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A Real World Pharmacovigilance Study of FDA Adverse Event Reporting System (FAERS) Events for Paxlovid and Molnupiravir

*Chao Yuan, MS[a], Haiqiang Liu, BS[b], Daoquan Wang, BS[a], Shunzhang Wang, BS[a], Xiangmei Zhang, BS[a], **

ABSTRACT

Background: Questions have been raised about the safety of paxlovid and molnupiravir as antiviral drugs for the treatment of COVID-19 since the pandemic.

Methods: We applied the FDA Adverse Event Reporting System (FAERS) to assess the safety by performing a disproportionality analysis to identify potential risks of paxlovid and molnupiravir. The protocol does not require ethics committee review because this study is based on a publicly available database.

Results: The number of paxlovid signals was higher than that of molnupiravir, with most signals of these two drugs overlapped. General disorders and administration site conditions (ROR: 0.52, 95% CI: 0.58- 2.18), infections and infestations (ROR: 0.18, 95% CI: 0.23-6.64), nervous system disorders (ROR: 1.41, 95% CI: 0.79-1.58) were the top 3 signals for paxlovid, with gastrointestinal disorders (ROR: 4.13, 95% CI: 0.27-4.54), skin and subcutaneous tissue disorders (ROR: 11.51, 95% CI: 0.10-12.92), nervous system disorders (ROR: 1.41, 95% CI: 0.79-1.58) for molnupiravir. Paxlovid-induced infections, skin and subcutaneous tissue disorders, and molnupiravir-induced musculoskeletal and connective tissue disorders, as well as potential safety signals on the heart, eyes and ears needlong-term observation, especially for signals not included in the instructions. However, it is important to note that these are all potential safety signals, and more research is needed to confirm whether these drugs are actually associated with these risks.

Conclusion: The adverse events on this study confirms most of the instructional information for paxlovid and molnupiravir, both drugs need to be monitored for risk signals such as acute respiratory failure, hematologic and lymphatic system.

INTRODUCTION

Starting from 2019, an outbreak of pneumonia of unknown origin from Wuhan, China, spread rapidly around world, causing a global pandemic Peeling et al. (2022) and immeasurable suffering to people worldwide Long et al. (2022). More than 80% of patients present with mild symptoms, while a small proportion of patients may be critically illed, especially the older patients and patients with comorbidities. Upper respiratory symptoms, fever, and altered taste/smell are the most common complaints Chavez et al. (2021). Extra-pulmonary complications are numerous and potentially serious, including cardiovascular, neurological, gastrointestinal and dermatological Pradhan et al. (2022). A lot of efforts have been made to treat COVID-19, such as vaccines Fernandes et al. (2022), and antiviral drugs [6]. Oral drugs are easy to use, especially since they can be self-administered by patients without hospitalization. Therefore, oral effective anti-COVID-19 drugs are an important weapon for mankind to overcome this epidemic Shariare et al. (2021).

Significant progress has recently been made in this area with the marketing approval of Merck Sharp & Dohme's oral anti-COVID-19 drug, molnupiravir, by the UK Medicines and Healthcare Products Regulatory Agency on November 4, 2021 Saravolatz et al. (2023). Its indication is mild to moderate cases of COVID-19 with at least one risk factor to progress severe disease.

Molnupiravir has become the first marketed oral anti-COVID-19 drug that could reduce the risk of hospitalization or death by 50% in COVID-19 patients world wile Jayk Bernal et al. (2022). Merck received emergency use authorizations from the Food and Drug Administration on Nov. 30.

[a] Department of Pharmacy, Weifang People's Hospital, Weifang, China.
[b] Department of Pharmacy intravenous admixture services, Weifang People's Hospital, Weifang, China.

Correspondence to: Xiangmei Zhang, Department of Pharmacy, Weifang People's Hospital, Weifang, China (261041), E-mail: zxm2259@163.com.

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Molnupiravir could block the synthesis of RNA-dependent RNA polymerase to inhibit the virus Kabinger et al. (2021). Pfizer announced that its development of the oral anti-COVID-19 drug paxlovid two days after Merck. Paxlovid is a combination of nirmatrelvir and low-dose ritonavir Reina et al. (2022), Buxeraud et al. (2022). It could reduce the risk of hospitalization or death in patients with mild or moderate COVID-19 by approximately 89% Mahase et al. (2021), FDA expended the emergency use authorization. The mechanism of paxlovid is to inhibit the activity of the 3-chymotrypsin-like protease of the new coronavirus Marzi et al. (2022).

The FDA Adverse Events Reporting System (FARES) database includes information about drug adverse event (AE) and medication error Li et al. (2023), Sakaeda et al. (2013). Risk signal mining of the FAERS database using appropriate signal mining techniques can effectively evaluate the post-marketing safety, and provide clinical reference to identify the potential reason of clinical signs/symptoms and abnormal laboratory test results that appear or worsen after drug administration in patients with COVID-19. The public can obtain data related to AE, drug instructions, national drug codes and recall reports from FAERS Yin et al. (2022). In this study, a comparative analysis of paxlovid and molnupiravir adverse reaction reports in FAERS was conducted to provide a reference for clinical use.

MATERIALS AND METHODS

Data source

Data for this study were obtained from the FAERS database, including all information collected by the FDA on adverse events or medication errors. Combined with the launch time of paxlovid and molnupiravir, the American standard code for information interchange (ASCII) data package was downloaded from the FAERS database for 5 quarters from Q4 2021 to Q4 2022 in accordance with the time to market for paxlovid and molnupiravir, it includes patient information, adverse events, drug information, and event outcomes.

Data cleaning and extraction

The downloaded 5 quarter data files were imported into MySQL5.7 software. The primary suspected drug (PS) of paxlovid and molnupiravir was retrieved and extracted through Navicat database management tool of the relevant ADE reports. The same names were combined, and ADEs was excluded with apparently no reference value, such as dose omission and product storage error, we excluded ADEs associated with primary disease. AEs were extracted by the International Dictionary for Drug Regulatory Activities (MedDRA) 24.1, and they are classified and described by the preferred term (PT) and system organ classification (SOC).

Statistical analysis

In this study, signal mining was performed by the reported odds ratio (ROR) by the proportional imbalance method [18]. A positive signal was determined when it was detected by ROR. The algorithm was based on a 2 × 2 contingency table (Table 1). Detection value criteria: the number of reports a ≥ 3; ROR value 95% CI lower limit > 1, suggesting a signal Saravolatz et al. (2023). When the frequency of the target ADE is higher than the threshold of the background frequency of the whole database, it represents a signal and the larger the signal value is, the association between the target drug and the suspected ADE is stronger.

Table 1: 2 × 2 contingency table for disproportionality analysis

	Drug of interest	**All other drugs**	**Total**
Adverse event of interest	a	b	a+b
All other adverse events	c	d	c+d
Total	a+c	b+d	a+b+c+d

RESULTS

Basic information of AE reports related to Paxlovid and molnupiravir

A total of 3089014 AE reports were collected, and 23235 AE reports were extracted by screening, including 21249 paxlovid-related reports and 1986 molnupiravir-related reports. There were 13375 (54.37%) AE reports for females, 7787 (40.01%) for males, and 2073 for unknow gender. The age was mainly 18-64 years (10172 cases, 47.87%) and 65-85 years (771 cases, 38.82%) (Table 2). The cases were mainly reported from the United States (17540 cases, 82.55%) and Japan (1355 cases, 68.23%) (Table 3).

Table 2: Clinical characteristics of patients treated with paxlovid and Molnupiravir in the FAERS database

		Paxlovid	**Molnupiravir**
Total numbers of reports		21249	1986
Age (years)	＜18	68 （0.32%）	24 （1.21%）
	18~64	10172 （47.87%）	535 （26.94%）
	65~85	6738 （31.71%）	771 （38.82%）
	＞85	424 （1.99%）	391 （15.61%）
	Not Specified	3847 （18.11%）	265 （13.34%）
Gender, n (%)	Male	6945 （32.68%）	842 （42.40%）
	Female	12366 （58.20%）	1009 （50.81%）
	Not Specified	1938 （9.12%）	135 （6.80%）
Reporter	Consumer	15385 （72.40%）	327 （16.47%）
	Healthcare Professional	5790 （27.25%）	1651 （83.13%）
	Not Specified	74 （0.35%）	8（0.4%）
Seriousness	non-Serious	18026 （84.83%）	1047 （52.72%）
	Serious	3223 （15.17%）	939 （47.28%）
Event year	2022年	21249 （100%）	1986 （100%）

Table 3: The counties of the cases reported by FAERS

	Paxlovid	**cases**
1	Americas	17540（82.55%）
2	Britain	331（1.56%）
3	Japan	222（1.04%）
4	France	211（0.99%）
5	Italy	99（0.47%）
6	Germany	74（0.35%）
	Molnupiravir	
1	Japan	1355（68.23%）
2	Americas	156（7.85%）
3	Australia	52（2.62%）
4	Italy	37（1.86%）
5	Germany	25（1.26%）

The main system signal detection results

The top 20 target drug-related AE signals in terms of association strength were gastrointestinal disorders, skin and subcutaneous tissue disorders, nervous system disorders, general disorders and administration site conditions, infections and infestations (Table 4).

Classification of each system/organ AE signal

In this study, the ROR methods of the proportional imbalance method were used to explore AE signals by excluding reports number ≤ 3 reports or 95% CI of ROR values < 1 to reduce the bias. Among the 23235 related AEs, the top 200 AE signals accounted for 68.8% of all reports, and the number of individual AE reports was ≥ 5. Therefore, screening the top 200 AE signals could provide a more comprehensive understanding of the AE signals of paxlovid and molnupiravir. Among the top 200 reported AE signals, 23 risk signals were showed statistically significant difference by ROR calculations (Table 5).

Discussions

As the COVID-19 pandemic continues, novel oral drugs are important for public health in relieving the symptoms and minimizing adverse outcomes Umakanthan et al. (2020). Paxlovid and molnupiravir have emerged as treatment options for some patients with COVID-19 Saravolatz et al. (2023), Singh et al. (2022), Islam et al. (2022).

They are approved for the treatment of adult or pediatric patients with high risk of progressing to severe COVID-19, but the clinical experience and evidence for these two new oral antiviral drugs are limited. As more patients have access to the drugs, we conducted a pharmacovigilance study using FAERS database to detect possible new adverse drug reactions.

In our study, a total of 21249 people experienced at least one adverse event after receiving paxlovid and 1986 people for molnupiravir as of December 31, 2022. According to the data collected, the elder population accounted for a greater proportion (63.62% for paxlovid and 56.78% for molnupiravir). Age is one of the important factors accounted for adverse drug reactions (ADRs) Han et al. (2022). The reason for the higher incidence of ADRs in the elder population for several reasons, include altered drug metabolizing enzyme activity, altered drug-receptor interactions, comorbidity with other diseases, and co-administration of drugs Davies et al. (2015), Loddo et al. (2022). The use of paxlovid and molnupiravir in the elderly population, as well as in patients with pre-existing diseases, are more susceptible to adverse reactions.

In pharmacovigilance databases such as FAERS, women typically account for a greater proportion of overall adverse event reporters (up to 60.1%).

Table 4: The top 20 target drug-related AE signals

SOC	Molnupiravir (1986)	Paxlovid (21249)
Blood and lymphatic system disorders	16	116
Cardiac disorders	46	354
Ear and labyrinth disorders	39	301
Eye disorders	45	360
gastrointestinal disorders	715	6285
General disorders and administration site conditions	320	14313
hepatobiliary disorders	9	106
Immune system disorders	18	267
infections and infestations	93	11083
Injury, poisoning and procedural complications	158	2721
investigations	100	1446
metabolism and nutrition disorders	43	641
musculoskeletal and connective tissue disorders	60	1019
nervous system disorders	426	8516
psychiatric disorders	88	5
product issues	8	595
renal and urinary disorders	26	362
Reproductive system and breast disorders	9	106
respiratory, thoracic and mediastinal disorders	118	3173
skin and subcutaneous tissue disorders	481	1418
Social circumstances	3	46
Surgical and medical procedures	22	109
vascular disorders	42	467

Table 5: Classification of each system/organ AE signal

SOC	Molnupiravir (1986)	Paxlovid (21249)	ROR	95% CI	95% CI
Blood and lymphatic system disorders	16	116	3.69	6.23	0.46
Cardiac disorders	46	354	3.51	4.79	0.39
Ear and labyrinth disorders	39	301	3.49	4.89	0.40
Eye disorders	45	360	3.38	4.62	0.41
gastrointestinal disorders	715	6285	4.13	4.54	0.27
General disorders and administration site conditions	320	14313	0.52	0.58	2.18
hepatobiliary disorders	9	106	2.26	4.48	0.87
Immune system disorders	18	267	1.80	2.91	0.90
infections and infestations	93	11083	0.19	0.23	6.64
Injury, poisoning and procedural complications	158	2721	1.59	1.88	0.74
investigations	100	1446	1.88	2.32	0.65
metabolism and nutrition disorders	43	641	1.80	2.46	0.76
musculoskeletal and connective tissue disorders	60	1019	1.58	2.06	0.82
nervous system disorders	426	8516	1.42	1.58	0.79
psychiatric disorders	88	5	489.13	1205.75	0.01
product issues	8	595	0.35	0.71	5.67
renal and urinary disorders	26	362	1.92	2.87	0.78
Reproductive system and breast disorders	9	106	2.26	4.48	0.87
respiratory, thoracic and mediastinal disorders	118	3173	0.99	1.19	1.22
skin and subcutaneous tissue disorders	481	1418	11.52	12.92	0.10
Social circumstances	3	46	1.73	5.58	1.85
Surgical and medical procedures	22	109	5.41	8.58	0.29
vascular disorders	42	467	2.42	3.33	0.57

There are multiple possible reasons that the adverse reactions of paxlovid and molnupiravir are reported more frequently in female than male, and in humans, there are significant differences in the activity of CYP450 enzymes for drug metabolism between genders Zanger et al. (2013). Ritonavir is a potential CYP3A4 inhibitor, whereas nirmatrelvir requires CYP3A4 inhibition for therapeutic effect Reis et al. (2022). Thus, gender differences in nirmatrelvir/ritonavir metabolism may make female more susceptible to adverse reactions. Molnupiravir is not a substrate of CYP450, which may be a possible reason for that female are more sensitive to chemical drug.

Unlike molnupiravir, which is primary reported by healthcare professionals, paxlovid has a higher consumer reporting rate. It may be related to the more widely use of paxlovid in the United States, whereas molnupiravir is used by only 7.85% of the population. It is believed that with the continued pandemic of COVID-19, the reporting group for molnupiravir may change under the conditions of more acceptance of molnupiravir in Europe and the United States. In our study, paxlovid showed a small proportion of serious ADRs (15.17%). The most common adverse events of paxlovid included general disorders and administration site conditions, infections and infestations, nervous system disorders and gastrointestinal disorders. And gastrointestinal disorders (including diarrhea, nausea and vomiting) and neurological disorders (taste inversions) were the most common adverse drug reactions in the instructions of paxlovid Chen et al. (2022), which is consistent with our study. Close attention should be paid to paxlovid-induced infections, skin and subcutaneous tissue disorders, upper respiratory tract congestion, sneezing, cough, nasal congestion, oropharyngeal pain, nasal leakage, and other respiratory, thoracic, and mediastinal disorders. Although these AEs are not shown in the instructions for paxlovid, special attention should be paid during treatment.

However, molnupiravir was associated with more serious AEs (47.28%), with the most common adverse events including gastrointestinal disorders, skin and subcutaneous tissue disorders, nervous system disorders. In the MOVe-OUT phase III trial study Thorlund et al. (2022), Johnson et al. (2022), the top adverse events were diarrhea, rash, nausea, COVID-19 pneumonia, vomiting, and dizziness, which is consistent with our study. While rash was observed during post-marketing was included in skin and subcutaneous tissue disorders, fever, decreased oxygen saturation, weakness, dyspnea, and cough, which may be related to the clinical manifestations of mild to critical SARS-CoV-2 infection. Although the most common AEs mentioned above are of concern, clinical practice focuses more on potential adverse events, such as seizures, sudden deafness, kidney injury, arrhythmia, and immune system disorders.

The current study has several limitations. FAERS is a spontaneous reporting system, but not all adverse events regarding drugs are reported to the FDA, which can be biased and incomplete, so underreporting, bias and absence of patient clinical information can affect signal mining results Li H et al. (2023), Peng et al. (2020), Guo et al. (2022). Adverse events in this study are related to paxlovid and molnupiravir separately without considering the effects of drug-drug interactions and patients' underlying diseases or comorbidities, so the signals generated by data mining do not represent a confirmed association between drugs and ADEs, it may require further clinical studies and assessmenta. What is more, the data are mainly from the European and American populations, so it may be different from the situation in China, further data is needed to verify whether the results are consistent with the Chinese population Yin et al. (2022). However, FAERS can provide a reference for the rational and safe use of drugs in China, and the data signal mining of large sample can provide a reference for drug safety research.

Conclusions

In conclusion, paxlovid and molnupiravir provide a new COVID-19 treatment option for patients. In our study, the signal mining of ADEs associated with paxlovid and molnupiravir using the ratio imbalance method by FAERS database showed to be associated with respiratory symptoms such as influenza-like illnesses and ADEs such as nausea and vomiting. ADEs such as influenza-like illnesses and gastrointestinal disorders were found to be strong associated with the drugs, which are consistent with the drug instructions, the risk of molnupiravir was higher. In addition, the identification of ADEs with strong signals, such as infections, skin and subcutaneous disorders, cardiovascular system, hematologic and lymphatic system disorders, which have not been documented in the drug instructions, give a warning to the clinic to carefully assess patients' risk factors of ADEs and to close monitoring of drug use to protect patients' benefits. We can provide recommendations for further research or monitoring, especially for the potential safety signals on the heart, eyes, and ears that require long-term observation. At the same time, we should also rely on a variety of complementary research methods to further clarify the safety of this class of drugs based on relatively adequate evidence.

DECLARATIONS

Data availability

The datasets generated and/or analysed during the

corresponding author on reasonable request.

Author contributions

Y.C contributed to conception and study design, Liu H.Q analyzed data, Wang D.Q prepared all Tables, and Wang S.Z took responsibility for the collection, integrity and accuracy of the data, Zhang X.M and Y.C drafted the main manuscript and approved the final version.

Disclosure statement

The authors declare no potential conflict of interest.

Competing interests

We declare no financial and personal relationships with other people or organizations

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