Int J Clin Exp Med 2018;11(9):9511-9519
www.ijcem.com /ISSN:1940-5901/IJCEM0080543

Original Article

Mirtazapine in combination with serotonin re-uptake inhibitors improves depression and anxiety in patients with PTSD

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Received May 29, 2018; Accepted June 27, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Objective: To investigate the efficacy of mirtazapine in combination with next-generation, antidepressant selective serotonin re-uptake inhibitors (SSRIs) in the treatment of patients with post-traumatic stress disorder (PTSD), and its influence on patient anxiety and depression. Methods: A total of 286 patients with PTSD and depression, and 172 with PTSD and anxiety were retrospectively analyzed. The patients were divided into 4 groups according to the treatment method received: the depression control group (n=165); the depression observation group (n=121); the anxiety control group (n=100); and the anxiety observation group (n=72). Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) and Pittsburgh Sleep Quality Index (PSQI) scores, and changes in serum levels of 5-hydroxytryptamine (5-HT) and noradrenaline (NE) in all patients were determined. Results: There was a Statistically significant difference in the overall effective and highly effective treatment rates between the control and observation groups (P<0.05). The HAMD, HAMA, and PSQI scores of patients in the two groups after 4 and 8 weeks of treatment decreased compared with pretreatment (P<0.05). The 5-HT levels of patients in the two control groups after 4 and 8 weeks of treatment were higher than those in the two observation groups (P<0.05). Treatment Emergent Symptom Scale (TESS) scores of patients in the two control groups after 4 and 8 weeks of treatment were higher than that in the two observation groups (P<0.05). Conclusions: Mirtazapine in combination with SSRIs can effectively improve depression, anxiety, and unhealthy psychological states in patients with PTSD and depression, as well those with PTSD and anxiety. This enhanced therapeutic effect and increased safety profile merits application in clinical settings.

Keywords: Mirtazapine, SSRIs, post-traumatic stress disorder, anxiety, depression

Introduction

Post-traumatic stress disorder (PTSD) is an individual, delayed-onset and persistent mental disorder caused by a cataclysmic or threatening event [1]. Along with the development of society and economy, humans experience increasing types of trauma, and more PTSDs caused by motor vehicle accidents, occupational injuries, and serious disease occur in addition to natural disasters [2, 3]. PTSD is usually concomitant with depression or anxiety. Similarly, depression/anxiety is also a common mental disorder that seriously affects physical and mental health. These patients will also have emotional disorders and bring appreciable burden to society [4, 5].

Currently, clinically common antidepressants/antianxiety drugs include selective serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitors (SSRIs), 5-HT and noradrenaline double-reuptake inhibitors, noradrenergic and specific 5-HT antidepressants, and 5-HT receptor antagonists, among others [6]. Many studies have noted the disadvantages of single antidepressant drugs, including long-onset time, poorer efficacy and short effective duration. Consequently, drug combinations have been a hot issue in therapy for depression [7, 8]. SSRIs improve extracellular levels of 5-HT, which binds to postsynaptic receptors by blocking the reuptake of 5-HT by synaptic neurons. Although antidepressants/antianxiety drugs are widely used in many countries, their effectiveness and safety have also been widely questioned [9, 10]. Mirtazapine is the first antidepressant/antianxiety drug with dual inhibitory effects on noradrenaline (NE) and 5-HT, which are impor-

Table 1. General Information

	Depression control	Depression observe	Statistic	*P*-value	Anxiety control	Anxiety observe	Statistic	*P*-value
Number	165	121			100	72		
Sex			0.025	0.875			0.018	0.894
Male	75 (45.5)	53 (43.8)			45 (45.0)	34 (47.2)		
Female	90 (54.5)	68 (56.2)			55 (55.0)	38 (52.8)		
Age (year)	42.5 ± 11.2	43.6 ± 10.9	0.830	0.407	43.3 ± 11.6	42.4 ± 12.3	0.489	0.625
Degree of education			0.196	0.658			0.081	0.776
Below Junior high school	109 (66.1)	76 (62.8)			52 (52.0)	35 (48.6)		
Junior high school or above	56 (33.9)	45 (37.2)			48 (48.0)	37 (51.4)		
Residence			0.798	0.372			0.264	0.607
Village	80 (48.5)	66 (54.5)			51 (51.0)	33 (45.8)		
City	85 (51.5)	55 (45.5)			49 (49.0)	39 (54.2)		
Types of trauma			0.414	0.813			0.612	0.736
Natural disaster	34 (20.6)	28 (23.1)			20 (20.0)	18 (25.0)		
Traffic Accident	115 (69.7)	80 (66.1)			67 (67.0)	45 (62.5)		
Other	16 (9.7)	13 (10.7)			13 (13.0)	9 (12.5)		

Table 2. Clinical Efficacy

	Number	Total effective rate	High effective	Effective	Non-effective
Depression control	165	135 (81.8)	86 (52.1)	49 (29.7)	30 (18.2)
Depression observe	121	113 (93.4)	89 (73.6)	24 (19.8)	8 (6.6)
Statistic		7.036	12.316	2.968	7.036
P-value		0.008	<0.001	0.085	0.008
Anxiety control	100	77 (77.0)	46 (46.0)	31 (31.0)	23 (23.0)
Anxiety observe	72	65 (90.3)	52 (72.2)	13 (18.1)	7 (9.7)
Statistic		4.244	10.697	3.036	4.244
P-value		0.039	0.001	0.081	0.039

tant factors affecting depression/anxiety. Mirtazapine has been widely used for treatment of patients with depression/anxiety due to its high cure rate and safety profile [11, 12].

This study investigated the efficacy and safety of mirtazapine in combination with SSRIs by retrospectively analyzing data from 458 patients with PTSD and depression, or PTSD and anxiety.

Materials and methods

Study subjects

A total of 286 patients with PTSD and depression, and 172 with PTSD and anxiety, who were admitted to the First Affiliated Hospital of Shihezi University Medical College, were retrospectively analyzed. The patients were divided into 4 groups according to the treatment method received: the depression control group (n=165); the depression observation group (n=121); the anxiety control group (n=100); and the anxiety observation group (n=72). The two control groups only received treatment with SSRIs, while the two observation groups received treatment with mirtazapine in combination with SSRIs. The diagnosis of patients with depression and/or anxiety was based on criteria from the Chinese Classification and Diagnostic Standard for Mental Diseases, Edition 3 [13]. All patients had single depression or anxiety, with no antidepressant treatment history before admission, had no allergic reactions to mirtazapine or SSRIs, and had no familial mental disease or organic psychosis. Patients with repeated suicidal thoughts or self-injurious behaviors, and those unable to communicate due to serious dementia, aphasia, consciousness disturbance, or alcohol abuse, were excluded. This study was approved by the Ethics Committee of the authors' hospital,

Table 3. Changes in HAMD score of patients with PTSD and depression

	Number	Prior treatment	After treatment of 4 weeks	After treatment of 8 weeks
Depression control	165	27.69 ± 2.72	22.17 ± 4.15[a]	15.36 ± 3.98[a,b]
Depression observe	121	27.58 ± 2.71	18.95 ± 2.17[a]	9.44 ± 1.33[a,b]
Statistic		0.339	7.791	15.732
P-value		0.735	<0.001	<0.001

Note: a, P<0.05, vs. before treatment; b, P<0.05, vs. after treatment of 4 weeks.

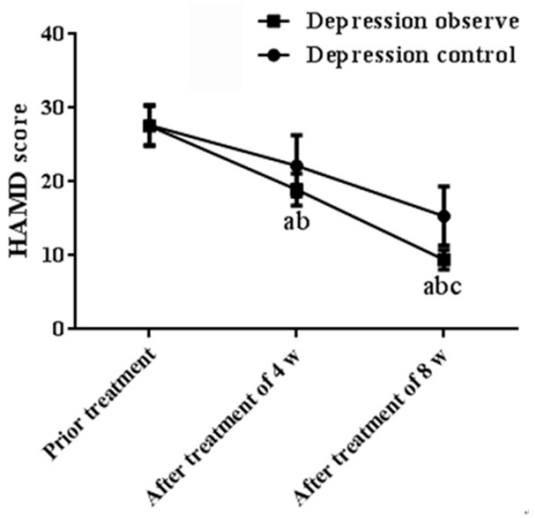

Figure 1. Hamilton Depression Scale (HAMD) scores compared with the depression control group (A) (P<0.05) after 4 weeks of treatment (B) (P<0.05) and after 8 weeks of treatment (C) (P<0.05).

and the patients or their family members provided informed written consent.

Treatment method

The two control groups only received treatment with SSRIs/sertraline (Shenzhen Xinguang United Pharmaceutical Co, Ltd. with GYZZ of H20060867) at a dose of 50 mg once per day (i.e, 50 mg/day). The two observation groups received treatment with mirtazapine (Shenzhen Simeiquan Biotechnology Co, Ltd. with GYZZ of H20100103) on the basis of treatment with SSRIs at a dose of 30 mg/day. Treatment of patients in the four groups lasted 8 weeks.

Observation indexes

Efficacy observation [14]: Changes in score reduction in the HAMA and HAMD were used as evaluation indexes, and changes in score reduction in HAMD or HAMA of patients in the four groups before treatment and after 8 weeks treatment were observed. A score reduction ≥ 60% was considered to be "highly effective", indicating the disease was cured or symptoms essentially disappeared. A score reduction of 30-59% was considered to be "effective", indicating the symptoms were improved or part of the symptoms disappeared. A score reduction <30% was considered to be "non-effective", indicating no change or worsening of symptoms. The total effective rate was calculated as the number of "highly effective" patients + number of "effective" patients)/total number of patients *100%.

Safety observation: This domain was evaluated using Treatment Emergent Symptom Scale (TESS) score.

The Pittsburgh Sleep Quality Index (PSQI) and changes in serum levels of 5-HT and NE of all patients before, and 4 and 8 weeks after treatment were determined. All peripheral blood samples were collected in the morning fasted condition by nurses in the authors' hospital; 5-HT and NE levels were assessed in the clinical laboratory of the same hospital.

Statistical analysis

SPSS version 19.0 (Asia Analytics, formerly SPSS China) was used. Enumeration data are expressed as n (%), and the X^2 test was used to compare ratios. Measurement data are expressed as $\bar{x}$ (i.e, mean) ± standard deviation. The rank sum test was used to compare the two groups, variance analysis was used for comparison among groups, and the least significant difference test was used for comparison between two groups, and repeated variance measurement experiment was used for comparison within a group at different times. Differences with P<0.05 were considered to be Statistically significant.

Results

General information

Of 286 patients with PTSD and depression, 165 (mean age, 42.5 ± 11.2 years) were allocated to the depression control group, and 121 (mean age, 43.6 ± 10.9 years) were allocated

Table 4. Changes in HAMA score of patients with PTSD and anxiety

	Number	Prior treatment	After treatment of 4 weeks	After treatment of 8 weeks
Anxiety control	100	31.88 ± 4.34	25.96 ± 3.34[a]	17.58 ± 3.31[a,b]
Anxiety observe	72	31.69 ± 4.25	20.57 ± 3.44[a]	9.15 ± 2.11[a,b]
Statistic		0.286	10.314	19.996
P-value		0.776	<0.001	<0.001

Note: a, P<0.05, vs. before treatment; b, P<0.05, vs. after treatment of 4 weeks.

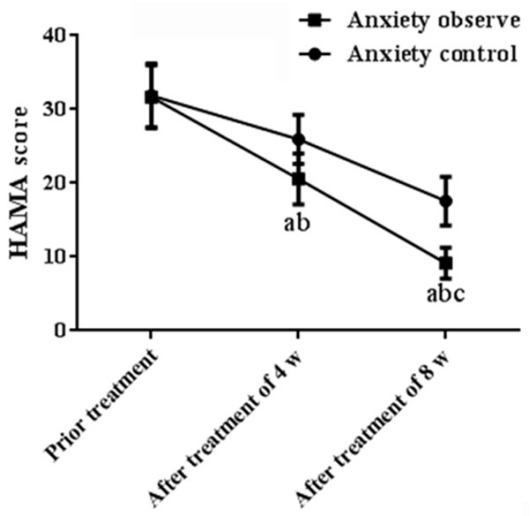

Figure 2. Hamilton Anxiety Scale (HAMA) scores compared with the anxiety control group A (P<0.05) after 4 weeks of treatment B (P<0.05) and after 8 weeks of treatment C (P<0.05).

to the depression observation group. There were no Statistical differences (P>0.05) between the groups in terms of sex, age, level of education, residence, or types of trauma. Of 172 patients with PTSD and anxiety, 100 (mean age, 43.3 ± 11.6 years) were allocated to the anxiety control group, and 72 (mean age, 42.4 ± 12.3 years) were allocated to the anxiety observation group. There were no Statistical differences (P>0.05) between the groups in terms of sex, age, level of education, residence, or types of trauma (**Table 1**).

Clinical efficacy

The overall treatment effectiveness rate in the depression control group was 81.9% (136 cases), in which the highly effective, effective, and non-effective rates were 52.4% (87 cases), 29.5% (49 cases), and 18.1% (30 cases), respectively. The overall treatment effectiveness rate in the depression observation group was 93.4% (113 cases), in which the high effective rate, effective rate and non-effective rate were 73.6% (89 cases), 19.8% (24 cases), and 6.6% (8 cases), respectively. There was a difference in the overall treatment effectiveness rate and highly effective rate between the two groups (P<0.05), whereas there was no difference in treatment effective rate (P>0.05).

The overall treatment effective rate in anxiety control group was 77.0% (77 cases), in which the highly effective, effective, and non-effective rates were 46% (46 cases), 31% (31.0 cases), and 23.0% (23 cases), respectively. The overall treatment effectiveness rate in the anxiety observation group was 90.3% (65 cases), in which the highly effective, effective, and non-effective rates were 72.2% (52 cases), 18.1% (13 cases), and 9.7% (7 cases), respectively. The overall treatment effectiveness and highly effective rates of patients were different between the two groups (P<0.05). However, there was no difference in the treatment effectiveness rate (P>0.05) (**Table 2**).

Changes in HAMD scores of patients with PTSD and depression

The mean HAMD scores in the depression control group before, and 4 and 8 weeks after treatment were 27.69 ± 2.72, 22.17 ± 4.15, and 15.36 ± 3.98, respectively. The mean HAMD scores in the depression observation group before, and 4 and 8 weeks after treatment were 27.58 ± 2.71, 18.95 ± 2.17, and 9.44 ± 1.33, respectively. There were no Statistically significant differences in HAMD scores between the two groups before treatment (P>0.05). However, the differences were found after 4 and 8 weeks of treatment (both P<0.05). Both the HAMD scores of patients in the two groups after 4 and 8 weeks of treatment decreased compared with before treatment (both P<0.05). HAMD scores of the patients in the two groups after 8 weeks of treatment decreased compared with a treatment duration of 4 weeks (P<0.05) (**Table 3**; **Figure 1**).

Table 5. PSQI score results

	Number	Prior treatment	After treatment of 4 weeks	After treatment of 8 weeks
Depression control	165	7.26 ± 1.11	6.56 ± 1.12[a]	3.15 ± 0.96[a,b]
Depression observe	121	7.24 ± 1.09	4.33 ± 1.03[a]	2.33 ± 0.85[a,b]
Statistic		0.152	17.231	7.495
P-value		0.879	<0.001	<0.001
Anxiety control	100	7.28 ± 1.25	6.28 ± 1.16[a]	3.34 ± 1.01[a,b]
Anxiety observe	72	7.27 ± 1.21	4.54 ± 1.13[a]	2.57 ± 1.03[a,b]
Statistic		0.052	9.810	4.892
P-value		0.958	<0.001	<0.001

Note: a, P<0.05, vs. before treatment; b, P<0.05, vs. after treatment of 4 weeks.

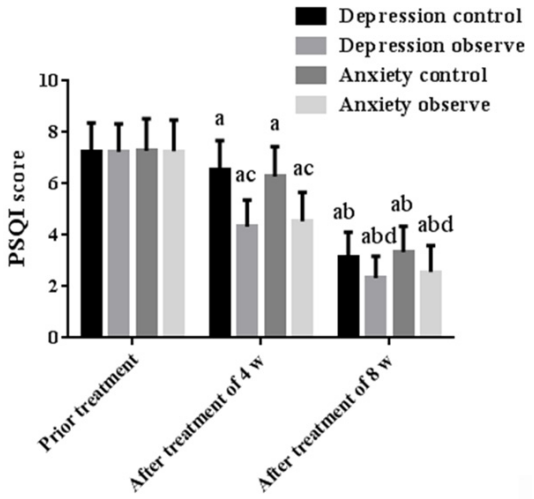

Figure 3. Pittsburgh Sleep Quality Index (PSQI) scores compared with the depression control group A (P<0.05) and the anxiety control group B (P<0.05) after 4 C (P<0.05) and 8 weeks of treatment D (P<0.05).

Changes in HAMA score of patients with PTSD and anxiety

The HAMA scores in the anxiety control group before, and 4 and 8 weeks after treatment were 31.88 ± 4.34, 25.96 ± 3.34, and 17.58 ± 3.31, respectively. The HAMA scores in the anxiety observation group before treatment, and 4 and 8 weeks after treatment were 31.69 ± 4.25, 20.57 ± 3.44, and 9.15 ± 2.11, respectively. There was no difference in HAMA scores between the two groups before treatment (P>0.05). However, there were differences after 4 and 8 weeks of treatment (both P<0.05). HAMA scores of patients in the two groups decreased after 4 and 8 weeks of treatment compared with pretreatment scores (P<0.05). HAMA scores in the two groups decreased after 8 weeks of treatment compared with treatment after 4 weeks (P<0.05) (**Table 4**, **Figure 2**).

Sleep quality improvement

There were no differences in pretreatment PSQI scores between the two groups of patients with PTSD and depression, or between the two groups of patients with PTSD and anxiety (all P>0.05). The PSQI scores of patients in the two control groups were higher at 4 and 8 weeks after treatment than those in the observation groups (all P<0.05). The PSQI scores of patients in the four groups after 4 and 8 weeks of treatment decreased compared with those before treatment (all P<0.05). The PSQI scores of patients in the four groups after 8 weeks of treatment were lower than that after 4 weeks of treatment (**Table 5**, **Figure 3**).

5-HT and NE test results

There were no differences in the levels of NE and 5-HT between the two groups of patients with PTSD and depression, or between the two groups of patients with PSTD and anxiety (all P>0.05). The levels of 5-HT in the two control groups after 4 and 8 weeks of treatment were lower than that in the two observation groups (P<0.05). The levels of NE in the two control groups after 4 and 8 weeks of treatment were lower than those in the two observation groups (all P<0.05). The levels of 5-HT in the four groups after 4 and 8 weeks of treatment increased compared with pretreatment levels (P<0.05). The levels of 5-HT in the four groups after 8 weeks of treatment were higher than those recorded after 4 weeks of treatment. The levels of NE in the four groups after 4 and 8 weeks of treatment increased compared with pretreatment levels (all P<0.05). The levels of NE in the four groups after 8 weeks of treatment were higher than that after 4 weeks of treatment (**Table 6**).

Safety assessment

TESS scores in the two control groups after 4 and 8 weeks of treatment were higher than

Table 6. 5-HT and NE test results of patients

		Number	Prior treatment	After treatment of 4 weeks	After treatment of 8 weeks
5-HT μg/L	Depression control	165	227.38 ± 36.59	252.22 ± 35.28[a]	302.49 ± 32.17[a,b]
	Depression observe	121	230.12 ± 33.72	309.64 ± 32.33[a]	358.64 ± 27.62[a,b]
	Statistic		0.647	10.456	28.627
	P-value		0.518	<0.001	<0.001
	Anxiety control	100	229.56 ± 34.17	277.86 ± 34.75[a]	313.17 ± 35.44[a,b]
	Anxiety observe	72	232.78 ± 35.02	306.59 ± 33.23[a]	352.56 ± 28.75[a,b]
	Statistic		0.780	12.571	30.771
	P-value		0.436	<0.001	<0.001
NE μg/L	Depression control	165	37.74 ± 5.15	45.56 ± 5.62[a]	54.33 ± 6.58[a,b]
	Depression observe	121	38.20 ± 5.33	69.22 ± 6.11[a]	106.45 ± 7.62[a,b]
	Statistic		0.736	12.519	15.201
	P-value		0.462	<0.001	0.012
	Anxiety control	100	38.36 ± 5.58	46.63 ± 5.82[a]	52.17 ± 6.49[a,b]
	Anxiety observe	72	38.97 ± 5.14	68.77 ± 5.95[a]	103.06 ± 6.88[a,b]
	Statistic		0.945	13.047	15.198
	P-value		0.345	<0.001	<0.001

Note: a, P<0.05, vs. before treatment; b, P<0.05, vs. after treatment of 4 weeks.

Table 7. TESS score results

	Number	After treatment of 4 weeks	After treatment of 8 weeks
Depression control	165	4.87 ± 1.46	3.43 ± 1.05
Depression observe	121	3.02 ± 1.25	1.33 ± 0.98
Statistic		11.252	17.205
P-value		<0.001	<0.001
Anxiety control	100	4.79 ± 1.52	3.38 ± 1.13
Anxiety observe	72	3.17 ± 1.36	1.59 ± 1.02
Statistic		9.316	13.801
P-value		<0.001	<0.001

Table 8. Adverse reactions results

	Number	Patients adverse reactions after treatment of 8 weeks
Depression observed	121	16
Anxiety observed	72	12
Total observation groups percent		14.5%
Anxiety control	100	31
Depression control	165	33
Total control groups percent		24.1%

those in the two observation groups (all P<0.05). The TESS scores in the four groups after 8 weeks of treatment were lower than that after 4 weeks of treatment (all P<0.05) (**Table 7**).

Adverse reactions

No serious adverse reactions occurred in the four groups of patients during the 8-week treatment period. Moderately adverse reactions occurred in 16 patients in the depression observation group and 12 in the anxiety observation group. The overall adverse reaction rate of patients in the observation groups was 14.5%. Adverse reactions occurred in 33 patients in the depression control group and in 31 in the anxiety control group. The overall adverse reaction occurrence rate in the control groups was 24.1%. There was a difference in the overall adverse reaction rate between the observation and control groups (P<0.05) (**Table 8**).

Discussion

The overall prevalence of PTSD in the general population is approximately 8%. The individual lifetime prevalence, however, can be as high as 58%, with female prevalence approximately double the prevalence in males [15]. Depression and anxiety are common complications of PTSD, with suicide rates as high as 15% [16, 17]. Therefore, it necessary to find effective and safe drugs for the treatment of patients

with depression/anxiety. Depression/anxiety is characterized by feeling down, inferiority and self-abuse, apathy, sleep disorders, and other symptoms caused by decreases in the levels of NE and 5-HT. If depression/anxiety is not treated effectively, the body will lose its ability to compensate for low levels of NE and 5-HT, which will further reduces endogenous levels, leading to more serious emotional disorders [18].

The efficacy and safety of mirtazapine in combination with SSRIs were investigated in this study by analyzing their therapeutic effect in patients with PTSD and depression/anxiety. Case data for 286 patients with PTSD and depression, and 172 with PTSD and anxiety, were retrospectively analyzed. Both the overall effective rate and highly effective rate of SSRIs for the treatment of PTSD and depression, and PTSD and anxiety, were lower than that of mirtazapine in combination with SSRIs. This is mainly because the cure rate of mirtazapine in combination with SSRIs in the treatment of patients with PTSD and depression, and patients with PTSD and anxiety, were higher than that of single SSRIs. The effective treatment rates in PTSD depression and PTSD anxiety were not different compared with single SSRIs.

Currently, the HAMA and HAMD are the two scoring scales most widely used for evaluation of depression and anxiety [19, 20]. Results of the present study demonstrated that scores of patients with PTSD and depression, and those with PTSD and anxiety, decreased and continuously decreased after treatment, while the degree of improvement in patients' HAMA and HAMD scores with mirtazapine in combination with SSRIs was significantly better than treatment with single SSRIs. Mirtazapine can simultaneously improve the levels of 5-HT and NE via a mechanism that increases the levels of 5-HT and NE by blocking the effect of the α1-adrenoreceptor, improving the sensitivity of brain 5-HT to the specific receptor, and increasing the levels of synaptic cleft 5-HT and NE receptors; thereby playing a central role in antidepression/antianxiety [21, 22]. Sertraline is a representative SSRI drug and mainly specific for 5-HT, which improves the extracellular level of 5-HT capable of binding to the postsynaptic receptor by blocking the reuptake of 5-HT in synaptic neurons [23, 24]. Therefore, the mechanisms of action of mirtazapine and SSRIs are different, and we suspect that this explains why mirtazapine in combination with SSRI can improve depression/anxiety. The test results of 5-HT and NE in this study demonstrated that the levels of 5-HT and NE in all patients increased and continuously increased after treatment. Moreover, the increased degrees of 5-HT and NE levels in patients receiving mirtazapine in combination with SSRIs were significantly higher than those of patients receiving single SSRIs. This also validates results supporting that the therapeutic effect of mirtazapine in combination with SSRIs in patients with PTSD and depression, and those with PTSD and anxiety, is better than that of single SSRIs.

We also analyzed the sleep quality of patients using the PSQI scale, which is the most widely used scale for evaluation of sleep quality in patients with sleep disorders as well as those with mental disorders [25]. Results of our study demonstrated the beneficial effects of mirtazapine in combination with SSRIs on the sleep quality of patients with PTSD and depression, as well as patients with PTSD and anxiety, which were significantly better than that of single SSRIs. Some investigators have reported that the ascending nerve fibers from nucleus raphes pontis and nucleus coeruleus can inhibit the reticular activating system of brain stem and, thus, participate in the regulation of sleep and wakefulness, in which the 5-HT neurons of the raphe nuclei participate in the regulation of non-rapid eye movement sleep, while the NE neurons at tail of the nucleus coeruleus mostly participate in the regulation of rapid eye movement sleep [26, 27]. The 5-HT system includes 5-HT1, 5-HT2, and 5-HT3 receptors, in which the 5-HT1 receptor is related to depression and anxiety, and the 5-HT2 and 5-HT3 receptors are associated with sleep [28]. Mirtazapine can selectively act on 5-HT1 receptors, thus improving depression/anxiety symptoms, and simultaneously block 5-HT2 and 5-HT3 receptors to improve sleep quality [29]. Mirtazapine can also act on NE, while SSRIs only affect 5-HT; therefore, we speculate that this explains why the improvement effect of mirtazapine in combination with SSRIs on sleep quality is better than that of single SSRIs.

We also analyzed the safety of mirtazapine and SSRIs in the treatment of patients with PTSD

and depression, as well as patients with PTSD and anxiety. Using the TESS score, which evaluates the safety of drug therapy in terms of severity, symptoms, and drug measures taken [30], no serious complications were recorded the during study. Both the TESS scores and total complication incidence rate of patients receiving mirtazapine in combination with SSRIs were lower than those of patients receiving single SSRIs. Mirtazapine is better tolerated, and modern pharmacology has proved that the low affinity of mirtazapine for α1-adrenergic and M-receptors will not cause postural hypotension and anticholinergic reactions, leading to higher patient compliance [31, 32]. This probably explains why mirtazapine in combination with SSRIs has a better safety profile in the treatment of patients with PTSD and depression, as well as those with PTSD and anxiety. Although the deeper cause remains unknown, we hope that this study can prompt further investigation in the future.

In conclusion, mirtazapine in combination with SSRIs can effectively improve depression, anxiety, and unhealthy psychological states in patients with PTSD and depression, as well those with PTSD and anxiety. This enhanced therapeutic effect and increased safety profile merits application in clinical settings.

Disclosure of conflict of interest

None.

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