

Managing medical and psychiatric comorbidities

Timothy Howell, MD, MA

The task of assessing and treating patients with combined medical and psychiatric problems can seem daunting, especially as patients become older, acquire chronic conditions, encounter acute illnesses, and take increasing numbers of medications. Add intercurrent social stressors as well as personality issues that affect how patients cope and this task can seem bewildering. But there has been significant progress made over the past few years in better appreciating how such factors may interact. Representative examples, which will be the focus of this article, include advances in the understanding of how vascular disease or diabetes and depression or cognitive impairment may interact and exacerbate each other. (For two other examples, epilepsy and end-stage renal disease, see the article by Bresnehan elsewhere in this issue.) In addition, evidence is emerging of how adequate treatment of depression may improve outcomes in vascular disease or diabetes, and vice versa. These significant advances in research at the interface of medicine and psychiatry are a source of valuable guidance.

Doctor Howell is an associate professor with the Department of Psychiatry and is the director of the Geriatric Psychiatry Fellowship Program at the University of Wisconsin-Madison.

Diagnostic Issues

The medical problems and medications that can cause psychiatric symptoms and syndromes are legion and the subject of entire books. For the purposes of this overview, the reader is referred to the accompanying table of physical disorders that can be associated with depression, anxiety, cognitive impairment (including delirium or dementia), and/or psychosis. (See Table 1.) The point to be emphasized here is that almost any medical problem or medication capable of causing a metabolic disturbance or direct effect on the central nervous system can present with psychiatric symptoms. The younger or older the patient is, the more likely this is to be the case. Patients with concomitant brain disease are also more vulnerable to such phenomena.

In addition to being aware of comorbid medical problems associated with psychiatric symptoms, one needs to have a higher index of suspicion if a patient's symptoms are more severe than expected, or are associated with a change in level of awareness. A change in personality, which may sometimes be subtle, is also reason for concern. Personality changes such as uncharacteristic lability of affect, aggression, suspiciousness, disinhibited behavior, or apathy, may go unnoticed by the patient, but can be picked up from collateral

sources of information such as family, friends, or others that have known the individual for some time. Additional clues of possible underlying or unrecognized medical problems include an unusual age for the onset of symptoms or the absence of anticipated family history.

One should also factor in how aging may influence the clinical presentation of an illness. For example, hyperthyroidism in a younger adult may generate symptoms of anxiety or hypomania, but can present in a geriatric patient atypically as depression or dementia (i.e. apathetic thyrotoxicosis). An additional caveat in working with patients with multiple medical problems and medications is the need to think multifactorially. Thus a patient with hypothyroidism, congestive heart failure, and severe osteoarthritis may develop a depressive disorder with several factors contributing to the mood disturbance—inadequate levels of thyroid hormone, disability due to dyspnea on exertion, and chronic pain associated with insomnia. Adequate treatment of the depressive disorder in such a context calls for each contributing factor to be identified and addressed. In turn, addressing each component of the depression will increase the likelihood of success in treating the comorbid medical problems. Therefore, by taking an ecological approach, one can avoid coming to

Table 1. Medical Conditions that Can Be Associated with Depression, Mania, Anxiety, Cognitive Impairment, and/or Psychosis

Neurodegenerative: Alzheimer disease, frontotemporal, Lewy body (D,A,C,P); Parkinson disease, Huntington disease (D,M,A,C,P),
Metabolic: electrolyte abnormality, hepatic or renal failure, anemia, porphyria (D,A,C,P); hypoxia, hypercarbia (D,A,C)
Endocrine: hypothyroidism(D,C,P); hyperthyroidism (D,M,A,C,P); hypoparathyroidism, hyperparathyroidism, Cushing's syndrome, Addison's disease (D,A,C,P); hypoglycemia (A,C), diabetes (D,A,C)
Cardiac: congestive heart failure (D, A,C); mitral valve prolapse, angina (A)
Normal pressure hydrocephalus (C,P)
Nutritional Deficiencies: B12, folate, niacin, thiamine (D,M,A,C,P)
CNS trauma (D,A,C,P)
Cancer (D,M,A,C,P)
Infection: CNS, sepsis, pneumonia, urinary tract (D,M,A,C,P)
Stroke (D,M,A,C,P)
Pulmonary embolus (A)
Seizures (D,A,C,P)
Immunological: lupus, sarcoidosis, CNS vasculitis (D,A,C,P)
Sleep apnea (D,C)
Toxicity: e.g. heavy metals (A,C,P), drugs (see Table 3)
Chronic pain (D,A)

Note: D=depression, M=mania, A=anxiety, C=cognitive impairment, P=psychosis.

premature closure in addressing the comorbidities, and identify—and then interrupt—vicious cycles whereby interacting medical and psychiatric problems exacerbate each other.

Treatment Issues

With the growing plethora of medications available for medical and psychiatric conditions, there has been a concomitant growth in awareness of the need to track how such medications can interact with

each other. Not only can medications enhance or interfere with each other's clinical efficacy, but they can also cause medical or psychiatric problems of their own through their interactions. Such interactions may be simply additive in nature, or due to pharmacokinetic and/or pharmacodynamic changes mediated by the cytochrome P450 enzyme system in the liver. The accompanying tables provide examples of some of the more clinically significant drug interactions of concern. (See Table 2.)

For example, of the selective serotonin reuptake inhibitors (SSRIs) paroxetine and fluoxetine, respectively, are more likely to interact with codeine (and thereby decrease its analgesic effects by interfering with its metabolism to morphine) or with beta-blockers (and thereby increase the likelihood of bradycardia or nightmares by elevating the serum levels of the beta-blockers), while sertraline and citalopram, respectively, are less likely to. One also needs to keep in mind the clinical rule of thumb that for a medication to reach a steady state in the body takes approximately five times the equivalent to that drug's half-life. Thus, for example, fluoxetine, and its active metabolite, norfluoxetine, with half lives of approximately two and eight days respectively, represent medications for which the onset of a significant drug interaction may be delayed by up to a few weeks. The interaction of drugs is a rapidly evolving area, and the reader is advised to stay abreast of current developments by checking periodically with a drug interaction Web site (e.g. www.medicine.iupui.edu/flockhart/) or subscribing to a drug interaction database that is updated regularly (e.g. www.micromedex.com/).

Beyond drug-drug interactions, potential drug-illness interactions also require careful consideration.

In addition to medications that can cause psychiatric symptoms (see Table 3), psychotropic medications themselves can have repercussions for coexisting medical problems. A recent survey of experts in geriatric psychiatry and geriatric medicine yielded a number of consensus recommendations. They suggested that, in general, clozapine, olanzapine, and conventional antipsychotics (especially low- and mid-potency) be avoided for patients with diabetes, dyslipidemia, or obesity. They recommended quetiapine as a first choice for patients with Parkinson's disease who required antipsychotic medication. They expressed a preference for avoiding the use of clozapine, ziprasidone, and conventional antipsychotics (especially low- and mid-potency) in patients with congestive heart failure or prolongation of the QTc interval on EKG. It was their consensus that risperidone, with quetiapine high second choice, was preferable in the context of cognitive impairment, diabetes, dyslipidemia, constipation, xerophthalmia, or xerostomia. These guidelines were qualified by a reminder that they were not to be used as a substitute for sound clinical judgment based upon the complexities of any specific individual patient.¹

Prognostic Issues

The presence of a psychiatric disorder may have an effect on the chances of a healthy individual developing a medical problem. Likewise, the patient with a medical illness who has a comorbid psychiatric problem may have a more guarded prognosis than one without the same mental illness. For example, in a recent evidence-based review of the relationship between depression and coronary artery disease (CAD), the presence of depression was determined to con-

fer a relative risk of 1.5-2.0 for the development of CAD in healthy individuals, and a relative risk of 1.5-2.5 for adverse cardiac events in patients with existing CAD. Identified behavioral links between depression and CAD include treatment adherence and lifestyle factors, as well as traditional risk factors such as smoking. Intriguingly, other depression-associated biological factors are implicated: alterations in the functioning of the autonomic nervous system and hypothalamic pituitary adrenal (HPA) axis, increased platelet activation (aggregation), endothelial dysfunction, and lowered heart rate variability.^{2,3} However, while there exists substantial evidence for a relationship between depression and CAD, there is still only marginal data based on prospective studies to support the efficacy of treating depression in improving clinical outcomes for CAD patients with depression.² Nonetheless, the results of large-scale clinical trials do suggest that the use of SSRIs may reduce adverse cardiac events in depressed patients with unstable angina or post-myocardial infarction. The inhibiting effects of SSRIs on platelet aggregation may also play a role in this context.⁴

Diabetes is another example of a medical illness that interacts in a multifactorial manner with psychiatric disorders. Patients with diabetes are at twice the risk for developing depression. In a recent meta-analysis of the prevalence of depression in adults with diabetes, the rates were 28% for women and 18% for men.⁵ Depression, in turn, can interfere with patients' efforts to manage their diabetes effectively. It also tends to be associated with hyperglycemia and with a higher risk for diabetic complications. Yet the rate of recognizing and treating depression appropriately in depressed diabetic patients is less than 25%.

Table 2. Examples of Potential Drug Interactions Mediated by the Cytochrome P450 System

	1A2	2C9/19	2D6	3A4
Inhibitors	fluvoxamine ciprofloxacin enoxacin mexiletene propafenone	valproate omeprazole fluoxetine fluvoxamine fluconazole ritonavir ticlopidine	ritonavir cimetidine fluoxetine paroxetine quinidine	grapefruit juice ketoconazole fluvoxamine nefazodone norfluoxetine ciprofloxacin erythromycin clarithromycin protease inhibitors methadone
Inducers	carbamazepine cigarette smoke broccoli	phenytoin barbiturates	carbamazepine	carbamazepine phenytoin
Substrates	caffeine clozapine fluvoxamine olanzapine tricyclics theophylline caffeine	barbiturates tricyclics fluvoxamine diazepam barbiturates warfarin glipizide glyburide	codeine fluoxetine paroxetine haloperidol risperidone tricyclics venlafaxine timolol metoprolol propranolol	protease inhibitors alprazolam fluvoxamine tricyclics nefazodone quetiapine carbamazepine ziprasidone cyclosporine mycins (some) estradiol statins (some)

The use of screening tools to facilitate the identification of depression in diabetic patients as well as utilization of a depression management approach, may improve outcomes (see the article by Halverson and Chan elsewhere in this issue). Thus far the data from controlled trials, although limited, show some promise that combined pharmacologic and psychological approaches are effective in improving glycemic control, overall functioning, and quality of life.⁶

Another area of increasing concern is the association of cognitive decline with Type II diabetes. With the combination of increasing numbers of older adults and rising levels of obesity in western societies, it is anticipated that the number of elderly with Type II diabetes will double over the next 20 years.⁷ It is well known that Type II diabetes is associated with higher risks for macrovascular disease (including CHD and stroke), as well as

microvascular disease (e.g. retinopathy, nephropathy, and peripheral neuropathy). It is becoming increasingly apparent that there may be an association between Type II diabetes and higher risk for mild cognitive impairment and dementia. Prospective data from the Epidemiology of Vascular Aging Study, for example, revealed that patients with diabetes had more than twice the risk for cognitive decline over a four-year period of follow-up.⁸ In a study of women with osteoporosis, over a period of three to six years, women with diabetes had a 74% increased risk for developing cognitive impairment, and that risk was proportional to the duration of the diabetes.⁹

The fact that prospective studies have demonstrated a 1.5 to 2.8 increase in the risk of vascular dementia in the context of diabetes comes as no surprise, given the strong link between Type II dia-

Table 3. Drugs Capable of Causing Psychiatric Symptoms: Depression, Mania, Anxiety, Cognitive Impairment, and/or Psychosis

Alcohol intoxication/withdrawal (D,A,C,P)
Analgesics, anti-inflammatory agents: narcotics, NSAIDs (D,A,C,P)
Anti-arrhythmics (D,A,C,P)
Antibiotics: e.g. gatifloxacin (D,A,C,P)
Anticholinergics (A,C,P)
Anticonvulsants (D,A,C,P)
Antidiarrheals: (A,C,P)
Antihistamines (A,C,P)
Antihypertensives: (D,A,C,P)
Antineoplastics: e.g. cisplatin (C,P)
Antitussives: e.g. dextromethorphan (M,C)
Antivirals: e.g. interferon (D,A,C,P)
Antidepressants: selective serotonin reuptake inhibitors (M,A), tricyclics (M,A,C,P)
Antipsychotics: atypical (D,M,A,C,P), typical (D,A,C,P)
Anti-Parkinsonians: dopaminergic (D,M,A,C,P)
Beta-blockers: (C,P)
Bronchodilators: theophylline, isoproterenol (A)
Cardiac drugs: calcium channel blockers, digoxin (D,A,C,P)
Cholinesterase inhibitors (D,A,C,P)
Decongestants: e.g. pseudoephedrine (A)
Diuretics: e.g. thiazides (D)
H2 blockers: e.g. cimetidine (D,M,C,P), ranitidine (C,P)
Hormones: steroids, thyroxine (D,M,A,C,P)
Lithium (A,C)
Organophosphates (A,C)
Sedatives, hypnotics, tranquilizers: (D,A,C,P)
Stimulants, caffeine (A,P)

Note: D=depression, M=mania, A=anxiety, C=cognitive impairment, P=psychosis.

betes and macrovascular disease. More intriguing is the fact that the same studies have revealed an approximately twofold increase in the risk of Alzheimer's disease in patients with diabetes.¹⁰ Both disorders are associated with amyloid deposition. Furthermore, advanced glycation end products have been demonstrated in the senile plaques and neurofibrillary tangles characteristic of Alzheimer's disease.¹¹ It may be, however, that Type II diabetes is associated with subclinical microvascular disease, which itself may cause cognitive impairment or which may act in synergy with Alzheimer's disease to accelerate the progression of cognitive decline. The cumulative effects of episodes of hypoglycemia, if severe and recurrent, have been associated with cognitive decline in children.⁷

Finally, in the last few years there has been heightened aware-

ness of the potential interactions between diabetes, schizophrenia, and antipsychotic medications. The prevalence of diabetes is higher in patients with schizophrenia than in the general population. A recent review concluded that a metabolic syndrome at the onset of schizophrenia (i.e. prior to treatment) as well as poor diet, lack of exercise, and high rates of smoking, may account for this trend. Additionally, antipsychotic medication may be associated with higher rates of food intake. Hence encouraging healthy changes in lifestyle may prove essential to improving the long-term outcomes of patients with schizophrenia.¹² The issue of associations between the newer atypical antipsychotics and glucose intolerance, diabetes mellitus, hyperlipidemia, and hyperleptinemia are controversial in the absence of rigorous prospective studies. A recent

ranking of the atypicals, based on currently available literature, rated the relative risk highest for clozapine and olanzapine, moderately high for quetiapine, and rather low for risperidone and ziprasidone.¹³ A similar review of the use of this class of medications with children and adolescents came up with similar rankings. The authors note that current published data suggests that the risk of weight gain was considerable with clozapine and olanzapine, moderate with risperidone and quetiapine, and low with ziprasidone and aripiprazole.

Conclusion


Clinical work with patients having multiple medical and psychiatric problems can be quite challenging for even very experienced medical professionals. But at the same time it can be very rewarding. Utilization of an ecological approach, one which tracks the interactions between medications, medical illnesses, psychiatric problems, personality styles, and social issues, can help to identify the ways in which an individual patient's various comorbid conditions interact. Such insights, with greater sensitivity and specificity for the unique aspects of each individual patient, can help busy clinicians avoid the hazard of premature closure in differential diagnosis and therapeutics. These insights can also help to identify and interrupt vicious cycles, which in turn may enhance the effectiveness of our clinical efforts.

References


1. Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Expert consensus panel for using antipsychotic drugs in older patients. using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004;65(Suppl 2):5-99.
2. Lett HS, Blumenthal JA, Babyak MA, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treat-

- ment. *Psychosom Med.* 2004; 66(3):305-315.
3. Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME. Coronary artery disease and depression. *Eur Heart J.* 2004;25(1):3-9.
 4. Jiang W, Krishnan RR. Should selective serotonin reuptake inhibitors be prescribed to all patients with ischemic heart disease? *Curr Psychiatry Rep.* 2004;6(3):202-209.
 5. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care.* 2001;24(6):1069-1078.
 6. Rubin RR, Ciechanowski P, Eggede LE, Lin EH, Lustman PJ. Recognizing and treating depression in patients with diabetes. *Curr Diab Rep.* 2004;4(2):119-125.
 7. Strachan MWJ. Cognitive decline and the older patient with diabetes. *Clinical Geriatrics.* 2002; 10(6):29-35.
 8. Fontbonne A, Berr C, Ducimetiere P, Alperovitch A. Changes in cognitive abilities over a four-year period are unfavorably affected in elderly diabetic subjects: results of the Epidemiology of Vascular Aging Study. *Diabetes Care.* 2001;24(2):366-370.
 9. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? study of Osteoporotic Fractures Research Group. *Arch Intern Med.* 2000;160(2):174-180.
 10. Ott A, Stolk RP, Hofman A, et al. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia.* 1996; 39(11):1392-1397.
 11. Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment, and dementia. *Diabet Med.* 1999;16(2):93-112.
 12. Peet M. Diet, diabetes and schizophrenia: review and hypothesis. *Br J Psychiatry Suppl.* 2004;47: S102-105.
 13. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs.* 2004;64(7):701-723.
 14. Stigler KA, Potenza MN, Posey DJ, McDougale CJ. Weight gain associated with atypical antipsychotic use in children and adolescents: prevalence, clinical relevance, and management. *Paediatr Drugs.* 2004;6(1):33-44.

They're Short,
missing teeth and
talk to
imaginary friends.
Obviously,
they need medical
attention.



It's a scientific fact that learning comes naturally to a young child. It's an unfortunate fact that cavities, colds and all kinds of 24-hour viruses do as well. Whether you're a doctor or a nurse, a dentist or an optometrist, a nutritionist or even a psychologist, we need you to donate your services for a few hours. With your help, we can make sure the bodies of our students are as healthy as their imaginations. To volunteer, call your local Head Start.

 **Nurture the future**
BE A HEAD START VOLUNTEER



TRANSCRIPTION

Toll-Free Phone Dictation
Handheld Recorders
HIPAA-compliant
voice file transfer

**Providing Individual
Attention and Superior
Transcription Since 1992**

*The right prescription
for your transcription*

*“Simply put, the best
transcription service I've had
in my 24 years of practice”*

Robert Hylland, M.D.
Muskegon, MI

**1-616-786-4665 info@qmedtranscription.com
www.qmedtranscription.com**