Schizophrenia Research 209 (2019) 135–140

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Co-treatment of buspirone with atypical antipsychotic drugs (AAPDs) improved neurocognitive function in chronic schizophrenia

Yu Wang [a,b], Xiao Yang [a,b], Xiuli Song [a,b], Liansheng Zhao [a,b,c], Jinxue Wei [a,b,c], Jixiang Wang [d], Hong Tian [d], Congyu Zheng [e], Min Wei [e], Qiang Wang [a,b], Wanjun Guo [a,b], Wei Deng [a,b], Tao Li [a,b], Xiaohong Ma [a,b,*]

[a] Psychiatric Laboratory and Mental Health Center, West China Hospital of Sichuan University, Chengdu, China
[b] West China Brain Research Center, West China Hospital of Sichuan University, Chengdu, China
[c] National Clinical Research Center on Mental Disorders (Changsha) of China, Changsha, China
[d] Dazhou Mental Health Center, China
[e] Mental Hospital of Liangshan Yi Autonomous Prefecture, China

ARTICLE INFO

Article history:
Received 1 March 2019
Received in revised form 13 April 2019
Accepted 5 May 2019
Available online 14 May 2019

Keywords:
Buspirone
APPDs
Co-treatment
Schizophrenia
Neurocognitive function

ABSTRACT

We conducted a 24-week, randomized, double-blind parallel-controlled trial to test whether buspirone is beneficial to improve cognitive deficits of schizophrenia because it remains unclear. Two hundred patients received in random order either co-treatment buspirone with AAPDs or monotherapy with AAPDs. All patients had been treated with a stable dosage of AAPDs for at least three months. The positive and negative syndrome scale (PANSS), Hamilton Depression Scale-24 (HAMD-24), and 14-item Hamilton Rating Scale for Anxiety (HAMA-14) were used to evaluate clinical symptoms. The short version of Wechsler Adult Intelligence Scale-Revised in China (WAIS-RC) was used to assess neurocognitive function. Social function and family burden were evaluated by Social Disability Screening Schedule (SDSS) and Family Burden Interview Schedule (FBIS). All patients were enrolled at baseline and followed up after 12 and 24 weeks. A total of 196 patients completed the trial, with 99 in the combined treatment group and 97 in the control group. During the intervention, the score of PANSS, HAMD-24, and HAMA-14 decreased slightly without group differences. Repeated measures ANOVA showed significant differences between the two groups in the score of arithmetic, similarities, picture completion, block design, SDSS, and FBIS ($P < 0.05$), but no difference was found with regard to the score of information, digital span test, or digital symbols ($P > 0.05$). In conclusion, co-treatment with buspirone and APPDs outperformed APPDs alone in improving cognitive deficit and reducing family burden of schizophrenia. Buspirone may be a promising candidate for co-treatment of schizophrenia-associated cognitive deficits.

1. Introduction

Schizophrenia is a severe, debilitating, and chronic mental disorder affecting approximately 0.7–1% of the population worldwide (Landek-Salgado et al., 2016), which is characterized by positive (hallucinations, delusions), negative (withdrawal, apathy, anhedonia), cognitive (working memory abnormalities, deficits of cognitive processing and attention), depressive, and anxiety symptoms (Sadock et al., 2009). As one of the core symptoms of schizophrenia, cognitive impairment is present in about 85% schizophrenic patients, involving attention, working memory, declarative memory, motivational performance, and executive function (Meltzer and Sumiyoshi, 2008). Cognitive symptoms have been associated with detrimental effects on patients' functional status and are the most stable symptoms over the course of illness (Sadock et al., 2009; Ghaleiha et al., 2010). Even if clinical symptoms improve or disappear, about 80% of patients will suffer from persistent cognitive impairment, resulting in their inability to live independently, to work and to learn (Zhao and Shi, 2015). A systematic review of 50 outcomes showed that only 13.5% of patients could rehabilitate clinically and socially (Jaaskelainen et al., 2013). According to data on the global disease burden (GBD) of schizophrenia that were published in 2016, about 21 million people worldwide were suffering from schizophrenia and >18 million were unable to achieve clinical and social rehabilitation (Charlson et al., 2018). Because of more direct or indirect costs, resources use and productivity loss, patients with schizophrenia usually need more care from family and society than those with other mental illnesses (Gupta et al., 2015). In Asian countries, about 70% patients are cared for by their families, which brings heavy burdens to the family in terms of including economy, social activities, and physical and mental health (Yu et al., 2017). Therefore, it is urgent that other effective measures be taken to improve cognition in chronic schizophrenia.

* Corresponding author at: Psychiatric Laboratory, Department of Psychiatry, West China Hospital of Sichuan University, #1 Ke Yuan 4th Road, Chengdu, Sichuan 610041, China.
E-mail address: maxiaohong@scu.edu.cn (X. Ma).

https://doi.org/10.1016/j.schres.2019.05.006
0920-9964/

The development of second-generation antipsychotic drugs has yielded some advances in reducing both positive and negative symptoms (Casey et al., 2009); however, they do not change much cognitive symptoms of schizophrenia (Owen et al., 2016). Goff et al. reported that the volume of left hippocampus in some patients with schizophrenia continued to shrink after 8 weeks' treatment with atypical antipsychotic drugs (AAPDs), which suggested that the cognitive function of the patients continued to decline (Goff et al., 2018). Another longitudinal study indicated that the volume of bilateral hippocampus in unmedicated patients significantly increased after treatment with aripiprazole, indicating aripiprazole had some positive effects on cognitive deficits (Bodnar et al., 2016). Therefore, they supposed that only a few AAPDs might improve cognitive function, which was related to their partial activation of 5-HT receptors (Jaaskelainen et al., 2013). Indeed, the serotonergic system is potentially an important target for pharmacologic agents (King et al., 2008; Akhondzadeh et al., 2009). In particular, 5-HT1A receptors are thought to be a favored therapeutic target for schizophrenia based on the following two evidences: (1) stimulation of 5-HT1A receptors can improve cognitive impairment in schizophrenia (Meltzer and Sumiyoshi, 2008; Sumiyoshi et al., 2001a, b; Sumiyoshi et al., 2007); and (2) agitation of 5-HT1A receptors can ameliorate antipsychotic-induced EPS (Ohno et al., 2008). Thus, 5HT1A receptor has proved to play an important role in cognitive enhancement.

Recently, some clinical studies were conducted to explore whether they could effectively improve cognitive impairment in schizophrenia. These data showed that the executive function, attention, and language memory of patients significantly improved after 6 weeks' combination treatments with AAPDs and 5HT1A agonist (Baba et al., 2015; Sumiyoshi et al., 2001a, b; Sumiyoshi et al., 2007). Animal researches focusing on 5HT1A agonist showed that it did not only increase cognitive flexibility, but reduce novel object recognition deficits induced by MK-801 and/or PCP (a non-competitive NMDAR antagonist) (Torrisi et al., 2017; Horiguchi and Meltzer, 2012). Another animal study conducted in Poland reported that buspirone enhanced neurogenesis in the opossum (Grabiec et al., 2009). Mori et al. also showed that chronic tandospirone treatment resulted in a significant increase in the number of doublecortin (DCX) positive cells per volume of dentate gyrus in a dose-dependent manner, which strongly suggested that 5-HT1A receptor partial agonists would be useful and beneficial in improving cognitive function through increased hippocampal neurogenesis (Mori et al., 2014). Besides, except for claimed 5-HT1AR partial agonist activity, buspirone is endowed with dopamine D3 receptor (D3R) antagonist activity (Bergman et al., 2013; Leggio et al., 2014). D3R play a fundamental role in the pathophysiology of schizophrenia. Torrisi et al. found that buspirone can effectively improve the deficit of temporal order recognition memory and schizophrenia-relevant abnormalities in wild-type mice (but not in D3R-null mutant mice) induced by MK-801 (Torrisi et al., 2017). These data provided strong evidence that buspirone may be successful in treating cognitive deficits in schizophrenia because of its activities of D3R antagonist and 5-HT1A receptor agonist. However, some studies also showed that buspirone was almost ineffective in remedying cognitive dysfunction (Maeda et al., 2014; Piškulić et al., 2009).

Considering that clinical symptoms may affect the cognitive performance of patients, we conducted a randomized, double-blind parallel-controlled trial to test the hypothesis that the addition of buspirone would improve various domains of cognition and psychopathology in patients who have chronic schizophrenia and are treated with AAPDs.

2. Methods

2.1. Participants

Chinese patients aged from 18 through 65 years old were recruited from two psychiatric hospitals in Sichuan Province during January 2017 to February 2018. All participants had confirmed the diagnosis of schizophrenia, based on the structured clinical interview for DSM-IV-TR for at least 1 year (First et al., 1997). Acute symptoms of illness were controlled by AAPDs and the patients were on a stable dose for at least three months, so as to attain the stable cognitive status (Woodward et al., 2005). As for the stable dose, it means that the dosage of the main antipsychotics has not changed in the past three months and throughout the trial. The exclusion criteria were: (1) having any other psychiatric disorders in Axis I or II; (2) having serious physical diseases, such as neurogenic diseases, endocrine diseases or metabolic disorders; (3) having any clinically significant abnormalities in vital signs or electrocardiogram; (4) being receiving hormones medication or electroconvulsive (ECT) therapy; (5) being pregnant or breast feeding; and (6) being in reproductive age without adequate contraception. All participants were given a complete description of the study before they provided written informed consent. The trial was approved by the Ethics Committee of West China Hospital of Sichuan University.

2.2. Study design

The 24-week study was a double-blind, randomized controlled trial (RCTs), involving two groups of patients with chronic schizophrenia. Eligible patients were assigned to receive either 24 weeks of co-treatment with AAPDs and buspirone (buspirone group) or AAPDs alone (control group). We randomized the patients using permuted blocks. We wrote the type of intervention on a piece of paper and put it in a sealed black box. For each patient who entered the study, we picked a box. One hundred patients were randomly allocated to buspirone group and another 100 patients to the control group. Patients received the addition of buspirone with dosing titration as follows: 5 mg twice daily during the 1st week, and 30 mg/day afterwards. To maintain the objectivity of the study, psychiatrists who conducted the clinical and neurocognitive assessments and patients were blinded to medication status throughout the study. Flow Diagram please read the supplementary materials.

2.3. Clinical and neurocognitive assessments

The presence and severity of schizophrenia symptoms were investigated using the positive and negative syndrome scale (PANSS) (Kay et al., 1987). Hamilton Depression Scale-24 (HAMD-24) and 14-item Hamilton Rating Scale for Anxiety (HAMA-14) were used to assess anxiety and depression symptoms of patients (Hamilton, 1959, 1960). Social Disability Screening Schedule (SDSS) was conducted to investigate clinical symptoms, cognitive function, quality of life, and social function (Handbook of Epidemiological Investigation on Mental Disorders, 1985). Assessment of the economic burden was performed using Family Burden Interview Schedule (FBIS) (Pai and Kapur, 1981). The short version of Wechsler Adult Intelligence Scale-Revised in China (WAIS-RC) was used to estimate neurocognitive function, mainly including speech comprehension, memory, attention, and perceptual organization (Gong, 1992). The seven subtests of WAIS-RC included information, arithmetic, digital symbol, digital span test, block design, picture completion, and similarities. For all patients, five clinical scales and cognitive function (WAIS-RC) were measured by a psychiatrist at baseline, 12, and 24 weeks after the start of research. The raw scores of PANSS, HAMD, HAMA, SDSS, and FBIS were measured, recorded, and analyzed. Regarding the seven subtests of WAIS-RC, primitive scores were converted into scores of the measuring scale, and higher scale score represented better neuropsychological performance (Gong, 1992).

To analyze the consistency of assessment among different researchers, ten professionally trained psychiatrists assessed 10 randomly selected patients with schizophrenia, respectively, before the trial. Assessment results showed that the internal consistency of different assessors was good and the intraclass correlation coefficient (ICC) was >0.90. More concretely, ICC of raters about WAIS-RC, PANSS, HAMD, HAMA, SSDD and FBIS scales were 0.94, 0.93, 0.97, 0.93, 0.92 and 0.93, respectively.

2.4. Statistical analysis

Group comparisons for demographic data were performed using independent *t*-tests for continuous variables and Chi-square tests for categorical data. Clinical as well as cognitive data were analyzed using separate 2 (treatment) × 3 (time) repeated measures ANOVAs. The between-subject factor, i.e. co-treatment with AAPDs and buspirone vs AAPDs alone, was denoted "Group," and the within-subject factor between time points was denoted "Time." A significant "Time × Group interaction" indicates a difference in response between the two treatment groups. Because of the exploratory nature of the analyses of outcomes, we did not correct for multiple comparisons. All statistical tests were two-tailed and 0.05 was set as the significance level throughout. IBM SPSS version 22 was used for statistical analyses.

3. Results

3.1. Clinical and demographic characteristics

Of 200 potential participants, four patients (one in the buspirone group and three in the control group) withdrew from the study due to lack of interest and time. Finally, 99 patients in the buspirone group and 97 patients in the control group completed the study. Basic demographic data such as age, gender, ethnicity, education, age at onset of illness, duration of illness, BMI, and history of smoking or alcohol were collected and there was no significant difference between the two groups (Table 1). The co-treatment atypical antipsychotic drugs were also list in Table 1. The duration of AAPDs treatment before baseline assessment was 144.1 ± 106.5 months (range: 13–444 months) for the buspirone group and 134.8 ± 99.4 months (range: 13–396 months) for the control group, which did not differ significantly between groups ($P = 0.529$).

3.2. Clinical psychopathology scales assessment

At baseline, we found no significant differences between the groups concerning the scores of PANSS, HAMD, or HAMA ($P > 0.05$), which means that the two groups are comparable at baseline. The score of PANSS from baseline (48.03 ± 12.95) to 12 W (44.22 ± 12.88) and 24 W (42.33 ± 12.61) after treatment had a slight decrease but failed to exhibit a significant difference among the three time points in the buspirone group. Similar pattern was also observed for HAMD and HAMA scores. Likewise, the scores of PANSS, HAMD, and HAMA all decreased slightly from baseline to 12 W and 24 W, but no significant difference was observed among the three time points in the control group (Table 1).

At baseline, we found no significant differences between the groups concerning the scores of SDSS and FBIS ($P > 0.05$). During the 24-week follow-up, both groups had similar reduction in the score of SDSS, while the score of FBIS presented completely opposite patterns in the two groups (Fig. 1). Based on results from the repeated measures ANOVA, we found an effect of Group on the scores of SDSS and FBIS ($P < 0.05$). The score of SDSS showed a significant effect of Time ($P < 0.001$) but the score of FBIS did not ($P > 0.05$). The repeated measures ANOVA revealed significant interaction between time of testing and treatment condition on the score of SDSS and FBIS ($P < 0.05$) (Table 2).

3.3. Neurocognitive assessment

At baseline, none of the 7 dimensions of WAIS-RC showed any significant differences between two groups ($P > 0.05$). During the intervention, both groups had similar increase patterns in scores of information, arithmetic, similarities, digital span test, and digital symbols. The scores of picture completion and block design increased significantly in the buspirone group, but not in the control group (Fig. 1).

Table 1
Demographics and clinical symptom scales characteristics of participants.

	Buspirone group (n = 99)		Control group (n = 97)		T/χ2	*P* value
	Mean (SD)	Range	Mean (SD)	Range		
Gender (male/female)	71/28		68/29		0.06	0.804
Age (year)	39.81(10.11)	18–64	39.02(9.56)	18–62	0.56	0.576
Age at onset of illness (year)	27.80(8.47)	10–46	27.78(7.49)	11–46	0.01	0.990
Duration of illness (year)	12.01(8.87)	1–37	11.24(8.28)	1–33	0.63	0.529
Antipsychotic medication						
Risperidone/quetiapine	49/21		42/23			
Clozapine/olanzapine	13/1		14/2			
Aripiprazole/ziprasidone	9/6		14/2			
Education (years)	6.89(3.68)	0–15	6.71(3.16)	0–13	0.36	0.718
BMI	23.79(3.76)		23.83(3.80)		0.08	0.936
Ethnicity (%)					1.45	0.229
Han	75.76		68.04			
Other	24.24		31.96			
Smoking yes/no (%)	33/66		30/67		1.30	0.718
Alcohol yes/no (%)	4/95		6/91		4.67	0.495
The score of PANSS						
Baseline	48.03(12.95)	30–87	47.49(12.32)	30–71	0.09	0.766
12 week	44.22(12.88)	30–86	45.60(12.32)	30–75	0.42	0.520
24 week	42.33(12.61)	30–86	44.30(12.23)	30–71	1.07	0.302
The score of HAMD-24						
Baseline	3.20(4.28)	0–20	3.23(4.30)	0–20	0.04	0.836
12 week	2.68(3.54)	0–22	2.38(3.25)	0–18	0.21	0.650
24 week	2.28(3.41)	0–21	1.94(3.59)	0–23	0.45	0.502
The score of HAMA-14						
Baseline	1.41(2.43)	0–9	1.44(2.45)	0–9	0.07	0.933
12 week	1.42(1.76)	0–7	1.18(2.10)	0–11	0.81	0.369
24 week	1.01(1.67)	0–8	0.81(1.77)	0–10	0.63	0.427

Abbreviations: BMI, body mass index; PANSS, the positive and negative syndrome scale; HAMD, Hamilton Depression Scale-24; HAMA, 14-item Hamilton Rating Scale for Anxiety; Mean, standard deviation (SD) and range are presented in the table. Group differences were tested by independent two-sample *t*-test and Chi-square tests, and no significant group differences were examined.

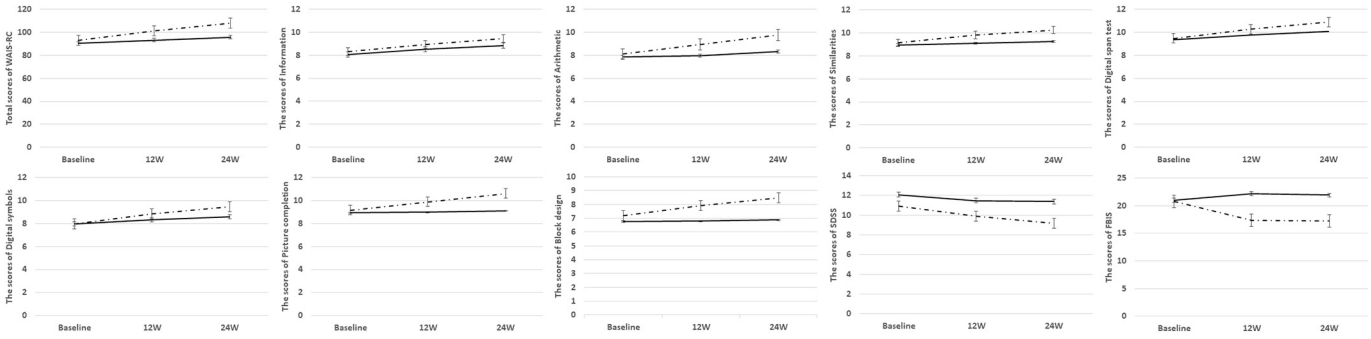

Fig. 1. Scores of three scales at baseline and Following 12 and 24 weeks. WAIS-RC, Wechsler Adult Intelligence Scale-Revised in China. The seven subtests of WAIS-RC included information, digital span test, digital symbols, arithmetic, similarity, picture completion, and block design. SDSS, Social Disability Screening Schedule; FBIS, Family Burden Interview Schedule. (—·— Buspirone group — Control group).

Table 2
Results on primary and secondary outcomes after 12 and 24 weeks of treatment.

	Buspirone group (n = 99)	Control group (n = 97)	Time *P* value	Group *P* value	Time * Group *P* value
	Mean (SD)	Mean (SD)			
Total scores of WAIS-RC					
Baseline	93.15(16.53)	90.43(14.56)			
12 week	101.18(18.54)	93.09(15.88)			
24 week	108.13(21.21)	95.75(17.41)	0.000	0.002	0.000
The scores of information					
Baseline	8.30(2.78)	8.04(2.17)			
12 week	8.92(2.78)	8.53(2.30)			
24 week	9.47(2.83)	8.82(2.48)	0.000	0.225	0.043
The scores of arithmetic					
Baseline	8.10(2.76)	7.88(3.11)			
12 week	8.94(2.85)	7.99(3.03)			
24 week	9.77(2.99)	8.31(3.13)	0.000	0.034	0.000
The scores of similarities					
Baseline	9.13(1.98)	8.97(1.68)			
12 week	9.83(2.19)	9.08(1.70)			
24 week	10.25(2.25)	9.25(1.69)	0.000	0.018	0.000
The scores of digital span test					
Baseline	9.48(2.51)	9.35(3.01)			
12 week	10.26(2.61)	9.76 (3.19)			
24 week	10.88(2.96)	10.09(3.41)	0.000	0.247	0.009
The scores of digital symbols					
Baseline	7.95(1.89)	7.95(1.65)			
12 week	8.85(2.05)	8.32(1.69)			
24 week	9.45(2.22)	8.57(1.76)	0.000	0.068	0.000
The scores of picture completion					
Baseline	9.16(2.17)	8.94(2.04)			
12 week	9.89(2.21)	8.99(2.03)			
24 week	10.61(2.62)	9.10(2.08)	0.000	0.005	0.000
The scores of block design					
Baseline	7.21(2.80)	6.75(2.45)			
12 week	7.93(2.95)	6.79(2.46)			
24 week	8.49(3.09)	6.88(2.53)	0.000	0.006	0.000
The scores of SDSS					
Baseline	10.92(4.97)	12.08(5.15)			
12 week	9.88(5.25)	11.48(5.77)			
24 week	9.18(5.44)	11.37(5.94)	0.000	0.031	0.002
The scores of FBIS					
Baseline	20.76(10.62)	21.00(10.53)			
12 week	17.37(9.59)	22.20(13.64)			
24 week	17.26(10.04)	21.91(14.03)	0.220	0.016	0.018

SDSS, Social Disability Screening Schedule; FBIS, Family Burden Interview Schedule; Mean, standard deviation (SD) and range are presented in the table; *P* values were analyzed using repeated measures analysis of variance. Columns represent effects of Time, Group and Time × Group interaction (treatment).

Further analysis of repeated measures ANOVA showed an effect of Group on scores of arithmetic, similarities, picture completion, and block design ($P < 0.05$), but not on scores of information, digital span test, or digital symbols ($P > 0.05$). A significant effect of Time was detected in all 7 dimensions of WAIS-RC ($P < 0.001$). The repeated measures ANOVA revealed significant interaction between time of testing and treatment condition on the scores of information, arithmetic, similarities, digital span test, digital symbols, picture completion, and block design ($P < 0.05$) (Table 2).

4. Discussion

Given that cognitive symptoms were viewed as major contributors to poor levels of psychosocial functioning among patients with schizophrenia, improvement of cognitive dysfunction was considered to be a crucial part of the overall treatment plan for the disorder. Extensive research has been directed towards development of the so-called "cognitive enhancers"; and scholars have concentrated on augmentation or accessory treatment strategies to remedy cognitive deficits.

In this study, we found that co-treatment with buspirone and APPDs had a more significant effect on improving the scores of arithmetic, similarities, picture completion, and block design than treatment with APPDs alone. Nevertheless, two groups failed to exhibit any significant differences in improving the scores of information, digital span test, or digit symbols. Subtests of information and digital symbols mainly represent general learning ability and motivational performance, while digital span test is used to evaluate attention and short-term memory. Arithmetic and similarities are used to measure the capacity of active attention, logical reasoning and generalization, while picture completion and block design usually represent more superior cognitive function such as visual discrimination/memory/comprehension, spatial relations identification, and coordination ability (Gong, 1992). Consistent with previous studies, this study indicated that co-treatment buspirone with APPDs outperformed APPDs alone in improving the capacity of logical reasoning, generalization, visual discrimination/memory/comprehension, spatial relations identification and coordination, and motivational performance in patients with schizophrenia (Sheikhmoonesi et al., 2015; Schreiber and Newman-Tancredi, 2014; Sumiyoshi et al., 2007; Uehara et al., 2015). More importantly, all participants of this study were in a stable condition, which meant that mental symptoms have little effect on cognitive performance. Therefore, it is reasonable to believe that the improvement of neurocognitive function is closely related to the pharmacological effects of buspirone.

As 5-HT1A receptor agonist, buspirone is thought to have aforementioned effects that are related to 5-HT1A receptor activation. Some clinical studies have been conducted to determine whether 5-HT1A agonists improve cognitive function in patients with schizophrenia and found that adjunctive treatment with 5-HT1A agonists and antipsychotics improved verbal learning and executive function in patients

with schizophrenia (Sumiyoshi et al., 2001a, b; Schreiber and Newman-Tancredi, 2014; Sheikhmoonesi et al., 2015; Sumiyoshi et al., 2007; Uehara et al., 2015). Animal researches indicated that combination therapy with 5-HT1A agonists and antipsychotics resulted in improved memory, attention, and executive function in rat/mice; but this effect was likewise offset by pretreatment with WAY 100635 (a selective 5-TH1A antagonist) (Li et al., 2004; Baba et al., 2015; Horiguchi and Meltzer, 2012; Nagai et al., 2009). Data on brain energy metabolism also supported the hypothesis that 5-HT1A agonist can improve cognitive deficits of schizophrenia (Sumiyoshi and Uehara, 2012). These findings were consistent with the present study of ours and provide further support for the concept that cognitive disturbances of schizophrenia are ameliorated by the stimulation of 5-HT1A receptors.

Furthermore, the mechanism by which 5-HT1A receptor agonists improve cognitive function has been considered to be related to the following factors. First, it is mediated by the enhancement of cortical dopamine neurotransmission (Huang et al., 2014; Horiguchi and Meltzer, 2012). Indeed, 5-HT1A receptors are strongly expressed in the prefrontal cortex, a region that is profoundly involved in the control of cognition and mood (Meltzer and Sumiyoshi, 2008). Some studies reported that 5-HT1A receptor agonists improve cognitive function by increasing extracellular dopamine level in the prefrontal cortex via 5-HT1A receptor activation (Huang et al., 2014; Meltzer and Sumiyoshi, 2008; Schreiber and Newman-Tancredi, 2014). More specifically, D3R plays a fundamental role in the pathophysiology of schizophrenia, which highly expresses in the nucleus accumbens (NAc) and medial prefrontal cortex (Nakajima et al., 2013; Bortolozzi et al., 2010; Clarkson et al., 2017). Previous researches showed that some antipsychotics that behave as selective D3R antagonists enhance cognitive functions in schizophrenia (Zimnisky et al., 2013; Nakajima et al., 2013). Some scholars even reported that whether buspirone can effectively improve cognitive performance in mice depends mainly on D3R (Torrisi et al., 2017). Leggio et al. also believed that buspirone has good clinical application prospects based on its strong D3 receptor antagonistic activity (Leggio et al., 2014). Second, dysfunction of γ-aminobutyricacid (GABA) interneurons has been suggested to be associated with the pathophysiology of schizophrenia, as the result of an imbalance between excitation and inhibition (E-I imbalance) in the cerebral cortex (Benes and Berretta, 2001; Lewis et al., 2012; Lewis et al., 2005). Clinical evidence suggests 5-HT1A agonists improve cognitive disturbances of schizophrenia through a mechanism that corrects E-I imbalance via the suppression of GABA neural function (Huang et al., 2014; Uehara et al., 2015). Findings from electrophysiological studies also indicated that cognitive benefits of 5-HT1A agonist are mediated by glutamate and GABA neurons (Lladó-Pelfort et al., 2012). Third, hippocampus is part of an altered circuitry that underlies aspects of cognitive impairment associated with schizophrenia, and deficits in hippocampal adult neurogenesis may disrupt cognitive processes that are dependent on newborn neurons (Mori et al., 2014). Researchers reported that 5-HT1A agonist treatment resulted in a significant increase in the number of DCX-positive cells per volume of the dentate gyrus, suggesting that 5-HT1A receptor agonists would be useful and beneficial in improving cognitive impairment through increased hippocampal neurogenesis (Schreiber and Newman-Tancredi, 2014; Mori et al., 2014). Taken together, buspirone may be a promising candidate for co-treatment of schizophrenia-associated cognitive deficits because of its activities 5-HT1A receptor agonist and D3R antagonist.

Besides, we also found that patients treated with a combination of buspirone and APPDs had a more significant decrease in the score of SDSS than those receiving the monotherapy of APPDs, which meant that social function improved more significantly in the combined therapy group. Moreover, the score of FBIS decreased substantially from the baseline to 12 W and 24 W in the combined-therapy group, but increased slightly in patients receiving AAPDs alone. These results indicate that patients treated with the combination of buspirone and APPDs had much better social function and lower family burden than those receiving AAPDs treatment alone despite the fact that taking buspirone might increase the patient's drug expenditure to some extent. The results also suggest strongly that buspirone may be a promising candidate for co-treatment of schizophrenia-associated impairments of social functioning and for reducing the burden of the family. Consistent with previous studies, 5-HT1A agonists could modestly improve cognitive performance in patients with schizophrenia when administered as an adjunct to antipsychotics (Schreiber and Newman-Tancredi, 2014; Mori et al., 2014; Uehara et al., 2015). Thus, the addition of buspirone to APPDs contributes to improving neurocognitive deficit and psychosocial function, and to reducing family burden.

The lack of placebos should be regarded as the biggest limitation of this study when interpreting the results because such inadequacy might exaggerate the results to some extent. Thus, placebo-controlled studies on the efficacy of buspirone in patients with schizophrenia are warranted. Besides, repeated measurement of WAIS-RC may exert some learning effects, which may also lead to the exaggeration of the results. Finally, the occurrence of adverse events was possibly underestimated because they were reported by participants themselves.

5. Conclusion

In conclusion, this study strongly suggests that co-treatment with buspirone and APPDs outperformed APPDs alone in enhancing neurocognitive performance in patients with schizophrenia, including the capacity of generalization, logical reasoning, visual discrimination/memory/comprehension, spatial relations identification and coordination and motivational performance. Therefore, buspirone may be a potential therapeutic medication for the treatment of schizophrenia. In particular, buspirone, through its 5-HT1A receptor agonist and D3R antagonist activity, may serve as a useful tool for improving cognitive deficits and social function and reducing family burden in patients with schizophrenia.

Conflict of interests

All authors declare that they have no conflicts of interest.

Contributors

Author Yu Wang, Xiao Yang, Xiu-li Song, Qiang Wang, Wan-jun Guo, Wei Deng, Tao Li and Xiao-hong Ma designed the study and wrote the protocol. Author Yu Wang, Ji-xiang Wang, Hong Tian, Cong-yu Zheng and Min Wei managed the literature searches and analyses. Authors Yu Wang and Lian-sheng Zhao and Jin-xue Wei undertook the statistical analysis, and author Yu Wang wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of the funding source

Funding for this study was provided by National Natural Science Foundation of China (Grant No. 81671344) and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (Grant No. ZY2016203). They had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgements

We thank Prof. Dong-tao Lin of Sichuan University for copyediting this manuscript and all individuals who have participated in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.006.

References

"Investigation Handbook" Compilation Committee. Handbook of Epidemiological Investigation on Mental Disorders. Beijing: Peoples' Medical Publishing House; 1985. p. 240–246. (Chinese).

Akhondzadeh, S., Mohammadi, N., Noroozian, M., Karamghadiri, N., Ghoreishi, A., Jamshidi, A.H., Forghani, S., 2009. Added ondansetron for stable schizophrenia: a double blind, placebo controlled trial. Schizophr. Res. 107 (2–3), 206–212.

Baba, S., Murai, T., Nakako, T., Enomoto, T., Ono, M., Shimizu, I., Ikeda, K., 2015. The serotonin 5-HT1A receptor agonist tandospirone improves executive function in common marmosets. Behav. Brain Res. 287, 120–126.
Benes, F.M., Berretta, S., 2001. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 25 (1), 1–27.
Bergman, J., Roof, R.A., Furman, C.A., Conroy, J.L., Mello, N.K., Sibley, D.R., Skolnick, P., 2013. Modification of cocaine self-administration by buspirone (Buspar®): potential involvement of D3 and D4 dopamine receptors. Int. J. Neuropsychopharmacol. 16 (2), 445–458.
Bodnar, M., Malla, A.K., Makowski, C., Chakravarty, M.M., Joober, R., Lepage, M., 2016. The effect of second-generation antipsychotics on hippocampal volume in first episode of psychosis: longitudinal study. BJPsych Open 2 (02), 139–146.
Bortolozzi, A., Masana, M., Díaz-Mataix, L., Cortés, R., Scorza, M.C., Gingrich, J.A., Toth, M., Artigas, F., 2010. Dopamine release induced by atypical antipsychotics in prefrontal cortex requires 5-HT(1A) receptors but not 5-HT(2A) receptors. Int. J. Neuropsychopharmacol. 13 (10), 1299–1314.
Casey, D.E., Daniel, D.G., Tamminga, C., Kane, J.M., Tran-Johnson, T., Wozniak, P., Abi-Saab, W., Baker, J., Redden, L., Greco, N., Saltarelli, M., 2009. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. Neuropsychopharmacology 34 (5), 1330–1338.
Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., McGrath, J.J., Whiteford, H.A., 2018. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr. Bull. 44 (6), 1195–1203.
Clarkson, R.L., Liptak, A.T., Gee, S.M., Sohal, V.S., Bender, K.J., 2017. D3 receptors regulate excitability in a unique class of prefrontal pyramidal cells. J. Neurosci. 37 (24), 5846–5860.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1997. User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version. American Psychiatric Pub, Washington, DC.
Ghaleiha, A., Noorbala, A.A., Farnaghi, F., Hajiazim, M., Akhondzadeh, S., 2010. A double-blind, randomized, and placebo-controlled trial of buspirone added to risperidone in patients with chronic schizophrenia. J. Clin. Psychopharmacol. 30 (6), 678–682.
Goff, D.C., Zeng, B., Ardekani, B.A., Diminich, E.D., Tang, Y., Fan, X., Galatzer-Levy, I., Li, C., Troxel, A.B., Wang, J., 2018. Association of hippocampal atrophy with duration of untreated psychosis and molecular biomarkers during initial antipsychotic treatment of first-episode psychosis. Jama Psychiat 75 (4), 370.
Gong, Y., 1992. Wechsler Adult Intelligence Scale-Revised in China Version. Hunan Medical College, Changsha, Hunan/China.
Grabiec, M., Turlejski, K., Djavadian, R.L., 2009. The partial 5-HT1A receptor agonist buspirone enhances neurogenesis in the opossum (Monodelphis domestica). Eur. Neuropsychopharmacol. 19 (6), 431–439.
Gupta, S., Isherwood, G., Jones, K., Van Impe, K., 2015. Productivity loss and resource utilization, and associated indirect and direct costs in individuals providing care for adults with schizophrenia in the EU5. Clinicoecon Outcomes Res 7, 593–602.
Hamilton, M., 1959. The assessment of anxiety states by rating. Br J Med Psychol 32 (1), 50–55.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Horiguchi, M., Meltzer, H.Y., 2012. The role of 5-HT1A receptors in phencyclidine (PCP)-induced novel object recognition (NOR) deficit in rats. Psychopharmacology 221 (2), 205–215.
Huang, M., Panos, J.J., Kwon, S., Oyamada, Y., Rajagopal, L., Meltzer, H.Y., 2014. Comparative effect of lurasidone and blonanserin on cortical glutamate, dopamine, and acetylcholine efflux: role of relative serotonin (5-HT)2A and DA D2 antagonism and 5-HT1A partial agonism. J. Neurochem. 128 (6), 938–949.
Jaaskelainen, E., Juola, P., Hirvonen, N., McGrath, J.J., Saha, S., Isohanni, M., Veijola, J., Miettunen, J., 2013. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr. Bull. 39 (6), 1296–1306.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
King, M.V., Marsden, C.A., Fone, K.C., 2008. A role for the 5-HT(1A), 5-HT4 and 5-HT6 receptors in learning and memory. Trends Pharmacol. Sci. 29 (9), 482–492.
Landek-Salgado, M.A., Faust, T.E., Sawa, A., 2016. Molecular substrates of schizophrenia: homeostatic signaling to connectivity. Mol. Psychiatry 21 (1), 10–28.
Leggio, G.M., Camillieri, G., Platania, C.B., Castorina, A., Marrazzo, G., Torrisi, S.A., Nona, C.N., D'Agata, V., Nobrega, J., Stark, H., Bucolo, C., Le Foll, B., Drago, F., Salomone, S., 2014. Dopamine D3 receptor is necessary for ethanol consumption: an approach with buspirone. Neuropsychopharmacology 39 (8), 2017–2028.
Lewis, D.A., Hashimoto, T., Volk, D.W., 2005. Cortical inhibitory neurons and schizophrenia. Nat. Rev. Neurosci. 6 (4), 312–324.
Lewis, D.A., Curley, A.A., Glausier, J.R., Volk, D.W., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 35 (1), 57–67.
Li, Z., Ichikawa, J., Dai, J., Meltzer, H.Y., 2004. Aripiprazole, a novel antipsychotic drug, preferentially increases dopamine release in the prefrontal cortex and hippocampus in rat brain. Eur. J. Pharmacol. 493 (1–3), 75–83.
Lladó-Pelfort, L., Santana, N., Ghisi, V., Artigas, F., Celada, P., 2012. 5-HT1A receptor agonists enhance pyramidal cell firing in prefrontal cortex through a preferential action on GABA interneurons. Cereb. Cortex 22 (7), 1487–1497.
Maeda, K., Lerdrup, L., Sugino, H., Akazawa, H., Amada, N., McQuade, R.D., Stensbøl, T.B., Bundgaard, C., Arnt, J., Kikuchi, T., 2014. Brexpiprazole II: antipsychotic-like and procognitive effects of a novel serotonin-dopamine activity modulator. J. Pharmacol. Exp. Ther. 350 (3), 605–614.
Meltzer, H.Y., Sumiyoshi, T., 2008. Does stimulation of 5-HT1A receptors improve cognition in schizophrenia? Behav. Brain Res. 195 (1), 98–102.
Mori, M., Murata, Y., Matsuo, A., Takemoto, T., Mine, K., 2014. Chronic treatment with the 5-HT1A receptor partial agonist tandospirone increases hippocampal neurogenesis. Neurology and Therapy 3 (1), 67–77.
Nagai, T., Murai, R., Matsui, K., Kamei, H., Noda, Y., Furukawa, H., Nabeshima, T., 2009. Aripiprazole ameliorates phencyclidine-induced impairment of recognition memory through dopamine D1 and serotonin 5-HT1A receptors. Psychopharmacology 202 (1–3), 315–328.
Nakajima, S., Gerretsen, P., Takeuchi, H., Caravaggio, F., Chow, T., Le Foll, B., Mulsant, B., Pollock, B., Graff-Guerrero, A., 2013. The potential role of dopamine D_3 receptor neurotransmission in cognition. Eur. Neuropsychopharmacol. 23 (8), 799–813.
Ohno, Y., Shimizu, S., Imaki, J., Ishihara, S., Sofue, N., Sasa, M., Kawai, Y., 2008. Evaluation of the antibradykinetic actions of 5-HT1A agonists using the mouse pole test. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 32 (5), 1302–1307.
Owen, M.J., Sawa, A., Mortensen, P.B., 2016. Schizophrenia. Lancet 388 (10039), 86–97.
Pai, S., Kapur, R.L., 1981. The burden on the family of a psychiatric patient: development of an interview schedule. Br. J. Psychiatry 138, 332–335.
Piškulić, D., Olver, J.S., Maruff, P., Norman, T.R., 2009. Treatment of cognitive dysfunction in chronic schizophrenia by augmentation of atypical antipsychotics with buspirone, a partial 5-HT1A receptor agonist. Hum. Psychopharmacol. Clin. Exp. 24 (6), 437–446.
Sadock, B., Sadock, V., Ruiz, P., 2009. Comprehensive Text of Book Psychiatry. Guilford Press, New York.
Schreiber, R., Newman-Tancredi, A., 2014. Improving cognition in schizophrenia with antipsychotics that elicit neurogenesis through 5-HT1A receptor activation. Neurobiol. Learn. Mem. 110, 72–80.
Sheikhmoonesi, F., Zarghami, M., Bahari Saravi, S.F., Khalilian, A., Ala, S., 2015. A triple-blinded, randomized, placebo-controlled trial to examine the efficacy of buspirone added to typical antipsychotic drugs in patients with chronic schizophrenia. J Res Mes Sci 20 (2), 140–145.
Sumiyoshi, T., Uehara, T., 2012. Serotonin-1A receptors and cognitive enhancement in schizophrenia: role for brain energy metabolism. Neuropsychiatric Disorders, pp. 127–140.
Sumiyoshi, T., Matsui, M., Nohara, S., Yamashita, I., Kurachi, M., Sumiyoshi, C., Jayathilake, K., Meltzer, H.Y., 2001a. Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. Am. J. Psychiatry 158 (10), 1722–1725.
Sumiyoshi, T., Matsui, M., Yamashita, I., Nohara, S., Kurachi, M., Uehara, T., Sumiyoshi, S., Sumiyoshi, C., Meltzer, H.Y., 2001b. The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. Biol. Psychiatry 49 (10), 861–868.
Sumiyoshi, T., Park, S., Jayathilake, K., Roy, A., Ertugrul, A., Meltzer, H.Y., 2007. Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr. Res. 95 (1–3), 158–168.
Torrisi, S.A., Salomone, S., Geraci, F., Caraci, F., Bucolo, C., Drago, F., Leggio, G.M., 2017. Buspirone counteracts MK-801-induced schizophrenia-like phenotypes through dopamine D3 receptor blockade. Front. Pharmacol. 8, 720.
Uehara, T., Sumiyoshi, T., Kurachi, M., 2015. New pharmacotherapy targeting cognitive dysfunction of schizophrenia via modulation of GABA neuronal function. Curr. Neuropharmacol. 13 (6), 793–801.
Woodward, N.D., Purdon, S.E., Meltzer, H.Y., Zald, D.H., 2005. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int. J. Neuropsychopharmacol. 8 (3), 457–472.
Yu, Y., Liu, Z.W., Tang, B.W., Zhao, M., Liu, X.G., Xiao, S.Y., 2017. Reported family burden of schizophrenia patients in rural China. PLoS One 12 (6), e179425.
Zhao, J.P., Shi, S.X., 2015. Chinese Guidelines for the Prevention and Treatment of Schizophrenia (Second Edition). China Medical Electronic Audio and. Video Publishing House.
Zimnisky, R., Chang, G., Gyertyán, I., Kiss, B., Adham, N., Schmauss, C., 2013. Cariprazine, a dopamine D(3)-receptor-preferring partial agonist, blocks phencyclidine-induced impairments of working memory, attention set-shifting, and recognition memory in the mouse. Psychopharmacology 226 (1), 91–100.