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Review Article

Psychiatric adverse events associated with the COVID-19 vaccines approved in the Republic of Korea: a systematic review

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ABSTRACT

This systematic review evaluated psychiatric adverse events (AEs) following vaccination against coronavirus disease 2019 (COVID-19). We included studies that reported or investigated psychiatric AEs in individuals who had received an approved COVID-19 vaccine in the Republic of Korea. Systematic electronic searches of Ovid-Medline, Embase, CENTRAL, and KoreaMed databases were conducted on March 22, 2023. Risk of bias was assessed using the Risk of Bias Assessment Tool for Non-randomized Studies 2.0. The study protocol was registered in the International Prospective Register of Systematic Reviews (CRD42023449422). Of the 301 articles initially selected, 7 were included in the final analysis. All studies reported on sleep disturbances, and 2 highlighted anxiety-related AEs. Sleep disorders like insomnia and narcolepsy were the most prevalent AEs, while depression was not reported. Our review suggests that these AEs may have been influenced by biological mechanisms as well as the broader psychosocial context of the COVID-19 pandemic. Although this study had limitations, such as a primary focus on the BNT162b2 vaccine and an observational study design, it offered a systematic, multi-vaccine analysis that fills a critical gap in the existing literature. This review underscores the need for continued surveillance of psychiatric AEs and guides future research to investigate underlying mechanisms, identify risk factors, and inform clinical management.

Keywords: Adverse effects; Anxiety; COVID-19 vaccines; Mental disorders; Sleep wake disorders; Systematic review

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Introduction

As a global health crisis, the coronavirus disease 2019 (COVID-19) pandemic has had profound

effects on nearly all aspects of society. In response to the pandemic, several vaccines have been introduced, with Pfizer-BioNTech's BNT162b2, Moderna's mRNA-1273, and Oxford-AstraZeneca's ChAdOx1 nCoV-19 predominantly utilized. As recorded on July 22, 2023, global administration surpassed 13 billion vaccine doses [1]. Despite the substantial benefits of the COVID-19 vaccines, safety concerns about these new vaccines persist. These concerns are often amplified by inaccurate media reporting, potentially heightening vaccine hesitancy in the public [2]. Hence, comprehensive understanding and precise reporting on the nature and prevalence of any adverse events (AEs) related to COVID-19 vaccines are crucial.

No medical intervention is entirely free from the potential for AEs, and COVID-19 vaccines are no exception. Following COVID-19 vaccination, AEs can present as a spectrum of physical symptoms and psychiatric manifestations. Serious, albeit rare, AEs such as myocarditis/pericarditis, thrombosis with thrombocytopenia syndrome, and Guillain-Barré syndrome have been reported [3]. Other less severe but notable symptoms have been consistently reported, including localized pain at the injection site, fatigue, headache, fever, nausea, and psychiatric symptoms such as anxiety and poor-quality sleep [4,5].

Of particular concern is the emergence of psychiatric symptoms after COVID-19 vaccination, an area of study that requires further exploration. The COVID-19 pandemic has already significantly impacted mental health worldwide, influenced in part by fear of the virus, lockdown mandates, and enforced social distancing [6,7]. Therefore, discerning the relationship between COVID-19 vaccination and the onset or exacerbation of psychiatric symptoms is highly important. To date, only one review has sought to synthesize the available evidence on this topic, focusing on published case reports [8].

Therefore, the present systematic review aimed to collate and analyze the existing literature on psychiatric AEs following COVID-19 vaccination. It sought to address the research question: What is the nature and extent of psychiatric AEs after COVID-19 vaccination, and what implications do these findings have for healthcare providers and policymakers?

HIGHLIGHTS

- This review systematically investigated psychiatric adverse events (AEs) following COVID-19 vaccination.
- In the studies reviewed, sleep disturbances such as insomnia and narcolepsy emerged as the most prevalent AEs, while depression was notably absent.
- Biological and psychosocial factors may influence the onset of these psychiatric AEs.
- The study fills a critical gap in the existing literature and calls for ongoing surveillance and further research.

Materials and Methods

The systematic review was conducted in accordance with the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [9], and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement [10]. The study protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (number: CRD42023449422). The authors are psychiatric and epidemiological experts and consultation was received from external reviewers specializing in the epidemiology of vaccine AEs.

Eligibility Criteria

Articles that matched the following criteria were considered: (1) studies of individuals vaccinated against COVID-19 with any vaccine approved in the Republic of Korea, including BNT162b2, mRNA-1273, Ad26.COV2.S, ChAdOx1 nCoV-19, NVX-CoV2373, and bivalent mRNA vaccines; (2) studies that reported on psychiatric AEs, with primary outcomes being anxiety and sleep disorders (e.g., narcolepsy and insomnia) and secondary outcomes covering panic attacks, depression, brain fog, and other psychiatric manifestations; and (3) either population-based or national-level studies.

Information Sources

A systematic electronic search of Ovid-Medline, Embase, CENTRAL, and the Korean database KoreaMed was conducted on March 22, 2023.

Search Strategy

The key terms included in the search were "COVID-19," "vaccine," "mental health," "sleep disorder," "depression," and "psychotic." A librarian was involved in establishing and conducting the search strategy. A manual search of the reference lists of relevant primary and review articles was also conducted to ensure comprehensiveness. The full electronic search strategy for each database is provided in Table S1.

Selection Process

Two reviewers (S.R. and M.C.) independently screened the titles and abstracts of all identified studies to assess eligibility for inclusion. Relevant full-text articles were then independently

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appraised by the same reviewers. Disagreements during the review process were addressed by consensus with a third review author (S.O.). The study selection was performed using Covidence software (Veritas Health Innovation) [11].

Data Collection Process

Two independent reviewers (S.R. and M.C.) conducted the data extraction process with one extracting the data and the other verifying the accuracy of the extracted data. The data extraction form included study characteristics and outcomes.

The data were primarily extracted from tables and figures within the studies, and supplementary files were consulted for additional detail when feasible. If supplementary material was not available, the intention-to-treat principle was used to impute missing data when possible.

Risk of Bias Assessment

The authors used the Risk of Bias Assessment Tool for Non-randomized Studies 2.0 to conduct a paired assessment for the risk of bias in the selected non-randomized studies [12].

Effect Measures

For each included study, continuous outcomes were presented as mean differences or hazard ratios, inverse-variance random-effects analysis and dichotomous outcomes were presented as odds ratios (ORs), and Mantel-Haenszel random-effects analysis with 95% confidence intervals (CIs) was applied to all outcome measures. The AEs in the vaccination studies were quantified using metrics such as rate ratios, ORs, or incidence rates and their 95% CIs.

Synthesis Methods

A meta-analysis was initially planned for studies demonstrating minimal heterogeneity. However, due to considerable heterogeneity and substantial differences in the study populations and methodologies among the included studies, conducting a meta-analysis was not feasible. Consequently, we pooled the results using a narrative synthesis, which provided a qualitative overview of the findings according to the synthesis without meta-analysis reporting guidelines [13].

Results

Study Selection

The initial search of the electronic databases yielded 301 articles. After removing duplicates, 222 articles remained. Of these, 83 were excluded based on title and abstract screenings, leaving 139 full-text reports for eligibility assessment. Ultimately, 7 studies were included in the final systematic review (Figure 1).

Study Characteristics

Of the 7 studies selected, all reported sleep disorders such as narcolepsy and insomnia. In addition, 2 studies documented cases of anxiety, while panic attacks, agitation, and brain fog were each reported in a single study. The characteristics and findings of the included studies are summarized in Table 1 [14–20].

Risk of Bias

The risk of bias assessment is presented in Figure S1 of the supplementary material. Notably, most studies demonstrated a low risk of bias, though there were concerns regarding outcome blinding and comparability of the target groups.

Results of Individual Studies

Sleep disturbance

One study focused on adolescents aged 12 to 18 years and found that the risk of developing sleep disturbances was significantly increased for those who received the BNT162b2 vaccine compared to those who were unvaccinated (IRR, 2.06; 95% CI, 1.01–4.24) [14]. Another self-controlled case-series study reported no significant difference in the

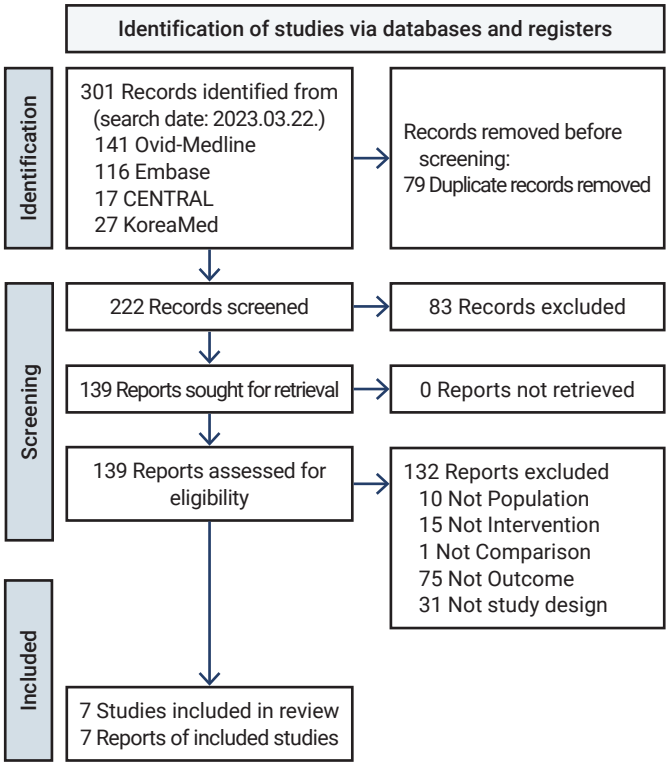

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analysis flow diagram for a systematic review of psychiatric adverse events following COVID-19 vaccination.

Table 1. Studies addressing psychiatric adverse events after COVID-19 vaccination

Study	Study site	Data source	Population (y)	No. of patients included in analysis	Intervention	Comparator	Study design	Outcome	Results
Wan et al. (2022) [15]	Hong Kong	National registry	People with type 2 diabetes (≥16)	141,224 BNT162b2 recipients	BNT162b2	Self-control	Self-controlled case series	Narcolepsy	The incidence of narcolepsy was not significantly different after vaccination with BNT162b2 (1st dose: IRR, 1.02; 2nd dose: IRR, 0.60) than before vaccination.
Wong et al. (2022) [18]	Hong Kong	National registry	Adults (≥18)	BNT162b2 1st: 1,308,820 BNT162b2 2nd: 1,116,677	BNT162b2	N/A	Retrospective observational study	Sleeping disturbance or disorder	The incidence rate of sleep disturbance by vaccine dose was as follows: BNT162b2 1st dose: 122 cases/100,000 doses; 167 cases/100,000 person-years BNT162b2 2nd dose: 91 cases/100,000 doses; 142 cases/100,000 person-years
Lai et al. (2022) [14]	Hong Kong	National registry	12–18	BNT162b2 1st: 138,141 BNT162b2 2nd: 119,664	BNT162b2	Unvaccinated	Retrospective observational study	Sleeping disturbance or disorder	A statistically significant difference in sleep disturbance was observed after the 2nd dose of the Pfizer vaccine compared to the unvaccinated group (IRR, 2.06; 95% CI, 1.01–4.24).
Lloyd et al. (2022) [16]	USA	Claim data	12–64	5,070,372 in Optum 7,445,051 in Healthcore 4,326,594 in CVS Health	BNT162b2, mRNA-1273, Ad26.COV2.S	Historical control (general population or influenza-vaccinated)	Nonconcurrent cohort study	Narcolepsy	The RR of narcolepsy and the frequency of narcolepsy cases per 100,000 doses of vaccine by data source and vaccine type are as follows: Optum: BNT162b2 RR 0.74; 2.6/mRNA-1273 RR 0.78; 3.2/Ad26.COV2.S RR 1.01; 4.9 HealthCore: BNT162b2 RR 1.07; 3.4/mRNA-1273 RR 1.02; 3.6/Ad26.COV2.S RR 0.94; 3.9 CVS Health: BNT162b2 RR 1.35; 3.4/mRNA-1273 RR 1.36; 3.8/Ad26.COV2.S RR 1.63; less than 5.5
Garcia-Alanis et al. (2022) [19][a)]	Mexico	National registry	Adults (≥18)	19,163 Individuals who reported adverse events	BNT162b2, ChAdOx1 nCoV-19, rAd26-rAd5, Ad5-nCoV, CoronaVac	N/A	Retrospective observational study	Anxiety, panic attack, insomnia, agitation	129 Cases of anxiety, 30 cases of panic attack, 25 cases of insomnia, and 11 cases of agitation were reported after COVID-19 vaccination with BNT162b2 or ChAdOx1 nCov-19.
Abdel-Qader et al. (2022) [17]	Jordan	National registry	Adults (≥18)	BNT162b2 1st: 418,517 BNT162b2 2nd: 192,074 ChAdOx1 nCoV-19 1st: 80,281 ChAdOx1 nCoV-19 2nd: 60,562	BNT162b2, ChAdOx1 nCoV-19	N/A	Prospective observational study	Insomnia, brain fog	The incidence of insomnia by vaccine type was as follows: BNT162b2 1st / 2nd dose: 1,182 cases (0.3%)/2,503 cases (1.3%) ChAdOx1 nCoV-19 1st / 2nd dose: 4.702 cases (5.9%)/2,558 cases (4.2%) The incidence of brain fog by vaccine type was as follows: BNT162b2 1st/2nd dose: 449 cases (0.1%)/152 cases (0.1%) ChAdOx1 nCoV-19 1st / 2nd dose: 5,103 cases (6.4%)/2,993 cases (4.9%)

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Table 1. Continued

Study	Study site	Data source	Population (y)	No. of patients included in analysis	Intervention	Comparator	Study design	Outcome	Results
Alkhalifah et al. (2023) [20]	Saudi Arabia	National registry	12–96	28,031 Individuals who reported adverse events	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19	N/A	Retrospective observational study	Anxiety, sleep disruption	The incidence of insomnia (p = 0.48)/sleep disruption (p = 0.022) by vaccine type was as follows: BNT162b2: 221 cases (0.58%)/487 cases (1.27%) ChAdOx1 nCoV-19: 207 cases (0.64%)/463 cases (1.44%) mRNA-1273: 5 cases (0.53%)/17 cases (1.79%)

COVID-19, coronavirus disease 2019; N/A, not applicable; IRR, incidence rate ratio; CI, confidence interval; RR, rate ratio.
[a]An estimated 88% of the total received vaccination with BNT162b2 or ChAdOx1 nCoV-19.

incidence of narcolepsy between the BNT162b2 vaccinated and unvaccinated patients with type 2 diabetes during the risk period versus the comparison period. The dose of the vaccine was also not linked to the outcome[15].

However, 3 studies did provide insights into the incidence rate of sleep disturbance by vaccine type [16–18], reporting 0.16 cases per 1,000 mRNA vaccine doses and 49.79 cases per 1,000 adenoviral vector vaccine doses. Two other studies, instead of reporting the total number of vaccinated individuals, highlighted the total AEs and specific cases of sleep disturbance [19,20]. One of these studies reported 25 cases of insomnia among 19,163 reported AEs after COVID-19 vaccination [19]. Another study revealed 487, 17, and 463 cases of sleep disturbance following vaccinations with BNT162b, mRNA-1273, and ChAdOx1 nCoV-19, respectively, as registered in the Saudi Arabia National Adverse Events Registry for recipients aged 12 to 96 years. These results showed a significant difference in the incidence of sleep disturbances by vaccine type (p = 0.022) [20].

Anxiety and cognitive AEs

Among the studies in our review, 2 reported anxiety-related AEs following COVID-19 vaccination [19,20]. One study noted that, out of 19,163 reported AEs, there were 129 cases of anxiety, 30 cases of panic attacks, and 11 cases of agitation [19]. The other study included 28,031 individuals who had reported 71,480 AEs. Of these, 221 (0.58%), 207 (0.64%), and 5 (0.53%) cases of anxiety were reported after the administration of the BNT162b, ChAdOx1 nCoV-19, and mRNA-1273 vaccines, respectively. However, no statistically significant differences were found in the proportion of anxiety cases between these vaccine types [20]. Regarding cognitive disturbances, another study reported incidences of brain fog following COVID-19 vaccination. Specifically, the mRNA vaccine was associated with 0.93 cases per 1,000 doses, whereas the adenoviral vector vaccine had a significantly higher incidence with 56.09 cases per 1,000 doses [17].

Discussion

The current review compiled findings from 7 studies investigating psychiatric AEs related to COVID-19 vaccines. Of the psychiatric manifestations observed after vaccination, sleep disturbance and anxiety were the most frequently reported. In contrast, depression was rarely documented. The selected studies all investigated AEs following vaccination with BNT162b2, and some studies included evaluations of the mRNA-1273, ChAdOx1 nCoV-19, and other vaccines. The varying incidence of sleep disorders among the different vaccine types suggests that a distinction in vaccine formulation or

its constituents might influence the susceptibility to specific adverse outcomes.

It is noteworthy that all studies included in our review reported sleep disorders such as insomnia or narcolepsy following COVID-19 vaccination. Although the biological mechanisms underlying these sleep disturbances remain elusive, several hypotheses have been proposed [21,22]. One recent study highlighted a link between postvaccination inflammatory reactions and certain hypothalamic circuits crucial to the sleep-wake cycle. Specifically, following peripheral activation of the innate immune system by the novel COVID-19 vaccines, pro-inflammatory cytokines potentially inhibit orexinergic neurons, resulting in enhanced sleepiness [21]. Alternately, the occurrence of postvaccination insomnia may be mediated by hyperarousal as well as inflammatory cytokines [23]. Stress and sleep share a significant correlation, with stressful life events often precipitating acute insomnia [24]. The inherent stress associated with receiving a novel COVID-19 vaccine during a global pandemic might activate the hypothalamic-pituitary-adrenal (HPA) axis, inducing a hyperarousal state that contributes to the onset of insomnia [25].

Two studies in this review reported anxiety and anxiety-related AEs after receiving a COVID-19 vaccination [19,20]. The emergence of postvaccination anxiety symptoms might be attributed to the HPA and immune axes [26], similar to the proposed mechanisms underlying sleep disturbances. Beyond these biological underpinnings, it is also vital to account for social and psychological influences. In the early stages of the COVID-19 pandemic, global anxiety levels escalated and were further exacerbated by the emergency authorization of new vaccines [27]. Given this context of widespread apprehension, we must be cautious about directly linking postvaccination anxiety symptoms solely to the vaccine. Monitoring the persistence of such anxiety reports over time remains essential.

Brain fog following immunization with COVID-19 vaccines was also reported in one study [17]. Brain fog is a nonspecific cognitive symptom characterized by lack of mental clarity, difficulty concentrating, and mental fatigue. This syndrome of cognitive impairment is commonly associated with post-COVID conditions (also called "long COVID") [28]. Several mechanisms have been suggested to explain brain fog after COVID-19 illness [29,30]. However, the association between COVID-19 vaccines and this cognitive impairment remains unclear. Postvaccination brain fog might be more closely linked to flu-like symptoms (e.g., headache, fatigue, fever) than to previously defined cognitive symptoms [31]. Interestingly, active safety surveillance data from Jordan showed a higher incidence of reported brain fog with the ChAdOx1 nCoV-19 vaccine than the BNT162b2 vaccine [17]. This suggests that systemic AEs such as headache, fatigue, and fever appear more prevalent following administration of the adenoviral vector vaccine than the mRNA counterpart [32]. Further research should be done to determine a direct link between the vaccine and genuine cognitive impairment.

One unanticipated observation from the studies included in our review was the absence of reports on postvaccination depression or psychosis. In contrast, a prior review identified 11 articles that documented 14 cases of psychiatric AEs, predominantly psychosis and mood disorders [8]. This discrepancy may be attributed to differences in study design. Our review sourced data from population-based or national-level studies, which are inclined to report the more common, milder AEs. In contrast, the earlier review was based on case reports, which tend to document the less frequent and more severe side effects like psychosis. Despite their relative infrequency in national databases of COVID-19 AEs, case reports of serious psychiatric AEs continue to be published with some regularity [8]. Regarding psychosis in particular, several hypotheses have been proposed to explain the potential mechanisms following COVID-19 vaccination [33,34], underscoring the need for careful monitoring of these reports.

In examining COVID-19 vaccine safety, our review specifically focused on psychiatric AEs. While 2 previous systematic reviews were conducted to assess the range of AEs following COVID-19 vaccination [35,36], it is notable that neither review distinctly categorized the psychiatric AEs. This lack of distinction can be attributed to the multifaceted nature of AE reporting and the challenges in isolating psychiatric symptoms from other systemic reactions. Our review attempts to fill this gap by specifically highlighting and analyzing psychiatric AEs. This focus is crucial, considering the potential impact of these AEs on the quality of life and the psychosocial burden they may impose.

Several limitations to our review need to be acknowledged. First, it predominantly relied on studies evaluating the BNT162b2 vaccine, with fewer studies examining other vaccines. This imbalance could skew the generalizability of our findings to other vaccines. Second, most of the selected articles were observational, which inherently poses a risk of uncontrolled confounding variables. Third, the lack of adequate control arms in most of the included studies precluded meta-analysis, limiting our ability to synthesize data quantitatively. Lastly, the literature we included revealed gaps in reporting serious psychiatric AEs like mood disorders and psychosis, highlighting areas for more comprehensive research.

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Conclusion

The current review identified a spectrum of psychiatric AEs following COVID-19 vaccination, with the notable prominence of sleep disturbances and anxiety. These AEs are relatively uncommon, nonserious, and seem to be multifactorial in nature. A direct causative link between the vaccines and psychiatric symptoms, however, has not yet been definitively established. Therefore, further research is essential to elucidate causality, determine potential risk factors associated with these AEs, and inform proactive measures. We support the need for ongoing surveillance and management of psychiatric reactions to COVID-19 vaccines, while acknowledging the pivotal role that vaccines continue to play in controlling the pandemic.

Supplementary Material

Table S1. Search strategies; **Figure S1.** Risk of bias. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0325.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
All data generated or analyzed during this study are included in this article. Other data are available upon request from the corresponding author.

Authors' Contributions
Conceptualization: MC, SO; Data curation: SR; Formal analysis: SR; Funding acquisition: MC, BJP; Investigation: SR, MC; Methodology: MC, SO; Project administration: MC; Resources: MC; Software: SR; Supervision: MC, BJP, OS; Validation: NKC, HSS, JHW, BJP; Visualization: SR; Writing–original draft: SR, MC, SO; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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