Turkish Medical Journal, 2024; 9(3),114-125.

Araştırma Makalesi / Research Article
https://doi.org/10.70852/tmj.1585694

EARLY ADVERSE EFFECTS AFTER COVID-19 VACCINE IN CHILDREN AND ADOLESCENTS WITH PSYCHIATRIC DISORDERS

Psikiyatrik Bozukluğu Olan Çocuk ve Ergenlerde Covid-19 Aşısı Sonrası Erken Yan Etkiler

Seda KAFALI[1], Selma TURAL HESAPCIOGLU[1], Dilan AYDIN AYVA[1], Duygu ASLANTAŞ[1], Mehmet Fatih CEYLAN[1]

Afiliasyon / Affiliation:
[1]Ankara Yildirim Beyazit University, Faculty of Medicine, Child and Adolescent Psychiatry Department, Ankara, Türkiye

Sorumlu Yazar / Correspondence:
Spec. Dr. Seda KAFALI
Ankara Yildirim Beyazit University Yenimahalle Education and Research Hospital Child and Adolescent Psychiatry Clinic, Ankara, Türkiye
E-mail: sedakafali94@gmail.com

Geliş / Received: 15.11.2024
Kabul / Accepted: 25.11.2024

Kongre / Congress:
09-12 Kasım 2022 tarihleri arasında Antalya, Türkiye'de düzenlenen 13th International Congress on Psychopharmacology & International Symposium on Child and Adolescent Psychopharmacology (ICP 2022)' de poster olarak sunulmuştur.

Cite as:
Kafali, S., Hesapcioglu Tural, S., Ayva Aydin, D., Aslantas, D., Ceylan, F. M. (2024). Early Adverse Effects After Covid-19 Vaccine in Children and Adolescents with Psychiatric Disorders. Turkish Medical Journal, 9(3),114-125. https://doi.org/10.70852/tmj.1585694

ABSTRACT

Objective: Vaccines for COVID-19 have reduced the severity of the infection and prevented deaths. Parents of children on psychopharmacological medications for psychiatric disorders were also referred to the hospital to learn whether the vaccine was safe for their children. It is not known until this period how chronic psychopharmacological drug use will interact with the vaccine. This study aimed to examine the early adverse effects of COVID-19 vaccines in children and adolescents aged 12-18 who have chronic psychiatric disorders and use psychopharmacological medications. **Method:** Post-vaccine short-term effects of 88 patients aged 12-18, who were followed up in the child and adolescent psychiatry clinic due to chronic psychiatric disorders and were using psychopharmacological medications, were monitored and compared with 88 vaccinated healthy controls. **Results:** Of the 88 patients, 80 (90.9%) were vaccinated with BNT162b2 (BioNTech) as the healthy control group; 8 (9.1%) were with Sinovac. Seventy-six (86.3%) of all patients were vaccinated with the second, and 21 (24%) were with the third dose. These were 83-second and 26-third doses for the control group. From all 45.4% of the patients were using antipsychotics. The cases were examined on the fourth and seventh days after vaccination. While the most frequently reported adverse effects after the first BNT162b2 dose in the patient group on the fourth day after vaccination were local pain (58.8%), fatigue (16.3%), redness (12.5%), and headache (11.3%), side affects first Sinovac dose in the patient group were local pain (75.0%), redness (25.0%), fatigue (25.0%). There was no significant difference between the patient and control groups receiving the BNT162b2 or Sinovac vaccine regarding adverse ffects on the fourth day. At the same time, in comparisons between patients diagnosed with psychiatric disorders, no statistical difference was found in terms of early adverse effects between the patients with and without antipsychotic use. **Discussion:** Our study shows that the vaccines mentioned in children and adolescents with psychiatric disorders are as safe and tolerable in terms of short-term side effects as in healthy individuals. This knowledge will be crucial in guiding evidence-based clinical decision-making and ensuring the safety of children and adolescents with psychiatric disorders.

Keywords: Adolescent, Antipsychotic, Child, COVID-19, Psychiatric disorder, Vaccine,

ÖZET

Amaç: COVID-19 aşıları enfeksiyonun şiddetini azaltmada ve ölümleri önlemede büyük bir gelişme olmuştur. Psikiyatrik bozukluklar nedeniyle psikofarmakolojik ilaç kullanan çocukların ebeveynleri de bu öncelikten yararlanmak amacıyla hastaneye başvurmuş ve ilk olarak aşının çocukları için güvenli olup olmadığını merak etmişlerdir. Kronik psikofarmakolojik ilaç kullanımının aşı ile nasıl etkileşeceği bu döneme kadar bilinmemektedir. Bu araştırmada COVID-19 aşılarının 12-18 yaş arası kronik psikiyatrik bozukluğu olup psikofarmakolojik ilaç kullanan çocuk ve ergenlerde erken dönem yan etkilerinin incelenmesi amaçlanmıştır. **Yöntem:** Çocuk ve ergen psikiyatri kliniğinde kronik psikiyatrik bozukluk nedeniyle takip edilen ve psikofarmakolojik ilaç kullanan 12-18 yaş arası 88 hastanın aşı sonrası kısa dönem yan etkileri takip edilmiş ve aşı olan 88 sağlıklı kontrolle karşılaştırılmıştır. **Bulgular:** Çalışmaya alınan hastaların 80'i (%90,9) BNT162b2 (BioNTech) aşısı; 8'i (%9,1) Sinovac aşısı olmuştu. Tüm hastaların 76'sı (%86,3) ikinci doz, 21'i (%24) ise üçüncü dozla aşılanmıştı. Kontrol grubu için 83 kişi ikinci dozu ve 26 kişi ise üçüncü dozu olmuştu. Antipsikotik kullanımı hastaların %45,4'ünde mevcuttu. Aşılar sonrası dördüncü ve yedinci günde olguların muayeneleri yapıldı. Aşı sonrası dördüncü günde hasta grubunda birinci BNT162b2 dozundan sonra en sık bildirilen yan etkiler lokal ağrı (%58,8), yorgunluk (%16,3), kızarıklık (%12,5) ve baş ağrısı (%11,3) iken, birinci Sinovac dozundan sonra ise lokal ağrı (%75,0), kızarıklık (%25,0), yorgunluktu (%25,0). Dördüncü gündeki yan etkiler açısından BNT162b2 ya da Sinovac aşısı yapılan hasta ve kontrol grupları arasında anlamlı bir fark yoktu. Aynı zamanda psikiyatrik bozukluk tanısı konulan hastalar arasındaki karşılaştırmalarda erken dönem yan etkiler açısından antipsikotik kullanan ve kullanmayanlarda istatistiksel farklılık bulunmadı.**Tartışma:** Bu çalışmada incelenen COVID-19 aşılarının, psikofarmakolojik ilaç kullanan psikiyatrik bozukluğu olan ergenler için kısa vadede güvenli olduğu bulunmuştur. Bu bilgiler, kanıta dayalı klinik karar alma süreçlerine rehberlik etmede ve psikiyatrik bozukluğu olan çocuk ve ergenlerin güvenliğini ve refahını sağlamada kritik öneme sahip olacaktır.

Anahtar Kelimeler: Antipsikotik, Aşı, COVID-19, Çocuk, Ergen, Psikiyatrik bozukluk

INTRODUCTION

COVID-19 vaccines have become a beacon of hope worldwide for preventing deaths and slowing the pace of the pandemic (Ophinni et al., 2020). As in adults, vaccination against COVID-19 is necessary for children to avoid transmission, achieve mass immunization, regain social life, and ensure continuity in education (Cauchemez et al., 2021; Kamidani et al., 2021; Sabu et al., 2022). The first two vaccines initially authorized in 2021 by the Ministry of Health in Türkiye were the BNT162b2 mRNA COVID-19 vaccine developed by Pfizer-BioNTech and Sinovac inactivated vaccine developed by Sinovac (Gedik et al., 2023). Early data from clinical studies have suggested that the BNT162b2 mRNA COVID-19 vaccine is safe in adolescents aged 12-15 years and highly immunogenic, while the Sinovac inactivated vaccine is immunogenic and safe in children aged 3-17 in studies (Frenck et al., 2021; Han et al., 2021). A meta-analysis examining ten different types of COVID-19 vaccines has reported that the most frequent adverse effects were injection site pain, fatigue, headache, muscle pain, and chills in children and adolescents (Gao et al., 2023). In previous studies in adults, post-vaccine fever, chills, itching, muscle and joint pain, headache, nausea, vomiting, diarrhea, constipation, cough, flu-like syndrome, abdominal pain, skin rash, allergic reactions, anaphylaxis, decreased appetite, increased sweating, paresthesia, edema (fascial, labial, glossal), blurred vision, respiratory distress, chest pain, restlessness, lymphadenopathy, Bell's palsy, rhythm disturbances, hypertension, Guillain Barre syndrome, myocarditis, pericarditis, acute myocardial infarction, appendicitis has been reported (Anand & Stahel, 2021; Chen et al., 2021; Mathioudakis et al., 2021; Mulligan et al., 2020; Oliver et al., 2020). According to Lee et al.'s study, it has been concluded that patients with a severe mental disorders are 2.3 times more likely to have severe COVID-19 outcomes than patients without a history of mental illness. Since the development of COVID-19 infection has been associated with an increased risk of morbidity and mortality, especially in the group with severe mental disorders should have been prioritized for vaccination (Lee et al., 2020; Mazereel et al., 2021; Veerman et al., 2021). Therefore, psychiatric disorders in children and adolescents, such as mood disorders, psychotic disorders, conduct disorders, and autism spectrum disorders, classified as severe mental disorders, can be considered a priority as they may lead to hospitalization and increase the risk of morbidity and mortality (Belfer & Nurcombe, 2007; Tural Hesapçıoğlu et al., 2024). Children and adolescents aged six months to 17 years with chronic diseases significantly have an increased risk of serious COVID-19, and they should have been offered to be vaccinated (WHO, 2021). Furthermore, a study demonstrated that children and adolescents with psychiatric disorders have an increased risk of hospitalization following COVID-19 infection (Chen et al., 2023). In August 2021, the Türkiye Ministry of Health announced that children and adolescents over 12 years of age with chronic diseases and those over 15 could be vaccinated on demand. COVID-19 vaccines have been applied for 16 years and above from July 2021, 15 years from August 2021, and 12 years from September 2021. After this decision, the families of many children and adolescents followed in our child and adolescent psychiatry clinic asked if it was appropriate for their children to be vaccinated while taking psychotropic medications. However, it was seen that there were no studies on the interaction between psychotropic drugs and COVID-19 vaccines and the adverse effects of the vaccines in children and adolescents who use psychotropic medications and in the literature. Given the lack of research on the interactions between psychotropic medications and COVID-19 vaccines and the potential adverse effects of these vaccines in children and adolescents using psychotropic drugs, this study was designed to fill this knowledge gap. Purpose to contribute to evidence-based decision-making and monitor the safety of vaccines in this vulnerable population.The first aim of this study was to examine the adverse effects of the COVID-19 vaccines in children and adolescents with psychiatric disorders. The second aim was to determine whether the adverse effects of the COVID-19 vaccine differ between children and adolescents with or without psychotropic drug use.

MATERIALS AND METHODS

Participants

The research was carried out on children and adolescents aged 12-18 who were followed up for at least three months with a psychiatric disorder in the Ankara Yildirim Beyazit University Yenimahalle Training and Research Hospital Child and Adolescent Psychiatry Clinic between November 2021 and February 2022. During the study period, 161 patients applied to the clinic, and 88 patients and their parents requested vaccination. Post-vaccination adverse event data for these patients were compared to demographically matched healthy adolescents between the ages of 12-18 who came to the hospital's COVID-19 vaccination clinic and did not have any psychiatric or medical diagnosis and agreed to participate in the study.

Procedure

The 88 patients with psychiatric disorders who decided to be vaccinated were followed up in the outpatient clinic on the 4th and 7th days of the vaccination. The adverse effects were recorded in the form prepared by the authors, which contains reported post-vaccine adverse effects in previous research (Anand & Stahel, 2021; Chen et al., 2021; Mathioudakis et al., 2021; Mulligan et al., 2020; Oliver et al., 2020). On the 4th day after vaccination, the clinician completed the form by asking about the adverse effects and physically examining the participant. The interview and examination were repeated on the 7th day. The Institutional Review Board approved the study protocol (10/11/2021, E-2021-58), and study procedures were performed according to the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. In addition, written informed consent/assent forms were obtained from all parents/legal guardians and subjects.

Data Collection Tool

The questionnaire about the adverse effects contained fever, chills, itching, muscle and joint pain, headache, nausea, vomiting, diarrhea, constipation, cough, flu-like syndrome, abdominal pain, skin rash, allergic reactions, anaphylaxis, appetite decreased, increased sweating, paresthesia, edema (fascial, labial, glossal), blurred vision, respiratory distress, chest pain, restlessness, lymphadenopathy, Bell's palsy, rhythm disturbances, hypertension, Guillain Barre syndrome, myocarditis, pericarditis, acute myocardial infarction (MI), appendicitis (Anand & Stahel, 2021; Chen et al., 2021; Mathioudakis et al., 2021; Mulligan et al., 2020; Oliver et al., 2020).

Statistical Analyses

IBM SPSS version 23.0, Microsoft Excel 365, and GraphPad Prism 8.4.2 were used for the statistical analyses. Statistical significance was defined as p values < 0.05. Frequencies and percentages were used to describe the characteristics of the patients and control groups. The chi-square test was used to compare adverse effects between groups. The two-sample t-test was used for parametric data to compare the two groups. The Mann–Whitney U test was used to compare the two groups for non-parametric data.

RESULTS

Table 1 presents the sociodemographic and clinical characteristics of vaccinated patients and controls. The patient group's body mass index was significantly higher. The control group had considerably higher repeated doses of vaccines. There was no statistical difference between groups regarding other sociodemographic and clinical characteristics.

Table 1. Sociodemographic and clinical characteristics of the vaccinated patients and controls

	Vaccinated patients (n=88)	Controls (n=88)	χ2 or U	p-value
Age (M, (IQR))	15 (3)	15 (3)	3.822	1.000
Sex (F, %)	61 (69.3%)	62 (72.9%)	0.276	0.599
Number of Doses	2 (1)	2 (2)	7.346	<0.001
BMI	22.09 (5.60)	20.70 (2.87)	7.720	0.005
Being infected with COVID-19	24 (27.6%)	14 (18.9%)	1.666	0.197
Being vaccinated with Sinovac (n=16)	8 (9.1%)	8 (9.1%)	<0.001	1.000
Being vaccinated with BNT162b2 (n=160)	80 (90.9%)	80 (90.9%)	<0.001	1.000
Only one dose vaccinated with BNT162b2	10 (11.3%)	5 (5.6%)	0.865	0.352
Only one dose vaccinated with Sinovac	2 (2.2%)	-		
Only two doses vaccinated with BNT162b2	49 (55.6%)	50 (56.8%)	0.106	0.744
Only two doses vaccinated with Sinovac	6 (6.8%)	7 (7.9%)		
Three doses vaccinated with BNT162b2	21 (23.8%)	25 (28.4%)	-*	0.615
Three doses were vaccinated with Sinovac	-	1 (1.1%)		

M: Median, IQR: Interquartile Range, F: Female, *: Fisher Exact Test was used.
BMI:Body Mass İndex

The doses of vaccination of the patients and controls are presented in Figure 1.

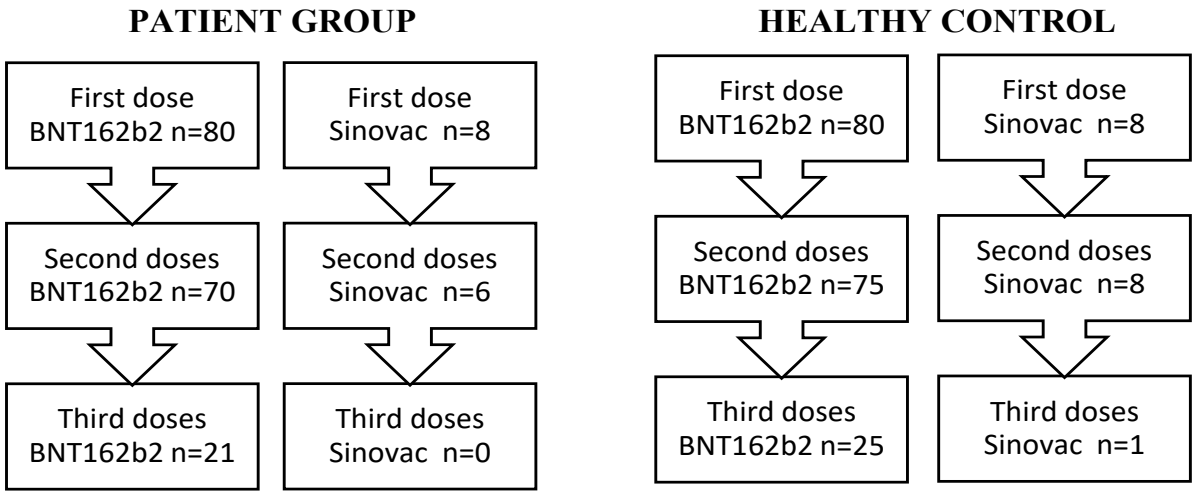

Figure 1. The doses of vaccination of the patients and controls

The most common psychiatric diagnosis of vaccinated patients was depression 43.2%, anxiety disorders 43.2%, and attention deficit hyperactivity disorder r (ADHD) 26.1%. Other diagnoses were intellectual disability 11.4%, obsessive-compulsive disorder 6.8%, bipolar disorder 5.7%, eating disorder 5.7%, autism spectrum disorder 5.6%, post-traumatic stress disorder 4.5%, substance use disorder 2.3%, conduct disorder 1.1%, schizophrenia 1.1% (A patient could have more than one comorbid diagnosis, Figure 2A). The number of patients who received the first dose of the vaccine is 88; 40 (45.4%) were using antipsychotics, and 48 (54.5%) were not using any antipsychotic drug but using antidepressants or anti-ADHD drugs or mood stabilizers (Figure 2B).

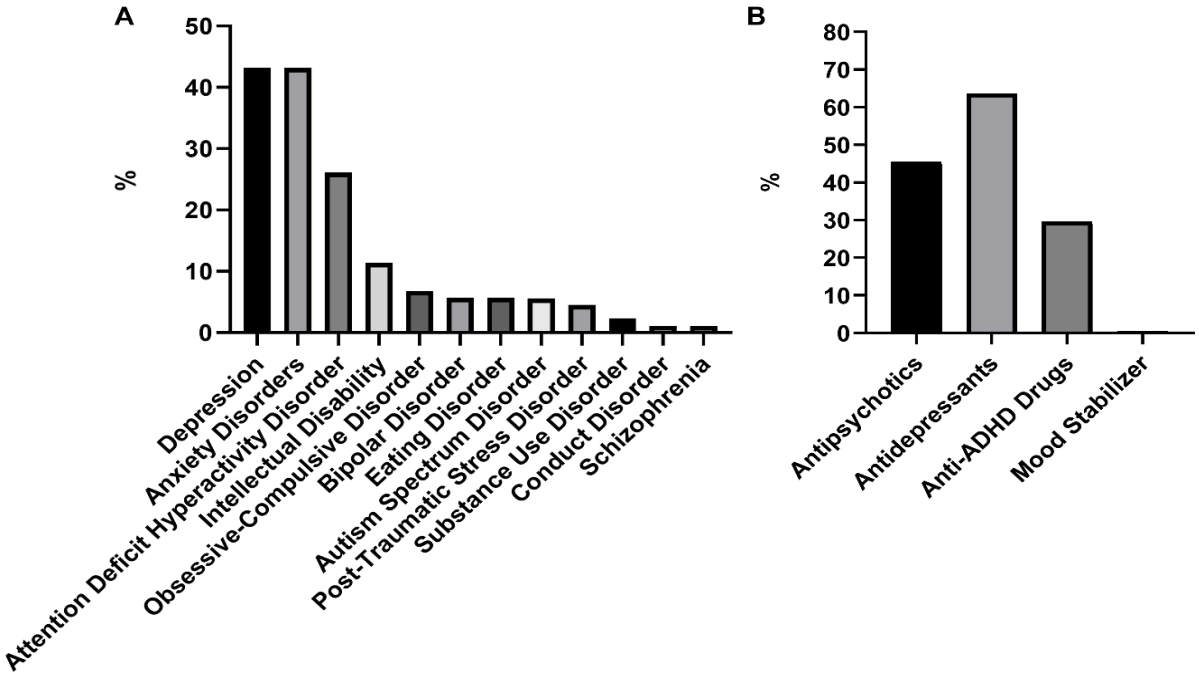

Figure 2. Distribution of the first dose of patients A. According to their diagnosis B. Psychiatric treatment

Short-term adverse effects of the vaccines are examined and compared between patients and the control group. The most frequent adverse effects of the BNT162b2 vaccinated patients group (n=80) were local pain (58.8%), fatigue (16.3%), and local redness (12.5%)(Tablo 2). There was no significant difference ($p<0.05$) between BNT162b2-vaccinated patients and BNT162b2-vaccinated controls (n=80) in terms of adverse effects. The same frequent side effects (local pain (75.0%), fatigue (25.0%) and local redness (25.0%) were observed in Sinovac-vaccinated patients (n=8), and there was no significant difference between Sinovac-vaccinated patients and Sinovac vaccinated controls (n=8, Table 2).

Table 2. Short-term side effects of the vaccines in patients with psychiatric disorders and controls after the first dose

	BNT162b2 vaccinated patients (n=80)	BNT162b2 vaccinated Control (n=80)	χ^2 or U	p	Sinovac vaccinated patients (n=8)	Sinovac vaccinated control (n=8)	χ^2 or U	p-value
LOCAL								
Redness	10 (12.5%)	12 (15.0%)	0.211	0.646	2 (25.0%)	1 (12.5%)	-*	0.500
Swelling	5 (6.3%)	7 (8.8%)	0.360	0.383	0 (0.0%)	1 (12.5%)	-*	0.500
Pain	47 (58.8%)	54 (67.5%)	1.316	0.251	6 (75.0%)	6 (75.0%)	-*	0.715
Itching	1 (1.3%)	5 (6.3%)	-*	0.105	1 (12.5%)	1 (12.5%)	-*	0.767
SYSTEMIC								
Fever	5 (6.3%)	4 (5.0%)	-*	0.500	**	**		
Fatigue	13 (16.3%)	21 (26.3%)	2.390	0.122	2 (25%)	2 (25%)	-*	0.715
Headache	9 (11.3%)	15 (18.8%)	1.765	0.184	0 (0.0%)	1 (12.5%)	-*	0.500
Shivering	**	**			1 (12.5%)	1 (12.5%)	-*	0.767
Muscle pain	4 (5.0%)	7 (8.8%)	0.879	0,349	0 (0.0%)	1 (12.5%)	-*	0.500
Joint pain	3 (3.8%)	2 (2.5%)	0.206	0.650	**	**	-*	0.500
Need for antipyretic /painkillers	4 (2.5%)	10 (21.3%)	2.818	0.160	**	**		
Cough	0 (0.0%)	2 (2.5%)	2.025	0.155	**	**		
Sleeping disorder	1 (1.3%)	0 (0.0%)	-*	0.500	**	**		
Restlessness	0 (0.0%)	1 (1.3%)	-*	0.503	1 (12.5%)	0 (0.0%)	-*	0.500
Tachycardia	1 (1.3%)	0 (0.0%)	-*	0.500	**	**		

*: Fisher Exact Test used for analysis. **: No statistics are computed because the variable is a constant.

No adverse effects such as vomiting, diarrhea, constipation, flu-like syndrome, abdominal pain, skin rash, itching (general), allergic reaction, loss of appetite, increased sweating, paresthesia, tinnitus, edema (fascial, labial, glossal), blurred vision, dyspnea, chest pain, lymphadenopathy, Bell's palsy, rhythm disorders, hypertension, Guillain Barre Syndrome, shingles, anaphylaxis, myocarditis, pericarditis, acute MI, appendicitis, epileptic seizure, cerebrovascular event, unconsciousness, delirium, death, hospitalization adverse effects were observed in any group. A decrease in the number of patients who received the second dose of the vaccine was observed. In total, 159 people received the second dose of the vaccine, 76 of whom were vaccinated patients and 83 of whom were in the control group. The most frequent adverse effects of the second BNT162b2 dose in the patient group (n=70) were local pain (35.7%), headache (8.6%), and local redness (8.6%). The need for antipyretics/analgesics was significantly higher in the BNT162b2 vaccinated control group compared to BNT162b2 vaccinated patients (p=0.039). All groups had no significant difference in other side effects (Table 3).

Table 3. Short-term side effects of vaccines in patients with psychiatric disorders and controls after the second dose

Short-term Side Effects of the Vaccines (First 4 days)	BNT162b2 vaccinated patients (n=70)	BNT162b2 vaccinated Control (n=75)	χ^2 or U	p	Sinovac vaccinated patients (n=6)	Sinovac vaccinated control (n=8)	χ^2 or U	p-value
LOCAL								
Redness	6 (8.6%)	9 (12.0%)	0.459	0.591	1 (16.7%)	1 (12.5%)	-*	0.692
Swelling	4 (5.7%)	6 (8.0%)	0.295	0.587	0 (0.0%)	0 (0.0%)	**	**
Pain	25 (35.7%)	35 (46.7%)	1.790	0.181	2 (33.3%)	2 (25.0%)	-*	0.594
Itching	1 (1.4%)	1 (1.3%)	-*	0.734	1 (16.7%)	1 (12.5%)	-*	0.692
SYSTEMIC								
Fever	4 (5.7%)	3 (4.0%)	-*	0.712	0 (0.0%)	0 (0.0%)	**	**
Fatigue	5 (7.1%)	7 (9.3%)	0.229	0.632	1 (16.7%)	1 (12.5%)	-*	0.692
Headache	6 (8.6%)	6 (8.0%)	0.016	0.901	1 (16.7%)	0 (0.0%)	-*	0.429
Diarrhea	0 (0.0%)	1 (1.3%)	-*	0.517	0 (0.0%)	0 (0.0%)		
Muscle pain	1 (1.4%)	2 (2.7%)	-*	0.526	0 (%)	1 (12.5%)	-*	0.571
Joint pain	1 (1.4%)	1 (1.3%)	-*	0.734	0 (0.0%)	1 (12.5%)	-*	0.571
Need for antipyretic /analgesics	1 (1.4%)	7 (9.3%)	-*	**0.039**	1 (16.7%)	0 (0.0%)	-*	0.429
Flu-like syndrome	0 (0.0%)	1 (1.3%)	-*	0.517	0 (0.0%)	0 (0.0%)	**	**
Abdominal pain	1 (1.4%)	0 (0.0%)	-*	0.483	0 (0.0%)	0 (0.0%)	**	**
Allergic reaction	1 (1.4%)	0 (0.0%)	-*	0.483	0 (0.0%)	0 (0.0%)	**	**

*: Fisher Exact Test used for analysis.

**: No statistics are computed because the variable is a constant.

There were no significant differences in comparisons for the 3rd BNT162b2 dose between patients (n=21) and controls (n=25).

Antipsychotic Use

Short-term adverse effects of the vaccines are examined and compared between the antipsychotic-using group and the patients without the antipsychotic-using group. The number of patients who received the first dose of the vaccine is 88; 40 (45.4%) of them were using antipsychotics. Of the 40 patients, 22 were using risperidone (55%), nine were using aripiprazole (22.5%), eight were using olanzapine (20%), two were using zuclopenthixol decanoate (5%), and one was using clozapine (2.5%), one was using quetiapine (%2.5). The median chlorpromazine equivalent dose of antipsychotics used by the patients was 50 mg/day, and the interquartile range (IQR) was 42 mg/day. The most frequent side effects in antipsychotic users after the first BNT162b2 dose were pain at the injection site (69.4%), redness (16.7%), and fatigue (13.9%). There was no significant difference between the first BNT162b2 dose-vaccinated patients with antipsychotic use (n=36) and those without antipsychotic use (n=44, Table 4).

Table 4. Side effects in antipsychotic users and non-users after the first dose.

	BNT162b2 vaccinated patients with antipsychotic use (n=36)	BNT162b2 vaccinated patients without antipsychotic use (n=44)	χ^2 or U	p	Sinovac vaccinated patients with antipsychotic use (n=4)	Sinovac vaccinated patients without antipsychotic use (n=4)	χ^2 or U	p-value
LOCAL								
Redness	6 (16.7%)	4 (9.1%)	1.039	0.308	2 (50%)	0 (0.0%)	-*	0.429
Swelling	2 (5.6%)	3 (6.8%)	0.054	0.596	0 (0.0%)	0 (0.0%)	**	**
Pain	25 (69.4%)	22 (50%)	3.089	0.079	2 (50%)	0 (0.0%)	-*	0.429
Itching	1 (2.8%)	0 (0.0%)	-*	0.450	0 (0.0%)	1 (25.0%)	-*	0.500
SYSTEMIC								
Fever	1 (2.8%)	4 (9.1%)	1.347	0.372	0 (0.0%)	0 (0.0%)	**	**
Fatigue	5 (13.9%)	8 (18.2%)	0.268	0.605	2 (50.0%)	0 (0.0%)	-*	0.429
Headache	4 (11.1%)	5 (11.4%)	-*	0.628	0 (0.0%)	0 (0.0%)	**	**
Chills	0 (0.0%)	0 (0.0%)	**	**	1 (25.0%)	0 (0.0%)	-*	0.500
Muscle pain	1 (2.8%)	3 (6.8%)	-*	0.623	0 (0.0%)	0 (0.0%)	**	**
Joint pain	1 (2.8%)	2 (4.5%)	-*	0.576	0 (0.0%)	0 (0.0%)	**	**
Need for antipyretic /analgesics	1 (2.8%)	3 (6.8%)	-*	0.623	0 (0.0%)	0 (0.0%)	**	**
Sleeping disorder	1 (2.8%)	0 (0.0%)	-*	0.450	0 (0.0%)	0 (0.0%)	**	**
Restlessness	0 (0.0%)	0 (0.0%)	**	**	1 (25.0 %)	0 (0.0%)	-*	0.500
Tachycardia	1 (2.8%)	0 (0.0%)	-*	0.450	0 (0.0%)	0 (0.0%)	**	**

*: Fisher Exact Test used for analysis.

**: No statistics are computed because the variable is a constant.

After the second BNT162b2 dose, local redness and local pain were significantly higher (respectively; p=0.01, p=0.015) in the antipsychotic-using patient group than non-users (Table 5).

Table 5. Short-term side effects in antipsychotic users and non-users after the second dose.

Short-term Side Effects of the Vaccines (First 4 days)	BNT162b2 vaccinated patients with antipsychotic use (n=34)	BNT162b2 vaccinated patients without antipsychotic use (n=36)	χ^2 or U	p	Sinovac vaccinated patients with antipsychotic use (n=2)	Sinovac vaccinated patients without antipsychotic use (n=4)	χ^2 or U	p-value
LOCAL								
Redness	6 (17.6%)	0 (0.0%)	-*	**0.010**	1 (9.1%)	0 (0.0%)	-*	0.333
Swelling	3 (8.8%)	1 (2.8%)	-*	0.286	0 (0.0%)	0 (0.0%)	**	**
Pain	17 (50.0%)	8 (22.2%)	5.877	**0.015**	2 (100.0%)	0 (0.0%)	-*	0.067
Itching	0 (0.0%)	1 (2.8%)	-*	0.514	0 (0.0%)	1 (25.0%)	-*	0.667
SYSTEMIC								
Fever	3 (8.8%)	1 (2.8%)	-*	0.286	0 (0.0%)	0 (0.0%)	**	**
Fatigue	3 (8.8%)	2 (5.6%)	-*	0.472	1 (50.0%)	0 (0.0%)	-*	0.333
Headache	5 (14.7%)	1 (2.8%)	-*	0.087	1 (50.0%)	0 (0.0%)	-*	0.333
Muscle pain	1 (2.9%)	0 (0.0%)	-*	0.486	0 (0.0%)	0 (0.0%)	**	**
Joint pain	1 (2.9%)	0 (0.0%)	-*	0.486	0 (0.0%)	0 (0.0%)	**	**
Need for antipyretic /painkillers	1 (2.9%)	0 (0.0%)	-*	0.486	1 (50.0%)	0 (0.0%)	-*	0.333
Abdominal pain	1 (2.9%)	0 (0.0%)	-*	0.486	0 (0.0%)	0 (0.0%)	**	**
Allergic reaction	0 (0.0%)	1 (2.8%)	-*	0.514	0 (0.0%)	0 (0.0%)	**	**

*: Fisher Exact Test used for analysis.

**: No statistics are computed because the variable is a constant.

An analysis was conducted for every group of antipsychotics. Individuals who solely use clozapine experienced abdominal pain more frequently following their second dose than those utilizing alternative antipsychotics (p=0.029).

SSRI Use

Of the patient group, 21 (23,9%) used SSRIs only. Fifteen patients used sertraline at a dose of 25-75 mg/day, five patients used fluoxetine at a dose of 20-30 mg/day, and only one patient used escitalopram at a dose of 10 mg/day. In patients using only SSRI, 19 (90,5%) received 1st dose of BNT162b2, and 2 (9,5%) received 1st dose of the Sinovac vaccine. Within the group that received the BNT162b2, 3 (15.8%) patients had fatigue, 2 (10.5%) had a fever, and 1 (5.3%) had swelling and redness, which was not significantly different from the control group. In contrast, neither of the two Sinovac-vaccinated patients reported any adverse effects. After the 19 first doses of BNT162b2, 17 received the second dose of the BNT162b2 vaccine, and there was also no significant difference when compared to the control group. One person who took Sinovac also had the second dose. Within those who took the second dose of BNT162b2, 4 (23.5%) patients experienced pain, 1 (5.9%) fever, and 1 (5.9%) headache.

Anti-ADHD Drug Use

Fifteen patients from the patient group were using only anti-ADHD medication: nine patients were using extended-release methylphenidate at a dosage of 18-36 mg/day, three patients were using modified-release methylphenidate at a dosage of 10-30 mg/day, two patients were using rapid-acting methylphenidate at a dosage of 20 mg/day, and one patient was using atomoxetine at a dosage of 70 mg/day.70 mg/day. Thirteen of 15 patients had received the first dose of BNT162b2, and 2 of them had received the Sinovac vaccine. After the first dose of vaccination, 7 (53.8%) patients had pain, 4 (30.8%) had fatigue, 2 (15.4%) had redness, 2 (15.4%) needed antipyretic /analgesic, 2 (15.4%) patients headache, muscle pain in 2 (15.4%) patients, joint pain

in 1 (7.7%) person, fever in 1 (7.7%) person. Eleven of those who received the first dose of BNT162b2 also received the second dose, and two people who received the first dose of Sinovac received the second dose. After the second dose of BNT162b2, 3 (27.3%) patients experienced pain, 1 (9.1%) fatigue, and 1 (9.1%) allergic reaction.

DISCUSSION

This study aims to evaluate the adverse effects of COVID-19 vaccines in children and adolescents with chronic psychiatric disorders using psychopharmacological medications. The control group appears to have received multiple doses of vaccines at a higher frequency ($p<0.001$). Early COVID-19 vaccine clinical trials primarily enrolled individuals from the healthy population, limiting data on individuals with chronic diseases who may have heightened safety concerns (Zhao et al., 2023). Studies show that vaccination rates increase as vaccine reliability and side effect information increases (Bianco et al., 2022; Xu et al., 2021). Informing families about current studies' efficacy and safety results can reduce vaccine hesitancy and be a valuable tool in public campaigns. There was no significant difference in adverse effects after the first dose in both vaccine groups, the patient and control groups. In a study conducted on 5 million adolescents aged 5-17, no significant increase in adverse effects was found between the ages of 5-11. In adolescents aged 12-17, an increase in the risk of hospitalization due to myocarditis was observed after the first and second doses of BNT162b2. In contrast, an increase in the risk of hospitalization due to epilepsy and demyelinating diseases was observed in females after the second dose. However, it was concluded that myocarditis was self-limiting, did not result in death, and the risk of seizures was high in those previously diagnosed with epilepsy (Copland et al., 2024). In another study, the incidence of myocarditis within 7 days after BNT162b2 vaccination among 5-17-year-olds was determined to be 40 per million (Hu et al., 2023). The findings of our study show that the vaccines mentioned in children and adolescents with psychiatric disorders are as safe and tolerable in terms of short-term adverse effects as in healthy individuals. When the vaccines' adverse effects were analyzed for patients and controls, there was a statistical difference for vaccinated patients with the second BNT162b2 dose; less antipyretic/analgesic use was observed in the patient group compared to the control group. The patient group may have had concerns regarding taking a new medication that might have interacted with the drugs they were currently taking. In the analyses conducted between patients using and not using antipsychotics, while no significant difference was observed between the groups after the first dose, local redness and local pain were significantly higher in the antipsychotic users after the second BNT162b2 dose. This situation may be related to changes in circulating cytokine levels associated with psychopharmacological drug use, which affect the local inflammatory response (Pollmächer et al., 2000). Aside from local pain and redness, no significant systemic side effects were detected, making it reliable except for these local adverse effects. This is the first trial of COVID-19 vaccines' adverse effects in children using psychiatric drugs. It is not known how chronic psychopharmacological drug use will interact with vaccines. There is still limited data in the literature on the evaluation of vaccine effects in children and adolescents using psychiatric drugs. The study's strengths, including clinician-conducted interviews and detailed questionnaires, significantly enhance the reliability of the findings and the comparative analysis of different medication classes (antipsychotics, SSRIs, and anti-ADHD drugs). This study fills a crucial void in the literature, providing essential insights that can inform future research and clinical practice. However, the cross-sectional design, which limits the assessment of long-term adverse effects, and the limited sample size necessitate further longitudinal research with larger cohorts to fully understand the long-term implications of vaccination in this vulnerable population. Future research should prioritize the identification of potential long-term side effects, optimizing vaccination strategies for this population, and exploring potential interactions between vaccines and psychiatric medications. This knowledge will be crucial in guiding evidence-based clinical decision-making and ensuring the safety and well-being of children and adolescents with psychiatric disorders.

CONCLUSION

Although the incidence and severity of COVID-19 are lower in the pediatric population than in adults, recent epidemiological studies suggest that the risk may be higher than initially assumed. Additionally, the need for social distancing and quarantine measures can negatively impact children's mental health and overall well-being, as it may require them to stay away from school and other activities. Children and adolescents with psychiatric disorders may experience a worsening of their condition when isolated from society and unable to attend school. It is important to prioritize their well-being since they may be at higher risk for morbidity and mortality related to their mental illnesses. This short-term study showed that BNT162b2 and Sinovac vaccines could cause non-serious common short term adverse and were safe and well tolerated during psychiatric treatments.

Funding: This research received no source of financial assistance.

Conflict of Interest: No potential conflict of interest relevant to this article was reported.

Acknowledgments: We thank the participants, their parents/caregivers, and Mehmet Emin Seker, MSc, for his technical support.

Author Contributions: STH and SK formulated the research questions, conducted the literature search, planned and designed the study. SK, DAA, MFC, DA collected patients' data. STH and SK performed the statistical analyses and wrote the article. STH and MFC critically checked and reviewed the manuscript and on the final drafts.

REFERENCES

Anand, P., & Stahel, V. P. (2021). Review the safety of Covid-19 mRNA vaccines: a review. Patient Saf Surg, 15(1), 20. https://doi.org/10.1186/s13037-021-00291-9

Belfer, M. L., & Nurcombe, B. (2007). The epidemiology and burden of child and adolescent mental disorder. The mental health of children and adolescents: An area of global neglect, 27-42.

Bianco, A., Della Polla, G., Angelillo, S., Pelullo, C. P., Licata, F., & Angelillo, I. F. (2022). Parental COVID-19 vaccine hesitancy: a cross-sectional survey in Italy. Expert review of vaccines, 21(4), 541-547.

Cauchemez, S., Bosetti, P., Kiem, C. T., Mouro, V., Consoli, A., & Fontanet, A. (2021). Education and mental health: good reasons to vaccinate children. Lancet, 398(10298), 387. https://doi.org/10.1016/s0140-6736(21)01453-7

Chen, F., Cao, H., Baranova, A., Zhao, Q., & Zhang, F. (2023). Causal associations between COVID-19 and childhood mental disorders. BMC psychiatry, 23(1), 922.

Chen, G., Li, X., Sun, M., Zhou, Y., Yin, M., Zhao, B., & Li, X. (2021). COVID-19 mRNA Vaccines Are Generally Safe in the Short Term: A Vaccine Vigilance Real-World Study Says. Front Immunol, 12, 669010. https://doi.org/10.3389/fimmu.2021.669010

Control, Centers for Disease, & Prevention. (2022). Clinical considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 vaccines among Adolescents and Young Adults. Centers for Disease Control and Prevention. Retrieved August 12, 2022. In.

Copland, E., Patone, M., Saatci, D., Handunnetthi, L., Hirst, J., Hunt, D. P., Mills, N. L., Moss, P., Sheikh, A., & Coupland, C. A. (2024). Safety outcomes following COVID-19 vaccination and infection in 5.1 million children in England. Nature Communications, 15(1), 3822.

Frenck, R. W., Jr., Klein, N. P., Kitchin, N., Gurtman, A., Absalon, J., Lockhart, S., Perez, J. L., Walter, E. B., Senders, S., Bailey, R., Swanson, K. A., Ma, H., Xu, X., Koury, K., Kalina, W. V., Cooper, D., Jennings, T., Brandon, D. M., Thomas, S. J., Türeci, Ö., Tresnan, D. B., Mather, S., Dormitzer, P. R., Şahin, U., Jansen, K. U., & Gruber, W. C. (2021, Jul 15). Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med, 385(3), 239-250. https://doi.org/10.1056/

NEJMoa2107456

Gao, P., Kang, L. Y., Liu, J., & Liu, M. (2023). Immunogenicity, effectiveness, and safety of COVID-19 vaccines among children and adolescents aged 2-18 years: an updated systematic review and meta-analysis. World J Pediatr, 1-14. https://doi.org/10.1007/s12519-022-00680-9

Gedik, M. S., Kilci, A. İ., Hakkoymaz, H., Küçük, Ö. F., Solak, Y., Basan, N. M., & Çıkrıkçı, Y. E. (2023). Evaluation of patients of vaccine side effects after the COVID-19 vaccine. Revista da Associacao Medica Brasileira (1992), 69(1), 147–152. https://doi.org/10.1590/1806-9282.20221035

Han, B., Song, Y., Li, C., Yang, W., Ma, Q., Jiang, Z., Li, M., Lian, X., Jiao, W., Wang, L., Shu, Q., Wu, Z., Zhao, Y., Li, Q., & Gao, Q. (2021). Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis. https://doi.org/10.1016/s1473-3099(21)00319-4

Hu, M., Wong, H. L., Feng, Y., Lloyd, P. C., Smith, E. R., Amend, K. L., Kline, A., Beachler, D. C., Gruber, J. F., & Mitra, M. (2023). Safety of the BNT162b2 COVID-19 vaccine in children aged 5 to 17 years. JAMA pediatrics, 177(7), 710-717.

Kamidani, S., Rostad, C. A., & Anderson, E. J. (2021). COVID-19 vaccine development: a pediatric perspective. Curr Opin Pediatr, 33(1), 144-151. https://doi.org/10.1097/MOP.0000000000000978

Lee, S. W., Yang, J. M., Moon, S. Y., Yoo, I. K., Ha, E. K., Kim, S. Y., Park, U. M., Choi, S., Lee, S.-H., & Ahn, Y. M. (2020). Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. The Lancet Psychiatry, 7(12), 1025-1031.

Mathioudakis, A. G., Ghrew, M., Ustianowski, A., Ahmad, S., Borrow, R., Papavasileiou, L. P., Petrakis, D., & Bakerly, N. D. (2021). Self-Reported Real-World Safety and Reactogenicity of COVID-19 Vaccines: A Vaccine Recipient Survey. Life (Basel), 11(3). https://doi.org/10.3390/life11030249

Mazereel, V., Van Assche, K., Detraux, J., & De Hert, M. (2021). COVID-19 vaccination for people with severe mental illness: why, what, and how? Lancet Psychiatry, 8(5), 444-450. https://doi.org/10.1016/S2215-0366(20)30564-2

Mulligan, M. J., Lyke, K. E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., Raabe, V., Bailey, R., Swanson, K. A., Li, P., Koury, K., Kalina, W., Cooper, D., Fontes-Garfias, C., Shi, P.-Y., Türeci, Ö., Tompkins, K. R., Walsh, E. E., Frenck, R., Falsey, A. R., Dormitzer, P. R., Gruber, W. C., Şahin, U., & Jansen, K. U. (2020). Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature, 586(7830), 589-593. https://doi.org/10.1038/s41586-020-2639-4

Oliver, S. E., Gargano, J. W., Marin, M., Wallace, M., Curran, K. G., Chamberland, M., McClung, N., Campos-Outcalt, D., Morgan, R. L., Mbaeyi, S., Romero, J. R., Talbot, H. K., Lee, G. M., Bell, B. P., & Dooling, K. (2020). The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep, 69(50), 1922-1924. https://doi.org/10.15585/mmwr.mm6950e2

Ophinni, Y., Hasibuan, A. S., Widhani, A., Maria, S., Koesnoe, S., Yunihastuti, E., Karjadi, T. H., Rengganis, I., & Djauzi, S. (2020). COVID-19 Vaccines: Current Status and Implication for Use in Indonesia. Acta Med Indones, 52(4), 388-412. https://www.ncbi.nlm.nih.gov/pubmed/33377885

Pollmächer, T., Haack, M., Schuld, A., Kraus, T., & Hinze-Selch, D. (2000). Effects of antipsychotic drugs on cytokine networks. Journal of psychiatric research, 34(6), 369-382.

Sabu, J. M., Zahid, I., Jacob, N., Alele, F. O., & Malau-Aduli, B. S. (2022). Effectiveness of the BNT162b2 (Pfizer-BioNTech) Vaccine in Children and Adolescents: A Systematic Review and Meta-Analysis. Vaccines, 10(11), 1880. https://www.mdpi.com/2076-393X/10/11/1880

Tural Hesapçıoğlu, S., Hacıosmanoğlu, C. D., Okuyucu, M., & Ceylan, M. (2024). Çocuk ve Ergen Psikiyatrisi Yataklı Tedavi Kliniğinde İzlenen Hastalarda Psikiyatrik Bozukluklar. Türk Tıp Dergisi, 9(1), 1-7.

Veerman, S. R. T., Bogers, J. P. A. M., Cohen, D., & Schulte, P. F. J. (2022). COVID-19: Risks, Complications, and Monitoring in Patients on Clozapine. Pharmacopsychiatry, 55(1), 48–56. https://doi.

org/10.1055/a-1562-2521

World Health Organization. (2021). Interim Recommendations for Use of the Pfizer–BioNTech COVID-19 Vaccine, BNT162b2, Under Emergency Use Listing: Interim Guidance, 8 January 2021. In: World Health Organization Geneva.

Xu, Y., Xu, D., Luo, L., Ma, F., Wang, P., Li, H., Li, Q., Wei, L., Diao, J., Liu, Y., Zhang, W., & Zheng, X. (2021). A Cross-Sectional Survey on COVID-19 Vaccine Hesitancy Among Parents From Shandong vs. Zhejiang. Frontiers in public health, 9, 779720. https://doi.org/10.3389/fpubh.2021.779720

Zhao, Y., Du, J., Li, Z., Xu, Z., Wu, Y., Duan, W., Wang, W., Zhang, T., Xu, J., & Wu, H. (2023). It is time to improve the acceptance of COVID-19 vaccines among people with chronic diseases: A systematic review and meta-analysis. Journal of Medical Virology, 95(2), e28509.