

being overweight, and refusal of eating. There was no binge eating, purging, or laxative misuse. Social isolation was a common feature in all three patients. Each girl withdrew from her family and peers, failed to attend online education, weighed herself every day, checked her body image in mirrors, engaged in discourse about weight gain, calculated calories, spent a lot of time on social media and the Internet (especially videos showing food recipes and people eating), and prepared food at home for family members. None of the patients had a premorbid psychiatric history, and their levels of academic success and peer relationships were described as good. Summaries of each case's background characteristics and clinical findings are given in Table 1.

The insight about their symptoms and clinical courses of all patients was partial. They did not want to apply to the child and adolescent psychiatric outpatient unit due to worry about being infected with COVID-19 at the hospital. One of the cases was monitored in the pediatric inpatient unit and the other two were monitored in the pediatric emergency unit. Tube feeding was not needed as they each agreed to adapt to an oral diet with the help of a nutritionist. They were each diagnosed with anorexia nervosa according to the DSM-5<sup>5</sup> and were followed at Marmara University Pendik Research and Training Hospital Child and Adolescent Psychiatry Clinic. One of the patients had anxiety symptoms in addition to anorexia nervosa and the other two had major depression. Patients were followed up with olanzapine and fluoxetine/sertraline combination medication, individual cognitive behavioral therapy, and family interviews weekly. There was no history of contact with COVID-19 or having COVID-19 in patients or their family members. Follow-up of patients continues at the same child and adolescent psychiatry clinic.

Chia *et al.* showed that dietary restriction for religious purposes, such as that observed during the practice of Ramadan, may not confer increased risk of eating disorder symptoms.<sup>6</sup> Also, there were no patients with these symptoms presenting to the Marmara University Pendik Research and Training Hospital Child and Adolescent Psychiatry Clinic during the 2019 Ramadan period. In another study, social isolation was associated with binge eating, not dietary restraint.<sup>7</sup> However, no study investigating the relation between social isolation and the onset of eating disorders has been observed in literature. Social isolation and quarantine may have important adverse psychological effects on the most vulnerable groups, such as adolescents, but it is not possible to say with three cases that social isolation and quarantine may cause eating disorders.


Written consent was taken from the participants. This study fulfills the ethical provisions of the Declaration of Helsinki.

### Disclosure statement

The authors declare no conflicts of interest.

### References

1. Wang G, Zhang Y, Zhao J *et al.* Mitigate the effects of home confinement on children during the COVID-19 outbreak. *Lancet* 2020; **395**: 945–947.
2. Sani G, Janiri D, Di Nicola M, Janiri L, Ferretti S, Chieffo D. Mental health during and after the COVID-19 emergency in Italy. *Psychiatry Clin. Neurosci.* 2020; **74**: 372.
3. Phillipou A, Meyer D, Neill E *et al.* Eating and exercise behaviors in eating disorders and the general population during the COVID-19 pandemic in Australia: Initial results from the COLLATE Project. *Int. J. Eat. Disord.* 2020; **53**: 1158–1165.
4. Temorshuizen JD, Watson HJ, Thornton LM *et al.* Early impact of COVID-19 on individuals with eating disorders: A survey of ~1000 individuals in the United States and The Netherlands. *MedRxiv*. 2020. <https://doi.org/10.1101/2020.05.28.20116301>
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. American Psychiatry Publishing, Arlington, VA, 2013.
6. Chia JLP, Fuller-Tyszkiewicz M, Buck K, Chamari K, Richardson B, Krug I. An ecological momentary assessment of the effect of fasting during Ramadan on disordered eating behaviors. *Appetite* 2018; **127**: 44–51.
7. Mason TB, Heron KE, Braitman AL *et al.* A daily diary study of perceived social isolation, dietary restraint, and negative affect in binge eating. *Appetite* 2016; **97**: 94–100.

Hatice Ünver, MD, PhD <sup>1</sup>, Ayşe Rodopman Arman, MD, PhD,<sup>2</sup>

Ayşe Burcu Erdoğan, MD, PhD<sup>2</sup> and Çağla İlbasmış, MD<sup>2</sup>

<sup>1</sup>Child and Adolescent Psychiatry Clinic, Marmara University Pendik Research and Training Hospital, and <sup>2</sup>Child and Adolescent Psychiatry Department, Marmara University Medical Faculty, Istanbul, Turkey

Email: [drhaticeunver@gmail.com](mailto:drhaticeunver@gmail.com)

Received 20 July 2020; revised 1 September 2020;

accepted 27 September 2020.

## Depressive symptoms in students during school closure due to COVID-19 in Shanghai

doi:10.1111/pcn.13161

Since the first identification of a patient with COVID-19, this infection has spread rapidly worldwide, with a high case fatality rate among the elderly and individuals with chronic diseases.<sup>1</sup> While this virus is less likely to cause serious illness in the younger generation, many affected countries have adopted school closure as a measure to prevent its spread among the community.<sup>2</sup>

Concerns may be raised about the adverse effects of school closure not only on education but also on the health of children. The drastic changes in children's lifestyles during school closure may deteriorate their mental health.<sup>3</sup> The present paper reports the changes in depressive symptoms among students in Shanghai caused by school closure due to the COVID-19 epidemic.

The present study was originally designed to assess health and health-associated factors using a web-based survey among schoolchildren (aged 6–17 years) and their parents from five schools across Shanghai, China. Details of the study procedure are described in Appendix S1. The first survey was conducted from 3 to 21 January 2020 (before school closure) and the second survey was conducted from 13 to 23 March 2020 (during school closure). Depression was assessed using the Children's Depression Inventory – Short Form (CDI-S)<sup>4</sup>; the total score ranges from 0 to 20, with a higher score indicating more depressive symptomatology. We also asked about the positive aspects of lifestyle change during school closure. We calculated the mean and SD of CDI-S scores before and during school closure and tested the difference using the paired *t*-test. A within-subjects analysis of variance was conducted to determine the interactions of Time × Subgroup (sex, school levels, and annual household income levels) in terms of CDI-S score. We declared statistical significance when  $P < 0.05$  for the paired *t*-test and  $P < 0.1$  for the interaction test.

Of 3042 students in the target schools, 2641 (87%) participated in the first survey. Of these, 2427 participated in the second survey. Overall, the mean CDI-S score significantly decreased between the two surveys: 4.19 before school closure and 3.90 during school closure ( $P < 0.01$ ). In stratified analyses, children in middle school showed a greater decrease in CDI-S scores than those in primary school ( $P$  for interaction = 0.09), whereas a lower CDI-S score during school closure was consistently observed across sexes and household income categories (Table 1). As regards positive aspects of lifestyle change during school closure, 71%, 80%, and 83% of children were satisfied with having more time 'at home,' 'with their parents,' and 'doing their own things,' respectively.

School closure with a stay-at-home policy should drastically decrease the opportunity for direct contact with persons other than family members, decrease physical activity, and increase the time of screen viewing, all of which may deteriorate the mental health of school children. However, the present result is at variance with the prior hypothesis; rather, we observed fewer depressive symptoms during school closure compared to those measured before the closure.

**Table 1.** Depression scores before and during school closure due to the COVID-19 pandemic among students in Shanghai

	Before school closure	During school closure	Mean differences	<i>P</i> -value <sup>†</sup>	<i>P</i> for interaction <sup>‡</sup>
Total ( <i>n</i> = 2427)	4.19 (2.82)	3.90 (2.56)	−0.29	<0.01	
Sex					0.21
Male ( <i>n</i> = 1242)	4.03 (2.63)	3.83 (2.57)	−0.20	<0.01	
Female ( <i>n</i> = 1185)	4.37 (3.00)	3.98 (2.55)	−0.39	<0.01	
School grade					0.09
Primary school ( <i>n</i> = 875)	3.89 (2.28)	3.77 (2.07)	−0.12	0.13	
Grade 1 ( <i>n</i> = 207)	3.43 (1.75)	3.53 (1.82)	0.11	0.44	
Grade 2 ( <i>n</i> = 198)	3.63 (1.77)	3.62 (1.84)	−0.01	0.95	
Grade 3 ( <i>n</i> = 165)	4.08 (2.36)	3.77 (1.82)	−0.32	0.10	
Grade 4 ( <i>n</i> = 171)	4.25 (2.70)	4.13 (2.56)	−0.11	0.57	
Grade 5 ( <i>n</i> = 134)	4.31 (2.79)	3.90 (2.26)	−0.41	0.08	
Middle school ( <i>n</i> = 1549)	4.36 (3.06)	3.97 (2.78)	−0.39	<0.01	
Grade 6 ( <i>n</i> = 558)	4.05 (2.79)	3.82 (2.72)	−0.23	0.07	
Grade 7 ( <i>n</i> = 417)	4.44 (3.02)	4.06 (2.66)	−0.38	<0.01	
Grade 8 ( <i>n</i> = 344)	4.56 (3.28)	3.92 (2.86)	−0.65	<0.01	
Grade 9 ( <i>n</i> = 230)	4.66 (3.37)	4.22 (3.01)	−0.43	0.02	
Annual household income (CNY)					0.19
<100 000 ( <i>n</i> = 277)	5.12 (3.50)	4.68 (3.33)	−0.44	0.02	
100 000–200 000 ( <i>n</i> = 677)	4.23 (2.76)	3.92 (2.56)	−0.31	<0.01	
>200 000–400 000 ( <i>n</i> = 767)	3.93 (2.65)	3.78 (2.43)	−0.15	0.09	
>400 000 ( <i>n</i> = 367)	3.92 (2.52)	3.82 (2.40)	−0.10	0.49	

Data are presented as mean (SD).

CDI-S, Children’s Depression Inventory – Short Form; CNY, Chinese Yuan.

<sup>†</sup>Calculated using paired *t*-test.

<sup>‡</sup>Calculated using within-subjects analysis of variance by the interaction effect of Time × Subgroup (sex, school levels [primary or middle school], or annual household income levels [<100 000, 100 000–200 000, >200 000–400 000, or >400,000 CNY]).

The present finding based on pre- and post-observation without a comparison group should be interpreted with caution. Nevertheless, this unexpected finding could be attributed to relatively good educational environments at home. In Shanghai, nearly all families own a personal computer or smartphone, which would have been used for communication with schools before the pandemic. Soon after school closure, each school started providing an online and TV program for education, and children received interactive education at home from their teacher and communicated with classmates on a daily basis. Such a remote educational system might have contributed to better mental health during school closure.

Children, especially those under high academic pressure, might have less stress in the home environment than at school. Analysis by school type showed that middle school students, who had a higher depressive score before school closure than primary school students, showed a greater decrease in depressive symptoms during school closure. This may partly reflect greater academic stress preparing for entrance examinations in middle school.<sup>5</sup> As regards the positive aspects of staying at home, most children reported being satisfied with having more time ‘at home,’ ‘with their parents,’ and ‘doing their own things.’ Taken together, a well-equipped home-schooling system, together with fewer stressors and the positive aspects of staying at home, may have jointly outweighed the potential harm of school closure to children’s mental health.

In conclusion, the present longitudinal study in Shanghai during the COVID-19 pandemic does not show any evidence of increased depressive symptoms among students after a 2-month school closure. Additional study is required to assess the long-term effect of school closure on the mental health and educational attainment of children.

**Acknowledgments**

This research was funded by the National Natural Science Foundation of China (grant 71804110) for Mi Xiang. The study protocol was approved

by the Ethics Committee of Shanghai, Jiao Tong University School of Medicine (SJUPN- 201813).

**Disclosure statement**

All authors have indicated they have no financial relationships relevant to this article to disclose.


**References**

- Centers for Disease Control and Prevention. People who are at higher risk for severe illness. [Cited 17 April 2020.] Available from URL: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html>
- United Nations Educational, Scientific and Cultural Organization. COVID-19 educational disruption and response. [Cited 17 April 2020.] Available from URL: <https://en.unesco.org/covid19/educationresponse>
- Wang G, Zhang Y, Zhao J, Zhang J, Jiang F. Mitigate the effects of home confinement on children during the COVID-19 outbreak. *Lancet* 2020; **395**: 945–947.
- Kovacs M. *Children’s Depression Inventory (CDI). Technical Manual Update*. Multi-Health Systems, North Tonawanda, NY, 2003.
- Zhao X, Selman RL, Haste H. Academic stress in Chinese schools and a proposed preventive intervention program. *Cogent Educ.* 2015; **2**: 1000477.

**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Appendix S1.** Methods of study sampling.

Mi Xiang, PhD,<sup>1†</sup> Shohei Yamamoto, MSc <sup>2,3†</sup> and Tetsuya Mizoue, MD, PhD<sup>2</sup>

<sup>1</sup>School of Public Health, Shanghai Jiao Tong University, Shanghai, China, <sup>2</sup>Department of Epidemiology and Prevention, National Center for Global Health and Medicine, Tokyo, and <sup>3</sup>Department of Rehabilitation Sciences, Kitasato University Graduate School of Medical Sciences, Kanagawa, Japan

Email: mizoue@hosp.ncgm.go.jp

<sup>†</sup>Drs Xiang and Yamamoto made equal contributions as first authors.

Received 5 June 2020; revised 12 August 2020;

accepted 28 September 2020.

## Combination therapy of brexpiprazole and aripiprazole for an adolescent patient with a first episode of schizophrenia: A case report

doi:10.1111/pcn.13151

One year before admission to our facility, an 18-year-old female high school student had presented with cognitive decline and reduced executive function. She presented grossly disorganized behavior accompanied by a mild fever and was tentatively diagnosed with encephalitis. She had no developmental issues, no history of illegal drug use, and no family history of psychiatric disorders. Neurologists conducted various tests, including tests of autoantibodies, cerebrospinal fluid, electroencephalography, and head MRI. Neither infection nor autoimmune disease was observed. Acyclovir infusion and steroid pulse therapy were performed as diagnostic treatments, but they were ineffective. The findings in total ruled out encephalitis. She gradually developed catatonic symptoms, and was transferred to our department. She was treated with lorazepam 1 mg/day, which led to partial relief of catatonic symptoms. Upon further communication with the patient, other symptoms, such as auditory hallucinations, loosening of association, and ego disorder as a delusion of control, were reported. She was then diagnosed with schizophrenia, and was initially treated with brexpiprazole, based on its tolerability, 1 mg/day, which was increased to 2 mg/day over a period of 1 week. She reported partial amelioration of her hallucinations. Brexpiprazole was increased to 4 mg/day. While brexpiprazole treatment was provided over a 4-week period, there was no further improvement in her symptoms. To improve her symptoms further, aripiprazole was added, 12 mg/day, and her hallucinations dramatically improved over a few days. She achieved remission with a combination of brexpiprazole (2 mg/day) and aripiprazole (12 mg/day). The combination therapy was continued until her discharge; the total length of her hospitalization was 3 months. Following discharge, she continued combination therapy, but aripiprazole was gradually discontinued over a period of 3 months because the patient complained of drowsiness. Treatment, then, was only with brexpiprazole, for a period 6 months. She has remained in remission on brexpiprazole treatment until the present. Patient consent was obtained for this report.

For treating adolescent girls with their first episode of schizophrenia, both brexpiprazole and aripiprazole are suitable in terms of low risk for weight gain, prolactin increase, and extrapyramidal symptoms.<sup>1,2</sup> In this case, brexpiprazole was selected based its lower potential to induce adverse effects, compared to aripiprazole, which are mediated by partial agonism of the D2 receptor. Our patient reported no adverse effects of brexpiprazole, but her symptoms were only partially improved with brexpiprazole alone. Brexpiprazole, 2 mg/day and greater, demonstrated

efficacy in patients with schizophrenia over a 6-week period.<sup>1, 3,4</sup> This suggests that in a subgroup of patients, as suggested in the current case, it could take more than 4–6 weeks for efficacy to occur with brexpiprazole monotherapy. Therefore, combination therapy of brexpiprazole with another second-generation antipsychotic (SGA) could be utilized as short-term treatment for first-episode schizophrenia patients. The mechanism of action of the current combination is unknown. The affinities of brexpiprazole and aripiprazole to D2 receptors as antagonists are similar. However, aripiprazole's partial agonism at the D2 receptor is greater than that of brexpiprazole, and brexpiprazole's antagonism of the 5-HT2A receptors is an order of magnitude greater than that of aripiprazole.<sup>5</sup> In our patient, it is speculated that the addition of aripiprazole compensated for brexpiprazole's weak D2 receptor agonism and any adverse effects mediated by D2 receptor antagonism by aripiprazole were suppressed by brexpiprazole's potent antagonism of the 5-HT2A receptor. It is possible that modulating dopaminergic functioning in this manner allowed for efficacy and reduced adverse effects. Furthermore, both brexpiprazole and aripiprazole have been reported to have antidepressant effects. The effects of brexpiprazole and aripiprazole on the dopamine system might have acted on affective components, such as anxiety and emotional stability, to improve our patient's condition.<sup>6</sup> In this case, a combination treatment of brexpiprazole and aripiprazole led to a shortened treatment period during the acute phase of schizophrenia, without side-effects. As remission was maintained with brexpiprazole alone, the findings suggest that aripiprazole could be effective as an additive treatment, with brexpiprazole, for acute treatment of schizophrenia.

In this case, there were no apparent adverse events with the combination therapy other than drowsiness. Although there are limited reports of adverse events with combination therapy used in psychiatric medicine, brexpiprazole in combination with antidepressants has been reported to lead to akathisia and tardive dyskinesia.<sup>7</sup> Atypical antipsychotics are generally prone to affect metabolism, electrolyte imbalance, and induced cardiovascular adverse effects.<sup>8</sup> Such side-effects could occur when brexpiprazole is used in combination with other atypical antipsychotics, including aripiprazole. Further studies are needed to establish an optimal treatment regime and to evaluate other combinations of SGA that show both efficacy and markedly reduced adverse effects compared to monotherapy.

### Disclosure statement

The authors have no conflicts of interest to declare.

### References

- Correll CU, Skuban A, Ouyang J *et al.* Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. *Am. J. Psychiatry* 2015; **172**: 870–880.
- DeLeon A, Patel NC, Lynn Crismon M. Aripiprazole: A comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin. Ther.* 2004; **26**: 649–666.
- Ishigooka J, Iwashita S, Tadori Y. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: A 6-week, randomized, double-blind, placebo-controlled study. *Psychiatry Clin. Neurosci.* 2018; **72**: 692–700.
- Kane JM, Skuban A, Ouyang J *et al.* A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr. Res.* 2015; **164**: 127–135.
- Maeda K, Sugino H, Akazawa H *et al.* Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J. Pharmacol. Exp. Ther.* 2014; **350**: 589–604.
- Romeo B, Blecha L, Locatelli K, Benyamina A, Martelli C. Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: Efficacy and safety. *J. Psychopharmacol.* 2018; **32**: 385–396.
- Fornaro M, Fusco A, Anastasia A, Cattaneo CI, de Berardis D. Brexpiprazole for treatment-resistant major depressive disorder. *Expert Opin. Pharmacother.* 2019; **20**: 1925–1933.