further illustrates the polypharmacy context in which adverse-event attribution must be interpreted. These comedication patterns highlight the complexity of adverse event attribution in this population and represent an important limitation of the current analysis.

# 4. DISCUSSION

Brexpiprazole exhibits a distinct neuropsychiatric adverse-event reporting pattern in Alzheimer's disease compared with its psychiatric indications, with delirium, falls, and agitation demonstrating consistent disproportionate reporting across all primary comparisons after Bonferroni correction. To our knowledge, this represents the first pharmacovigilance analysis directly comparing neuropsychiatric adverse event profiles across all three FDA-approved indications for brexpiprazole using post-marketing surveillance data. Building on prior FAERS work by Jiang et al. and Qi et al. characterizing brexpiprazole adverse events in MDD augmentation and general safety surveillance, this study extends the comparison to include the recently approved Alzheimer's disease indication [3, 4]. The temporal analysis further revealed that by 2025, Alzheimer's disease became the most frequently represented brexpiprazole indication in FAERS, surpassing MDD (408 vs 354 reports), underscoring the growing post-marketing safety surveillance priority for this population.

The delirium signal — the largest observed in this analysis (ROR 32.91 vs MDD) — warrants careful interpretation, potentially reflecting a combination of drug-related effects, underlying dementia vulnerability, and coding differences between reporters in older dementia settings, who may use "delirium" for presentations coded as "confusional state" in psychiatric settings. The substantial attenuation of this signal from ROR 32.91 to 3.62 when delirium and confusional state were combined in the collapsed MedDRA sensitivity analysis supports coding heterogeneity as a contributing factor, though the signal remained statistically significant after this adjustment, suggesting a genuine pharmacovigilance concern. Falls also demonstrated marked disproportionate reporting (ROR 8.06 vs MDD), yet were not significantly disproportionate compared to quetiapine users with Alzheimer's disease (ROR 1.02), suggesting the possibility of a class effect across antipsychotics in older dementia patients rather than a brexpiprazole-specific risk. Hallucination reporting was markedly elevated versus MDD (ROR 10.01) and strengthened further when restricted to patients aged ≥ 65 years (ROR 30.59), yet showed no significant disproportionality versus schizophrenia patients (ROR 1.08), reflecting the high baseline hallucination burden in that reference group. Neuroleptic malignant syndrome, while significantly elevated versus MDD (ROR 11.47), was reported significantly less frequently with brexpiprazole than quetiapine in Alzheimer's patients (ROR 0.23), suggesting that the NMS signal may reflect population vulnerability in older dementia patients rather than brexpiprazole-specific

pharmacology. The consistently lower reporting of akathisia, tardive dyskinesia, and dyskinesia in Alzheimer's patients compared to psychiatric groups may reflect lower brexpiprazole doses used in the ADBP indication, cognitive impairment limiting self-reporting of subjective movement symptoms, or shorter treatment duration in this population.

The agitation signal (ROR 5.09 vs MDD) requires particular interpretive caution, as agitation represents both the FDA-approved indication for brexpiprazole in Alzheimer's disease and a reported adverse event in FAERS — a dual role that precludes distinguishing therapeutic failure, disease progression, and genuine adverse drug effect within spontaneous reporting data. Regardless of mechanism, the finding that agitation is reported at fivefold higher rates in Alzheimer's patients than MDD patients warrants careful monitoring for treatment response versus adverse drug effect in clinical practice. The mortality data in this analysis — with death reported in 32.1% of Group A cases compared to 2.7% in Group B — are consistent with the existing FDA boxed warning for increased mortality risk with antipsychotic use in older patients with dementia-related psychosis, though the high mortality rate in Group A reflects the advanced age and disease severity of this population and cannot be attributed to brexpiprazole specifically. These findings may support heightened attention to fall risk, delirium, concomitant CNS depressants, and symptoms suggestive of neuroleptic malignant syndrome when brexpiprazole is used in older adults with Alzheimer's disease.

Several limitations of this study should be acknowledged. As with all spontaneous reporting analyses, FAERS data cannot establish causality — reported associations reflect disproportionate reporting patterns rather than confirmed adverse drug reactions, and findings should be interpreted as hypothesis-generating signals requiring confirmation in prospective studies. The absence of a denominator in spontaneous reporting systems precludes calculation of incidence rates, and reporting biases — including underreporting, stimulated reporting following the 2023 FDA approval, and differential reporting intensity across indication groups — may have influenced observed signals. Confounding by indication represents the most substantive limitation: the three groups differ markedly in age (median 83 vs 52 vs 43 years), cognitive status, comorbidity burden, and comedication profiles, and observed differences in adverse event reporting may reflect these population characteristics rather than differential drug effects. While the age-restricted sensitivity analysis and quetiapine active comparator analysis partially address this concern, residual confounding cannot be excluded. Because age was missing in more than half of reports in every group, the age-restricted sensitivity analysis may itself be subject to selection bias. Marked differences in reporter type across indication groups may also contribute to differential event coding and recognition, particularly for clinically defined events such as delirium and neuroleptic malignant syndrome, which are more likely to be identified and labeled by clinicians than by consumer reporters. The unspecified "Dementia" cases (n = 202, 29.6%) were classified into Group A under a prespecified temporal assumption based on their submission after the May 2023 approval; while methodologically justified, this assumption introduces potential misclassification risk, and this classification was not independently confirmed against a sensitivity analysis excluding these cases. The relatively recent ADBP approval creates temporal asymmetry — Group A reports span only 2.5 years compared to 10 years for Groups B and C — which may amplify

reporting intensity through a pattern compatible with the Weber effect, independent of true adverse event rates. Dose information is inconsistently captured in FAERS and was not available for analysis; the lower brexpiprazole doses used in the ADBP indication (0.5–2 mg) compared to psychiatric indications (2–4 mg) may partially explain the lower movement disorder reporting observed in Alzheimer's patients. Comedication data were available for only 27.0% of Group A cases, limiting the characterization of polypharmacy contributions to observed signals. Finally, agitation and depression — the primary indications for Groups A and B respectively — also appear as reported adverse events in their respective groups, precluding distinction between therapeutic failure and genuine adverse drug effect; depression reported as an adverse event in Group B may reflect inadequate treatment response rather than a drug-specific effect, analogous to the agitation overlap in Group A.

These findings highlight the need for dedicated prospective pharmacovigilance studies in brexpiprazole-treated Alzheimer's patients, incorporating standardized neuropsychiatric assessments, falls surveillance, and delirium monitoring protocols with individual patient-level data, addressing limitations inherent to spontaneous reporting frameworks. Future studies should examine the dose-response relationship between brexpiprazole exposure and neuropsychiatric adverse events in dementia populations, clarify the contribution of comedication burden to observed signals, and compare brexpiprazole prospectively against both placebo and active comparators including quetiapine in real-world dementia care settings, including a sensitivity analysis excluding unspecified dementia cases. The increase in FAERS reporting volume documented in this analysis — with Alzheimer's disease surpassing MDD as the most frequently represented brexpiprazole indication by report volume within two years of approval — underscores the urgency of this research agenda. Brexpiprazole reports associated with Alzheimer's disease showed a different neuropsychiatric reporting pattern from reports for psychiatric indications, particularly for delirium, falls, and agitation. These findings should be interpreted in light of substantial differences in age, indication, reporter type, and reporting period, and warrant confirmation using denominator-based real-world data.

## DECLARATIONS

# Conflicts of Interest

The authors declare that they have no conflicts of interest.

# Ethics Approval

This study used only publicly available, de-identified data from the FDA Adverse Event Reporting System and was exempt from institutional review board approval in accordance with the HHS Common Rule (45 CFR 46.104). No patient consent was required.

# Consent to Participate

Not applicable.

### Consent for Publication

Not applicable.

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# Author Contribution

M.H.A.Z. conceived the study, performed the data analysis, interpreted the results, and drafted the manuscript. A.A.J. contributed to study design, interpretation of findings, and critical revision of the manuscript. Both authors read and approved the final manuscript.

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AI assistance (Claude, Anthropic) was used for R programming guidance. All clinical decisions, data interpretation, analytical methodology, and final manuscript content were reviewed and approved by the authors. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

# Data Availability

The data used in this study are publicly available from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). The datasets analyzed during the current study are available through the FDA FAERS Quarterly Data Extract Files.

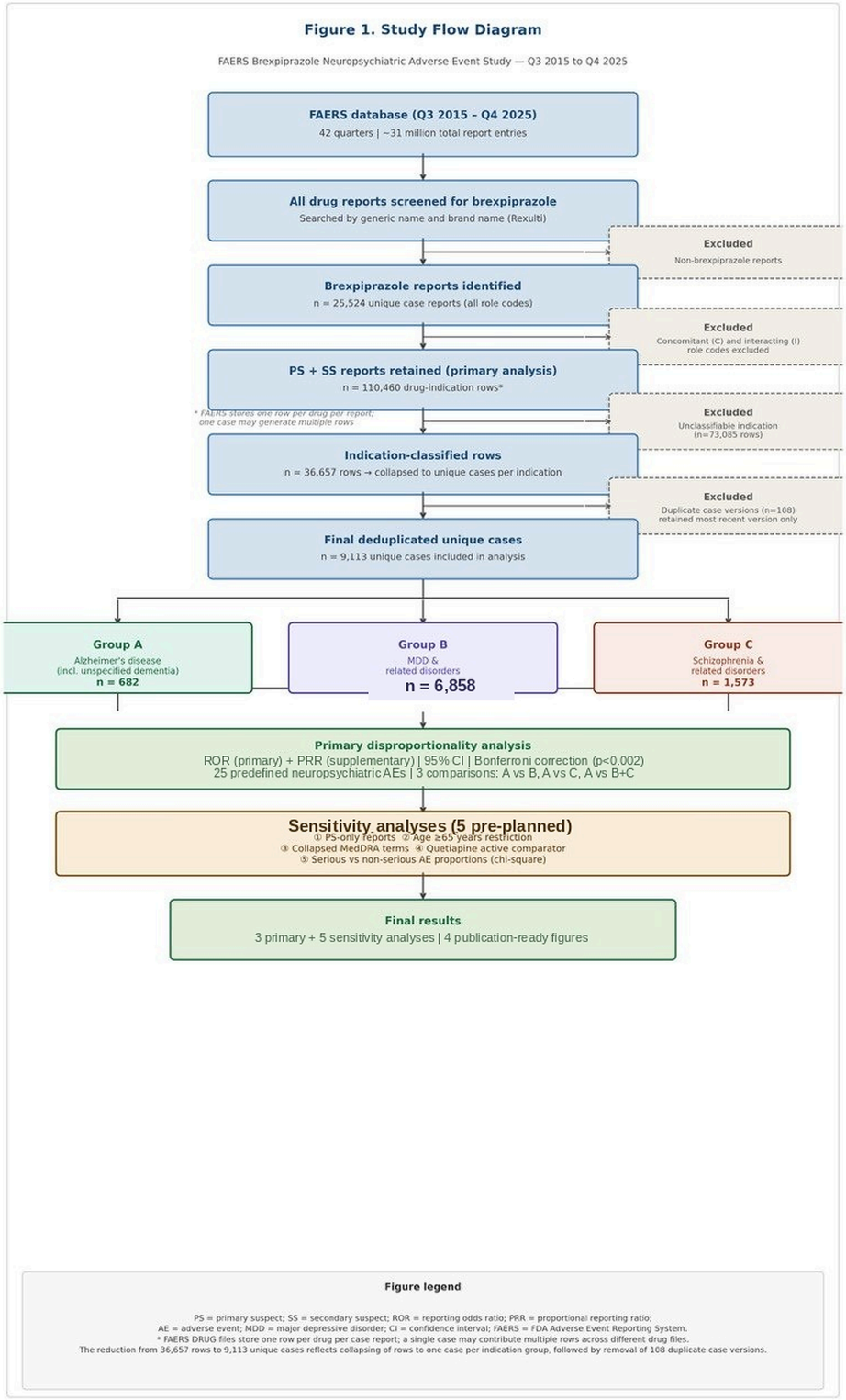
# Code Availability

The R code used for data processing and statistical analyses is available from the corresponding author upon reasonable request.

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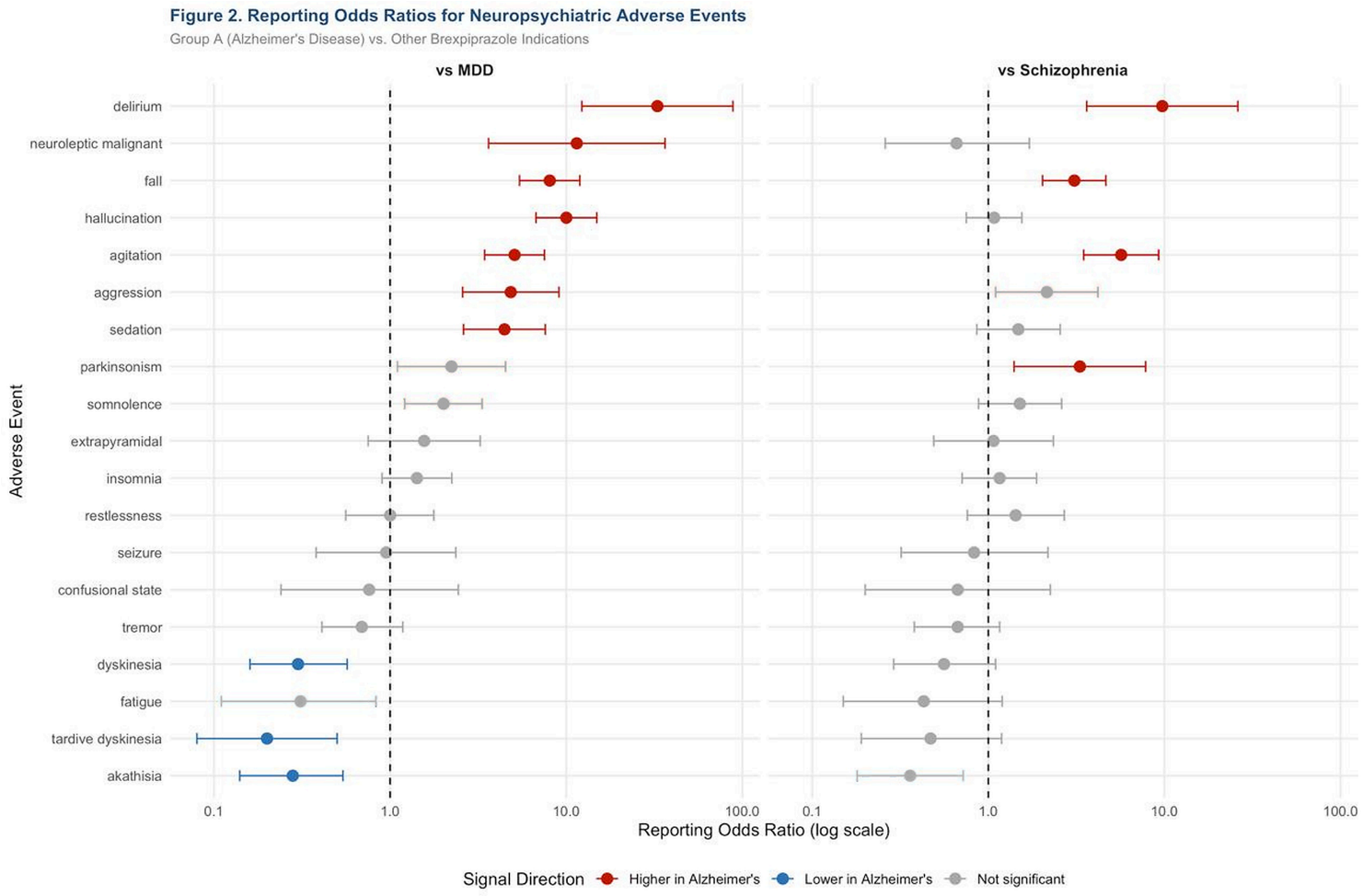
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# Figures



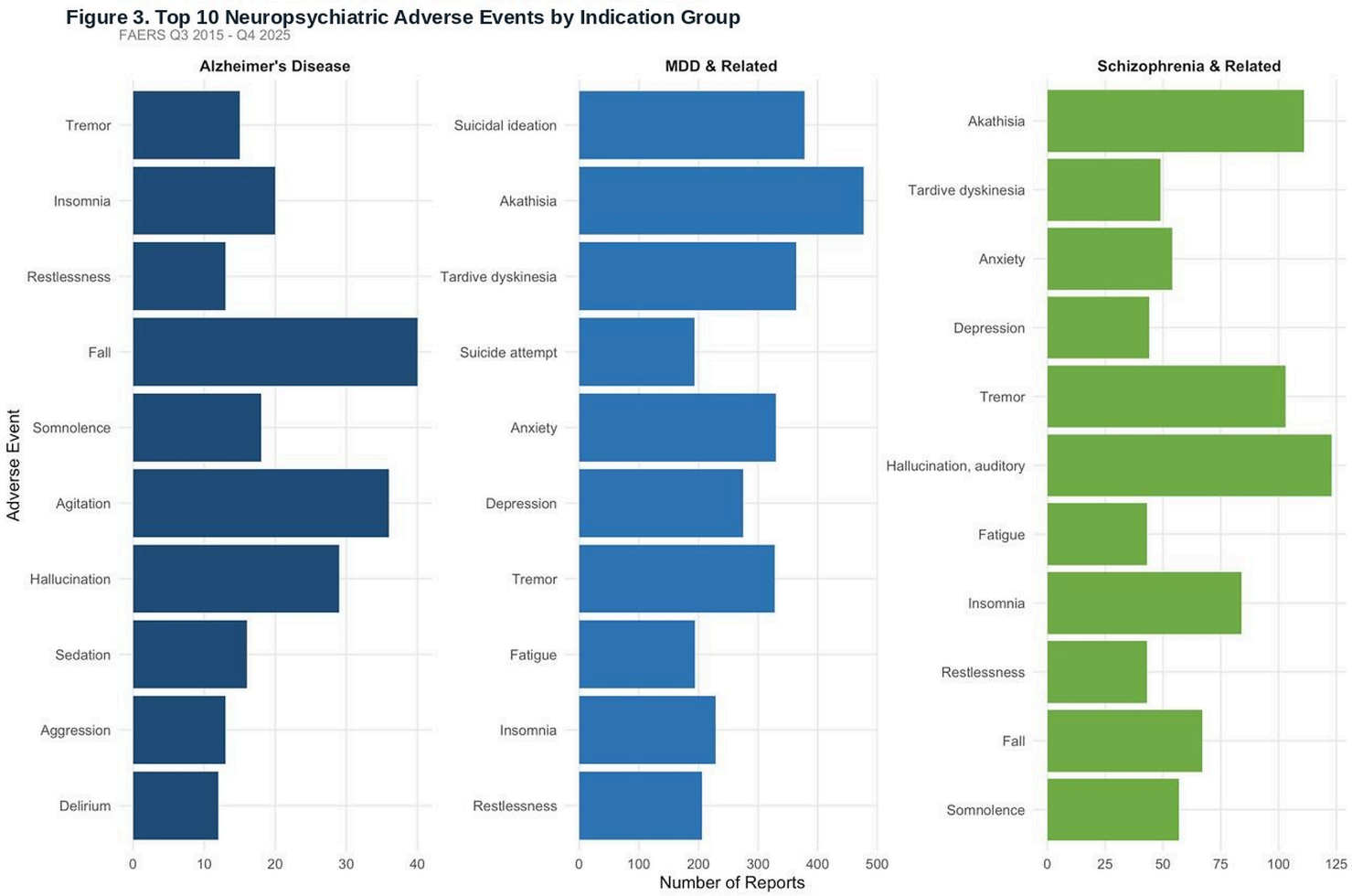

## Figure 1

Study flow diagram showing participant selection from the FDA Adverse Event Reporting System (FAERS). PS = primary suspect; SS = secondary suspect; ROR = reporting odds ratio; PRR = proportional reporting ratio; AE = adverse event. *FAERS DRUG files store one row per drug per case report; one case may contribute multiple rows. The reduction from 36,657 classified rows to 9,113 unique cases reflects collapsing to one case per indication group followed by removal of 108 duplicate case versions.



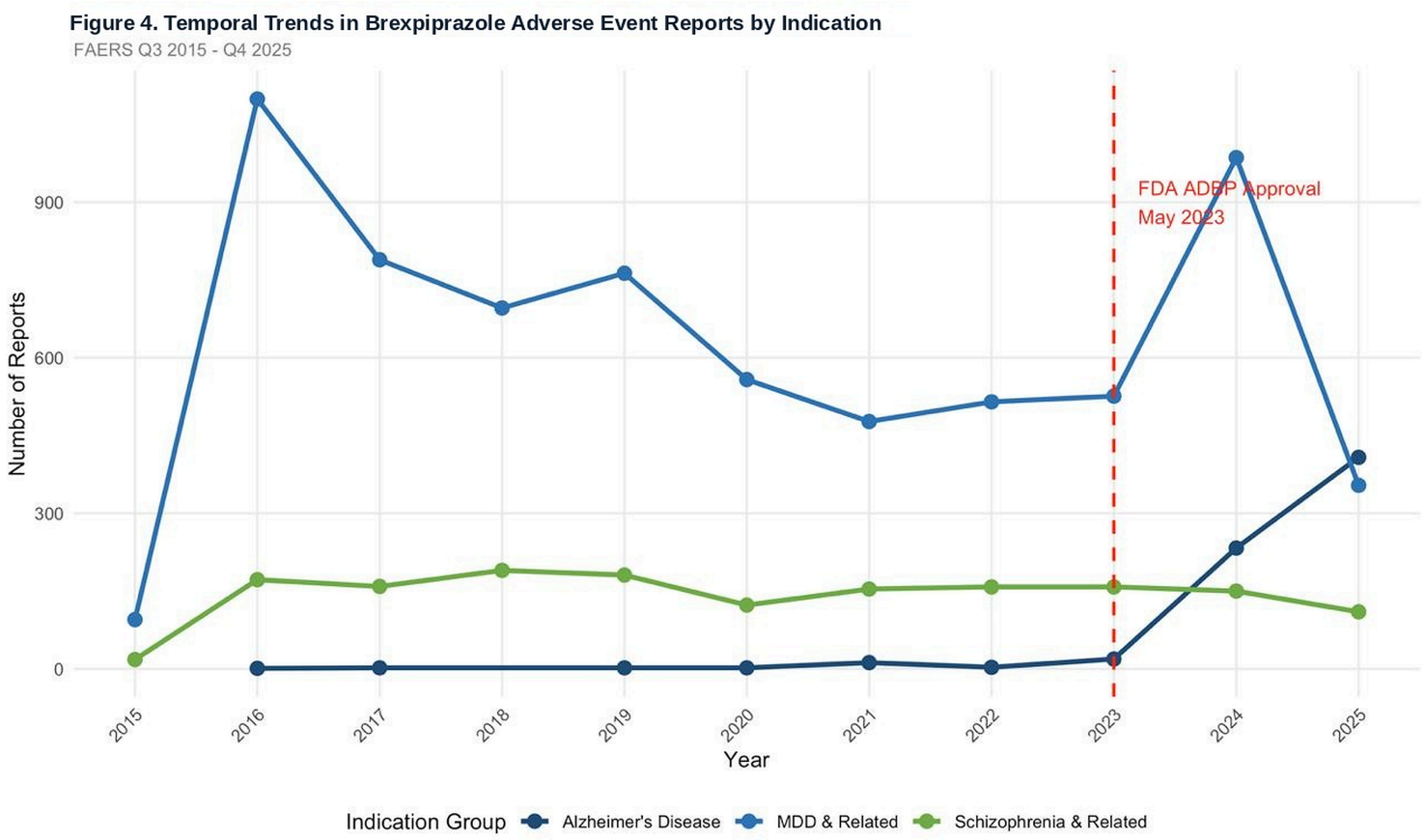

## Figure 2

Forest plot showing Reporting Odds Ratios (ROR) with 95% confidence intervals for neuropsychiatric adverse events in Group A (Alzheimer’s disease) versus Group B (MDD and related disorders) and Group C (Schizophrenia and related disorders). Red circles indicate signals significantly higher in Alzheimer’s disease; blue circles indicate signals significantly lower; gray circles indicate non-significant associations. Dashed vertical line represents ROR=1.0 (no disproportionality). X-axis is on a log scale. All signals shown survived Bonferroni correction ($p<0.002$) unless otherwise indicated.




## Figure 3

Top 10 neuropsychiatric adverse events by indication group. Bar charts show the number of reports for each adverse event in Group A (Alzheimer’s disease, dark blue), Group B (MDD and related disorders, light blue), and Group C (Schizophrenia and related disorders, green). Note that x-axis scales differ across panels to allow visualization of Group A findings.




## Figure 4

Temporal trends in brexpiprazole adverse event reports by indication group, FAERS Q3 2015 – Q4 2025. The dashed vertical red line indicates the May 2023 FDA approval of brexpiprazole for agitation associated with Alzheimer’s disease (ADBP). Group A (Alzheimer’s disease, dark blue), Group B (MDD and related disorders, light blue), Group C (Schizophrenia and related disorders, green). The crossover of Group A above Group B in 2025 reflects a rapid increase in FAERS reporting for the Alzheimer’s indication.