

A Proposed Protocol for the Investigation of the Safety and Efficacy of the COVID-19 Vaccine for Patients with Psychosis and Pilot Safety Findings from a Chinese Psychiatrist's Self-Experiment

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Abstract

We present a study protocol designed to test the safety and efficacy of the 2019 Coronavirus Disease (COVID-19) vaccine in patients with major psychotic disease. A secondary objective is to investigate optional vaccination methods for these patients. In a self-experiment, a Chinese psychiatrist examined the safety and efficacy of the COVID-19 vaccine under clinical use of typical antipsychotic agents and sedatives (olanzapine, duloxetine, and diazepam). For patients with extremely drug-resistant conditions, the safety of the COVID-19 vaccine under electroconvulsive therapy was also investigated. The entire study process was recorded on high-definition video. This clinical study protocol is, to our knowledge, the first of its kind. Our findings will shed new light on the protection of patients with psychotic diseases from COVID-19 infection.

Keywords: COVID-19 Vaccine; Psychotic disease; Olanzapine; Duloxetine; Diazepam; Electroconvulsive therapy

Introduction

In the context of the COVID-19 pandemic, many institutes have made major efforts to identify a drug that effectively treats COVID-19 infection. To date, however no such treatment has been discovered, and the COVID-19 vaccine is the only effective method to protect against infection. Vaccination programs have been initiated in many countries, with reports of some vaccine-related adverse events. In China, reported side effects of the COVID-19 vaccine include mild fever, influenza-like symptoms, muscle pain, and local reactions at the injection site; rare serious adverse events, such as anaphylactic shock and cardiovascular and cerebrovascular events, have not been observed.

Patients with major psychotic disorders, such as schizophrenia, bipolar disorder, and depression, and those with pre-psychosis, have been reported to be more susceptible than the general population to COVID-19 [1-6]. Many factors contribute to this enhanced susceptibility [4,7-10]. Significantly increased risks of COVID-19 development have been documented in patients with depression and those with schizophrenia (adjusted odds ratios, 7.64 and 7.3 respectively), and patients with COVID-19 and mental disorders have been found to be at increased risk of death [1].

More notably, many studies have revealed a reciprocal pattern of deterioration between COVID-19 and major psychotic disorders, which has a gradually increasing trend [4,8-10]. Although the mechanisms underlying the destructive effects of COVID-19 on the immune system remain unclear, increasing evidence indicates that this destruction plays pivotal roles in the episode, progress, and deterioration of infected patients [11-15]. At the same time, the COVID-19 vaccine has been confirmed to generate an immune response, with antibody production to block infection [15-18]. Notably, many hypotheses have involved immune system disturbance in the pathological mechanisms of major mental disorders [19-24]. Antipsychotics and antidepressants have been suggested to normalize such disturbance, improving psychotic symptoms [25-34]. These reciprocal effects of the immune system and drugs used to treat mental disorders, however, are controversial. In general, it might be reasonable to conclude that the immune system is the common pathway influenced by the COVID-19 vaccine and drugs such as antipsychotic agents and antidepressants [11-38]. This common pathway should include sophisticated reciprocal interactions and reaction cascades, which may involve immunoglobulin, cytokines, complements, and adhesion molecules. Thus, the safety and efficacy of the COVID-19 vaccine may be influenced by drugs used to treat mental disorders. Investigation of the vaccine's safety and efficacy in humans with confirmed blood concentrations of antipsychotic agents, antidepressants, and diazepam is needed; such research must be performed with healthy individuals before being expanded to include patients with psychosis. To date, no such study has been conducted with a Chinese population. Human studies of this type are needed because animal models of psychosis cannot mimic the traits of patients with psychosis, many of which involve the brain.

In our opinion, psychiatrists should be the vanguard of such research, volunteering to serve as study subjects, followed by healthy volunteers and, finally, patients with psychosis. Many physicians have conducted self-experimentation to explore new methods to treat patients. For example, Professor Forssmann (1904-1979) inserted a 65-cm-long catheter into his elbow vein and advanced it to the right atrium, confirming its location radio graphically after self-administering contrast agent, thereby obtaining the first radiographic image of cardiac catheterization.

Study objectives

This study protocol was designed to examine the safety and efficacy of the COVID-19 vaccine for patients with major psychotic disorders under drug treatment. We advocate the performance of three

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Received date: October 11, 2021; Accepted date: October 26, 2021; Published date: November 02, 2021

Citation: Sun Y, Lin C, Chen J, Qianchen L, Yang W, et al. (2021) A Proposed Protocol for the Investigation of the Safety and Efficacy of the COVID-19 Vaccine for Patients with Psychosis and Pilot Safety Findings from a Chinese Psychiatrist's Self-Experiment. J Infect Dis Ther 9:479.

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sub-studies to meet this goal. First, psychiatrists should volunteer as study participants, as they are most familiar with the side effects of antipsychotics and other drugs used to treat mental disorders. Thus, sub-study 1 should be conducted to test the safety and efficacy of the COVID-19 vaccine in volunteer psychiatrists via the administration of recommended clinical doses of an antipsychotic agent, an antidepressant, and diazepam; \geq 1-month and \geq 6-month regimens of these drugs and the efficacy index (which measures the equivalence of antibody production to that in healthy individuals administered only the vaccine) should be used for assessment. The hypotheses for this sub-study are that the COVID-19 vaccine will induce no severe allergic reaction by the antipsychotic agents, and that vaccine-induced antibody production will not be disturbed by the drug regimens, leading to serious adverse events. Sub-study 2 should investigate the safety and efficacy of the COVID-19 vaccine in healthy volunteers administered recommended clinical doses of an antipsychotic agent, an antidepressant agent, and an anti-anxiety agent, respectively. The objectives and hypotheses are the same as in sub-study 1. Sub-study 3 should be conducted in the same manner and with the same hypotheses as sub-study 2, but with patients with schizophrenia, bipolar disorder, depression, and severe anxiety administered the respective diseasespecific drugs.

Design and Methods

The flow of the study is illustrated in Figure 1. Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA). Normally distributed data are expressed as means \pm standard deviations and non-normally distributed continuous data are expressed as medians with interquartile ranges. Categorical variables are presented as numbers and percentages. Differences between groups in demographic and clinical characteristics and total therapeutic agent dosages over the 6-month study period were compared using Analysis of Variance (ANOVA) or the Kruskal-Wallis rank-sum test and the chi-squared test or Fisher's exact test, as appropriate. The homogeneity of variance was evaluated for the ANOVA using the Levene test. Greenhouse-Geisser correction was applied when the sphericity assumption was not met. To correct for missing values due to poor treatment response or transfer to another hospital, the last observation carried forward method was used to supply 6-month follow-up data.

For each disease, as the seropositive conversion rate in the COVID-19 vaccinated population is about 85%, the following formula was used to estimate the required sample size (N):

Where P is the seropositive conversion rate, Q=1-P, d is the allowable error (5%), and t is the statistic of significance (1.96 at the significance level of 0.05). The total sample required was determined to be 196 cases. Considering the potential for 20% loss to follow-up, 245 samples are required. As the estimated adverse reaction rate in the COVID-19 vaccinated population is about 30%, the required sample size was estimated to be 323 cases. Considering the potential for 20% loss to follow-up, 404 samples are required. We took the maximum value of the two assessments, i.e., 404 cases, as the overall required sample size. Hence, the totally sample size of three diseases (major depression disorder, bipolar disorder, schizophrenia), we will totally recruit 1300 participants.

Sub-study 1

Dr. Chuanjun Zhuo and 15 psychiatrists on his team volunteered to participate in sub-study 1 to test the safety and validity of COVID-19 vaccination. We are using the Sinovac vaccine (SVA.US; SINOVAC Life Sciences Co., Ltd., Beijing, China) under treatment with antipsychotic, antidepressant, and anti-anxiety agents. Two hours before receiving the COVID-19 vaccine (we are using the Sinovac vaccine (SVA.US; SINOVAC Life Sciences Co., Ltd., Beijing, China), valuated psychiatrists underwent MRI and EEG examinations to confirm that his brain structure and function were normal. Thirty minutes after vaccination, venous blood was collected for examination by a third-party institute to confirm the absence of antipsychotic drugs in the doctor's system. Two hours thereafter, the psychiatrists took antipsychotic, antidepressant, and anti-anxiety agents (at patient treatment doses). They were then monitored in the ICU for a total of 72 hours, including monitoring to detect any acute or chronic allergic reaction. The injection site was checked every 4 hours for the first 24 hours and hourly thereafter. For the first 24 hours, blood was collected every 4 hours to characterize the drug trajectories and to detect any effect of the vaccine on those trajectories; thereafter, blood was collected every day. For the first 24 hour, the doctors' urine and feces were collected for the examination of residual drug concentrations. MRI and EEG were performed at 12, 24, 36, and 48 hours to monitor brain function. Immune indices in blood were also analyzed, and any relationship between the immune system reaction and drug metabolism trajectory was characterized. All blood samples were conducted in duplicate, for third-party confirmation of the findings. At 25th hour, the psychiatrists took the second doses of the same drugs. From 26 hours to 72 hours, venous blood was collected every 12 hours to confirm the drug concentrations. After the initial 72-hours monitoring period, EEG and MRI will be performed to examine the brain at the 48th hour and 72nd hour. Any side effects that occur during this period will be recorded. After 48 hours ICU observation, after 72 hours monitoring in the ICU, the psychiatrists will be free to resume normal activities, with continuation of the drug regimens and collection of venous blood every 48th hour for the analysis of drug concentrations. Immune indices will be examined to characterize the immune reaction trajectory. MRI and EEG will be performed weekly. Any side effects that occur during this period will be recorded, and COVID-19 antibody testing will be performed during the 6-month study period. All procedures will be documented by HD video recording.

Sub-study 2

600 valuated psychiatrists and 600 healthy volunteers will be recruited from several communities in Tianjin, a city in northern China with a population of 1600, 0000, and Wenzhou, a city in southern China with a population of 900, 0000. Recruitment of native, resident individuals will be performed in the two regions to avoid bias with regard to genetic features potentially influencing vaccine safety and efficacy. The participants will be divided into three groups taking, respectively. Each group will comprise 50 individuals each from Tianjin and Wenzhou. The inclusion criteria will be: 1) Age 18-55 years, 2) No COVID-19 vaccine contraindication, 3) And voluntary consent to study participation. Exclusion criteria will be: 1) Allergic constitution; 2) Internal, neurological, immune-system, or hematological disease; 3) Mental disorder; and 4) Surgical disease that may affect the nervous or immune system. The procedure used for sub-study 1 will be used for this study, with the exceptions of healthy volunteer participation and administration of one drug to each participant (Figure 2).

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Sub-study 3

For this sub-study, patients (target n=1200) will be recruited from several hospitals in Tianjin and Wenzhou. The participants will be native to these regions and will be allocated to treatment groups as described for sub-study 2. After the safety was confirmed, according to the G* Power 3.1 manual, assuming a 15% dropout rate in each group and to enable the observation of significant effects at α =0.05 with a statistical power of 0.8, a total of 12, 00, 000 participants will be needed. The inclusion and exclusion criteria described for sub-study 2 will be applied, with the additional criterion that patients treated with more than one drug will be excluded. The procedure used for sub-study 1 will be used for this study (Figure 3).

The back-up study

We have prepared a contingency plan to investigate the safety and efficacy of the COVID-19 vaccine in patients requiring Electroconvulsive Therapy (ECT). This study will be completed in six steps. First, valuated psychiatrists and healthy volunteers will undergo 12 ECT sessions after COVID-19 vaccination to test the safety of the vaccine in people receiving ECT. Second, valuated psychiatrists and healthy volunteers will undergo three post-vaccination ECT sessions per week to test the efficacy of the vaccine under ECT. Thereafter, valuated patients will undergo ECT sessions in the same way, followed by the performance of the same procedures with the valuated psychiatrists and volunteers. All procedures will be the same as in the pharmacological arm of the study, including the monitoring of life indices and HD video recording (Figure 4).



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Outcome measures

(1) Short and long-term safety of the COVID-19 vaccine in patients with psychosis receiving pharmacological treatment or ECT.

Detailed index measure: all adverse events and side effects.

(2) Short and long term efficacy of the COVID-19 vaccine in patients with psychosis receiving pharmacological treatment or ECT. The COVID-19 antibody survival time in the human body will be the primary variable observed [39-42].

Detailed index measures: all adverse events and side effects, and efficacy index determination, should be HD video recorded.

Strategies to treat serious adverse events and side effects

The occurrence of adverse events and side effects, including any

complaints reported by patients and/or recorded by physicians, will be evaluated. According to the physical signs and changes in life indices, symptomatic treatment will be administered immediately. The most serious possible adverse events, including anaphylactic shock, will be treated in a timely manner by emergency doctors, and will prompt the termination of the study. Data on all reports and treatment of adverse events and side effects, and on symptomatic treatment effects, will be collected for further research purposes. HD video recording will capture the possible occurrence and treatment of adverse events and side effects.

Results

Anticipated results

The long-term safety and efficacy of the COVID-19 vaccine for

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patients with psychosis are anticipated to be ideal.

Discussion

I, Chuanjun Zhuo, a senior psychiatrist in China (Chinese ID no. 3708027197610231511, medical doctor license no. 110120000030033), am the director of the Key Laboratory of Real-Time Tracing of Brain Circuits of Neurology and Psychiatry (Tianjin Medical University Affiliated Tianjin Fourth Center Hospital). I conducted the selfexperimental portion of this study because patients with psychosis are as human as everyone, and action, rather than debate, is urgently needed for these patients. I made the decision to simultaneously receive one maximum recommended clinical dose each of olanzapine (20 mg for schizophrenia), venlafaxine (225 mg for depression), and diazepam (10 mg to improve the clinical effect or for serious anxiety or alcohol dependence) to rapidly test the safety of the COVID-19 vaccine for patients taking these drugs, despite the associated risks, thereby encouraging the participation of healthy individuals and patients in further testing of the vaccine as quickly as possible. In addition, I underwent ECT twice a week to confirm the safety of COVID-19 vaccination for patients receiving this treatment. I felt no serious side effect of ECT. For transparency and validity, my entire experience was documented on HD video and can be viewed freely (Figure 5).



Conclusion

As elderly individuals and those with the conditions encompassed by the exclusion criteria will not participate in the study, the safety and efficacy of the COVID-19 vaccine in these populations will not be investigated. Such investigation can be undertaken only with the establishment of a high safety profile for a COVID-19 vaccine.

Acknowledgments

We thank Professor Hongjun Tian and Professor Xiaodong Lin, who used their salaries to support me in performing this study, and Dr. Jianyue Chen, Dr. Qianchen Li, Dr. Cong Yao, Dr. Weiliang Yang, Dr. Tao Fang, Dr. Jing Ping, Dr. Ziyao Cai, and all the other workers in the department of cardiology, psychiatry, and ICU to protect me during the entire study procedure. Express my heartfelt thanks to them.

Statement of Conflict of Interest

The authors declare that they have no conflicts of interest.

References

 Huang Y, Wang Y, Wang H, Liu Z, Yu X, et al. (2019) Prevalence of mental disorders in China: a cross-sectional epidemiological study. Lancet psychiat 6:211-224.

- Xiang YT, Yu X, Sartorius N, Ungvari GS, Chiu HF (2012) Mental health in China: challenges and progress. Lancet 380:1715-1716.
- Wang Q, Xu R, Volkow ND (2021) Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World Psychiat 20: 124-130.
- Koreki A, Nakane J, Kitada S, Hamaya T, Ishii H, et al. (2020) Impact of COVID-19 on psychiatric day care services. Asian J Psychiatr 54:102442.
- Huang C, Huang L, Wang Y, Li X, Ren L, et al. (2021) 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-232.
- Du S, Cao Y, Zhu Q, Yu P, Qi F, et al. (2020) Structurally resolved sars-cov-2 antibody shows high efficacy in severely infected hamsters and provides a potent cocktail pairing strategy. Cell 183:1013-1023.
- Solmi M, Fornaro M, Ostinelli EG, Zangani C, Croatto G, et al. (2020) Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: A large scale systematic meta-review of 78 adverse effects. World Psychiat 19: 214-232.
- Maripuu M, Bendix M, Öhlund L, Widerström M, Werneke U (2020) Death associated with coronavirus (covid-19) infection in individuals with severe mental disorders in sweden during the early months of the outbreak-an exploratory cross-sectional analysis of a population-based register study. Front Psychiat 11: 609579.
- De Picker LJ, Yolken R, Benedetti F, Borsini A, Branchi I, et al. (2021) Viewpoint | European COVID-19 exit strategy for people with severe mental disorders: Too little, but not yet too late. Brain Behav Immun 94: 15-17.
- Bouabdallaoui A, Taouihar S, El Aidouni G, Aabdi M, Alkouh R, et al. (2021) The impact of mental health on COVID 19 disease progression: Case report. Ann Med Surg 68: 102543.
- Starr TN, Greaney AJ, Addetia A, Hannon WW, Choudhary MC, et al. (2021) Prospective mapping of viral mutations that escape antibodies used to treat COVID-19. Science 2021; 371: 850-854.
- White KM, Rosales R, Yildiz S, Kehrer T, Miorin L, et al. (2021) Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A. Sci 371:926-931.
- 13. Sette A, Crotty S (2021) Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 184: 861-880.
- Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, et al. (2021) Global absence and targeting of protective immune states in severe COVID-19. Nature 591: 124-130.
- Koenig PA, Das H, Liu H, Kümmerer BM, Gohr FN, et al. (2021) Structureguided multivalent nano bodies block SARS-CoV-2 infection and suppress mutational escape. Science 371.
- Lavine JS, Bjornstad ON, Antia R (2021) Immunological characteristics govern the transition of COVID-19 to endemicity. Science 371:741-745.
- Dai L, Gao GF (2021) Viral targets for vaccines against COVID-19. Nat Rev Immunol 21: 73-82.
- Wauters E, Van Mol P, Garg AD, Jansen S, Van Herck Y et al. (2021) Discriminating mild from critical COVID-19 by innate and adaptive immune single-cell profiling of bronchoalveolar lavages. Cell Res 31: 272-290.
- 19. Al-Diwani AAJ, Pollak TA, Irani SR, Lennox BR (2017) Psychosis: An autoimmune disease? Immunol 152: 388-401.
- Müller N (2020) A brief history of immunological research into psychosis and pathways for immune influence of the brain. Curr Top Behav Neurosci 44:1-8.
- Minichino A, Senior M, Brondino N, Zhang SH, Godwlewska BR, et al. Measuring disturbance of the endocannabinoid system in psychosis: A Systematic review and meta-analysis. JAMA Psychiat 76: 914-923.
- Ezeoke A, Mellor A, Buckley P, Miller B (2013) A systematic, quantitative review of blood autoantibodies in schizophrenia. Schizophr Res 150: 245-251.
- 23. Steiner J, Frodl T, Schiltz K, Dobrowolny H, Jacobs R, et al. Innate immune cells and c-reactive protein in acute first-episode psychosis and schizophrenia: Relationship to psychopathology and treatment. Schizophr Bull 46: 363-373.
- Essali N, Goldsmith DR, Carbone L, Miller BJ (2019) Psychosis as an adverse effect of monoclonal antibody immunotherapy. Brain Behav Immun 81: 646-649.

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- 25. Dinesh AA, Islam J, Khan J, Turkheimer F, Vernon AC (2020) Effects of antipsychotic drugs: Cross talk between the nervous and innate immune system. CNS Drugs 34:1229-1251.
- Hendouei N, Saghafi F, Shadfar F, Hosseinimehr SJ (2019) Molecular mechanisms of anti-psychotic drugs for improvement of cancer treatment. Eur J Pharmacol 856:172402.
- Perlman K, Benrimoh D, Israel S, Rollins C, Brown E, et al. (2019) A systematic meta-review of predictors of antidepressant treatment outcome in major depressive disorder. J Affect Disord 243: 503-515.
- Røge R, Møller BK, Andersen CR, Correll CU, Nielsen J (2012) Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr Res 140: 204-213.
- Robichon K, Patel V, Connor B, La Flamme AC (2020) Clozapine reduces infiltration into the CNS by targeting migration in experimental autoimmune encephalomyelitis. J Neuroinflammation 17:53.
- 30. Gerasimou C, Tsoporis JN, Siafakas N, Hatziagelaki E, Kallergi M, et al. A Longitudinal Study of Alterations of S100B, sRAGE and Fas Ligand in Association to Olanzapine Medication in a Sample of First Episode Patients with Schizophrenia. CNS Neurol Disord Drug Targets 17: 383-388.
- Chan MK, Cooper JD, Bot M, Birkenhager TK, Bergink V, et al. Blood-based immune-endocrine biomarkers of treatment response in depression. J Psychiatr Res 83: 249-259.
- Baumeister D, Ciufolini S, Mondelli V (2016) Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment? Psychopharmacology 233: 1575-1589.
- McNamara RK, Lotrich FE (2012) Elevated immune-inflammatory signaling in mood disorders: A new therapeutic target? Expert Rev Neurother 12:1143-1161.

- 34. Ganguli R, Brar JS, Rabin BS (1994) Immune abnormalities in schizophrenia: evidence for the autoimmune hypothesis. Harv Rev Psychiatry 2:70-83.
- 35. Bardají A, Sevene E, Cutland C, Menéndez C, Omer SB, et al. (2021) The need for a global COVID-19 maternal immunisation research plan. Lancet 397:e17-e18.
- 36. Lv H, Wu NC, Tsang OT, Yuan M, Perera R, et al. (2020) Cross-reactive Antibody Response between SARS-CoV-2 and SARS-CoV Infections. Cell Rep 2020; 31: 107725.
- 37. Quartuccio L, Fabris M, Sonaglia A, Peghin M, Domenis R, et al. (2021) Interleukin 6, soluble interleukin 2 receptor alpha (CD25), monocyte colonystimulating factor, and hepatocyte growth factor linked with systemic hyperinflammation, innate immunity hyperactivation, and organ damage in COVID-19 pneumonia. Cytokine 140: 155438.
- Shaan Lakshmanappa Y, Elizaldi SR, Roh JW, Schmidt BA, Carroll TD, et al. (2021) SARS-CoV-2 induces robust germinal center CD4 T follicular helper cell responses in rhesus macaques. Nat Commun 12: 541.
- Mishra S, Kass DA (2021) Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 18:400-423.
- Noonan J, Bobik A, Peter K (2020) The tandem stenosis mouse model: Towards understanding, imaging, and preventing atherosclerotic plaque instability and rupture. Br J Pharmacol.
- 41. Silva KAS, Emter CA (2020) Large Animal Models of Heart Failure: A Translational Bridge to Clinical Success. JACC Basic Transl Sci 5:840-856.
- 42. Vieira-Rocha MS, Sousa JB, Rodriguez-Rodriguez P, Morato M, Arribas SM, et al. Insights into sympathetic nervous system and GPCR interplay in fetal programming of hypertension: a bridge for new pharmacological strategies. Drug Discov Today 25:739-747.