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Association of posttraumatic stress disorder with increased prevalence of metabolic syndrome

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Abstract

Objective—Few studies have compared prevalence rates of metabolic abnormalities in antipsychotic-treated patients with different psychiatric disorders, including posttraumatic stress disorder (PTSD). In this study, we examined components of metabolic syndrome among middle-aged and older patients with psychiatric disorders.

Method—In the study, 203 outpatients older than 40 years and with psychotic symptoms that needed antipsychotic treatment were enrolled. Among them, 65 had a diagnosis of schizophrenia, 56 had dementia, 49 had mood disorder, and 33 had PTSD. Clinical evaluations included medical history, use of psychotropic and other medications, adverse effects, physical examination, and clinical laboratory tests for metabolic profiles.

Results—Overall, the prevalence rates of metabolic syndrome were 72% in patients with PTSD, 60% in those with schizophrenia, 58% in those with mood disorder, and 56% in those with dementia. There were significant differences in body mass index, diastolic blood pressure, waist circumference, and high-density lipoprotein cholesterol among the 4 diagnostic groups. Posttraumatic stress disorder, schizophrenia, and mood disorder groups had significantly higher body mass indexes compared with the dementia group. The PTSD group also had significantly higher diastolic blood pressure compared with the dementia and mood disorder groups.

Conclusions—Posttraumatic stress disorder may be associated with worsened metabolic profile. The overall frequency of metabolic syndrome and its components in patients with PTSD taking antipsychotics seemed to be at least equivalent, if not slightly worse, compared with that in patients with schizophrenia, dementia, or a mood disorder.

Metabolic syndrome is a significant risk factor for cardiovascular disease and diabetes.[1,2] The prevalence of metabolic syndrome is higher in people older than 40 years than in those younger than 40 years, with the highest rates being among women older than 60 years.[3] Metabolic syndrome and its components have also been shown to be more common in individuals with schizophrenia, [4–6] bipolar disorder, [4,6–8] and major depressive disorder.[4,6,9] In recent years, there has been considerable focus on the role of atypical antipsychotics in elevating the risk of metabolic syndrome.[10,11] Although patients with posttraumatic stress disorder (PTSD) are often prescribed atypical antipsychotics off-label,[12–17] metabolic syndrome has only recently been studied in this population.

There is some evidence that PTSD is associated with increased rates of metabolic syndrome [6,18–20] and its components, including being overweight and obese [21–24] as well as dyslipidemia.[21,25] Jakovljevic et al [18] examined the prevalence of metabolic syndrome among 47 Croatian war veterans with PTSD and found that 31.9% met criteria for it, far exceeding the rate in a middle-aged Croatian nonclinical comparison group (8.9%). In contrast, a larger sample of 100 male Croatian combat veterans with PTSD had a metabolic syndrome prevalence rate of 35%, compared with 41.8% in an at-risk sample of 79 Croatian male patients needing medical care.[20] These investigators also found that the prevalence of

metabolic syndrome was significantly related to severity of PTSD; the rate in veterans with severe PTSD was 66.7%, compared with 23.3% in veterans with low-intensity PTSD. Similarly, Violanti et al [19] reported a study on police officers and found that people with the most severe PTSD symptoms had a significantly higher prevalence of metabolic syndrome (50%) than those with subclinical symptoms (15.1%). Vieweg et al [24] noted that the high prevalence of being overweight and obese in their sample of veterans with PTSD could not be explained by psychotropic medications typically associated with weight gain. Diabetes has also been shown to be more prevalent in patients with PTSD [21,26–28]; however, one study reported that trauma was associated with increased likelihood of diabetes, but PTSD did not mediate this relationship.[29]

A higher frequency of diseases related to metabolic syndrome has been linked to PTSD. For example, stroke was significantly more common in female veterans with PTSD.[22] The results for heart disease have been mixed, with some studies reporting PTSD to be associated with higher rates of heart disease,[21,30] but not others.[22,26] Although previous studies show that individuals with a severe mental illness had a higher prevalence of metabolic syndrome than individuals who have no mental illness, to our knowledge, no studies have compared rates of metabolic syndrome across mental illness diagnostic groups in older adults.

In the present investigation, we sought to compare the risk of metabolic abnormalities across diagnostic groups among middle-aged and older patients receiving antipsychotics for schizophrenia, PTSD, mood disorder, and dementia with psychosis. We hypothesized that patients with schizophrenia and PTSD would have a higher prevalence of metabolic syndrome including each of its components than patients with mood disorder or dementia. We should stress the fact that the antipsychotics are approved by the Food and Drug Administration primarily for schizophrenia and bipolar disorder, and their use in other conditions is considered off-label. Furthermore, there are black-box warnings issued by the Food and Drug Administration regarding an increased risk of strokes and mortality with these drugs in elderly patients with dementia.[31,32] The decision to prescribe antipsychotics to the patients in this study was made by the respective clinical psychiatrists treating those individuals.

METHODS

Here we present an analysis of baseline data from an ongoing National Institute of Mental Health (NIMH)-funded investigation examining metabolic, cardiovascular, and cerebrovascular effects in patients older than 40 years who had psychotic symptoms that, according to the patients' own treating psychiatrists, needed treatment with antipsychotics. This research is being conducted at the NIMH-funded Advanced Center for Innovation in Services and Intervention Research for the study of older patients with psychosis at the University of California, San Diego (UCSD), and Veterans Affairs San Diego Healthcare System. The study has been approved by the UCSD institutional review board, and all the participants have provided written informed consent. Participants enrolled in this investigation completed a baseline evaluation and will have follow-up assessments at 6 and 12 weeks and every 3 months thereafter. The present paper is restricted to baseline data from the available sample, which include the following: (1) medical history and use of psychotropic and other medications, as well as neurologic and other physical examination results; (2) anthropomorphic measurements for obesity; (3) psychopathology, medication adverse effects, and everyday functioning; and (4) clinical laboratory results for metabolic profiles.

Subjects

The patients were recruited from psychiatric clinics at UCSD and the Veterans Affairs San Diego Healthcare System as well as from nursing homes and board-and-care homes in San Diego County. All the patients had their conditions diagnosed by their primary psychiatrists, many of whom are on the clinical faculty of the UCSD Department of Psychiatry. The patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for schizophrenia/schizoaffective disorder, psychosis associated with mood disorder, dementia, PTSD, or psychotic disorder not otherwise specified.[33] Patients with active substance abuse in the past 30 days or unstable medical conditions were excluded. Twelve patients with a diagnosis of psychotic disorder not otherwise specified were excluded from the following analyses in view of the small number of patients in this group.

Assessment

Medical History, Use of Psychotropic and Other Medications, and Neurologic and Other Physical Examination

Two trained physician assistants obtained detailed medical history about medical illnesses, known risk factors for metabolic abnormalities, and treatment for these conditions. Physical comorbidity was evaluated with the Cumulative Illness Rating Scale for geriatrics.[34] In addition to having their vital signs and blood pressure recorded, each patient had a neurologic and other physical examination, including a specific assessment for stroke using the National Institutes of Health Stroke Scale.[35] For the blood pressure assessment, subjects were seated quietly for at least 5 minutes before the measurement was made. Two blood pressure readings were recorded at least 30 seconds apart using a sphygmomanometer. The mean of the 2 readings for both systolic and diastolic pressures was computed and used as the record of blood pressure.[36]

Information regarding past and present treatment with antipsychotic and other medications potentially impacting metabolic conditions was also obtained. Specifically, the study physician assistants went through a medication checklist with each patient, including all categories of relevant medications such as antipsychotics, antidiabetes medications, lipid-lowering agents, and antihypertensives, and carefully recorded past and current use.

Anthropomorphic Measurements for Obesity

Height was measured using a wall-mounted stadiometer, and weight, by a western digital indicator to the nearest tenth of a kilogram. Body mass index (BMI), a standardized method to estimate overall obesity, was determined from these values (kg/m^2). The waist, hip, and thigh circumferences in centimeters were assessed using a measuring tape. The maximum waist circumference was measured at the level of the umbilicus, and the hip, at the maximum horizontal circumference of the hips. All the measurements were taken with the subject in a standing position (the arms at rest along the body) and in apnea fixed at the mid respiratory phase.

Psychopathology and Medication Adverse Effects

We used standardized rating scales to evaluate psychopathology, movement disorders, cognitive impairment, and everyday functioning. Psychopathology was assessed with the Brief Psychiatric Rating Scale [37] and the Hamilton Depression Rating Scale.[38] Movement disorders were rated according to a modified Simpson-Angus Scale [39] for extrapyramidal symptoms and the Abnormal Involuntary Movement Scale [40] for tardive dyskinesia. In patients with dementia, the Mini-Mental State Examination [41] and Dementia Rating Scale of Mattis [42] were used to assess level of cognitive impairment.

Before the enrollment of subjects, raters were trained on the administration of assessments. With regard to interrater reliability, an intraclass correlation coefficient of 0.80 or higher was established. All raters hired after the study was initiated were trained and passed reliability training tests before evaluating the subjects.

Clinical Laboratory Examinations for Metabolic Measures

All blood samples were collected by a nurse working in the General Clinical Research Center at UCSD, and the laboratory testing was done at the UCSD Medical Center-certified clinical laboratory. The blood for the chemistry panel that included fasting plasma glucose and the lipid panel (total, high-density lipoprotein [HDL], and low-density lipoprotein cholesterol, and triglycerides) was drawn in the early morning, after at least 12 hours of fasting.[43,44] A diagnosis of metabolic syndrome was made on the basis of the following 5 conditions, namely, waist circumference, blood pressure, fasting blood glucose, triglycerides, and HDL cholesterol, according to criteria of the American Heart Association (AHA).[45] The cutoff criteria for each component of metabolic syndrome are as follows: waist circumference, greater than 40 in (>102 cm) in men and greater than 35 in (>88 cm) in women; blood pressure, 130/85 mm Hg or higher; fasting glucose level, 100 mg/dL or higher; triglyceride level, 150 mg/dL or higher; and HDL cholesterol level, less than 40 mg/dL in men and less than 50 mg/dL in women. If patients endorsed using antidiabetic, antihypertensive, or antilipemic medications, we counted them as meeting the respective criteria even if their glucose, blood pressure, or lipid levels were normal.[45] Anyone having 3 or more conditions meeting the AHA cutoff criteria was considered to have metabolic syndrome.

Statistical Analysis

Continuous variables were assessed for normality of distribution, and appropriate transformations were performed when necessary. The raw percentages of rates for metabolic syndrome and its components were compared between the different psychiatric diagnostic groups. These rates were then adjusted for age, sex, and treatment duration in view of significant differences in these variables between the diagnostic groups. The adjusted percentages of metabolic syndrome for each diagnosis were computed by creating logistic regression models adjusting for age, sex, and treatment duration, and then, using the sample means for each of the covariates, the model was used to predict proportions of patients in each of the 4 diagnostic groups. Between-group comparisons of categorical variables were made using $[chi]^2$ tests. Group comparisons were performed on continuous variables with Welch analysis of variance (ANOVA), and post hoc analyses between groups were carried out on the variables having significant differences on ANOVA. The comparisons between groups adjusting for age, sex, and treatment duration were performed using linear regression with robust tests of heteroscedastic consistent covariance matrix.[46] All comparisons were 2-tailed, with $P < 0.05$ considered statistically significant.

RESULTS

The first 203 patients who completed the baseline evaluation are included in this analysis. The demographic and clinical characteristics of the 4 diagnostic groups (schizophrenia, mood disorder, dementia, and PTSD) are presented in Table 1. The mean age of entire sample was 65.9 years (range, 40–94 years); 67% were men, and 85% were currently taking antpsychotics. The dementia group was significantly older and had a higher percentage of women than the other diagnostic groups. The schizophrenia group had a lower level of education and a lower percentage of white patients. The proportion of patients currently taking antipsychotics was lower in the dementia group than in patients with mood disorder or PTSD. The mean duration of prior antipsychotic use was shorter in the patients with

dementia compared with the other groups. Among the patients taking antipsychotics, the percentages of patients on specific atypical agents (including olanzapine) were not different across the 4 diagnostic groups. None of the participants was on clozapine. The proportions of patients currently taking antidiabetic, cholesterol-lowering, and antihypertensive drugs did not differ among the 4 diagnostic groups.

Rates of the Metabolic Syndrome and Each of Its Abnormal Components

Using the AHA criteria,[45] 72% of patients with PTSD, 60% of those with schizophrenia, 58% of those with mood disorder, and 56% of those with dementia were classified as having metabolic syndrome (Fig. 1). Because older age and female sex have been associated with an increased risk of metabolic syndrome in the general population,[3] and age and sex were significantly different among the 4 diagnostic groups, we adjusted the rates of metabolic syndrome and its components by age, sex, and duration of prior antipsychotic treatment. The adjusted rates of metabolic syndrome in patients with PTSD, schizophrenia, mood disorder, and dementia were 73%, 61%, 58%, and 54%, respectively. Pairwise comparison showed a significant difference between patients with PTSD and those with dementia.

There were significant differences in BMI ($P < 0.001$), diastolic blood pressure ($P = 0.033$), waist circumference ($P = 0.002$), and HDL cholesterol ($P = 0.012$) among the 4 diagnostic groups. The PTSD, schizophrenia, and mood disorder groups had higher BMIs than the patients with dementia ($P < 0.001$). The PTSD group had higher diastolic blood pressure compared with the dementia ($P = 0.011$) and mood disorder groups ($P = 0.008$). The waist circumference in patients with schizophrenia, mood disorder, and PTSD was greater than in those with dementia. The HDL cholesterol level was lower in the participants with PTSD ($P < 0.001$), schizophrenia ($P = 0.033$), and mood disorder ($P = 0.026$) compared with that of the dementia group, with the PTSD participants having the lowest HDL level of all the groups.

To eliminate the possible confounding effects of age, sex, and duration of antipsychotic treatment on the prevalence of metabolic syndrome, we further analyzed the data after adjusting for these variables and found that the group differences in BMI and diastolic blood pressure remained significant. Adjusting for treatment duration alone, we found that the group differences in BMI, diastolic blood pressure, waist circumference, and HDL cholesterol remained significant. Adjusting for sex alone resulted in BMI, waist circumference, and diastolic blood pressure being different between the groups, whereas an adjustment for age alone resulted in all the group differences becoming nonsignificant.

Although we did not specifically assess PTSD severity, we examined correlations between the Brief Psychiatric Rating Scale total and psychosis subscale scores [37,47] and each component of metabolic syndrome in these patients. No significant correlations were found between any of the metabolic outcomes and severity of symptoms in patients with PTSD.

DISCUSSION

Metabolic syndrome was common in middle-aged and older patients with psychotic disorders, especially in those with PTSD. The rates of metabolic syndrome and some of its components in patients with PTSD taking antipsychotics were statistically equivalent to (and numerically worse than) those in patients with schizophrenia, although the schizophrenia group had a longer duration of prior neuroleptic exposure.

The mean prevalence of metabolic syndrome in the US population in the National Health and Nutrition Examination Survey was 44% in people older than 40 years, with the rate being higher in women than in men.[3] The 60% rate of metabolic syndrome in our patients

with schizophrenia was higher compared with the 42.7% rate reported in the Clinical Antipsychotic Trials of Intervention Effectiveness.[5] However, the Clinical Antipsychotic Trials of Intervention patient sample was younger, and that study used the Adult Treatment Panel III criteria for metabolic syndrome with a higher glucose cutoff.

The 72% prevalence rate of metabolic syndrome in our PTSD group is not only higher than that in the general US population but also higher than the previously reported rates of 16% to 67% among patients with PTSD.[18–20] However, the prior investigations used the National Cholesterol Education Program/Adult Treatment Panel III criteria,[48] and 2 of the groups were from Croatia, which has a lower (8.6%) rate of metabolic syndrome in the general population [18] than the 24% to 27% rate in the United States.[3] We did not find significant correlations between the metabolic outcomes and severity of symptoms in patients with PTSD, although they all were deemed to need antipsychotics, suggesting that they probably had severe illness.

Possible mechanisms explaining the link between PTSD and metabolic abnormalities include lifestyle factors, medications, and physiologic dysregulation due to long-term overactivation of the body's stress-response pathways. Posttraumatic stress disorder, schizophrenia, and mood disorders are all associated with an increased risk of having lifestyle behaviors that can predispose to metabolic syndrome, such as smoking, unhealthy diets, sedentary habits, and alcohol and drug abuse. Among the atypical antipsychotics, clozapine and olanzapine have the highest risk of causing weight gain and metabolic abnormalities.[49–51] However, the rates of olanzapine use were equivalent among the 4 diagnostic groups, and no patient was on clozapine. Therefore, it is unlikely that differences in prior antipsychotic use could fully explain the higher rates of metabolic abnormalities seen among patients with PTSD. It is possible, however, that differences in antipsychotic dosages could have contributed to variations in metabolic risk across the groups.

Potential physiologic explanations associating chronic stress with metabolic syndrome include allostatic load, hypothalamic-pituitary-adrenal axis dysregulation, and autonomic nervous system imbalance.[52,53] Examples of allostatic state in PTSD include exaggerated startle response, sleep disturbance, and heightened sympathetic tone indicated by higher resting heart rates, blood pressure, and cardiovascular, electromyographic, and skin conductance responses to reminders of the traumatic event.[30,54] Hypothalamic-pituitary-adrenal axis activation may result in increased glucocorticoid levels, which have been linked to abdominal obesity, which in turn leads to increased insulin resistance.[55,56] Through such mechanisms, PTSD itself could be associated with increased likelihood of metabolic syndrome, and antipsychotics might further increase that risk.

Our study has several limitations. First, our PTSD sample size was relatively small, and all diagnoses were based on clinical assessment rather than on a structured interview such as the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[33] Second, women were underrepresented. Third, we did not have detailed information on prior antipsychotic use including types and dosages of medications. Finally, this study used a convenience sample referred from clinics, and the prescription of antipsychotics had been based on the individual treating psychiatrist's decision rather than on randomization. It is thus possible that the prescribers chose medications such as olanzapine for patients at lower risk of developing metabolic syndrome.

Despite these limitations, our results suggest that PTSD carries liability for metabolic complications, along with a significant mental health burden, and indicates a need for caution in using antipsychotics in this patient population. Further study is needed to confirm these findings and to guide the development of optimally tailored prevention and

intervention efforts targeting metabolic changes in patients with PTSD and other disorders associated with psychotic symptoms.

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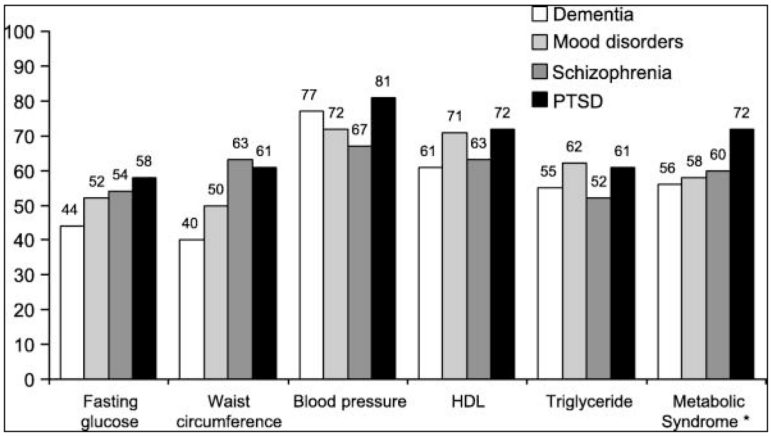

Figure 1.

Percentage of patients with metabolic syndrome and with each component above cutoff point among 4 diagnostic groups. The AHA criterion for blood glucose level of 100 mg/dL or higher was used. Patients taking antidiabetic, antihypertensive, and antilipemic medications were also considered to meet criteria even if they had normal glucose, blood pressure, or lipid levels.

Table 1

Demographic and Clinical Characteristics of Middle-Aged and Older Patients with 4 Different Psychotic Disorders

	Diagnostic Groups									
	Dementia With Psychosis (n=56)		Mood Disorder With Psychosis (n=49)		Schizophrenia (n=65)		PTSD (n=33)			
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P****	**Post hoc**
Age, yr	77.2	9.8	67.1	13.2	58.3	10.6	59.7	10.5	<0.001	D> M> S, P
Education level, yr	13.7	2.8	14.0	3.1	12.4	2.8	13.7	2.5	<0.05	D, P, M >S
Duration of antipsychotic treatment, mo	44.4	36.1	129.4	133.1	253.3	162.9	173.4	160.6	<0.001	S>P, M>D
Number of metabolic syndrome conditions	2.8	1.3	3.0	1.4	2.9	1.5	3.3	1.4	0.459	—
BMI	26.1	5.0	29.5	7.8	29.8	6.8	30.4	4.3	<0.001	D<M, S, P
Diastolic blood pressure, mm Hg	69.4	9.7	69.3	8.6	72.8	9.1	75.1	9.7	0.015	D, M <P
Systolic blood pressure, mm Hg	126.2	18.6	126.4	15.8	123.4	19.7	132.7	15.2	0.089	—
Waist circumference, in	36.9	5.2	40.3	7.2	41.0	6.4	39.9	7.0	0.002	D<M, S, P
Fasting glucose level, mg/dL	100.0	23.1	109.9	44.6	119.7	78.5	114.2	41.3	0.088	—
HDL cholesterol level, mg/dL	51.9	18.7	44.8	12.6	44.3	18.5	41.4	10.3	0.012	D>M, S, P
Triglyceride level, mg/dL	123.5	115.1	140.5	87.6	149.6	120.6	127.3	61.1	0.558	—
Categorical variables	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Sex										
Male	31	55	30	61	48	74	29	88	<0.01	D<S, P; M<P
Female	25	45	19	39	17	26	4	12		(% male)
Ethnicity										
White	47	84	40	82	42	64	21	64	<0.05	D, M > S, P
Nonwhite	9	16	9	18	23	37	12	36		(% White)
On antidiabetic drugs	6	11	11	22	16	25	7	21	0.351	—
On statins	20	34	22	45	15	23	15	45	0.058	—
On antihypertensive drugs	30	54	29	59	28	43	22	67	0.234	—
Currently on antipsychotics†	42	75	46	94	55	89	30	91	<0.01	M, P>D

*Welch ANOVA for continues variables and χ^2 for categorical variables.

†The percentage of patients taking atypical antipsychotics or rate of olanzapine use was not significantly different between the diagnostic groups.

D indicates dementia with psychosis; M, mood disorder with psychosis; P, PTSD; S, schizophrenia.