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Incidence of narcolepsy symptoms after taking COVID-19 vaccines: a Jordanian cross-sectional study

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Purpose: Sleeping disorders were reported in many patients who took vaccines during previous pandemics. We aim to investigate the relationship between coronavirus disease 2019 (COVID-19) vaccines and the incidence of narcolepsy symptoms in the Jordanian population.

Materials and Methods: We used a descriptive, cross-sectional, online self-administered survey conducted between December 2022 and May 2023. The survey targeted males and females above the age of 18 years who took any type of COVID-19 vaccine, had no chronic diseases, and had no sleep disorders prior to taking the vaccine. The survey was distributed via social media platforms.

Results: A total of 873 participants were included in this study, consisting of 44.4% males and 55.6% females, with the majority being in the 18–29 age group. Most participants (79.8%) received two vaccine doses, with the Pfizer vaccine being the most common. Nearly half of the participants reported excessive daytime sleepiness. Sleep paralysis and hypnagogic hallucinations were reported by a notable proportion of participants, but no significant differences were found among the vaccine types. Sleep attacks and fragmented nighttime sleep were associated with the number of vaccine doses received, suggesting a possible influence of the dose count on these symptoms. The presence of excessive daytime sleepiness, sudden loss of muscle tone, sleep paralysis, and hypnagogic hallucinations showed no significant association with the number of doses taken.

Conclusion: We hypothesize a possible link between COVID-19 vaccination and the emergence of narcolepsy symptoms in Jordanian individuals. Additional investigations and continuous monitoring to determine the extent of the risk and uncover potential mechanisms behind this connection should be performed.

Keywords: Narcolepsy, COVID-19 vaccines, Sleep wake disorders, Orexins

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which affects the upper and lower respiratory tracts [1]. It was first identified in the city of Wuhan-China in late 2019 before becoming a global pandemic [2]. According to "Our World in Data," between January 2020 and June 2023, the total reported cases of COVID-19 were about 767 million people and the total deaths of it were approximately 6.93 million [3].

The first COVID-19 vaccine to be approved by the U.S. Food and Drug Administra-

tion was Pfizer-BioNTech in December 2020 [4]. Four types of vaccines approved to be used in Jordan. These are Pfizer-BioNTech vaccine (Pfizer, New York, NY, USA), Oxford-AstraZeneca vaccine (AstraZeneca, Cambridge, UK), Sinopharm vaccine (Sinopharm, Beijing, China), and Sputnik V vaccine (Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia) [5]. Like the other vaccines, these have some adverse effects. Systemic side effects include fever, headaches, fatigue, vomiting, diarrhea, muscle pain, joint pain, cough, nausea, dyspnea, impaired appetite, dizziness, mucosal abnormalities, pruritus, hypersensitivity, syncope, asthenia, rhinorrhea, malaise, sore throat, oropharyngeal pain, hives, and nasal congestion [6]. Local side effects to the injection site include pain, induration, erythema, pruritus, and muscle weakness [6]. Sleep disturbances were reported after taking certain vaccines [7].

COVID-19 vaccines have altered the course of the pandemic dramatically, saving about 10 million lives in its first year [8]. However, its side effects should not be disregarded and must be addressed in order to improve compliance with the future vaccinations [9]. Sleep disturbance as minor to moderate side effects after Pfizer-BioNTech COVID-19 vaccination was reported [10,11].

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis [12]. The diagnosis of narcolepsy is made by the clinical features along with the supportive biomarkers: evidence of rapid eye movement sleep periods soon after sleep onset; cerebrospinal fluid orexin deficiency; and positivity for HLA-DQB1*06:02 [13].

In a cohort study published in 2021, sleep-related side effects were reported after taking the ASO3-adjuvanted H1N1 pandemic influenza vaccine [7]. These include daytime napping, attention deficit, nightmares, nocturnal waking, and sleep talking [7]. In the same study, all of the included patients reported symptoms of narcolepsy with different percentages of its symptoms [7]. In another systemic review and meta-analysis study made in 2018, an increased incidence of narcolepsy was noted in many countries after the pandemic H1N1 influenza vaccination campaign in 2009–2010 [14]. This study reported an increased relative risk of narcolepsy by 5 to 14-fold in children and adolescents and 2 to 7-fold in adults [14].

This study seeks to examine the correlation between COVID-19 vaccines and the manifestation of narcolepsy symptoms among the population of Jordan. Furthermore, it aims to explore the potential mechanisms through which these vaccines could contribute to or pose a risk for narcolepsy.

Materials and Methods

Study design

In our study, we used a descriptive, cross-sectional, online self-administered survey between December 2022 and May 2023. The aim of this study is to establish the relationship between COVID-19 vaccines and the occurrence of narcolepsy symptoms in Jordanian population. Also, another goal is to study the mechanism of which these vaccines may cause, or be a risk factor of, narcolepsy.

An anonymous questionnaire was distributed via social media platforms, including Facebook, Instagram, WhatsApp, and Twitter across Jordan. No direct contact with the participants was made during data collection.

Study population

The study included males and females over the age of 18 years, took any type of COVID-19 vaccine, has no chronic diseases, and has no sleep disorder prior to taking the vaccine. Exclusion criteria were males and females below the age of 18 years, who has any chronic diseases, has a sleep disorder of any kind or has failed to complete at least 80% of the questionnaire.

Study tool

An online-based questionnaire created via Google Forms online survey software (Google LLC, Mountain View, CA, USA) was used in this study. It was first developed in Arabic and then translated into English. Back-translation into Arabic was used to ensure comprehensibility and content validity.

The questionnaire consists of 25 detailed self-report questions covering six integral domains. The first domain is the inclusion and exclusion criteria (four questions). The second domain deals with sex, the number of doses, the type of vaccine received, and the time passed since taking the last dose of the vaccine in months (four questions). The third category includes questions related narcolepsy symptoms after vaccination (16 questions) and the last question was about people's opinion regarding whether these symptoms were related to COVID-19 vaccines or not.

A pilot study was conducted that included 25 participants to look for any faults that might exist and ensure the validity and reliability of the overall questionnaire. Accordingly, the

survey was reviewed again by a group of consultants from the Department of Neurology at New Zarqa Governmental Hospital to ensure the validity of the construction prior to distribution. The 25 participants in the pilot study were excluded from the main study and subsequent analyses.

Data collection procedure

An anonymous free online survey was used to collect responses over 6 months, directing males and females who have received at least one dose of the COVID-19 vaccine and live in Jordan. The questionnaire was shared and advertised via several social media groups, and participants were encouraged to share it with their friends and families in order to maximize the sample size. It took less than 5 minutes to complete all the questions.

The ethical committee at New Zarqa Governmental Hospital approved this observational cross-sectional study (approval number: ZNH-220710). This study was carried out in accordance with the Helsinki Declaration regulations. In our study, the ethical standards of voluntary participation were followed, and the participants' rights to privacy, anonymity, and self-determination are protected. Informed consent was waived. The aims of the study were explained, and the confidentiality of the data collected was ensured.

Statistical analysis

In our analysis, we used IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis in the form of means (standard deviation) was used in describing the collected data. Chi-square test was used to examine the relationship between study factors. Statistical significance was defined as a p-value equal to or less than 0.05.

Results

A total of 990 participants have completed the form. However, 873 met the inclusion criteria and 17 participants were excluded from this study.

These results represent 873 participants of the Jordanian population who received COVID-19 vaccines. The tables depict the demographic characteristics of the participants and the distribution of various cataplexy symptoms and their relationship with the vaccination history.

The presented research findings in Table 1 outline the demographic distribution and vaccination-related attributes of the study participants. The sample comprised 388 males (44.4%) and 485 females (55.6%). In terms of age, the majority fell within the 18–29 age group (51.2%), followed by the 30–49 years group (27.8%) and individuals over 50 years (21%). Among the participants, a significant proportion received two vaccine doses (79.8%), while 16.4% received three doses, 2.9% received a single dose, and 0.9% received four doses. The Pfizer vaccine was the most administered (58.6%), followed by Sinopharm (28%), AstraZeneca (6.3%), and a mixed vaccine regimen (7.1%). Furthermore, a considerable proportion of participants (68.8%) had received their first dose more than a year ago, while 25.7% received it within 7–12 months, and 5.5% received it within 6 months.

Table 1. The demographic characteristics and vaccination history of the participants (N=873)

Characteristic	No. (%)
Sex	
Male	388 (44.4)
Female	485 (55.6)
Age group (yr)	
18–29	447 (51.2)
30–49	243 (27.8)
≥50	183 (21.0)
No. of doses taken	
Single dose	25 (2.9)
2 Doses	697 (79.8)
3 Doses	143 (16.4)
4 Doses	8 (0.9)
The type of vaccine taken	
Pfizer	512 (58.6)
Sinopharm	244 (28.0)
AstraZeneca	55 (6.3)
Mixed	62 (7.1)
The time period from the 1st dose	
≤6 mo	48 (5.5)
7–12 mo	224 (25.7)
>1 yr	601 (68.8)

In this research, participants were surveyed regarding various cataplexy symptoms and their vaccination history. The results were summarized in Table 2. Approximately half of the participants (48.7%) reported experiencing excessive daytime sleepiness. Among those with excessive daytime sleepiness, the distribution of vaccine types taken showed a slightly higher prevalence of Pfizer (50.6%) and Sinopharm (48.8%) vaccines. Furthermore, a significant portion of participants (53.2%) reported never experiencing a sudden loss of muscle tone (cataplexy). Interestingly, recipients of the AstraZeneca vaccine re-

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Table 2. Distribution of various cataplexy symptoms and their relationship with the vaccination history (N=873)

Variable	Total	The type of vaccine taken					No. of doses taken				
		Pfizer	Sinopharm	AstraZeneca	Mixed	p-value	1	2	3	4	p-value
Excessive daytime sleepiness						0.23					0.31
Yes	425 (48.7)	259 (50.6)	119 (48.8)	23 (41.8)	24 (38.7)		10 (40.0)	348 (49.9)	65 (45.5)	2 (25.0)	
No	448 (51.3)	253 (49.4)	125 (51.2)	32 (58.2)	38 (61.3)		15 (60.0)	349 (50.1)	78 (54.5)	6 (75.0)	
Sudden loss of muscle tone (cataplexy)						0.74					0.029
Never	464 (53.2)	259 (50.6)	134 (54.9)	34 (61.8)	37 (59.7)		20 (80.0)	352 (50.5)	84 (58.7)	8 (100.0)	
Rarely	70 (8.0)	45 (8.8)	17 (7.0)	4 (7.3)	4 (6.5)		1 (4.0)	61 (8.8)	8 (5.6)	0	
More than once a month	124 (14.2)	79 (15.4)	33 (13.5)	5 (9.1)	7 (11.3)		0	101 (14.5)	23 (16.1)	0	
More than once a week	137 (15.7)	83 (16.2)	34 (13.9)	9 (16.4)	11 (17.7)		1 (4.0)	118 (16.9)	18 (12.6)	0	
Daily	78 (8.9)	46 (9.0)	26 (10.7)	3 (5.4)	3 (4.8)		3 (12.0)	65 (9.3)	10 (7.0)	0	
Sleep paralysis						0.45					0.86
Yes	178 (20.4)	112 (21.9)	48 (19.7)	8 (14.6)	10 (16.1)		4 (16.0)	142 (20.4)	31 (21.7)	1 (12.5)	
No	695 (79.6)	400 (78.1)	196 (80.3)	47 (85.4)	52 (83.9)		21 (84.0)	555 (79.6)	112 (78.3)	7 (87.5)	
Hypnagogic hallucinations						0.45					0.80
Yes	137 (15.7)	72 (14.1)	43 (17.6)	10 (18.2)	12 (19.3)		4 (16.0)	106 (15.2)	25 (17.5)	2 (25.0)	
No	736 (84.3)	440 (85.9)	201 (82.4)	45 (81.8)	50 (80.7)		21 (84.0)	591 (84.8)	118 (82.5)	6 (75.0)	
Sleep attacks						0.017					0.67
Yes	219 (25.1)	141 (27.5)	62 (25.4)	6 (10.9)	10 (16.1)		8 (32.0)	172 (24.7)	38 (26.6)	1 (12.5)	
No	654 (74.9)	371 (27.5)	182 (74.5)	49 (89.1)	52 (83.9)		17 (68.0)	525 (75.3)	105 (73.4)	7 (87.5)	
Fragmented nighttime sleep						0.015					0.016
Yes	369 (42.3)	230 (44.9)	105 (43.0)	14 (25.4)	20 (32.3)		6 (24.0)	306 (43.9)	57 (39.9)	0	
No	504 (57.7)	282 (55.1)	139 (57.0)	41 (74.6)	42 (67.7)		19 (76.0)	391 (56.1)	86 (60.1)	8 (100.0)	

Values are presented as number (%).

corded the lowest percentage of sudden loss of muscle tone compared to recipients of other vaccinations (38.2%). A notable proportion of participants reported experiencing sleep paralysis (20.4%) and hypnagogic hallucinations (15.7%). However, there was no significant difference in the distribution of vaccine types taken among those who reported these symptoms. Additionally, sleep attacks were reported by 25.1% of the participants, and those experiencing sleep attacks showed a slightly higher prevalence of Pfizer (27.5%) and Sinopharm (25.4%) vaccines. Lastly, fragmented nighttime sleep was reported by 42.3% of the participants, and those with this symptom showed a higher prevalence of Pfizer (44.9%) and Sinopharm (43.0%) vaccines. There was a significant association between sleep attacks and fragmented nighttime sleep with the type of vaccine taken (p-value=0.017 and 0.015, respectively).

There was no significant association between the number of doses taken and the presence of excessive daytime sleepiness. Similar findings were observed for the symptoms of sudden loss of muscle tone (cataplexy), sleep paralysis, and hypnagogic hallucinations. However, participants who reported experiencing sleep attacks showed a significant association with the number of doses taken (p-value=0.017). Additionally, fragmented nighttime sleep was significantly associated with the number of doses (p-value=0.015). These findings suggest that the occurrence of sleep attacks and fragmented nighttime sleep may be influenced by the number of doses received.

Discussion

Our study investigated the incidence of narcolepsy symptoms following COVID-19 vaccination in the Jordanian population. Our findings revealed a notable occurrence of narcolepsy symptoms among vaccinated individuals.

Previous research has linked the adjuvanted pandemic influenza A (H1N1) vaccines, such as Pandemrix, with an increased risk of narcolepsy in certain populations [15,16]. These studies primarily focused on European populations and suggested an association between Pandemrix vaccination and narcolepsy, particularly in children and adolescents [15,16]. The underlying mechanism for this association is hypothesized to involve an autoimmune response triggered by the vaccine [17].

In our study, we observed a concerning incidence of narcolepsy symptoms following COVID-19 vaccination. These findings are significant and warrant further investigation into the potential association between COVID-19 vaccines and narcolepsy. It is important to note that our study did not explore the specific mechanisms underlying this observed association. However, a recent hypothesis proposed that proinflammatory cytokines interleukin (IL) 1 (IL-1a and IL-1b) and tumor necrosis factor-α (TNF-α) may propagate a peripheral inflammatory response after vaccination, causing reactogenic sleepiness and narcolepsy symptoms [18].

The innate immune system communicates information to the brain through cytokine signaling [19,20], and this includes the processing of reactogenic systemic symptoms that may indicate disrupted arousal states, such as increased sleepiness and decreased sleep quality. However, there is a scarcity of studies investigating changes in sleep following vaccination [20,21].

The study suggested that orexin hypothalamic neurons, which are essential neural substrates in the brain that regulate wakefulness, arousal, and appetite, and mediate some aspects of sickness behavior [22], have a major role in the occurrence of sleepiness following activation of the innate immune system in response to certain COVID-19 vaccines [18]. The study concluded a possible connection between reactogenic inflammatory factors and the hypothalamic circuits involved in regulating the sleep-wake cycle. This response activates a specific group of GABAergic neurons as well as inhibitory neurons from sleep-promoting regions, resulting in the inhibition of wake-promoting orexin neurons. Additionally, the adenosinergic modulation of sleep-wake signals, in the context of neuron-glial interactions, may also play a role in this process.

The emergence of narcolepsy symptoms following COVID-19 vaccination raises several critical considerations [23]. First, it is essential to differentiate between coincidental occurrences and causation. Although we observed an increased incidence of narcolepsy symptoms, additional studies employing rigorous methodologies are necessary to establish a causal relationship between COVID-19 vaccination and narcolepsy symptoms [24]. Addressing these symptoms is crucial because sleep deprivation and other sleep disorders have been linked to many chronic diseases. These include hypertension, diabetes, stroke, obesity, and depression [25].

Furthermore, it is crucial to evaluate the specific COVID-19 vaccine formulations used in our study population and their potential contribution to the observed narcolepsy symptoms. The examination of vaccine components, including adjuvants or other ingredients. Several studies linked sleepiness and other narcolepsy symptoms to the vaccine formulations and how they might trigger an immunologic response, causing reactionary sleepiness [10,26-29]. The majority of these studies reported immuno-reactogenic responses to the vaccines or a component of them [10,27-29].

These findings highlight the importance of post-vaccination surveillance and pharmacovigilance systems to identify and assess potential adverse events associated with COVID-19 vaccines. Robust monitoring systems can promptly detect and evaluate any safety concerns, ensuring the ongoing safety and effectiveness of vaccination campaigns.

It is worth noting that our study has certain limitations. The cross-sectional design restricts our ability to establish a temporal relationship between vaccination and the onset of narcolepsy symptoms. Additionally, the study's sample size and scope may limit the generalizability of our findings to larger populations. In addition, the online questionnaire was disseminated via social media, which carries a high risk of selection and reporting bias, and the questionnaire could have been circulated among anti-vaxxers. However, based on our knowledge of the study population, this is highly unlikely.

Future studies should aim to address these limitations and further investigate the association between COVID-19 vaccination and narcolepsy.

In conclusion, our study suggests a potential association between COVID-19 vaccination and the development of narcolepsy symptoms in the Jordanian population. These findings emphasize the need for further research and ongoing surveillance to determine the magnitude of the risk and to identify potential mechanisms underlying this association. Assessing the risk-benefit ratio of COVID-19 vaccination in relation to narcolepsy is crucial to guide public health decision-making and ensure the safety of vaccination efforts.

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