

ASSESSMENT OF NEUROPSYCHIATRIC ADVERSE DRUG REACTIONS ASSOCIATED WITH MONTELUKAST: A PHARMACOVIGILANCE DATABASE STUDY

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1.ABSTRACT

Montelukast is a leukotriene receptor antagonist, which is used to treat asthma, allergic rhinitis and exercise induced bronchospasm. The medicine is viewed as effective and is widely used, but rising reports of neuropsychiatric adverse drug reactions have raised concerns about its safety profile. Several post-marketing reviews and regulatory safety warnings have noted the potential link between montelukast and psychiatric adverse effects. The present study was designed to assess the neuropsychiatric adverse medication events related to montelukast by using pharmacovigilance data from the WHO VigAccess database. A retrospective observational study was conducted to collect and analyze reported neuropsychiatric adverse events associated with montelukast medication. Reported side effects included anxiety, sadness, sleeplessness, nightmares, hostility, irritability, hallucinations and suicide ideation. Descriptive statistical analysis was applied to estimate

the frequency and distribution of the reported adverse events. Insomnia (22.7%) and anxiety (20.3%) were the most commonly reported neuropsychiatric adverse medication reactions, followed by depression (16.0%) and nightmares (14.1%). Severe psychiatric adverse effects, such as hallucinations and suicidal ideation, were reported less frequently but were clinically

relevant. The findings of this study echo prior indications that there may be an association between montelukast use and neuropsychiatric side effects. The study highlights the necessity of continued pharmacovigilance, adequate patient counseling and early detection of psychiatric problems during montelukast medication. Increased understanding of these adverse effects among health care providers may help enhance patient safety and appropriate usage of montelukast.

KEYWORDS: Adverse drug reactions, Asthma, Drug safety, Leukotriene receptor antagonist, Neuropsychiatric adverse drug responses, Pharmacovigilance.

2. INTRODUCTION

Montelukast is a selective leukotriene receptor antagonist (LTRA) often used for asthma, allergic rhinitis and exercise induced bronchospasm. It works by inhibiting the cysteinyl leukotriene receptors, therefore decreasing airway inflammation, bronchoconstriction, mucus secretion, and allergic responses. Montelukast is widely utilized in clinical practice due to its oral administration, strong patient compliance and efficacy in both adults and children. It is primarily indicated for prophylactic and long-term management of asthma, avoidance of exercise-induced bronchospasm, and treatment of seasonal and perennial allergic rhinitis, particularly in individuals who are not effectively controlled with conventional medications.^[1,2]

Montelukast has therapeutic value, however in recent years, there have been increasing concerns over the safety profile of montelukast, particularly with relation to neuropsychiatric adverse drug events (ADRs). Neuropsychiatric ADRs are psychiatric or neurological symptoms that arise after drug administration and may impair the quality of life of a patient and treatment adherence. The following neuropsychiatric problems have been reported in patients treated with montelukast in post-marketing reports and clinical studies: anxiety, depression, sleeplessness, nightmares, irritability, aggression, hallucinations, behavioral changes, and suicidal ideation. These side effects have been observed in montelukast medication in adult and pediatric patients. These psychiatric signs are unpredictable and may be severe, and clinical attention to the safety of montelukast has grown. Regulatory agencies, such as the United States Food and Drug Administration (FDA) and the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), have also issued safety communications emphasizing the need for monitoring of neuropsychiatric symptoms in patients receiving montelukast.^[3-5]

Pharmacovigilance plays a significant role in detecting, assessing, analyzing, and preventing adverse drug reactions and other drug-related disorders. Continuous monitoring of adverse drug reactions (ADRs) is conducted via spontaneous reporting systems and international safety databases, which allows for the detection of rare and major adverse effects that could not be thoroughly assessed during the clinical trial phase. However, underreporting of ADRs is a serious concern in pharmacovigilance practice and might impair the proper risk assessment. WHO VigiAccess offers valuable information on worldwide adverse drug reaction data and helps to uncover patterns of drug safety signals. In 2020, after assessing reports of significant mental health adverse effects, including suicide thoughts and behaviors, the FDA added a boxed warning to reinforce existing safety warnings for montelukast. The warning urged vigilance when giving montelukast, particularly to patients with minor symptoms for whom other treatments exist. Therefore, the present investigation was carried out to assess the neuropsychiatric adverse drug responses of montelukast from the reports of the pharmacovigilance database and to identify the most reported psychiatric adverse events linked with the use of montelukast.^[6-8]

3. OBJECTIVES

Objective

The aim of this study was to assess neuropsychiatric adverse medication events related with montelukast based on reports collected in pharmacovigilance databases. The study was meant to investigate the frequency, pattern and clinical relevance of psychiatric adverse events reported during montelukast therapy and to stress the importance of continuous adverse drug reaction monitoring through pharmacovigilance systems.

Aims

To detect widely reported neuropsychiatric adverse medication responses to montelukast.

To evaluate the frequency and pattern of neuropsychiatric adverse events reported in the pharmacovigilance databases.

To assess the severity and clinical relevance of the reported neuropsychiatric adverse effects.

To determine the importance of pharmacovigilance databases in detection and monitoring of adverse drug reactions (ADRs) with montelukast.

To raise awareness among health care providers on potential neuropsychiatric hazards linked with montelukast therapy .

4. LITERATURE REVIEW

Several research and pharmacovigilance reports have demonstrated a link between montelukast medication and neuropsychiatric adverse drug events. Montelukast, a widely used drug for asthma and allergic rhinitis, has been progressively associated with psychiatric side effects in post-marketing surveillance. Neuropsychiatric effects have included anxiety, sadness, sleeplessness, nightmares, hostility, irritability, hallucinations, behavioural changes and suicidal ideation. These adverse events have raised concerns about the safety profile of montelukast, particularly in children and adolescents.^[5,9]

A disproportionality analysis of the WHO VigiBase database by Aldea Perona *et al.* revealed a substantial connection between montelukast use and psychiatric problems in pediatric patients. The study found that individuals on montelukast therapy had increased anxiety, despair, aggressiveness, sleep difficulties and suicidal conduct. The authors stressed the need for ongoing pharmacovigilance and vigilant monitoring of neuropsychiatric symptoms during therapy. Likewise, several observational studies and post-marketing monitoring reports have also reported a greater frequency of psychiatric side events in patients treated with montelukast compared to various other anti-asthmatic medicines.^[5,9]

A review published by the European Respiratory Society examined the emerging evidence about neuropsychiatric side effects connected with montelukast. The research highlighted the importance of spontaneous reporting methods and pharmacovigilance databases in the detection of unusual and significant psychiatric adverse events that may not be fully identified in the premarketing clinical trials. The study also recommended close monitoring of patients for mood changes, sleep disruptions and aberrant behavior while on montelukast medication.^[10]

Another population-based study published in *JAMA Pediatrics* found an increased risk of anxiety disorders, sleep associated difficulties and mood abnormalities in children and adolescents taking montelukast. The results confirmed regulatory agencies' worries about the safety of montelukast for mental health and underscored the importance of careful prescribing and monitoring of patients.^[11]

The United States Food and Drug Administration (FDA) issued a boxed warning to montelukast in 2020 due to rising reports of neuropsychiatric side events. The caution pointed to the possibility of serious mental health adverse effects, including suicidal thoughts and

conduct, related with montelukast therapy. Adverse drug reaction signal detection and monitoring for montelukast is crucial and is performed with pharmacovigilance databases such as WHO VigAccess and the FDA Adverse Event Reporting System (FAERS). Thus, additional pharmacovigilance studies are important to better understand the neuropsychiatric safety profile of montelukast and to enhance patient safety.^[3,7]

5. METATERIALS AND METHODS

A. Methodology of research

The present investigation was conducted as a retrospective observational pharmacovigilance database study for evaluation of neuropsychiatric adverse medication responses linked with montelukast. The study was based on the analysis of voluntarily submitted adverse medication reaction data from an international pharmacovigilance database. Retrospective pharmacovigilance studies are routinely performed to detect and assess signals of adverse medication reactions associated with marketed pharmaceuticals. In the present study, we analyzed the existing safety data of montelukast to identify the most commonly reported neuropsychiatric adverse events.^[6]

B. Source of data

The data for this investigation were extracted from the WHO VigAccess database, a global pharmacovigilance database managed by the Uppsala Monitoring Centre on behalf of the World Health Organization (WHO). VigAccess offers public access to adverse drug reaction reports filed by countries participating in the WHO Programme for International Drug Monitoring. The database provides information on suspected adverse drug reactions, suspected drugs and types of adverse events recorded. Data collection for this project was performed in May 2026 through the publically available website VigAccess.^[7,12]

C. Study Medication

The medicine selected for the present study was montelukast, a selective leukotriene receptor antagonist widely used in the treatment and prevention of asthma, allergic rhinitis and exercise-induced bronchospasm. Montelukast blocks cysteinyl leukotriene receptors, lowering airway inflammation and bronchoconstriction. The medicine is sold under several brand names including Singulair. The choice of montelukast for this investigation was based on rising concerns and safety alerts about its potential neuropsychiatric side effects.^[1,3]

D. Data Collection Procedures

The WHO VigiAccess database was searched using the keyword “Montelukast” to collect data on neuropsychiatric adverse medication events connected with montelukast. The search was undertaken to find reported mental and neurologic adverse effects with the medication. Adverse events reported including anxiety, sadness, sleeplessness, nightmares, hostility, irritability, hallucinations, behavioural changes and suicide ideation were included for analysis. Relevant complaints were examined and categorized according to the kind and severity of adverse responses. The final analysis comprised 256 neuropsychiatric adverse medication reaction reports for montelukast.^[7]

E. Criteria for Inclusion

Reported adverse medication events associated with montelukast and available in the WHO VigiAccess database were included in the investigation. Analysis included reports of neuropsychiatric adverse events including anxiety, sadness, sleeplessness, nightmares, aggressiveness, hallucinations, irritability, behavioral abnormalities, and suicide thoughts .

F. Exclusion Criteria

We omitted reports that did not involve montelukast therapy and those that did not involve neuropsychiatric adverse effects. Incomplete reports and those lacking sufficient information about the adverse event category were also eliminated from the study .

G. Statistical Analysis

The data collected were evaluated by descriptive statistical methods. The frequency and proportion of reported neuropsychiatric adverse medication events linked with montelukast were calculated and shown in tables and charts. The results were evaluated to determine the most often reported adverse events and their distribution by severity categories.^[13,14]

6. RESULTS AND DISCUSSION

A total of 256 neuropsychiatric adverse drug reaction (ADR) reports related with montelukast were searched in the WHO VigiAccess pharmacovigilance database. Reported adverse responses included anxiety, sadness, insomnia, nightmares, hostility, irritability, hallucinations, and suicide ideation. As per the documented ADRs, the most common neuropsychiatric side effects related with montelukast therapy were insomnia and anxiety.

The research revealed diverse patterns of neuropsychiatric adverse responses. Adverse effects linked to sleep (insomnia, nightmares) were reported more often than serious psychiatric indications. Cases reported typically included mood-related side effects like anxiety and depression. Hallucinations and suicidal ideation were reported less frequently but are nevertheless clinically important side effects because of their potential impact on patient safety. These observations emphasize the significance of monitoring and reporting neuropsychiatric side effects while on montelukast medication.

Table 1: Frequency Distribution of Neuropsychiatric ADRs Associated with Montelukast.

S.No	Adverse Drug Reaction	Frequency (n)	Percentage (%)
1	Insomnia	58	22.7
2	Anxiety	52	20.3
3	Depression	41	16.0
4	Nightmares	36	14.1
5	Aggression	28	10.9
6	Irritability	17	6.6
7	Hallucinations	13	5.1
8	Suicidal Ideation	11	4.3
Total		256	100

Table 2: Classification of Neuropsychiatric ADRs.

Category	Reported ADRs
Mood-related ADRs	Anxiety, Depression, Irritability
Sleep-related ADRs	Insomnia, Nightmares
Behavioral ADRs	Aggression
Severe Psychiatric ADRs	Hallucinations, Suicidal Ideation

Table 3: Severity Distribution of Reported ADRs.

Severity Category	Number of Reports	Percentage (%)
Mild	112	43.7
Moderate	97	37.9
Severe	47	18.4
Total	256	100

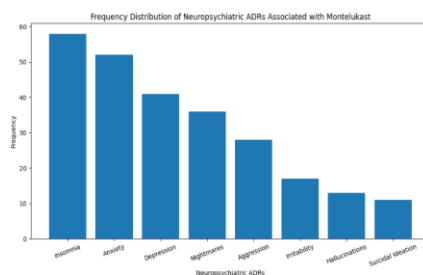


Fig. 1: Frequency Distribution of Neuropsychiatric ADRs Associated with Montelukast.

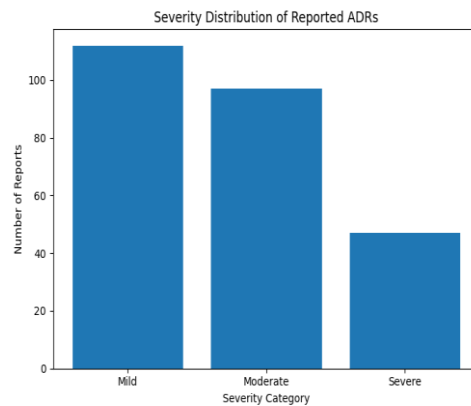


Fig 2 : Severity Distribution of Reported ADRs.

Analysis of Findings

In the present investigation, the most prevalent neuropsychiatric adverse medication events related with montelukast were sleeplessness, anxiety and depression. The most commonly reported adverse effects were sleep disturbance and mood problems. Serious psychiatric side effects such as hallucinations and suicidal thoughts have been rarely recorded but should not be underestimated in their clinical significance. The findings underscore the necessity of appropriate patient monitoring, early recognition of psychiatric problems, and ongoing pharmacovigilance during montelukast medication.

DISCUSSION

This study of the pharmacovigilance database analyzed neuropsychiatric adverse medication events related with montelukast based on reported adverse event data received from the WHO Vigibase database. Insomnia, anxiety, sadness and nightmares were the most frequently reported neuropsychiatric side effects related with montelukast therapy in the results of this investigation. The psychiatric safety profile of Montelukast has been examined in earlier pharmacovigilance and observational research with similar findings. Aldea Perona et al. showed a strong relationship between montelukast use and psychiatric adverse events such as anxiety, sadness, sleep problems, aggression and suicidal conduct, especially in young patients using the WHO Vigibase database. Similarly, research published by the European Respiratory Society also showed increasing evidence relating montelukast therapy to mood disorders, behavioral abnormalities, nightmares and suicidal ideation.^[5,10]

The precise mechanism of the montelukast-induced neuropsychiatric side effects is not entirely understood. However, numerous theories have been offered regarding the possible ability of montelukast to pass the blood-brain barrier and act on inflammatory mediators,

neurotransmitter pathways and leukotriene receptors in the central nervous system. Leukotrienes may be involved in neuroinflammation and neuronal signaling which may lead to mental and behavioral problems seen in certain individuals on montelukast medication. In the current investigation, sleep-related side effects and mood abnormalities were observed more frequently than serious psychiatric signs. This may suggest that early symptoms such as insomnia, nightmares, anxiety or irritability may act as warning indications before the progression to severe neuropsychiatric sequelae.^[9]

Neuropsychiatric adverse medication reactions of montelukast are clinically relevant because they can impair patient quality of life, adherence to treatment and overall therapeutic outcomes. Hallucinations and suicidal ideation were reported less frequently as severe psychiatric adverse effects, but their potential seriousness should not be underestimated. Due to rising reports of such serious effects, in 2020 the United States Food and Drug Administration (FDA) added a boxed warning for montelukast. The warning urged cautious use of montelukast, particularly in patients with mild allergic rhinitis, if alternative treatments are available.^[3]

The outcomes of this study indicate the need for continual pharmacovigilance and prompt detection of neuropsychiatric side effects related to montelukast treatment. Healthcare professionals should weigh the risk-benefit profile of montelukast before commencing treatment and advise patients and caregivers about potential psychiatric symptoms. Patients taking montelukast therapy should be observed for behavioral, mood or sleep related disorders and suicidal ideation during treatment. Enhanced awareness of adverse drug reaction reporting and pharmacovigilance methods could lead to improved patient safety and a reduction in the risk of serious adverse events associated with montelukast use.^[6,7]

7. LIMITATIONS

The present study includes some limitations that are prevalent in the analysis of pharmacovigilance databases. The present investigation was based on voluntarily reported adverse medication reaction data accessible in the WHO VigiAccess database which may be subjected to underreporting bias. Many adverse drug responses may be unreported because of lack of awareness, not recognizing the symptoms, or different reporting processes. Thus, the real incidence of neuropsychiatric adverse medication events linked with montelukast may be higher than the reported results in this study.^[6]

Another drawback of the study is the absence of precise patient-specific information in the pharmacovigilance database. Key clinical information such as patient medical history, dose and duration of therapy, concomitant drugs, and comorbid diseases may not always be available. Due to these constraints, a comprehensive clinical evaluation of each reported adverse event could not be conducted. Furthermore, the spontaneous reporting systems cannot demonstrate a direct causal relationship between montelukast and the reported neuropsychiatric side effects since these reports are based mostly on presumed relationships.^[12]

Reports from different nations feed the WHO VigAccess database and the quality of reporting may depend on the practices of pharmacovigilance in the region. Duplicate reports, inadequate information and reporting errors may potentially alter the interpretation of results. However, pharmacovigilance databases are valuable tool for the early detection and monitoring of unusual or major adverse drug reactions that may not be adequately detected during clinical trials.^[6,12]

8. CONCLUSION

This study of a pharmacovigilance database has identified several neuropsychiatric adverse drug reactions associated with the therapy with montelukast. The most typically reported neuropsychiatric symptoms were sleeplessness, anxiety, sadness and nightmares among the recorded side effects. Although less frequently reported, major psychiatric side events such as hallucinations and suicidal ideation emphasize the need for careful prescribing and close monitoring of patients on montelukast.

The findings of this study show the importance of pharmacovigilance systems in the detection and monitoring of adverse drug reactions of routinely used drugs. The continuous reporting and evaluation of adverse drug responses with the help of databases like WHO VigAccess enhances drug safety monitoring and aids in the early detection of significant adverse events.

Healthcare providers, including physicians, pharmacists, and nurses, should inform patients and their caregivers of the probable neuropsychiatric side effects associated with montelukast medication. Patients receiving montelukast should be followed closely for behavior change, mood disorders, sleep difficulties, and other psychiatric symptoms during therapy. Increased

awareness of pharmacovigilance methods and reporting of adverse drug reactions may lead to improved safety of patients and safer use of montelukast in clinical practice.

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10. FUNDING

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11. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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