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RESEARCH

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A pharmacovigilance study of olanzapine/samidorphan based on FDA Adverse Event Reporting System (FAERS)

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Abstract

Objects The olanzapine/samidorphan (OLZ/SAM) combination is being regarded as a new strategy to combat weight gain induced by olanzapine (OLZ), and its safety is of significant concern. Specifically, as samidorphan is an opioid receptor-related drug, issues related to its potential for dependence and withdrawal symptoms deserve attention. This study aims to provide a comprehensive analysis of adverse events (AEs) associated with the OLZ/SAM.

Methods This study is a pharmacovigilance study based on the analysis of reports from the FDA Adverse Event Reporting System (FAERS) utilizing the Openvigil online analysis platform for the period from January 1, 2023, to June 30, 2024. Signal results were reported as Reporting Odds Ratios (ROR) along with 95% confidence intervals. A binary logistic regression model was used to analyze the association between the OLZ/SAM and specific AEs.

Results This study included 86 reports of AEs associated with the OLZ/SAM and 4,678 reports related to OLZ. In terms of frequency of OLZ/SAM-related AEs, off-label use ($N=12$) and drug withdrawal syndrome ($N=11$) were reported most frequently. Among various system organ classes, the highest frequency of AEs was observed in neurological disorders (SOC) ($N=23$). We identified 15 signals associated with the OLZ/SAM. The results of the stepwise regression analysis indicated that in all models, the OLZ/SAM was significantly associated with drug withdrawal syndrome when compared to OLZ ($p<0.01$).

Conclusion The long-term safety of the OLZ/SAM warrants attention, particularly concerning drug withdrawal syndrome.

Keywords Olanzapine, Samidorphan, Adverse event, Drug withdrawal syndrome, Pharmacovigilance study

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Introduction

Olanzapine (OLZ) is a commonly used second-generation antipsychotic (SGA) worldwide, noted for its lower rate of discontinuation compared to other first-line SGAs in long-term studies [1, 2]. Considering of weight gain and other metabolic adverse effect induced by OLZ, the utilization was declined from 2005 to 2014 in the USA, in addition to be relegated to second-line SGA by Schizophrenia Patient Outcomes Research Team (PORT) in 2010 [3, 4]. The tendency was also echoed in European, Asian, and South American such as Denmark and Turkey, however, except China where the amount of prescription of olanzapine remained to be the second most among SGAs according to a national survay [5].

Samidorphan (SAM) is a novel opioid antagonist. Preclinical studies have demonstrated that the opioid system plays a crucial role in regulating food reward, feeding behavior, and metabolism [6–8]. The combination drug formulation of OLZ plus SAM is designed to provide the antipsychotic efficacy of OLZ while mitigating weight gain and associated metabolic abnormalities. A 4-week Phase 3 study demonstrated that the OLZ/SAM significantly improved overall PANSS and CGI-S scores compared to placebo, while also reducing weight gain relative to OLZ alone [4]. Both systematic reviews and evidence-based analyses of clinical trials have also demonstrated that OLZ/SAM is comparably effective to OLZ while exhibiting better tolerability regarding weight gain [9, 10]. The open-label randomized controlled trial (RCT) indicated that potential adverse effects of OLZ/SAM may include drowsiness and altered taste, among others [11]. However, there is limited information regarding other adverse effects of the OLZ/SAM. Given that OLZ/SAM interacts with opioid receptors, clinicians may express concerns about opioid receptor-related issues such as dependence, drug withdrawal, and other related effects. Currently, our understanding of the adverse reactions associated with OLZ/SAM remains insufficiently comprehensive.

The FDA approved OLZ/SAM in May 2021 for the treatment of schizophrenia and bipolar I disorder in adults [12, 13]. Currently, our understanding of the safety profile of this combination is not complete. Pharmacovigilance studies based on the FAERS database are essential for gaining a comprehensive understanding of adverse drug reactions and can provide valuable references for further mechanistic research and clinical practice [14, 15]. The objective of this study is to comprehensively evaluate the safety of the OLZ/SAM.

Methods

Data source

The data for this study were sourced from the OpenVigil website (https://openvigil.sourceforge.net/). OpenVigil is an open, online analysis platform based on the FDA Adverse Event Reporting System (FAERS). This study downloaded all reports related to drug name of "olanzapine/samidorphan" and "olanzapine" from January 1, 2023, to June 30, 2024.

Processing

According to the official website, OpenVigil has cleaned and processed the FAERS data, which includes removing duplicate reports and merging multiple files. We included reports where the role_code was listed as the primary suspect (PS) or the second suspect (SS), and where the patients were older than 18 years of age. We extracted demographic information, prognosis, adverse events, drug information, and indications from the reports for further analysis. Adverse events (AEs) were identified by preferred terms, which were coded using MedDRA version 24.1.

Statistics

Measurement data are presented as means and standard deviations (SD), while categorical data are expressed as counts and percentages. The relative odds ratio (ROR) and 95% confidence interval (CI) were calculated to assess disproportionality between cases and non-cases. To further investigate the association between the OLZ/SAM and AEs, and to compare it specifically with OLZ, reports involving both OLZ/SAM and OLZ were included. After adjusting for age, gender, indication, and reporter country, stepwise regression was employed to calculate the odds ratios (OR) for the association between the drugs and specific adverse events. The dosage of the study drug was not included in the analysis, as less than 50% of the reports contained complete dosage information.

Results

Characteristics of reports

This study included reports of 86 cases related to OLZ/SAM and 4,678 cases related to OLZ. Among the total reports, individuals aged 18–65 represented the majority—81.8% overall, 98.8% for OLZ/SAM, and 81.6% for OLZ. The proportion of female patients was higher in reports concerning OLZ/SAM compared to male patients (64.3% vs. 35.7%), whereas it was lower in reports for OLZ (43.4% vs. 55.0%). The United States, Canada, and France were the top three countries contributing to the OLZ-related reports. Since OLZ/SAM is available only in the United States, 98.9% of these reports originated from there, with one report missing the regional information. The most common indications for both OLZ and OLZ/SAM were bipolar disorder (5.7% and 27.9%, respectively) and schizophrenia (16.3% and 22.3%, respectively). Although OLZ/SAM has only been approved by the FDA

for the treatment of bipolar disorder and schizophrenia, there were 12 reports of off-label use. See Table 1 for further details.

Olanzapine/samidorphan associated adverse events

Among the 86 reports, 19 AEs, each with at least three reported cases, were identified. Figure 1A illustrates the various AEs and their corresponding frequencies. The reported frequency of off-label use and drug withdrawal syndrome exceeded 10 cases. The frequencies of adverse events related to contraindicated products, weight gain, sedation, and drug ineffectiveness were reported in decreasing order. Somnolence, lethargy, hyperhidrosis, and false-positive drug screen results were reported with a frequency of four cases each. Other reported adverse events included weight loss, nausea, muscle spasms, increased appetite, hypersomnia, dysarthria, dizziness, and elevated blood glucose levels. The frequency of increased aggression was reported in three cases. Figure 1B displays the log (ROR) and 95% confidence intervals for PTs, with the lower limits of 15 of the ROR95% confidence intervals exceeding 1. When comparing the same PT signals in OLZ (see supplementary materials, Table S1), we found that muscle spasms emerged as a positive signal in OLZ/SAM, whereas no such signal was observed for OLZ.

We categorized the 19 PTs into 10 different primary system organ classes (SOCs) and found that "Nervous system disorders" were the most frequently reported (see Fig. 2A, B). Five of the PTs are related to the nervous system, identified as sedation, lethargy, somnolence, dizziness, and dysarthria. Additionally, the SOCs for skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, gastrointestinal disorders, psychiatric disorders, and metabolism and nutrition disorders each contained only one PT.

Table 1 Characterization of the included reports

Characteristics	Total (*N* = 4764)	Olanzapine/Samidorphan (*N* = 86)	Olanzapine (*N* = 4678)
Age in report			
18–65	3898(81.8%)	82(98.8%)	3816(81.6%)
65+	866(18.2%)	4(1.2%)	862(18.4%)
Gender			
Male	2604(54.7%)	30(35.7%)	2574(55.0%)
Female	2085(43.8%)	54(64.3%)	2031(43.4%)
Unknown	75(1.6%)	2(2.4%)	73(1.6%)
Reporter country(top 3)			
	US, 968(20.3%)	US, 85(98.9%)	US, 883(18.9%)
	CA, 695(14.6%)	Unknown, 1(1.1%)	CA, 675(14.4%)
	FR, 451(9.5%)		FR, 451(9.6%)
Indication			
Bipolar disorder	291(6.1%)	24(27.9%)	267(5.7%)
Schizophrenia	1057(22.2%)	14(16.3%)	1043(22.3%)
Other mental illness	1720(36.1%)	12(14.0%)	1708(35.5%)
Unknown	1696(35.6%)	36(41.9%)	1660(35.5%)

The relationship between olanzapine/samidorphan and drug withdrawal syndrome

To further investigate whether the AE of drug withdrawal syndrome is associated with OLZ/SAM, we conducted a cross-sectional analysis that included all reports of OLZ/SAM and OLZ, totaling 4,764 reports. The results are presented in Table 2. In Model 1, without adjusting for covariates, we found a significant direct association between OLZ/SAM and drug withdrawal syndrome ($p < 0.01$). In Model 2, after adjusting for gender and age, the results continued to demonstrate a direct relationship between the combination and drug withdrawal syndrome ($p < 0.01$). Finally, in Model 3, after adjusting for all covariates, including gender, age, indication, and reporter country, the results still indicated a significant correlation between the combination and drug withdrawal syndrome ($p < 0.01$).

Discussion

In this pharmacovigilance study utilizing the FAERS database, we analyzed the AEs related to OLZ/SAM. We identified 19 OLZ/SAM-related AEs with more than 3 reports. Among these, 15 showed positive signals in the disproportionality analysis, including muscle spasms. Our further analysis found that OLZ/SAM was associated with drug withdrawal syndrome, which occurred at a higher incidence compared to OLZ. These findings provide additional references for researchers and clinicians.

Our study found that the AEs associated with OLZ/SAM was focused on nervous system disorders. Similar AEs (with the exception of dysarthria) were reported in an earlier randomized double-blind phase 2 study [11]. Furthermore, associations between OLZ/SAM and these AEs were also found in OLZ. Numerous studies have indicated that OLZ can result in side effects such as drowsiness [16, 17]. It is challenging to definitively attribute these nervous system adverse events to OLZ in the combination, as opposed to SAM. SAM functions as an opioid receptor inhibitor, specifically antagonizing μ-receptors while partially activating κ- and δ-receptors [18, 19]. Given its pharmacological properties, SAM may also induce a sedative effect through the activation of the κ-receptor. The comparison of the magnitude of risk for nervous system AEs between OLZ/SAM and OLZ requires further investigation.

After adjusting for covariates in our analysis, we found that OLZ/SAM had a higher proportion of reported drug

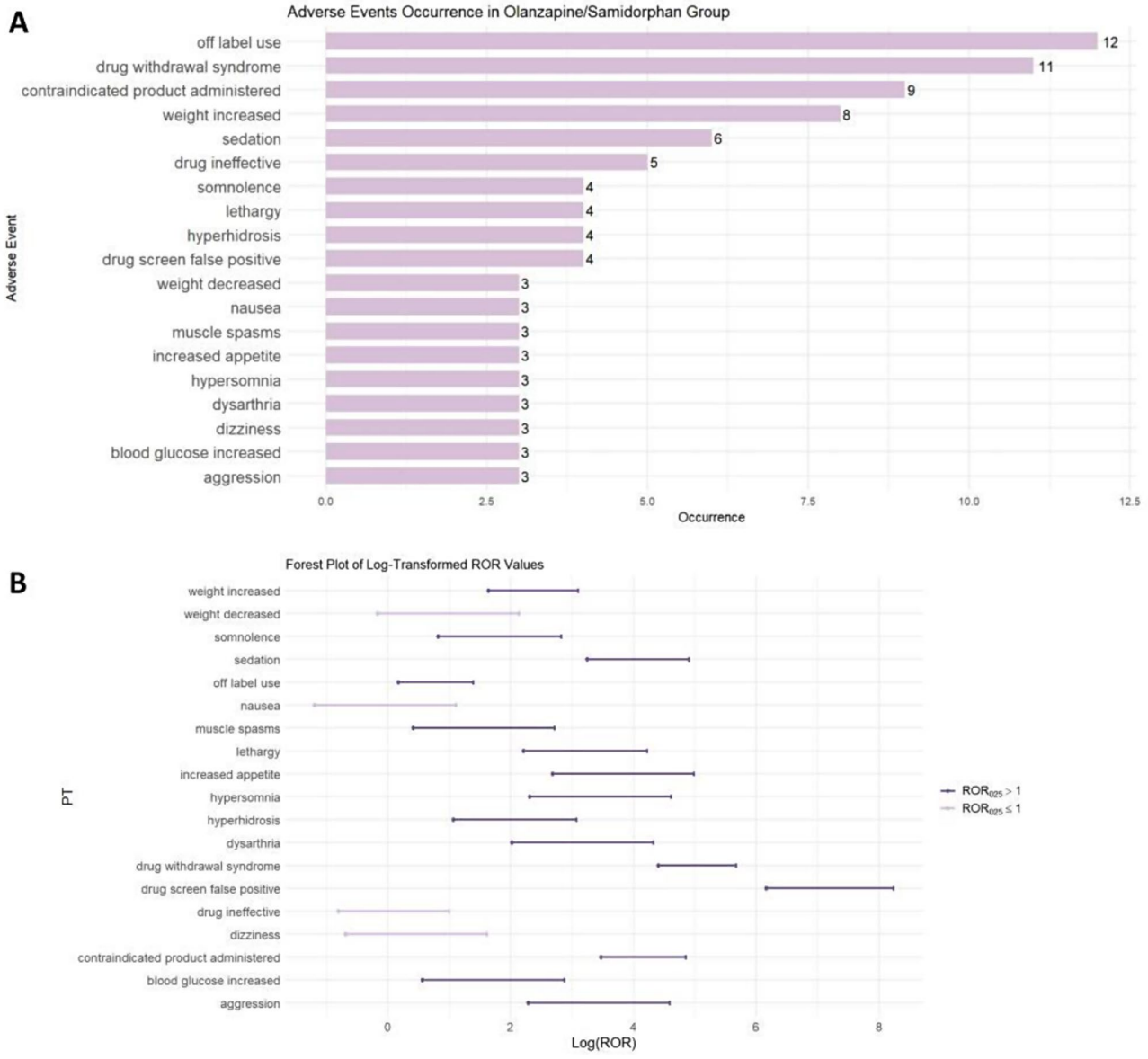

Fig. 1 Disproportional analysis of adverse events (AEs) in olanzapine/samidorphan. (**A**) Bar plot illustrates the number of adverse eventsassociated with the olanzapine/samidorphan combination. (**B**) The displays the log(ROR) and 95% confidence intervals (CIs) for adverse events (AEs) associated with the olanzapine/samidorphan combination. A lower bound of the ROR 95% confidence interval greater than 1 is represented in deep purple, while a lower bound that does not exceed 1 is shown in light purple

withdrawal syndromes compared to olanzapine. It may suggest that OLZ/SAM has a higher incidence of drug withdrawal syndrome than olanzapine. Withdrawal syndrome from OLZ may include symptoms such as psychiatric manifestations, neurological symptoms, cholinergic rebound, and movement disorders [20, 21]. Due to the limitations of the study itself, we do not have specific information regarding the manifestations and severity of withdrawal syndrome associated with OLZ/SAM.

Our study demonstrated an association between OLZ/SAM and muscle spasms. According to the drug labeling, muscle spasms associated with OLZ/SAM may be due to drug-induced extrapyramidal reactions [22]. However, we cannot rule out that muscle spasms may also be one manifestation of opioid withdrawal. A case report described a patient who experienced muscle spasms after taking OLZ/SAM [23]. Initially, clinicians suspected it to be an acute dystonic reaction to OLZ and administered treatment, but it was ineffective. Subsequently, they concluded that opioid withdrawal might be the underlying cause of the symptoms. Our study did not include information on other commonly used medications, and we could not determine whether patients were concurrently using other opioid substances. As a result, we are unable

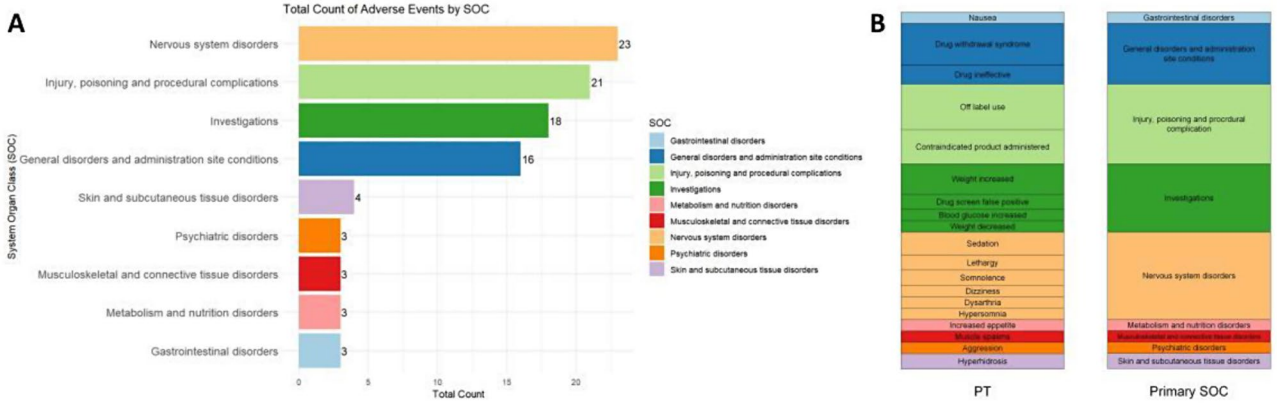

Fig. 2 Reports related to adverse events (AEs) associated with the olanzapine/samidorphan combination within various System Organ Classes (SOCs). (**A**) Bar plot illustrates the number of AEs related with the olanzapine/samidorphan combination, categorized by SOC. (**B**) Bar plot displays the preferred terms (PTs) and SOCs associated with AEs related to the olanzapine/samidorphan combination. The colors represent the relationships between different PTs and SOCs

Table 2 Analysis the association between olanzapine/samidorphan and drug withdrawal reactions

	OR (95%CI), *p* value					
	Model 1		**Model 2**		**Model 3**	
	OR (95%CI)	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**
Drug						
Olanzapine	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Olanzapine/Samidorphan	**20.64 (9.64, 41.22)**	**<0.01***	**23.64 (10.82, 48.60)**	**<0.01***	**27.24 (10.27, 75.39)**	**<0.01***
Age in report			0.99 (0.98, 1.01)	0.56	0.99 (0.97, 1.01)	0.29
Gender						
Female			1 (Ref.)		1 (Ref.)	
Male			2.08 (1.09, 4.17)	<0.05	1.99 (1.03, 4.00)	<0.05
Unknown			1.98 (0.10, 10.93)	0.53	1.69 (0.09, 9.99)	0.63
Indication						
Bipolar disorder					1 (Ref.)	
Schizophrenia					2.25e + 06 (0.00, 7.06e + 82)	0.98
Other mental illness					9.80e + 06 (0.00, 1.20e + 87)	0.98
Unknown					6.14e + 06 (0.00, 1.19e + 90)	0.98
Reporter country						
Non-US					1 (Ref.)	
US					1.43 (0.60, 3.04)	0.38

* The adjusted *p*-value is < 0.05, determined using the Benjamini-Hochberg (BH) method

OR: odds ratio. 95% CI: 95% confidence interval

Model 1: no covariates were adjusted

Model 2: adjusted for age, gender

Model 3: adjusted for age, gender, indication and reporter country

to further exclude the effects of these other drugs, which represents a limitation of our research.

Opioid use disorder remains one of the most concerning AEs associated with opioid receptor-related medications. Although the pharmacological properties of SAM, which include antagonizing μ-receptors while partially activating κ- and δ-receptors, may contribute to its lower potential for dependence and drug withdrawal symptoms compared to conventional opioid medications, there are still concerns regarding its long-term safety. Several case reports have documented instances of drug withdrawal syndrome associated with SAM in combination with other medications [24, 25]. Further investigation is required to determine the underlying mechanisms that contribute to the occurrence of withdrawal reactions, specifically whether they relate to the combination of particular drugs and their respective dosages. We are currently unable to further explain our findings, as the number of covariates included in our study was limited, and the events observed were relatively few. We hope that our results will garner sufficient attention regarding the long-term safety of OLZ/SAM, particularly concerning drug withdrawal syndrome.

Additionally, no association was found between OLZ/SAM and cardiovascular AEs. Previous studies have indicated that OLZ may carry some risk of cardiovascular toxicity [26]. An pharmacovigilance study based on FAERS found that OLZ was associated with prolonged QT intervals on the electrocardiogram [27]. In our research, we did not observe any cardiovascular event-related AEs associated with OLZ/SAM, including QT prolongation. This finding is consistent with the results of a thorough QT (TQT) study of OLZ/SAM, which also indicated that OLZ/SAM did not show significant QT prolongation [28]. It is hypothesized that that SAM may mitigate factors contributing to cardiovascular events, such as obesity and metabolic abnormalities.

This study has several limitations. First, our research is based on data from the FAERS and relies on the Openvigil online analysis platform for data cleaning. Common limitations of spontaneous reporting studies, such as missing data and duplicate reports, also affect our research [29, 30]. Openvigil employs standardized data quality and cleaning procedures, enhancing the reproducibility and robustness of findings in such studies [31]. Second, we did not include a sufficient number of covariates in our regression analysis. Although dosage plays a crucial role in the occurrence of adverse events, we could not incorporate it into the adjustments due to significant missing data. Additionally, we were unable to adjust for variables related to disease severity and compliance, as these data were either unavailable or severely lacking in the database. Finally, our study only compared OLZ/SAM to OLZ, without comparing it to other antipsychotic medications. We believe that the most important aspect is to compare the safety of OLZ/SAM, as an alternative solution to counteract OLZ-induced weight gain, with the safety of OLZ itself. This comparison represents the primary objective of our study.

Conclusion

Based on our analysis of adverse event reports related to OLZ/SAM in the FAERS database, we found that OLZ/SAM may have a higher risk of drug withdrawal syndrome compared to OLZ. Clinicians should take this into careful consideration when contemplating OLZ/SAM as a substitute for OLZ. Furthermore, the long-term safety of OLZ/SAM warrants continued attention.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00869-4.

Supplementary Material 1

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The for this study were sourced from the FAERS database and analyzed using the Openvigil online analysis platform for disproportionality analysis. The information, results, or interpretations presented in this study do not reflect any opinions of the FDA or Openvigil.

Author contributions

Luyao He, Lei Zhang, Mengting Shen, Yan Li and Huafang Li participated in the conception and design of the work; Luyao He, Mengting Shen and Yan Li did the data analysis; Lei Zhang, Yan Li and Huafang Li validated the data; Luyao He wrote the first draft; All authors had the final responsibility for the decision to submit for publication.

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Data availability

The data for this study are available from OpenVigil at https://openvigil.sourceforge.net.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Financial disclosure

Not applicable.

Competing interests

The authors declare no competing interests.

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