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"SAFETY PROFILE OF MIRTAZAPINE: A REAL-WORLD DISPROPORTIONALITY ANALYSIS OF FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) "

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Abstract

Introduction: Mirtazapine is an antidepressant drug that produces both noradrenergic and serotonergic activity. It is effective in treating of mild to severe depression. Proper evidence pointing to the safety of Mirtazapine is not established. The need for post-marketing surveillance (PMS) is considered most essential. This study was aimed to generate signal for unreported adverse drug reactions for Mirtazapine.

Materials and Methods: Our study retrospectively analyzed the AEs reported entered in the Adverse Events Reporting System (FAERS) databases in the last 10-years during the period of Jan 2011 to June 2020. Disproportionality analysis was done using Reporting Odds Ratio, Proportional Reporting Ratio, and Information Component with 95% confidence interval.

Results: A disproportionality analysis was done for 41 adverse events, out of these, signal for 11 adverse events was found. ROR values 10.17 being the highest for abulia and 2.22 being the lowest for homicidal Ideation. The PRR value was 10.17 being the highest for abulia and 2.22 being the lowest for homicidal ideation. The IC025 value was 1.87 for abulia and 0.27 for homicidal Ideation.

Conclusion: The present study using the Adverse Events Reporting System (FAERS) databases maintained by the FDA suggested new safety signals for Mirtazapine. Still more cohort and epidemiological studies are recommended to validate these results.

Keywords: Mirtazapine, Disproportionality analysis, Safety Signals.

Introduction

Anti depressants remains the cornerstone of treatment for depression by a primary care physician [1]. Mirtazapine is known to have noradrenergic (NA) and specific serotonergic properties, making it a drug of choice for the treatment of major depression [2]. It is especially helpful in patients with depression who are anxious; this drug has been shown to reduce anxiety and has even been used to relieve preoperative anxiety and insomnia in patients having gynecologic surgery [3,4]. It is always difficult to find all adverse effects of a drug in clinical trials because of its restricted sample size, limited exposure time, reduced follow-up, exclusion of special population, and subjects with co-morbidities. Hence the need for post-marketing surveillance (PMS) emerges and plays a vital role in identifying new signals. World Health Organization (WHO) defines signal as "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented". [5,6] Signal detection plays a crucial in pharmacovigilance as it helps in identifying new Adverse events of marketed drugs.

FDA collects and maintains data that provides safety information for its regulated products. The FDA currently receives approximately two million adverse events each year from health care professionals, manufacturers, and consumers. All the reports are entered in the FDA Adverse Events Reporting System (FAERS) databases maintained by the FDA for subsequent analyses to identify potential safety issues. Recently data mining methods have become more common for data

analysis and FDA has recommended its use to the pharmaceutical industry. [7]

All ICSRs in FDA database are automatically coded with MedDRA, the Medical Dictionary for Regulatory Activities (MedDRA) coding system, which refers to a group of terms belonging to a System Organ Class.[8] In Pharmacovigilance Signal detection is the process of searching and identifying a safety signals from a varied data source. The utmost common basis for signals comes from the spontaneous reporting systems. Preferred Term (PT) level of analysis has been shown to have the best combination of sensitivity and positive predictive value for signal detection.[9]

Disproportionality approaches are widely used to detect the statistical relationship between products and events in the databases of safety reports. Various disproportionality evaluation methods are widely used for detecting a signal. These methods associate the observed count for a product-event combination with an expected count. Disproportionality procedures always look for surprising frequencies of reports in the dataset in valuation with general reporting frequencies.[10] Newly Identified safety signals are defined as the Disproportionately Reported Combinations (DRCs). The Proportional Reporting Ratio (PRR) is the fundamental concept for many disproportionality methods. [11,12]

Proportional Reporting Ratio (PRR) is a simple way to measure of how common an adverse event for a particular drug compared to the event in overall database.It can also roughly measure the strength of the association and determine if there is a disproportionate reporting of a particular adverse event with a particular drug compared to other adverse events and other drugs. The Reporting Odds Ratio (ROR) are the odds of an adverse reaction occurring with any Pharmaceutical Products, compared to the odds of the same event taking place with all other Pharmaceutical products available in the database. Computing the ROR in spontaneous report databases offers an advantage over the PRR. It allows for Measuring of the relative risk, and emphases attention on which people or reports should be included or excluded from the control series, permitting more deliberate elimination of biases [13]

The information component (IC) can measure the disproportionality between the observed and the expected reporting of a drug- ADR pair. IC_{025} is the lower end of a 95% credibility interval for the Information Component. A positive IC value designates that a particular drug- Adverse Reaction pair is reported more often than expected, based on all the reports in the database. On the other hand, a negative IC value means that the drug-ADR pair is reported less frequently than expected. The higher the value of the IC, the more the combination stands out from the background. Data regarding the real-world safety of Mirtazapine is lacking, hence our study was aimed to generate signal for unreported adverse drug reactions of Mirtazapine using disproportionality analysis in food and drug administration adverse events reporting system (FAERS) database.

Methodology

AE reports from the FAERS database were used for the study. An attempt was made to detect serious AEs for Mirtazapine which are not identified during premarketing stage. The FDA publishes FAERS files every quarter (i.e., four files each year). Every quadrant file had details about the demographics, reactions, statistics, and drugs associated with the AE reported in that quadrant. Our study retrospectively analyzed the AEs reported in last 10 year reports starting from 1St quarter of 2011 Q1 to 2nd Quarter of 2020 Q2. In the first step, case IDs of Mirtazapine was isolated from drug file. All individual AEs based on MedDRA, SOC and PT level recorded on Mirtazapine reports were identified to describe the spectrum of toxicities. Severe outcomes included life-threatening events or those causing hospitalization, disability, or death. Few repeatedly reported clinically relevant and rare ADRs were chosen and evaluated for IC, ROR and PRR. For the evaluation of each AE number of Ni (The event of interest), Nj (Drug of interest), Nij (Both events of interest and drug of interest) were listed. The further calculation was carried out for IC025, ROR and PRR to find the correlation between Mirtazapine and AE.

Statistical Analysis

We analyzed adverse events caused by investigating drugs, but not by disease state. The threshold for statistical significance was predefined as a PRR of ≥2.0 with a Chi-squared test statistic of ≥4.0, at least three reports (n ≥3) of that preferred term (PT), IC with IC-2SD>0, and A ROR signal was defined positive when the number of cases > 3, the lower limit of 95% confidence interval (CI) > 1.0, and ROR value was > 2.0. Any PT that met all of these three criteria was disproportionally reported for Mirtazapine at a higher rate than expected.[14]

Results

A total of 15278658 ADR reports were recorded during 10-year reports starting from 1st January of 2011to 30th June 2020. Out of these, 28354 ADR reports were primarily or secondarily suspected by Mirtazapine.

Data mining and clinical review: A total of 258 PTs were identified by using data mining algorithms. Clinically relevant 41 PTs were selected for which signal detection process was performed. 11 New AEs were identified that were disproportionately reported with the use of Mirtazapine by using data mining techniques. The majority of PTs were related to Cardiovascular system, reproductive system, psychiatric and Ophthalmic problems.

Positive signals identified using PRR:

The PRR values for 11 PTs ranged from *10.17 being the highest for abulia and 2.22 being the lowest for homicidal ideation*. The PRR values for other selected adverse events were,6.96 Cardiac Hypertrophy,5.14 for Long QT Syndrome,4.15 for Logorrhoea,3.72 for miosis, 3.67 for Suicidal Behaviour,3.44 for Catatonia,2.77 for Bradyphrenia,2.50 for Priapism followed by 2.37 for somnambulism. All the values are presented in table 1.

Positive signals identified using ROR:

The ROR values for 11 PTs ranged from *10.17 being the highest for abulia and 2.22 being the lowest for homicidal ideation*. The ROR values for other selected adverse events were,6.96 Cardiac Hypertrophy,5.14 for Long QT Syndrome,4.16 for Logorrhoea,3.73 for miosis, 3.67 for Suicidal Behaviour,3.44 for Catatonia,2.76 for Bradyphrenia,2.50 for Priapism followed by 2.37 for somnambulism. All the values are presented in table 1.

Positive signals identified using IC_{025} values:

The IC_{025} values for 11 PTs ranged from *2.85 being the highest for abulia and 0.27 being the lowest for homicidal ideation*. The IC_{025} values for other selected adverse events were,1.40 Cardiac Hypertrophy, ,1.36 for miosis, 1.35 for Long QT Syndrome,1.30 for Logorrhoea, 1.08 for Suicidal Behaviour, 1.09 for Catatonia,0.78 for Bradyphrenia, 0.58 for somnambulism followed by 0.57 for Priapism. All the values are presented in table 1. All the values are presented in table 1.

Table:1 . Data mining algorithm values of all clinically relevant reactions associated with Mirtazapine.

S.NO	Event associated with Mirtazapine	PRR Value	ROR value	IC 025 value
1	Priapism	2.50	2.50	0.57
2	Cardiac Hypertrophy	6.96	6.96	1.40
3	Long QT Syndrome	5.14	5.14	1.35
4	Logorrhea	4.15	4.15	1.30
5	Catatonia	3.44	3.44	1.09
6	Bradyphrenia	2.77	2.76	0.78
7	Suicidal Behaviour	3.67	3.67	1.08
8	Somnambulism	2.37	2.37	0.58
9	Homicidal Ideation	2.22	2.22	0.27
10	Abulia	10.17	10.17	1.87
11	Miosis	3.72	3.73	1.36

Discussion

In the last two decades, many countries are involved in the collection of suspected ADR's to generate their database. They strongly believe that data mining in their respective databases can help their pharmacovigilance systems in identifying new, rare, previously unknown, ADRs. Data mining methods include statistical techniques, including cluster analysis, link analysis, deviation detection, and disproportionality assessment, which can be used to determine and assess new signals. The use of a measure of disproportionality is currently applied in various countries. Variables such as reporting Odd Ratio (ROR) and proportional reporting ratio (PRR), have been proposed to evaluate a reported signal. Disproportionality analysis is quick and inexpensive and can generate automatic signals from large databases.

FDA collects and maintains data (Adverse Events Reporting System (FAERS) database) that provide safety information for its regulated products and considered as one of the largest database. An attempt was made to detect serious AEs for Mirtazapine which are not identified during premarketing stage.

There is a definite correlation between cardiovascular diseases and depressive disorders. higher risk of mortality due to cardiovascular events has been reported in patients suffering from psychiatric disorders such as depression. [15,16] Cardiovascular patients should be individually evaluated to their potential risks and benefits from antidepressant therapy. In our study few signals are identified in the cardiovascular system which includes Cardiac Hypertrophy and QT prolongation. Periodical monitoring with the ECG is also required to detect probable QT prolongation or other substantial ECG abnormalities. although antidepressants have been shown to be effective in reducing the symptoms of depression there is concern that rates of suicide and self-harm may be increased by treatment, particularly in younger people. In our study we identified suicidal ideation and Homicidal Ideation as a new signal. [17,18] In our study we reported few cases of catatonia. Historically, antipsychotics are considered one of the culprits for catatonia or worsening a catatonic conundrum or even leading to Neuroleptic Malignant Syndrome (NMS).[19]

Limitations of the Study

Disproportionality studies should be only considered as tentative in the context of signal detection. They do not let quantification of the true risk. a slightly increased ROR value does not suggest a risk of AEs in clinical practice. They cannot assure causality and cannot be used to evaluate the incidence of an Adverse Event. Despite these limitations, the findings can offer an update for healthcare professionals to closely follow-up on patients prescribed with these drugs.

Conclusion

To conclude, disproportionality studies are more important today, when there is a growing demand for more safe drugs. The present study using the FAERS database suggested few safety signals for Mirtazapine. Since this study was based on a spontaneous reporting database there are chances of potential biases, Intensive drug monitoring, cohort, and epidemiological studies are recommended to validate the results.

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