Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LETTER TO EDITOR

Adverse drug reactions associated with ivermectin use for COVID-19 reported in the World Health Organization's pharmacovigilance database

Keywords Ivermectin; Pharmacovigilance; COVID-19

Abbreviations

ADRs	adverse drug reactions
COVID-19	coronavirus disease 2019
PT	preferred terms
WHO	World Health Organization

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, numerous drugs have been proposed for the management of the infection. Among them, ivermectin has been the subject of many scientific studies evaluating its potential antiviral efficacy. Despite the fact that it has never been proven that ivermectin can be effective in the management of COVID-19 [1,2], North American and European tabloids as well as some public health policies began to mention it as a potential anti-COVID-19 treatment in May 2020 which led to its off-label use in several countries [3].

In 2021, a correspondence by Temple et al. showed an increasing number of calls regarding ivermectin exposure related to COVID-19 at a Poison Center in Oregon, USA [4]. Ivermectin has already been studied for its safety in various indications. It is well known that the use of ivermectin in individuals highly infected with loaisis, a parasitic disease endemic in Central Africa, may cause severe neurological adverse drug reactions (ADRs) [5,6]. In 2018, Chandler at al. reported 28 cases of serious neurological adverse events after the administration of ivermectin where loaisis infection was not reported [7]. In 2021, through an analysis of the World Health Organization (WHO) pharmacovigilance database, the occurrence of serious neurological adverse reactions was highlighted in areas where loiasis was not endemic [8].

We reviewed all ADRs reported with ivermectin and recorded in VigiBase®, the World Health Organization's ADRs database.

We highlighted a considerable increase in ivermectine-related reports since May 2020 (758 reports in 2018, 542 reports in 2019, 1418 reports in 2020 and 1252 reports in 2021).

From May 1st 2020 to December 21, 2021, a total of 1777 cases were reported with ivermectin specifying an indication for COVID-19. Gastrointestinal and neurological effects were the most reported. Among 53 cases considered as serious, the most frequently reported concerned neurologic disorders (11 cases including 1 encephalitis, 1 coma and 1 death), respiratory disorders (8 cases including 2 deaths), gastrointestinal disorders (8 cases including 1 death) and cardiac disorders (5 cases including 2 deaths by cardiac arrest). Four overdoses were reported and were mostly associated with neurologic disorders. Among these 4 cases, 2 were life threatening and 1 caused/prolonged a hospitalization. Table 1 summarizes characteristics of the 35 serious cases (including 6 deaths) where ivermectin was reported as the single suspect. The most reported preferred terms (PT) among those cases were: overdose, use of product in an unapproved indication, abdominal pain, pruritus and vomiting.

Among the 6 deaths, 4 were male and 2 were female, 1 patient was 20-years-old, 4 were between 50- and 80-years-old, and 1 patient was of unknown age. For 3 cases, death was the only term reported. The other 3 cases report the following PTs:

- confusional state, septic shock and digestive disorders;
- abnormal state sensation and acute respiratory distress syndrome;
- cardiac arrest, serious myasthenia and nervous system disorder.

It is not excluded that these effects also reflect the lack of effectiveness of ivermectin in the management of COVID-19. These findings call for extreme caution when using ivermectin, especially since there is no current scientific evidence to support its use in the treatment of COVID-19.

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Table 1 Characteristics of serious cases reported with ivermectin as single suspect.

Characteristics	Reported cases ($n = 35$)
Sex ratio (M/F)	1.5
Age (median [minimum, maximum])	51 [13,79]
Reporting region (*n*, %)	
North America	13 (37.1%)
Europe	9 (25.7%)
Asia	7 (20.0%)
Latin America	6 (17.1%)
Seriousness criterion (*n*, %)[a]	
Death	6 (17.1%)
Life threatening	9 (25.7%)
Disabling/incapacitating	2 (5.7%)
Hospitalization	16 (45.7%)
Other important condition	18 (51.4%)
System organ class [SOC] (*n*, %) [b]	
Nervous system disorders	10 (28.6%)
Injury, poisoning, procedural complications	9 (25.7%)
General disorders and administration site conditions	8 (22.9%)
Investigations	7 (20.0%)
Gastrointestinal disorders	7 (20.0%)
Respiratory, thoracic, mediastinal disorders	7 (10.4%)
Infections and infestations	6 (17.1%)
Skin and subcutaneous tissue disorders	4 (11.4%)
Psychiatric disorders	4 (11.4%)
Metabolism and nutrition disorders	3 (8.6%)
Cardiac disorders	3 (8.6%)
Eye disorders	2 (5.7%)
Ear and labyrinth disorders	2 (5.7%)
Musculoskeletal, connectives tissues disorders	2 (5.7%)
Vascular disorders	1 (2.9%)
Social circumstances	1 (2.9%)

[a] Each case can correspond to multiple seriousness criteria.
[b] Each case can correspond to 1 or more SOCs.

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Our study is based on the use of VigiBase®, a global pharmacovigilance database, with information from a variety of sources. The likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The Uppsala Monitoring Centre has provided the data but the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, National Centers, or WHO.

Disclosure of interest

The authors declare that they have no competing interest.

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