

Nonpsychiatric Disorders Associated with Depression

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Although depression is recognized as a common problem in primary care, that it is frequently associated with nonpsychiatric disorders is not well known. In this study, the charts of all 157 patients at a university family practice center diagnosed with depression during a 12-month period were reviewed retrospectively. In addition to demographic data, the presence of nonpsychiatric conditions known to be associated with depression and the physician's initial diagnosis were determined and statistically analyzed. At least one associated nonpsychiatric disorder was evident in 47.8 percent of the patients. The use of at least one drug known to be associated with depression was noted in 43.3 percent of the patients. Yet, only 7.6 percent of the charts indicated a recognition by the physicians that the patients had an associated nonpsychiatric disorder. Those which were recognized tended to have endocrine disorders. By increasing physician sensitivity, coupled with a complete history and physical examination, a greater number of these nonpsychiatric conditions can be diagnosed. Treatment of the contributing disorder may alleviate the depressive symptomatology.

Clinical depression today is a symptom complex. It has assumed major proportions under the stress of twentieth century America by the fact that at least 15 to 30 percent of the population will have at least one depressive episode in their lifetime.¹ At a primary care center in Boston, de-

pression was the second most frequent problem, accounting for 10 percent of all problems and seen in 32 percent of the patients.²

Drugs (Table 1) and various medical illnesses (Table 2) have long been known to cause or at least be associated with the symptom complex of depression as described by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*.¹⁰ Between 5 and 42 percent of psychiatric patients have been found to have a physical illness contributing to their psychiatric problems; in fact, the problems of 9.1 percent of psychiatric outpatients were felt to be secondary to an underlying medical disorder.⁷

Though antidepressant therapy can be used to treat the neurovegetative symptoms of depression

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Table 1. Drugs Associated With Depression

Analgesics—Anti-inflammatory agents	Antiparkinsonian agents ^{3,5}
Ibuprofen ³	Cytotoxic agents ^{3,5}
Indomethacin ^{3,5}	Hormones
Baclofen ⁵	ACTH ^{3,5}
Opiates ³	Corticosteroids ^{3,5}
Pentazocine ³	Estrogen ⁶
Phenacetin ³	Oral contraceptives ^{3,5,6}
Phenylbutazone ³	Immunosuppressive agents ³
Anticonvulsants ^{3,5}	Tranquilizers
Antihistamines ³	Barbiturates ^{3,5}
Antihypertensive agents	Major tranquilizers ^{3,5}
Clonidine ³	Minor tranquilizers ^{3,5}
Guanethidine ³	Miscellaneous
Hydralazine ³	Alcohol ³
Methyldopa ^{3,5}	Amphetamine withdrawal ^{3,5}
Propranolol ^{3,5}	Caffeine ⁴
Reserpine ^{3,5}	Cimetidine ⁵
Antimicrobials	Digitalis ³
Ampicillin ³	Disulfiram ^{3,5}
Cycloserine ³	Fenfluramine ³
Dapsone ³	Halothane ⁵
Griseofulvin ³	LSD (lysergic acid diethylamide) ³
Isoniazid ^{3,5}	Methysergide ³
Metronidazole ³	Metrizamide ⁵
Nalidixic acid ^{3,5}	Phenylephrine ⁵
Nitrofurantoin ³	
Procaine penicillin ⁵	
Streptomycin ³	
Sulfonamides ³	
Tetracycline ³	
Trimethoprim sulfa ³	

whatever the cause, if a nonpsychiatric disorder contributing to the symptomatology can be identified, treatment of that disorder may alleviate the depressive symptoms. This study was performed to assess the presence of nonpsychiatric conditions potentially contributing to depression. Undertaken in an ambulatory setting, the study's results are presented to increase physicians' awareness of and sensitivity to these associated conditions.

Methods

Over a 12-month period, from July 1978 through June 1979, 157 new cases of depression were diagnosed by six residents and ten attending physicians at The Ohio State University Family Practice

Center. The patients' charts were reviewed retrospectively for the presence of active nonpsychiatric conditions known to be associated with depression as listed in Tables 1 and 2, a family history of depression, and an initial diagnosis of depression related to nonpsychiatric conditions. The diagnosis of depression was made either on clinical grounds by applying DSM-III criteria, or by using an objective instrument—Popoff's Index of Depression¹¹ or the Minnesota Multiphasic Personality Inventory (MMPI).

In a comprehensive study seeking a cause-and-effect relationship, it would be necessary to select a matched control group. However, because this study focused on the presence of nonpsychiatric disorders that may be contributing to the de-

Table 2. Medical Disorders Associated With Depression

Collagen-Vascular	Infectious
Giant cell arteritis ^{7,9}	Brucellosis ⁹
Gout ⁹	Encephalitis ⁹
Periarteritis nodosum ⁹	Hepatitis ^{7,9}
Rheumatoid arthritis ⁹	Infectious mononucleosis ^{7,9}
Systemic lupus erythematosus ^{7,9}	Influenza ^{8,9}
Endocrine	Malaria ⁹
Acromegaly ^{8,9}	Pneumonia ^{7,9}
Diabetes mellitus ⁹	Syphilis ⁹
Hyperadrenalism ^{7,9}	Tuberculosis ^{7,9}
Hyperparathyroidism ^{7,9}	Metabolic
Hyperthyroidism ^{7,9}	Decreased bicarbonate ^{7,9}
Hypoadrenalism ^{7,9}	Hyperkalemia ^{7,9}
Hypoglycemia ⁹	Hypocalcemia ⁹
Hypoparathyroidism ^{7,9}	Hypokalemia ^{7,9}
Hypopituitarism ⁷	Hypomagnesemia ^{7,9}
Hypothyroidism ^{7,9}	Hyponatremia ^{7,9}
Menopause ^{7,9}	Increased bicarbonate ^{7,9}
Postpartum ⁷	Uremia ^{7,9}
Gastrointestinal	Neoplasm
Cirrhosis ^{8,9}	Intracranial ⁷
Inflammatory bowel disease ^{8,9}	Leukemia ^{8,9}
Pancreatitis ⁹	Lymphoma ^{8,9}
Whipple's disease ^{8,9}	Oat cell carcinoma ^{8,9}
Hypovitaminosis	Pancreatic ^{8,9}
Ascorbic acid ⁹	Neurologic
Folate ⁹	Chronic subdural hematoma ⁹
Iron ⁹	Huntington's disease ⁹
Niacin ^{7,9}	Multiple sclerosis ^{8,9}
Pernicious anemia ^{7,9}	Organic brain syndrome ^{8,9}
Pyridoxine ⁹	Miscellaneous
Thiamine ⁹	Amyloidosis ^{8,9}
	Psoriasis ⁹
	Sarcoidosis ⁹
	Wilson's disease ^{7,9}

pressive symptomatology in depressed patients, it was decided to delimit the scope to include only depressed patients. The vertical nature of the study seeking nonpsychiatric disorders active at the single point in time when the diagnosis of depression occurred made selection of a matched control group inappropriate.

The data were analyzed statistically using a criterion probability level of $P \leq .05$. Statistical analyses included the chi-square test, Fisher's exact probability test, Student's *t* test, and one-way analysis of variance with Scheffé post hoc tests. Analyses were conducted in an attempt to identify

factors that should alert the physician to search for associated nonpsychiatric conditions.

Results

Although the Family Practice Center population is 59 percent female and has a mean age of 32 years, the depressed population in this study was 77 percent female with a mean age of 38.9 years. In addition, 75.8 percent of the depressed population were white and 22.9 percent were black; 45.2 percent were married. Of the unmarried patients, 25.5 percent were single, 18.5 percent were divorced, 4.5 percent were separated, and 6.4 percent were

Table 3. Frequency of Associated Nonpsychiatric Conditions Observed

Cause	No. (%)
Minor tranquilizer use	26 (16.6)
Menopause	17 (10.8)
Major tranquilizer use	12 (7.6)
Opiate use	12 (7.6)
Alcohol use	12 (7.6)
Caffeine use	11 (7.0)
Estrogen use	10 (6.4)
Propranolol use	9 (5.7)
Oral contraceptive use	6 (3.8)
Barbiturate use	5 (3.2)
Methyldopa use	4 (2.5)
Antihistamine use	4 (2.5)
Amphetamine use	3 (1.9)
Pneumonia	3 (1.9)
Hepatitis	3 (1.9)
Hypothyroidism	3 (1.9)
Hypoglycemia	3 (1.9)
Organic brain syndrome	2 (1.3)
Multiple sclerosis	2 (1.3)
Reserpine use	1 (0.6)
Postpartum	1 (0.6)
Systemic lupus erythematosus	1 (0.6)
Hypoadrenalism	1 (0.6)
Hypokalemia	1 (0.6)
Hyperthyroidism	1 (0.6)

widowed. Of the 68 patients for whom psychiatric family histories were available, 27.9 percent indicated a history of depression.

With 65.6 percent of the patients diagnosed as depressed on clinical grounds alone, the initial diagnosis made by the physician recognized an associated nonpsychiatric condition in only 7.6 percent of the cases. However, upon review of the charts, 47.8 percent of the patients were found to have at least one nonpsychiatric condition known to be associated with depression; one patient had six such disorders. The frequencies of particular nonpsychiatric conditions found in this study are presented in Table 3. The use of drugs known to be associated with depression was found in 43.3 percent of the patients. While the charts can be expected to be complete in terms of medications taken by the patient, evidence of other nonpsychiatric conditions was often not available.

Table 4. Relationship Between Family History and Presence of Nonpsychiatric Disorder

Family History of Depression	Presence of at Least One Nonpsychiatric Disorder	
	Absent	Present
Negative	19	31
Positive	13	6
$\chi^2=5.15, df=1, P\leq.025$		

Table 5. Relationship Between Nonpsychiatric Disorder Recognition and the Number of Nonpsychiatric Disorders Present

	Number	
	1	>1
Not recognized	23	40
Recognized	10	2
Fisher's exact probability test, $df=1, P=.003$		

Hence, with that limitation in mind, the frequencies presented represent minimal numbers.

Statistical analysis revealed that, in those with a known family history, patients without any identifiable nonpsychiatric disorders more frequently had a family history of depression ($P \leq .025$ by chi-square test) as shown in Table 4. In addition, Table 5 demonstrates that an initial diagnosis recognizing a nonpsychiatric disorder associated with depression was more commonly made when only one nonpsychiatric disorder was found as opposed to more than one ($P = .003$ by Fisher's exact probability test).

Analysis of specific groups of nonpsychiatric conditions was conducted. Table 6 demonstrates that patients with endocrine disorders tended to be female ($P \leq .025$ by chi-square test). Their mean age of 44.4 years was significantly older than the 37.9 year mean for those without endocrine disorders ($P \leq .005$ by Student's t test; a test for homogeneity of variances showed that the variances were not homogeneous). This was expected be-

Table 6. Relationship Between Sex and Endocrine Disorders

	Presence of at Least One Endocrine Disorder	
	Present	Absent
Female	23	98
Male	1	35
$\chi^2=5.63, df=1, P\leq.025$		

cause of the large percentage of patients diagnosed as menopausal in the study population. However, Table 7 demonstrates that those with endocrine disorders were more likely to be recognized as such by the initial diagnosis ($P = .003$ by Fisher's exact probability test).

When marital status was analyzed in terms of the use of drugs possibly contributing to depression, it was found that those patients who suffered a marital loss (divorced, separated, or widowed) had a greater frequency of such drug usage ($P \leq .005$ by chi-square test) as shown in Table 8. This finding may be related to the high frequency of use of alcohol and major or minor tranquilizers that was noted in this group.

Discussion

The nature of the association between depression and nonpsychiatric disorders is unclear. Indeed, because depression and many of these nonpsychiatric disorders are common, they may simply coexist. However, though a cause-and-effect relationship between these medical disorders and depression has not been proven, bioamine abnormalities have been noted with estrogen, progesterone,⁶ opiate, and alcohol use³ as well as in vitamin B₆ deficiency.⁶ When depression is associated with a medical disorder, the psychiatric symptoms can precede or be the sole manifestation of the contributing disease.⁷ On the other hand, medical illness is the single most frequent precipitant of depression in the elderly.¹²

Though it has been reported that endocrine disease is the most common cause of psychiatric symptoms in women, drugs are also commonly as-

Table 7. Relationship Between Endocrine Disorders and Recognition of Nonpsychiatric Disorders

	Presence of at Least One Endocrine Disorder	
	Present	Absent
Not recognized	18	127
Recognized	6	6
Fisher's exact probability test, $df=1, P=.003$		

Table 8. Relationship Between Drug Use and Marital Status

	Drug Use	
	Present	Absent
Single	16	24
Married	23	48
Marital loss	29	17
$\chi^2=10.91, df=2, P\leq.005$		

sociated with depression, especially in the elderly. It has been claimed that from 2 to 3 percent of patients display psychiatric symptoms from the medications they take⁷; in fact, at least 200 drugs are known to be associated with depression, accounting for 3 percent of the prevalence of depression being related to drug ingestion.³ Hence, depression may be of iatrogenic origin. On the other hand, depressed patients may self-medicate themselves with alcohol, opiates, or tranquilizers. This may account for their association with depression and/or increase depressive symptomatology.

No matter what the nature of the association between depression and nonpsychiatric disorders is, there are implications to its management. Though it is true that antidepressant therapy can treat the neurovegetative symptoms of depression whatever the cause, the tricyclic medications are not without risk. Aside from their cardiotoxic effects, their suicidal potential is well known. A safer and more logical initial approach to depres-

sion associated with nonpsychiatric conditions is to treat the potentially contributing disorder. Removal of a possibly offending medication should be considered. Such an approach may result in reduction in depressive symptoms.

If recognition of this association has management implications, how sensitive are physicians to the recognition of these conditions? This study found that, although 47.8 percent of the patients had at least one associated condition, only 7.6 percent of these cases were recognized initially. That most of the patients recognized as such had only one nonpsychiatric condition in retrospect suggests that once one condition was recognized, the physician failed to search further. Apparently, the physicians in this study were more sensitive to endocrine disorders.

Once physicians are attuned to nonpsychiatric conditions known to be associated with depression, there are historical clues that can increase detection. Hall et al reported that most patients with "medically induced" psychiatric symptoms are between 40 and 60 years old (though 25 percent are under 30 years of age) and have a negative family history of psychiatric disease.⁷ In addition, from 70 to 80 percent of "medically induced" psychiatric symptoms have a recent—between six and nine months—clearly defined onset. Yet, 80 percent of the primary disorders can be recognized with a detailed evaluation.⁷

Based upon this study, physicians should suspect a nonpsychiatric disorder if the depressed patient lacks a family history of depression. Women and older patients should always be evaluated for endocrine disorders, and those patients suffering a marital loss (separation, death, or divorce) should be questioned for drug use, especially alcohol and major or minor tranquilizers. In general, a thorough drug history is essential in evaluating the depressed patient.

However, the retrospective nature of this study presents limitations. The lack of uniformity in diagnosis raises questions concerning identification of the sample for lack of sensitivity. But once diagnosed, the diagnostic accuracy is assumed to be high.¹³ In addition, the use of antidepressants and counseling prevents evaluation of the role of these associated disorders by resolution of the depression. Finally, the setting of this study may limit its generalizability.

It is concluded that in depressed patients, a

nonpsychiatric disorder possibly contributing to the depressive symptoms is commonly present. Nearly one half of those diagnosed as depressed were found to have an associated nonpsychiatric disorder, though few were recognized as such. Therefore, the physician must be alert to search for organic disease. Not only is such evaluation important to the possible health implications of the contributing disorder, but it may alter the treatment approach as well. Physician sensitivity to the presence of these nonpsychiatric disorders must be increased and a detailed evaluation of depressed patients encouraged.

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