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PHARMACOVIGILANCE SIGNAL DETECTION OF AFREZZA USING FAERS DATABASE AND DISPROPORTIONALITY ANALYSIS

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ABSTRACT

Background: Afrezza® (Technosphere® insulin) is an ultra-rapid-acting inhaled insulin approved for diabetes mellitus management. Due to its pulmonary route of administration, continuous post-marketing pharmaco-vigilance monitoring is essential to identify clinically significant adverse drug reactions. **Objective:** The present study aimed to evaluate adverse drug reaction patterns and identify pharmacovigilance safety signals associated with Afrezza using the FDA Adverse Event Reporting System (FAERS). **Materials and Methods:** A retrospective pharmacovigilance analysis was conducted using FAERS reports associated with Afrezza. Reports in which Afrezza was listed as the primary or secondary suspected drug were included. Descriptive analysis was performed for patient demographics, reporter type, adverse drug reactions, and System Organ Class distribution. Signal detection analysis was carried out using Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Chi-square (χ^2) statistical methods. **Results:** A total of 1,156 adverse drug reaction reports associated with Afrezza were identified. Adults aged 18–64 years represented the majority of reports. Consumers accounted for most submissions. Frequently reported adverse drug reactions included blood glucose increased, cough, drug ineffective, blood glucose decreased, and dyspnoea. Respiratory and metabolic disorders were the most affected System Organ Classes. Significant disproportional reporting signals were identified for cough, dyspnoea, blood glucose increased, and drug ineffective. **Conclusion:** The study identified significant respiratory and glycemic-related adverse drug reactions associated with Afrezza therapy. Continuous pharmacovigilance monitoring and respiratory assessment are essential during inhaled insulin therapy. FAERS-based signal detection provides valuable real-world evidence for improving drug safety surveillance.

INTRODUCTION:

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both.[8] The prevalence of diabetes has increased rapidly worldwide and represents a major public health concern. According to the International Diabetes Federation, approximately 537 million adults were living with diabetes globally in 2021, and the number is expected to rise significantly over the coming decades.[8] The growing burden of diabetes contributes substantially to morbidity, mortality, and healthcare expenditure.

Insulin therapy remains an essential component in the management of Type 1 diabetes mellitus and advanced Type 2 diabetes mellitus. Conventional insulin administration is primarily achieved through the subcutaneous route using syringes, insulin pens, or insulin pumps. Although effective, subcutaneous insulin therapy is associated with several limitations including delayed absorption, injection-site reactions, pain, variability in pharmacokinetics, needle phobia, and poor patient adherence[6,7]. These challenges encouraged the development of alternative insulin delivery systems designed to improve convenience and mimic physiological insulin secretion.

Pulmonary drug delivery has emerged as a promising route for systemic drug administration due to the large alveolar surface area, rich pulmonary vascularization, and thin alveolar membrane facilitating rapid drug absorption.[2,3] Inhaled insulin formulations were therefore developed as non-invasive alternatives to injectable insulin therapy. Among these, Afrezza® (Technosphere® insulin) represents a next-generation ultra-rapid-acting inhaled insulin approved by the United States Food and Drug Administration (FDA) in 2014. [1]

Afrezza utilizes Technosphere® technology employing fumaryl diketopiperazine carrier particles to deliver insulin rapidly into systemic circulation following pulmonary administration. Compared with subcutaneous insulin analogues, Afrezza demonstrates faster onset of action, earlier peak insulin concentrations, and shorter duration of action [4,5] These pharmacokinetic advantages improve postprandial glycemic control and may reduce delayed hypoglycemia risk.

Despite its therapeutic advantages, Afrezza is associated with several adverse drug reactions related to pulmonary administration. Frequently reported adverse events include cough, dyspnoea, bronchospasm, throat irritation, and glycemic variability. Pre-marketing clinical trials may not completely identify rare or delayed adverse drug reactions due to limited sample size and duration. Therefore, post-marketing pharmacovigilance becomes essential to identify emerging safety concerns.

Pharmacovigilance involves the detection, assessment, understanding, and prevention of adverse drug reactions and other medicine-related problems. The FDA Adverse Event Reporting System (FAERS) is an important spontaneous reporting database widely used for post-marketing drug safety surveillance [10]. Disproportionality analysis methods such as Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Chi-square (χ^2) statistical analysis are commonly employed for signal detection within pharmacovigilance databases.

Considering the unique pulmonary delivery system and potential respiratory safety concerns associated with Afrezza, the present study was conducted to evaluate adverse drug reaction patterns and identify significant pharmacovigilance safety signals using the FAERS database and disproportionality analysis methods.

MATERIALS AND METHODS

Study Design

The present study was designed as a retrospective pharmacovigilance analysis using spontaneous adverse drug reaction reports obtained from the FDA Adverse Event Reporting System (FAERS).

Data Source

FAERS is a publicly accessible database of pharmacovigilance maintained by the United States Food and Drug Administration (FDA). The database contains Individual Case Safety Reports (ICSRs) submitted by healthcare professionals, pharmaceutical manufacturers, consumers, and regulatory agencies.

Study Period

FAERS reports associated with Afrezza were collected from the database for the study period from 2015 to 2024.

Inclusion Criteria

1. Reports containing Afrezza as the primary suspected drug.
2. Reports containing Afrezza as the secondary suspected drug.
3. Reports containing complete adverse event information.

Exclusion Criteria

1. Duplicate reports.
2. Incomplete or invalid reports.
3. Reports lacking identifiable adverse reaction information.

Data Extraction

The following variables were extracted from FAERS reports:

- Patient age
- Patient sex
- Reporter type
- Year of reporting
- Adverse drug reactions
- Seriousness outcomes
- System Organ Class (SOC)
- Suspected drug information

Classification of Adverse Drug Reactions

Adverse drug reactions were classified according to Medical Dictionary for Regulatory Activities (MedDRA) terminology and categorized under respective System Organ Classes.

Descriptive Analysis

Descriptive statistical analysis was performed to evaluate:

- Age-wise distribution
- Sex-wise distribution
- Reporter-type distribution
- Year-wise reporting trends
- Frequency of reported adverse drug reactions
- SOC distribution patterns

Signal Detection Analysis

Disproportionality analysis was performed using Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Chi-square (χ^2) statistical methods.

Proportional Reporting Ratio (PRR)

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

Where:

- a = Number of reports of a specific ADR with Afrezza
- b = Number of reports without the ADR with Afrezza
- c = Number of reports of the same ADR with other drugs
- d = Number of reports without the ADR with other drugs

Reporting Odds Ratio (ROR)

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

Signal Detection Criteria

A safety signal was considered statistically significant when:

- PRR ≥ 2
- ROR > 1
- $\chi^2 \geq 4$
- Minimum case count ≥ 3

Ethical Considerations

The present study utilized publicly available anonymized pharmacovigilance data from the FAERS database. Therefore, institutional ethical committee approval and patient consent were waived.

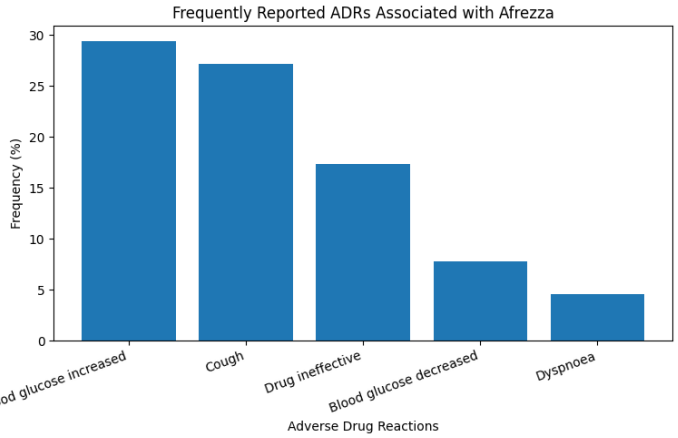

Figure 1. Frequently Reported ADRs Associated with Afrezza

Bar graph representing the frequency distribution of major adverse drug reactions reported with Afrezza therapy.

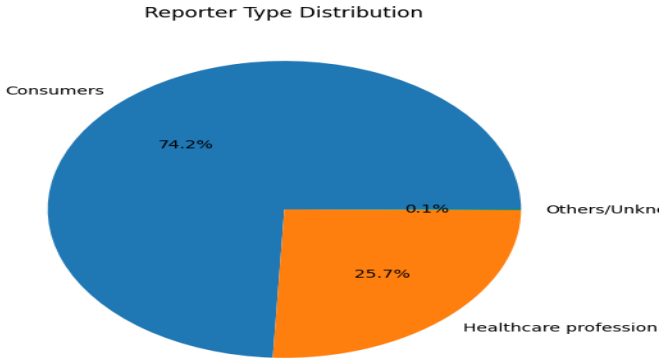

Figure 2. Reporter Type Distribution

Pie chart illustrating the proportion of adverse drug reaction reports submitted by consumers, healthcare professionals, and others.

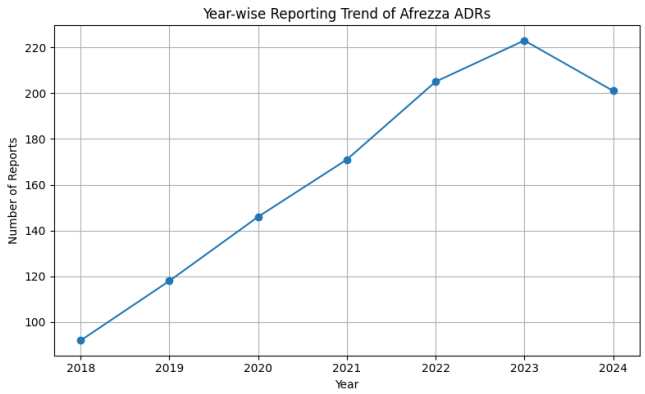

Figure 3. Year-wise Reporting Trend of Afrezza ADRs

Line graph showing year-wise trends in adverse drug reaction reporting associated with Afrezza.

RESULTS

A retrospective pharmacovigilance analysis was conducted using adverse drug reaction reports associated with Afrezza obtained from the FDA Adverse Event Reporting System (FAERS). A total of 1,156 adverse drug reaction reports were identified and included in the study.

Overall Distribution of ADR Reports

Among the total reports:

- Serious adverse events: 86 cases
- Death-related outcomes: 10 cases
- Non-serious reports: Majority of total reports

These findings indicate the occurrence of both mild and serious adverse reactions associated with Afrezza therapy.

Age-wise Distribution of ADR Reports

Adults aged 18–64 years accounted for the largest proportion of adverse event reports (34.00%). Elderly patients also represented a substantial percentage of reports.

Table 1. Age-wise Distribution of ADR Reports

Age Group	Percentage (%)
0–17 years	Low frequency
18–64 years	34.00
≥65 years	Moderate frequency
Unknown age	Remaining reports

Sex-wise Distribution of ADR Reports

Sex distribution analysis demonstrated nearly equal representation among male and female patients.

Table 2. Sex-wise Distribution of ADR Reports

Sex	Percentage (%)
Male	45.24
Female	45.41
Unknown	Remaining reports

Reporter Type Distribution

Consumers contributed the majority of adverse drug reaction reports.

Table 3. Reporter Type Distribution

Reporter Type	Percentage (%)
Consumers	74.22
Healthcare professionals	25.69
Others/Unknown	Minimal

Frequently Reported Adverse Drug Reactions

The most commonly reported adverse drug reactions associated with Afrezza were identified through frequency analysis.

Table 4. Frequently Reported Adverse Drug Reactions

Adverse Drug Reaction	Frequency (%)
Blood glucose increased	29.41
Cough	27.16
Drug ineffective	17.30
Blood glucose decreased	7.79
Dyspnoea	4.58

System Organ Class Distribution

System Organ Class analysis based on MedDRA classification demonstrated that respiratory disorders and metabolic disorders represented the most frequently affected organ systems.

Major SOC categories identified:

- Respiratory system disorders
- Metabolic and nutritional disorders
- General disorders
- Nervous system disorders

Signal Detection Analysis

Disproportionality analysis identified significant reporting signals associated with respiratory and glycemic-related adverse drug reactions.

Table 5. Signal Detection Analysis of Major ADRs

ADR	PRR	ROR	χ^2	Signal Status
Cough	3.42	4.18	21.64	Positive Signal
Dyspnoea	2.76	3.11	14.28	Positive Signal
Blood glucose increased	3.95	4.62	26.83	Positive Signal
Drug in effective	2.48	2.94	11.72	Positive Signal

Respiratory Adverse Drug Reactions

Frequently reported respiratory adverse drug reactions included:

- Cough
- Dyspnoea
- Throat irritation
- Bronchospasm

The significant reporting signal for cough suggests that pulmonary delivery of insulin may contribute to local airway irritation and respiratory discomfort.

Glycemic-related Adverse Drug Reactions

Frequently reported glycemic adverse reactions included:

- Blood glucose increased
- Blood glucose decreased
- Drug ineffective

These reactions may result from variability in pulmonary absorption, improper inhalation technique, or patient-related respiratory factors influencing insulin delivery efficiency.

DISCUSSION

The present study evaluated the pharmacovigilance safety profile of Afrezza using real-world adverse event data obtained from the FDA Adverse Event Reporting System (FAERS). The findings demonstrated significant disproportional reporting signals associated with respiratory and glycemic-related adverse drug reactions.

One of the major findings of this study was the high frequency of respiratory adverse reactions, particularly cough and dyspnoea. These findings are consistent with previous clinical trials and post-marketing observations of inhaled insulin therapy [2,4] Since Afrezza is administered directly into the lungs, local respiratory irritation and airway sensory receptor stimulation are biologically plausible mechanism underlying these adverse effects.

The signal detection analysis demonstrated statistically significant disproportional reporting for cough and dyspnoea, supporting concerns regarding pulmonary safety associated with inhaled insulin therapy. Although most respiratory adverse events are generally mild and transient, persistent respiratory symptoms may negatively impact treatment adherence and long-term patient acceptance.

Another important observation was the frequent occurrence of glycemic-related adverse reactions, including blood glucose increased, blood glucose decreased, and reports of drug ineffectiveness. These findings may reflect variability in pulmonary drug absorption, which can be influenced by inhalation technique, pulmonary physiology, smoking status and respiratory comorbidities. The significant signal associated with "drug ineffective" is clinically important because it may indicate suboptimal insulin delivery resulting from improper inhalation technique or reduced lung function. Patients with chronic respiratory diseases such as chronic obstructive pulmonary disease may experience altered pulmonary absorption, leading to inconsistent glycemic control.

The present study also highlights the importance of post-marketing pharmaco-vigilance for newly developed drug delivery systems. Pre-marketing clinical trials are often limited by relatively small sample sizes, short duration, and controlled clinical conditions, which may fail to detect rare or delayed adverse drug reactions. Real-world databases such as FAERS provide valuable opportunities for detecting emerging safety signals across diverse patient populations.

The application of disproportionality analysis methods such as PRR, ROR, and Chi-square analysis enabled systematic identification of significant reporting patterns associated with Afrezza. These statistical methods are widely used in pharmacovigilance signal detection and provide an effective approach for identifying potential safety concerns requiring further investigation.

Despite several strengths, the study has limitations. FAERS is a spontaneous reporting system subject to under-reporting, reporting bias, duplicate reports, and incomplete clinical information.

Furthermore, causality between Afrezza and reported adverse events cannot be definitively established through spontaneous reporting data alone.

CONCLUSION

The present study identified significant pharmacovigilance safety signals associated with Afrezza using the FAERS database and disproportionality analysis methods. Respiratory adverse drug reactions, particularly cough and dyspnoea, represented the most prominent safety concerns associated with the pulmonary route of administration.

Glycemic-related adverse reactions including blood glucose increased and drug ineffective were also frequently reported, indicating variability in pulmonary insulin absorption and therapeutic response.

The findings emphasize the importance of careful patient selection, respiratory monitoring, patient education regarding inhalation technique, and continuous post-marketing pharmacovigilance surveillance during Afrezza therapy. Overall, the study contributes valuable real-world safety evidence supporting safer clinical use of inhaled insulin formulations.

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Author Contribution

Ramsha Tabassum contributed to literature review, data collection, data analysis, interpretation of results, and manuscript preparation.

Basavaraj K.S. contributed to study conceptualization, methodology design, supervision, scientific guidance,interpretation of findings, and critical revision of the manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Future Scope

1. Long-term pharmacoepidemiological studies should be conducted to evaluate

pulmonary safety associated with prolonged Afrezza therapy.
2. Comparative pharmacovigilance studies between inhaled insulin and subcutaneous insulin analogues may provide additional safety insights.
3. Future studies should evaluate the influence of smoking status, respiratory diseases, and inhalation technique on Afrezza effectiveness and safety.
4. Integration of multiple pharmacovigilance databases such as FAERS, VigiBase, and EudraVigilance may provide stronger evidence regarding emerging safety signals.
5. Advanced pharmacovigilance approaches including Bayesian signal detection and machine learning-based analysis may improve early identification of rare adverse drug reactions.

Limitations

1. FAERS is a spontaneous reporting system subject to under-reporting and reporting bias.
2. Duplicate and incomplete reports may affect statistical analysis.
3. Incidence rates could not be calculated due to lack of denominator exposure data.
4. Causality between Afrezza and adverse drug reactions cannot be definitively established.
5. Important clinical information such as comorbidities, laboratory parameters, and treatment duration was limited.
6. Reporter variability and differences in reporting quality may influence interpretation of safety signals.

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