Original Contribution

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Patients with Posttraumatic Stress Disorder with Comorbid Major Depressive Disorder Require a Higher Dose of Psychotropic Drugs

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Summary: Major depressive disorder (MDD) has been associated with stressful life events and with posttraumatic stress disorder (PTSD). PTSD and MDD comorbidity was also reported to be associated with greater symptom severity and lower levels of functioning. However, the characteristics of pharmacotherapy for PTSD with MDD are not fully understood. To understand this relationship, we conducted a retrospective review using medical charts at the Department of Neuropsychiatry, Kurume University Hospital. Information from 55 patients with PTSD was analyzed. Five cases were excluded after re-evaluation of the PTSD diagnosis. A higher rate of type II trauma was observed in the PTSD with MDD group (50.0%) than in the PTSD-only group [13.6%; χ^2 (1, n = 50) = 7.26, $p<0.01$]. Patients with comorbid MDD were significantly older, had more severe PTSD symptomatology, and a longer duration of treatment. They also received higher doses of psychotropic drugs, regardless of the type (antidepressants, antipsychotics, benzodiazepines), than the PTSD-only group. Our results showed that comorbid MDD is associated with higher doses of psychotropic drugs, suggesting difficulties in treatment.

Key words posttraumatic stress disorder, major depressive disorder, pharmacotherapy, comorbidity, antipsychotics, benzodiazepines

INTRODUCTION

Posttraumatic stress disorder (PTSD) is one of the typical psychiatric illnesses that occur after a traumatic event. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) lists four major categories of PTSD symptoms: intrusive (including flashbacks), avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity [1]. The lifetime prevalence of PTSD in the general adult population of the United States is 6.8% [2].

Traumatic experiences are categorized as either type I or type Ⅱ trauma [3]. Type I trauma is a single traumatic event such as accidental injury or natural disaster. Type Ⅱ trauma results from long-lasting or repeated exposure to extreme stress, such as interpersonal physical violence or sexual abuse. Combat trauma is often considered type I trauma; however, it involves long-lasting violent events along with a mixture of fear, anxiety, and despair, as well as pride, excitement, and patriotism that comes closer to type Ⅱ trauma [4].

Type Ⅱ trauma is also called complex trauma and increases risk for a symptom profile distinguishable from PTSD, commonly referred to as complex PTSD [5,6]. Complex PTSD includes the defining symptoms of PTSD (re-experiencing, avoidance/numbing, and hyperarousal) as well as a range of disturbances in self-regulatory capacities such as emotion regulation difficulties, disturbances in relational capacities, alterations in attention and consciousness (e.g., dissociation), adversely affected belief systems, and somatic

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Abbreviations: CAPS, Clinician-Administered PTSD Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; IES-R, Impact of Event Scale-Revised; MDD, major depressive disorder. PTSD, posttraumatic stress disorder; SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

distress or disorganization [6].

The major guidelines for the treatment of PTSD (e.g., [7]) recommend selective serotonin reuptake inhibitors (SSRIs) as a first-line pharmacotherapy. For example, the practice guideline of the American Psychiatric Association indicated that SSRIs have proven efficacy for PTSD symptoms in short- and intermediate-term trials. In addition to finding a reduction in PTSD symptoms, studies with SSRIs have suggested that SSRI treatment promotes improvement in functional status and quality of life. However, several studies of combat-related PTSD [8,9] demonstrated that the occurrence of PTSD symptoms did not significantly differ between SSRI and placebo groups at 10 or 12 weeks in randomized-controlled studies.

Antipsychotic medications are regarded as potential candidates for adjunctive treatment in patients who have partially responded to an SSRI or a serotonin/norepinephrine reuptake inhibitor (SNRI), including patients with co-occurring psychotic symptoms [10]. A multicenter retrospective survey conducted in Japan showed that among 185 patients with PTSD using paroxetine, antipsychotics were co-prescribed in 28.1% of the study cases, and logistic regression analysis revealed that co-administration of antipsychotics predicts insufficient efficacy of paroxetine [11]. Another survey of pharmacological treatment for PTSD after large-scale disasters showed that 27.6% of the study participants received antipsychotics [12]. Ooka et al. [13] conducted a medical chart review for patients with PTSD from 1997 to 2006 at the Kurume University Hospital. They found that 101 out of 120 patients received pharmacotherapy. SSRIs were prescribed to about half of the patients, and antipsychotics were prescribed to 19.8% of the patients. They also found that the rate of prescribing antipsychotics was higher in patients with multiple-traumatic experiences than in those who had experienced only one traumatic event in their lifetime.

Major depressive disorder (MDD) has been associated with stressful life events and with PTSD. The co-occurrence rate of MDD in PTSD is 51–82% [14,15]. This comorbidity was also associated with greater symptom severity [16-19] and lower levels of functioning [19]. However, the characteristics of the pharmacotherapy for PTSD with MDD are not fully understood.

The aim of this study was to examine the symptom severity and the pharmacological treatment patterns of patients with PTSD as compared with those suffering from PTSD with comorbid MDD. We hypothesized that patients with PTSD and comorbid MDD would show more severe PTSD symptoms and take a higher dose of psychotropic drugs than PTSD-only patients.

MATERIALS AND METHODS

Samples

A retrospective review was conducted using medical charts at the Department of Neuropsychiatry, Kurume University Hospital. The survey period was limited to the period from August 2005 to July 2014 because electronic medical insurance records at Kurume University were only available starting in 2005. Fifty-five cases with PTSD were extracted. PTSD and MDD diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders (4th edn, text revision) (DSM-IV-TR) criteria [20]. Five cases were excluded after a re-evaluation of the PTSD diagnosis by two psychiatrists who were experienced in diagnosing PTSD.

Data collection

Demographic data (gender, age, academic background), the number and contents of traumatic events, duration until the first medical examination, age at the first medical examination, comorbidities of MDD and/or panic disorder, pharmacological and nonpharmacological treatment (i.e., counseling by clinical psychologists in addition to the usual treatment by psychiatrists), duration of the treatment, PTSD symptom assessment scored by the Clinician-Administered PTSD Scale (CAPS), and/or the Impact of Event Scale-Revised (IES-R) were collected from the medical charts. IES-R is a 22-item self-rating scale for the screening of post-traumatic stress symptoms [21]. Scores range from 0 to 88, and the cut-off point is 24/25 in the Japanese version of the IES-R [22]. The CAPS is the gold standard to assess symptoms of PTSD. We used the validated Japanese version of the CAPS [23]. This instrument allows quantification of the frequency and intensity of each of the 17 symptoms of PTSD according to the DSM-IV [24]. A diagnosis of PTSD can be made based on the CAPS. In addition, for the calculation of correlations and regression analyses, the CAPS total score (frequency plus intensity) can be used. The CAPS has excellent psychometric properties, with test-retest reliability ranging from 0.90 to 0.98 across the 17 items, and an internal consistency of 0.94 [24-26]. Comorbid disorders of MDD and panic disorder were diagnosed according to DSM-IV-TR [20].

Data analysis

Data analysis was performed by IBM SPSS soft-

ware (Version 21). Fisher's exact tests were used when comparing two nominal variables. The Student's t-test was used to compare the means from different groups. Bivariate associations among the variables were estimated using Pearson's product-moment correlations. Logistic regression analysis was used to measure the relationship between the categorical dependent variable (with or without MDD) and the independent variables. Results were considered significant if the p value was <0.05. Cohen's d was used for the effect sizes, of which small (around 0.20), medium (0.50), and large (0.80) sizes were shown.

Ethical issues

This research received approval from the ethics review board at Kurume University (No. 14025). Authors followed the ethical guidelines for epidemiological research by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare, Japan.

RESULTS

Demographic and clinical characteristics of the patients (Table 1)

Eighty-four percent of patients were female. A higher percentage of patients experienced Type I trauma (66.0%) than Type Ⅱ trauma. PTSD symptom severity was measured using a self-rating scale (IES-R) in most cases and was assessed by the CAPS in about half of the patients.

Pharmacological treatment (Table 2)

About two-thirds of the patients were prescribed benzodiazepines. SSRIs were prescribed to 27 patients. The duration of treatment in patients given antipsychotics (46.5±43.2 months) was significantly longer than that in patients not taking antipsychotics [16.7±27.2 months, $t(48) = 2.92$, $p<0.01$]. There were no significant differences in the mean IES-R scores between patients taking or not taking antipsychotics.

Characteristics of patients with comorbid major depression (Table 3, Table 4)

A higher rate of type Ⅱ trauma was observed in the PTSD with comorbid MDD group (50.0%) than in the PTSD-only group [13.6%; $\chi^2(1, n=50) = 7.26$, $p<0.01$]. The PTSD with comorbid MDD group tended to have more counseling sessions than the PTSD-only group (42.9% vs. 13.6%; $\chi^2(1, n = 50) = 5.00$, $p<0.05$). The PTSD with comorbid MDD group had more severe PTSD symptoms, a longer duration of treatment, and received a higher dose of psychotropic drugs than the PTSD-only group. There were no age differences between the PTSD with comorbid MDD group and the PTSD-only group; however, a medium effect size was observed according to the calculated Cohen's d. Logistic regression analysis (using the forward stepwise with the likelihood ratio test) was conducted to determine the relationship between variables and comorbid MDD, adjusting for possible differences and background characteristics (gender, age, type of trauma, counseling, SSRI use, antipsychotic use, benzodiazepine use, duration of treatment, IES-R, comorbid of panic disorder) (Table 4). The final model could differentiate 79.5% of the whole sample [$\chi^2(3) = 23.0$, $p<0.001$]. The type of trauma, benzodiazepine use, and IES-R significantly predicted comorbid MDD, and the odds ratios were 16.4, 14.3, and 1.09 respectively. This result suggests that patients experiencing type Ⅱ trauma were more likely to experience comorbidity with MDD, were more likely to be treated with benzodiazepines, and were more likely to show more severe PTSD symptoms.

DISCUSSION

We demonstrated that PTSD patients with comorbid MDD experienced more severe PTSD symptoms, longer treatment periods, and higher doses of psychotropic drugs. After adjusting the variables, type II trauma, benzodiazepine use, and PTSD symptom severity by IES-R predicted comorbid MDD. Our finding that posttraumatic stress symptoms were more severe in the comorbid MDD group is consistent with previous studies [16-19]. A study by Elhai et al. [16] using a community sample demonstrated that PTSD and MDD symptoms appeared to have a single, unitary construct, and that MDD symptoms were more pathological than PTSD symptoms. In another study, participants were categorized into four diagnostic groups (no PTSD–no MDD, no PTSD with MDD, PTSD without MDD, PTSD with MDD), and the results revealed that the PTSD with MDD group reported the most severe symptoms [17]. A recent meta-analysis showed a higher comorbidity rate of MDD among patients from the military and those who experienced interpersonal traumas than civilian samples and victims of natural disasters [27]; our finding that type Ⅱ trauma survivors tend to have a higher rate of comorbid MDD is consistent with this result. The longer treatment period in the comorbid MDD group

TABLE 1.
Demographic and clinical characteristics of the patients (n = 50)

demographic variables			
Gender	Male	8	(16.0%)
	Female	42	(84.0%)
age (years old)	average (SD)	29.22	(14.3)
	median	25.0	
	minimum	9	
	maximum	65	
academic background	junior high school	9	(18.0%)
	high school	9	(18.0%)
	vocational school	12	(24.0%)
	junior college	1	(2.0%)
	university	10	(20.0%)
	other/ unknown	9	(18.0%)
age at onset	average (SD)	27.6	(14.5)
duration until first visit (month)	average (SD)	32.9	(78.2)
duration of treatment (month)	average (SD)	31.6	(38.8)
traumatic events	sexual abuse	22	(44.0%)
	motor vehicle accident	10	(20.0%)
	crime victims	7	(14.0%)
	domestic violence	4	(8.0%)
	accidental injury	3	(6.0%)
	bullying, physical punishment at school	2	(4.0%)
	childhood abuse	1	(2.0%)
	other	1	(2.0%)
number of comorbidity: major depression	Yes	28	(56.0%)
	No	22	(44.0%)
number of comorbidity: panic disorder	Yes	7	
	No	43	
measures			
IES-R (n = 44)	average (SD)	56.0	(15.4)
	median	56.5	
CAPS (n = 25)	average (SD)	82.9	(23.4)
	median	92	
	minimum	32	
	maximum	122	

and a higher dose of psychotropic drugs were believed to be partially influenced by the severity of PTSD symptoms.

The frequency at which benzodiazepines were prescribed was relatively high. The cumulative total number of benzodiazepine prescription is larger as sleep inducing effect (n = 37) than anxiolytic effect (n = 19). The high rate of benzodiazepine prescriptions is not in line with the treatment guidelines, which do not recommend benzodiazepine use for PTSD patients (e.g., [7]). However, it has been reported that more than 30% of veterans in the USA with PTSD continue to

TABLE 2.
Pharmacological treatment

measures	number of patients	mean (mg)	SD
imipramine equivalent dose of antidepressants	28	105.3	86.8
chlorpromazine equivalent dose of antipsychotics	25	329.3	370.0
diazepam equivalent dose of benzodiazepines	33	14.8	13.5
mood stabilizers	7	N/A	N/A

TABLE 3.
Group differences between posttraumatic stress disorder (PTSD) only and PTSD with major depressive disorder (PTSD+MDD)

variables	PTSD only (n = 22)		PTSD+MDD (n = 28)				
	M	SD	M	SD	t(48)	p	Cohen's d
age	25.36	12.1	32.3	15.3	1.77	0.08	0.51
duration of treatment (months)	12.3	20.9	46.8	42.9	3.46	0.001	1.00
imipramine equivalent dose of antidepressants	23.4	33.7	86.8	99.4	2.86	0.006	0.83
chlorpromazine equivalent dose of antipsychotics	44.3	99.5	259.3	378.3	2.59	0.01	0.75
diazepam equivalent dose of benzodiazepines	4.87	7.9	13.6	14.9	2.65	0.01	0.76
IES-R	48.5	13.8	62.3	13.9	3.31	0.002	0.96

TABLE 4.
Logistic regression analysis predicting major depression comorbidity

predictor	B	SE	OR	Wald Statistic	95% CI	p
trauma type, type Ⅱ	2.80	1.21	16.37	5.38	[1.54, 174.01]	0.02
benzodiazepine use, yes	2.67	1.11	14.31	5.72	[1.61, 126.59]	0.02
IES-R	0.09	0.03	1.09	7.27	[1.02, 1.16]	0.01

CI = confidence interval for odds ratio (OR); IES-R = Impact of Event Scale-Revised

receive benzodiazepines [28,29]. Female, older age, and longer time since PTSD diagnosis were independently associated with benzodiazepine use in veterans [29]. Another study found that compared with SSRIs/SNRIs only, the adjusted risk of mental health hospitalization was greater among patients prescribed SSRIs/SNRIs and benzodiazepines concurrently [30]. Our data suggest that the medical doctors in Kurume University Hospital should reduce benzodiazepine use for patients with PTSD.

Several limitations of this study require consideration. We could not obtain data on the severity of major depression symptoms because only a few patients had been asked to fill out self-rating scales such as the Beck Depression Inventory, Zung's Self-rating Depression Scale, and/ or Hamilton Depression Rating Scale. Similarly, we cannot discuss the relationships between each core PTSD symptom and MDD comorbidity and prescription patterns because only half of the patients had CAPS data and IES-R could not be evaluated for each PTSD symptom. This study was a cross-sectional study; therefore, we cannot discuss causality.

In conclusion, we found differences in patient characteristics and prescription patterns between patients with PTSD only and those with PTSD and MDD. Our results have important clinical implications for traumatized victims. We should evaluate traumatized patients not only with PTSD assessment scales, but also with MDD assessment scales because comorbid MDD might be associated with difficulties in treatment. More prospective studies are needed to explore the relationship between PTSD and co-occurring MDD.

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