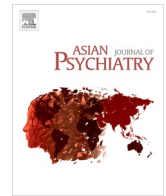




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Short communication

Psychiatric adverse reactions to COVID-19 vaccines: A rapid review of published case reports

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ABSTRACT

We aimed to review the available reports of psychiatric adverse reactions to COVID vaccines. Electronic databases such as PubMed and Google scholar were combed to identify relevant reports. We found a total of 11 reports describing 14 cases of psychiatric reactions; these were mostly altered mental states, psychosis, mania, depression, and functional neurological disorder. The index case was commonly a young or middle-aged adult. All reports pertained to the use of either mRNA or vector-based vaccines. Symptom onset was within 10 days of vaccination in all cases; as such, this seems to be a high-risk period warranting vigilance.

1. Introduction

The ongoing COVID-19 pandemic represents the biggest public health crisis of our times with profound negative consequences on the health and livelihoods of people, social networks, and global economies. Based on prior experience with infectious pandemics, vaccination is considered to be the most effective solution to combat the ongoing pandemic. Regulatory bodies, such as the Food and Drugs Administration, have granted emergency use authorization for vaccines to circumvent the need for lengthy trials and limit the progress of the pandemic (Pandey et al., 2021). Following recovery from COVID-19 infection, a range of neuropsychiatric manifestations have been described; these have been attributed to a host of possible mechanisms including dysregulated immunomodulation (Jasti et al., 2021). It is of interest that this journal has had a focus on disseminating information related to psychiatric implications of COVID-19 (Tandon, 2021).

Since vaccination against COVID 19 virus induces an immune reaction similar to the actual infection, it can be expected to trigger similar sequelae. Case reports describing various psychiatric manifestations following COVID-19 infection have already appeared in literature. To date, there has been no attempt to synthesize available evidence in this regard despite its obvious practice and policy implications. Therefore, we conducted, what we believe, to be the first such review of reports pertaining to psychiatric sequelae following COVID-19 vaccination.

2. Search strategy and study selection

Two independent investigators searched MEDLINE through PubMed, without any search filters, and Google scholar using combinations of the following keywords: “COVID-19”, “SARS-CoV-2”, “vaccination” or “vaccine” to identify potentially relevant reports of psychiatric adverse events following COVID-19 vaccination. Additionally, reference lists of retrieved articles were hand searched to identify further articles that may have been missed in the search. We included all reports that described any primary psychiatric manifestation following administration of the vaccine; reports that described exacerbations of primary neurological conditions such as multiple sclerosis were excluded as were reports of encephalitis unless the presentation included psychiatric symptoms. There was no restriction on age. The search was updated till February 1, 2022 and yielded 396 results. Generated reports were screened independently by two investigators to identify articles that described psychiatric complications following COVID-19 vaccination. We found a total of 11 reports describing 14 cases that fit the a priori criteria; relevant data such as demographic details of the subject, type of vaccine administered, and nature and timeline of symptoms were extracted. The reports are grouped under broad diagnostic categories and discussed below. Table 1 summarizes the reports. As the aim of this report was to produce timely information in an emerging area, we did not conduct a risk of bias assessment for the included reports.

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3. Acute confusional states

There were three reports of altered mental status characterized by disorientation, hallucinations, and labile affect within 0–10 days of vaccination. These presentations were reported after second dose of ChAdOx1 nCoV-19 vaccine (Takata et al., 2021), mRNA-1273 COVID-19 vaccine (Hilaire et al., 2021), and first dose of AstraZeneca COVID-19 vaccine (Roberts et al., 2021), respectively. Two of these described males over 50 years of age (Hilaire et al., 2021; Roberts et al., 2021) and one described a 22-year-old female (Takata et al., 2021). None of them had a previous psychiatric history. Autoimmune encephalitis screen was negative for all of them. The patients were given inpatient supportive care and symptoms resolved in a week.

4. Psychosis

Five cases of psychosis were reported as an adverse effect of COVID vaccines. Reinfield and colleagues reported a 31-year-old male who developed psychotic symptoms after the 1st dose of an mRNA-based COVID-19 vaccine, and markedly worsened three weeks later after receiving the second dose. This patient had pre-morbid schizotypal personality traits; as such, the authors suggested that the vaccine could have been an epiphenomenon of the onset of schizophrenia (Reinfield et al., 2021). An 18-year-old woman developed psychotic symptoms on the same day of receiving 1st dose of AstraZeneca vaccine. Symptoms

started few hours after the vaccination with irrelevant talk. Over the next three days, it progressed to irritability, delusions of persecution and reference, and visual hallucinations. Because of the temporal correlation and because other causes, including delirium were excluded, a diagnosis of vaccine associated psychosis was considered (Grover et al. 2022). Similarly, Giné-Servén et al. described two cases of acute psychosis within a week following receipt of AstraZeneca vaccine (Giné-Servén et al., 2021). Another case of acute psychosis with catatonic features in a 20-year-old female was reported following 1st dose of the Pfizer-BioNTech COVID-19 vaccine (Flannery et al., 2021). Notably, all these reports described psychosis after Covid vaccination in young individuals.

5. Affective disorders

We found two reports of mania and one of depression following COVID vaccination. Yesilkaya et al. described two male patients, who presented with manic symptoms. Both of them had dysphoric mood, irritability, increased speech, delusions, and absent insight. One of them developed symptoms on the same day of 2nd dose of BNT162b2 mRNA vaccine and the other patient developed symptoms one day after his 1st dose (Yesilkaya et al., 2021). Another 74-year-old male developed depression after receiving the 1st dose of ChAdOx1-S/nCoV-19 adenoviral vector vaccine. Symptoms started two days after vaccination. Prominent symptoms were tiredness, low mood, dryness of mouth,

Table 1
- Psychiatric adverse events following COVID-19 vaccination.

S. No	Author, year	Age/sex of patient	Name of vaccine received (vaccine type)	Reported psychiatric adverse event	Time lag for onset of adverse event after vaccination	Key clinical features
1.	Takata et al. (2021)	42/F	Second dose of ChAdOx1 nCoV-19 vaccine (Viral vector vaccine)	Altered mental status	Few days	Alert but disoriented to time, person and place, agitated with labile affect, hallucinations (visual and tactile)
2.	Hilaire et al. (2021)	54/M	Second dose mRNA-1273 vaccine (mRNA vaccine)	Altered mental status	1 day	Altered mental status, headache and high fever. History of type 2 diabetes mellitus, atrial flutter, hypothyroidism, well-controlled seizure disorder, and a remote history of traumatic brain injury
3.	Roberts et al. (2021)	51/M	First dose of AstraZeneca vaccine (Viral vector Vaccine)	Altered Mental status	10 days	Disoriented to time and place, disordered thought, labile mood, auditory hallucinations
4.	Grover et al. (2022)	18/F	First dose of AstraZeneca's Vaxzevria (Viral vector vaccine)	Psychosis	Same day	Irritability, irrelevant speech, decreased sleep, delusions of persecution and reference, visual hallucinations.
5.	Flannery et al. (2021)	20 s/F	First dose of the Pfizer-BioNTech COVID-19 vaccine (mRNA Vaccine)	Psychosis	1 week	Decreased sleep, anxiety, auditory hallucinations, catatonia.
6.	Reinfield et al. (2021)	31/M	First dose mRNA-based COVID-19 vaccine (mRNA Vaccine)	Psychosis	Not specified	Auditory hallucinations, grandiose and erotomaniac delusions. History of Schizotypal traits
7.	Giné-Servén et al. (2021)	Not mentioned	AstraZeneca COVID-19 vaccine (Viral vector vaccine)	Psychosis (2 cases)	Acute (7 h and 12 days)	Cycloid psychosis-like phenotype and marked cognitive impairment
8.	Yesilkaya et al. (2021)	42/M	First dose of the BNT162b2 mRNA (mRNA vaccine)	Mania with psychotic symptoms	1 day	Irritability; sleeplessness; dysphoric mood; increased psychomotor activity; persecutory and referential delusions; loosening of associations
		57/M	Second dose of the BNT162b2 mRNA vaccine (mRNA vaccine)	Mania with psychotic symptoms	Same day	Increased speech; increased psychomotor activity; decreased sleep; nihilistic delusion
9.	Uvais (2021)	74/M	First dose of ChAdOx1-S/nCoV-19 vaccine (Viral vector vaccine)	Depression	2 days	Low mood, dryness of mouth, lack of interest in activities, marked reduction in appetite, and difficulty in initiating sleep.
10.	Ercoli et al. (2021)	41/M	First dose	Functional neurological disorder	Same day	Bilateral facial paralysis Left-sided facial hypoesthesia which resolved spontaneously
11.	Butler et al., 2021	38/F	First dose of the Pfizer-BioNTech SARS-CoV-2 vaccine (mRNA vaccine)	Functional neurological disorder	Same day	Left-sided arm weakness in distal muscles and forearm. Downward deviation of the angle of the mouth to the left and tongue deviation to the right. Hoover's sign positive.
		36/F	Second dose dose of Moderna SARS-CoV-2 vaccine (mRNA Vaccine)	Functional neurological disorder	Same day	Weakness in right hand and new onset right-leg limping Hoover's sign positive.

anhedonia, reduced appetite, and insomnia (Uvais, 2021).

6. Functional neurological disorder (FND)

Three cases of functional neurological disorder have been reported following vaccination. In one of the cases, a 41-year-old man presented with bilateral facial paralysis after receiving Covid vaccine. The symptom was transient and resolved within an hour. But the patient again presented with left-sided facial hypoesthesia two weeks later. Detailed neurological examination was unremarkable, except for the tactodolorific hypoesthesia of left side. Sensory disturbance resolved completely after two weeks (Ercoli et al., 2021). Butler et al. discussed two cases of middle-aged women with FND, who presented with motor weakness and other variable neurological symptoms. They had developed the symptoms one day after the first dose of the Pfizer-BioNTech SARS-CoV-2 vaccine and few hours following the second dose of Moderna SARS-CoV-2 vaccine, respectively. Further evaluation and neuroimaging did not reveal any organic cause. Hoover's sign was positive for both the patients. They were diagnosed with FND based on positive neurological signs and symptom variability (Butler and Michael, 2021).

7. Discussion

Almost half of the included reports described cases of young or middle-aged adults. This observation is consistent with findings from Phase III randomized controlled trials and federally sponsored surveillance programs (Baden et al., 2021; Klein et al., 2021). Both sexes appear to be equally affected; no clear preponderance could be made out probably owing to the limited number of reports. Prior cohort studies and reviews have reported an association between female sex and adverse effects after COVID vaccination (Beatty et al., 2021; Vassallo et al., 2021); this has been explained by higher vaccine reactivity among women and the role of hormonal, microbiota, and genetic responses (Venkatakrishnan et al., 2021).

Almost half of the psychiatric manifestations reported were following administration of the Oxford-Astrazeneca vaccine, a viral vector vaccine. Prior comparisons have shown that viral vector-based vaccines are associated with greater systemic side effects compared to mRNA vaccines (Klugar et al., 2021; Menni et al., 2021). However, a greater number of adverse reports with a vaccine may also be linked to it being around for a relatively longer period of time, as in the case of the Astrazeneca vaccine which received an early approval for use. No psychiatric adverse effects have been reported with the use of whole virus inactivated vaccines. Though the exact reasons are unclear, this may be linked to its weaker immunogenicity compared to mRNA vaccines (Lim et al., 2021).

More than two-third of the adverse effect reports followed receipt of the first vaccine dose. Currently, there is no consensus on how to manage psychiatric adverse reactions following vaccination. Specifically, whether to restrict the second dose or switch to another vaccine available remains unclear. In the reports reviewed, psychiatric symptom onset was noted within 0–10 days after receipt of the first dose of vaccine. Hence, increased monitoring for psychiatric adverse effects may be warranted during the first two weeks following COVID vaccination.

The occurrence of psychosis following vaccination may be mediated by immune response of the body against the SARS-CoV-2. Specifically, the administration of vaccine elicits a cellular immune reaction which leads to T-helper cell mediated outpouring of pro-inflammatory cytokines (Grover et al., 2022). In some individuals, this may lead to cytokine storm and NMDA receptor hypofunction with a resultant increase in dopamine; this may trigger a psychotic state (Grover et al., 2022). Other hypothesized causes for psychosis post-vaccination include anti-NMDA encephalitis (Flannery et al., 2021; Hilaire et al., 2021). Majority of the index cases had no prior history of psychiatric illness before receipt of vaccine. A history of prior COVID-19 infection before vaccination has

been linked to greater odds of physical adverse reactions (Beatty et al., 2021). Whether this is true for psychological adverse reactions merit further investigation. A COVID negative test status at the time of presentation was mentioned in five cases while one patient had tested COVID positive four months before the index presentation; for others, this data was not available.

To conclude, vaccination, in general, is a safe procedure. However, a small minority experience major psychiatric adverse reactions following COVID-19 vaccination. It must be emphasized that a causal link between COVID-19 vaccines and reported adverse effects cannot be made due to the uncontrolled nature of the observations. Nevertheless, based on current evidence, young age and receipt of viral vector vaccines may have a greater association with such reactions, particularly within the first 10 days of receipt. There is a need to systematically collect data on psychiatric side effects of COVID-19 vaccines. To this effect, we recommend maintaining registries, both at primary and tertiary care centers, to aid data gathering and identification of risk factors. This will also potentially inform preventive strategies. There is a need to evolve a consensus on monitoring and managing psychiatric adverse reactions following COVID-19 vaccination.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to the contents of the manuscript.

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