Key Words: evidence-based, comorbidity, clinical trials, medical illness, epidemiology, depression and medical illness

Evidence-Based Treatment of Psychiatric Disorders with Comorbid Medical Illnesses: The Need for Large Simple Clinical Trials

Warren D. Taylor, MD, P. Murali Doraiswamy, M.B.,B.S., and K. Ranga R. Krishnan, M.B.,B.S

Psychopharmacology Bulletin. *2007;40(4):5-11.*

When discussing psychiatric illnesses in the elderly, one cannot ignore coexisting medical problems. With aging, there is a rapid increase in the prevalence of medical disorders including cancer, Alzheimer's disease, stroke, heart disease, and arthritis. It is often these illnesses, not depression, anxiety or other psychiatric symptoms, which bring patients in to see their physician; however the interaction between psychiatric disorders and these illnesses have at best been poorly studied or at worst ignored. The reciprocal relationship between these illnesses is deserving of more intensive study, particularly examining how the treatment of one may influence or be influenced by the other.

The topic of medical illnesses coexisting with various psychiatric disorders, such as bipolar disorder, psychosis, anxiety, and addiction, is broad. It also varies with the psychiatric disorder in question. For this editorial, we will use depression, a common psychiatric disorder in the elderly, as an example.

Depression and Medical Illness

What is the association between depression and medical illness? Epidemiologic studies have demonstrated relationships between depression and cardiac disease,[1–5] diabetes,[6] cancer,[7,8] chronic pain,[9] HIV and AIDS,[10] and urinary incontinency,[11] among others. The coexistence of depression and these illnesses is critical as depression may increase the risk of having poorer disease control or adverse outcomes of these illnesses.[12–13] Interestingly, medical comorbidities overall do not appear to influence antidepressant treatment outcomes.[14–17] This would suggest that medical

Dr. Taylor is a clinical associate in the Division of Geriatric Psychiatry at the Duke Medical Center's Pain and Palliative Care Clinic in Durham, NC. Dr. Doraiswamy is chief of the Division of Biological Psychiatry and director of clinical trials and Dr. Krishnan is professor and chair of the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center in Durham, NC.

To whom correspondence should be addressed: Warren D. Taylor, MD, Duke University Medical Center, DUMC Box 3903, Durham, NC 27710; Phone: (919) 668-7887; Fax: (919) 681-7668; E-mail: Taylo066@mc.duke.edu

comorbidity should not be viewed as an impediment to antidepressant treatment, but the presence of untreated depression may worsen the impact of that disease on the patient.

The relationship between depression and medical disease is often reciprocal. For example, cardiovascular disease may contribute to depression by increasing the risk for subcortical cerebrovascular ischemic disease, which itself is associated with depression (Table 1).[18–21] This concept is the foundation behind the "vascular depression" hypothesis,[22–24] which proposes that late-life depression may be caused or exacerbated by cerebrovascular disease. Other hypotheses could be formulated to explain the association between depression and other medical illnesses.

PREVALENCE OF MEDICAL ILLNESS IN DEPRESSED POPULATIONS

The prevalence of both depression and medical comorbidity are dependent upon the population being sampled. For example, in studies of populations in long-term care facilities where residents have more severe medical illnesses, depressive symptoms may be seen in 30–40% of patients, with 12–16% meeting *DSM-IV* criteria for major depression.[25–27] For studies of community-dwelling elders, the same issue applies: from where are patients recruited?

A recent study examined the association between depression and medical comorbidity in an academic family medicine clinic.[28] Out of the 1997 patients who agreed to participate, 541 (29.7%) had high levels of depression or anxiety, defined as a score greater than 30 on the Duke Anxiety-Depression Scale (DUKE-AD[29]). Overall, they found that subjects reporting high levels of depression and anxiety also had high rates of medical illnesses (Table 2). In particular, subjects with depression were more likely to have diagnoses of headache, osteoarthritis, abdominal pain, and diabetes mellitus. Greater disability and pain appeared to be persistent indicators of high anxiety and depression

TABLE 1

POSSIBLE MECHANISMS UNDERLYING THE RELATIONSHIP BETWEEN DEPRESSION AND CORONARY HEART DISEASE

- More severe cardiac disease is more likely to be accompanied by depression[36]
- Poor adherence to medical treatment regimens[37,38]
- Sympathetic and neuroendicrine dysfunction[39,40]
- Low heart rate variability, which may represent autonomic dysfunction[41]
- Changes in QTc interval post-myocardial infarction[42]
- Increase in platelet activation and aggregation[43,44]
- Immune dysfunction and increased inflammatory processes[45]

Taylor, Doraiswamy, and Krishnan. *Psychopharmacology Bulletin*. Vol. 40. No. 4. 2007.

TABLE 2

PREVALENCE OF COMMON MEDICAL ILLNESS IN PRIMARY CARE PATIENTS WITH DEPRESSION SYMPTOMS

DIAGNOSIS	PREVALENCE (N = 541)
Asthma	2.8 (15)
Diabetes Mellitus	8.5 (46)
Coronary Heart Disease	2.6 (14)
Hypertension	14.8 (80)
Osteoarthritis	2.8 (15)
Gastroesophageal Reflux	2.4 (13)
Pain Syndromes	
Abdominal Pain	4.1 (22)
Back Pain	5.4 (29)
Headache	4.4 (24)
Joint Pain	4.4 (24)
Limb Pain	2.8 (15)

Data reported as percentage (number reporting illness[28]).

Taylor, Doraiswamy, and Krishnan. *Psychopharmacology Bulletin*. Vol. 40. No. 4. 2007.

TABLE 3

PREVALENCE OF SELF-REPORT OF MEDICAL ILLNESS IN A GROUP OF DEPRESSED ELDERLY SUBJECTS PARTICIPATING IN A TERTIARY CARE DEPRESSION RESEARCH STUDY

DIAGNOSIS	PREVALENCE (N = 361)
Asthma	7.2 (26)
Diabetes Mellitus	11.9 (43)
Heart Problems	23.5 (85)
Hypertension	44.3 (160)
Arthritis	59.0 (213)
Cancer (All types)	7.8 (28)
Emphysema or Chronic Bronchitis	7.8 (28)
Gastrointestinal Ulcers	6.9 (25)
Hardening of the arteries	10.8 (39)

Data reported as percentage (number reporting illness).

Taylor, Doraiswamy, and Krishnan. *Psychopharmacology Bulletin*. Vol. 40. No. 4. 2007.

symptom levels after controlling for other variables.

In contrast, we examined the prevalence of medical illnesses in a cohort of 361 depressed elderly subjects participating in a longitudinal research study of late-life depression in a tertiary care academic medical center. Medical comorbidity was measured by a self-report questionnaire asking about the presence of several medical conditions derived from questions included in the NIMH Epidemiological Catchment Area program.[30]

We found high rates of illness in this population (Table 3). In particular, arthritis (59%), hypertension (44%), and cardiovascular disease (asked as "heart trouble," 23%) were particularly common in this group. Overall, this group was more medically ill than was found when depressive symptoms were examined in a primary care setting. Part of the difference may have been due to age: the primary care study examined patients spanning the strata of age groups, while the longitudinal depression study focused on elderly patients, aged 60 years and older. Regardless, this shows that medical illnesses are quite common in depressed populations.

WHAT DOES THE EVIDENCE TELL US ABOUT ANTIDEPRESSANT THERAPY IN MEDICALLY ILL PATIENTS?

Fortunately most evidence suggests that the coexistence of medical illnesses does not influence antidepressant treatment outcomes.[14–17] In other words, antidepressant treatments can still be effective in medica lly ill populations. However, there is only limited research demonstrating safety of antidepressant agents in medically ill populations or how successful antidepressant treatment may impact medical outcomes.

Some of the best evidence we have in these areas is in depression and cardiac disease, specifically the ENRICHD (Enhancing Recovery in Coronary Heart Disease) and SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) studies. While the ENRICHD study examined a cognitive-behavioral therapy intervention,[31] SADHART examined sertraline in the treatment of post-myocardial infarction. The SADHART trial concluded that sertraline treatment is safe and effective in this population[32] and is associated with improved quality of life after hospitalization.[33] Moreover, data from this study has resulted in an improved understanding of platelet activation in patients with depression and coronary heart disease.[34] Similar trials are ongoing in other disease states, such as a study of sertraline in the prevention of depression in stroke patients (the SADBRAIN study).

But are these studies sufficient? Often studies examining cardiac outcomes examine extremely large numbers of subjects. For example, a study of clopidogrel as adjunctive therapy to aspirin in patients with unstable angina examined over 12,000 subjects,[35] a sizeable difference from the 369 subjects examined in the SADHART trial or even the 2481 patients examined in the ENRICHD study. Such larger numbers of subjects may be necessary to detect rare adverse events that occur with antidepressant treatment in these medically ill populations.

Unfortunately, we cannot glean much knowledge from past antidepressant trials. Most efficacy studies have an extensive list of exclusion criteria, some of the more com m on ones are detailed in Table 4.

TABLE 4

COMMON EXCLUSION CRITERIA IN ANTIDEPRESSANT CINICAL TRIALS

- Cognitive impairment (typically a Mini-Mental State Exam score <24)
- Suicide risk
- Serious/unstable medical disorders
- Seizure disorders
- Other psychiatric diagnoses other than that being studied. For depression, this may include dysthymia, addictions, personality disorders, anxiety disorders, or psychotic disorders including psychotic depression
- Prior nonresponse to treatment

List drawn from a review of the two largest published clinical trials of selective serotonin reuptake inhibitors in depressed elderly patients[46,47] and a meta-analysis of exclusion criteria used in depression trials in younger populations.[48]

Taylor, Doraiswamy, and Krishnan. *Psychopharmacology Bulletin*. Vol. 40. No. 4. 2007.

Unfortunately this list excludes a large number of patients seen in dinical practice! There has been a trend towards greater indusion of subjects with coexisting medical illnesses such as stable hypertension or diabetes. Although such indusion may provide some safety and efficacy data of the use of antidepressants in those populations, it does not provide information for antidepressant treatment in more serious illnesses such as unstable angina, myocardial infarction, or stroke.

WHERE DO WE GO FROM HERE?

We know that depression and medical illnesses are comorbid and we know that they can have reciprocal relationships. We need better data on safety and effectiveness of antidepressants in patient populations at high risk to become depressed (such as post-stroke patients) and in populations where depression increases medical morbidity and mortality (such as in people who are post-myocardial infarction, or have congestive heart failure). Data on antidepressant treatment and outcomes of chronic illnesses, such as diabetes mellitus and hypertension, are also urgently needed.

Studies should follow the example set by the large cardiology studies. Large, simple, more indusive effectiveness studies are critically important for these populations. Currently there is a great need for antidepressant treatment with little evidence to support the safety or effectiveness of our interventions. To provide the safest and most effective treatment for our patients, this needs to change.

DISCLOSURE

Dr. Taylor has received honoraria from Pfizer, Inc. and Wyeth. He has also served as a speaker for Janssen Pharmaceutica. ✤

REFERENCES

1. Carney RM, Rich WM, Tevelde A, Saini J, Clark K, Jaffe AS. Major depressive disorder in coronary artery disease. *Am J Cardiol*. 1987;60:1273-5.
2. Gonzalez MB, Snyderman TB, Colket JT, et al. Depression in patients with coronary artery disease. *Depression*. 1996;4:57-62.
3. Forrester AW, Lipsey JR, Teitelbaum ML, DePaulo JR, Andrzejewski PL. Depression following myocardial infarction. *Int J Psychiatry Med*. 1992;22:33-46.
4. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA*. 1993;270:1819-25.
5. Jiang W, Alexander J, Christopher E, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med*. 2001;161:1849-56.
6. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24:1069-78.
7. Craig TJ, Abeloff MD. Psychiatric symptomatology among hospitalized cancer patients. *Am J Psychiatry*. 1974;131:1323-7.
8. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. *JAMA*. 1983;249:751-7.
9. Campbell LC, Clauw DJ, Keefe FJ. Persistent pain and depression: a biopsychosocial perspective. *Biol Psychiatry*. 2003;54:399-409.
10. Penzak SR, Reddy YS, Grimsley SR. Depression in patients with HIV infection. *Am J Health Syst Pharm*. 2000;57:376-89.
11. Nygaard I, Turvey C, Burns TL, Crischilles E, Wallace R. Urinary incontinence and depression in middle-aged United States women. *Obstet Gynecol*. 2003;101:149-56.
12. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med*. 2001;63:619-30.
13. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care*. 2000;23:934-42.
14. Krishnan KRR, Doraiswamy PM, Clary CM. Clinical and treatment response characteristics of late-life depression associated with vascular disease: a pooled analysis of two multicenter trials with sertraline. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001;25:347-51.
15. Krishnan KRR. Comorbidity and depression treatment. *Biol Psychiatry*. 2003;53:701-6.
16. Miller MD, Lenze EJ, Dew MA, et al. Effects of cerebrovascular risk factors on depression treatment outcomes in later life. *Am J Geriatr Psychiatry*. 2002;10:592-8.
17. Gill D, Hatcher S. Antidepressants for depression in medical illness. Cochrane Database Syst Rev. 2003(3).
18. Krishnan KRR, Goli V, Ellinwood EH, France RD, Blazer DZ, Nemeroff CB. Leukoencephalopathy in patients diagnosed as major depressive. *Biol Psychiatry*. 1988;1988:519-22.
19. Taylor WD, Steffens DC, MacFall JR, et al. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry*. 2003;60:1090-6.
20. Coffey CE, Wilkinson WE, Weiner RD, et al. Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. *Arch Gen Psychiatry*. 1993;50(1):7-16.
21. Greenwald BS, Kramer-Ginsberg E, Krishnan KRR, Ashtari M, Aupperle PM, Patel M. MRI signal hyperintensities in geriatric depression. *Am J Psychiatry*. 1996;153:1212-5.
22. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-22.
23. Krishnan KRR, McDonald WM. Arteriosclerotic depression. *Med Hypotheses*. 1995;44:111-5.
24. Krishnan KRR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry*. 1997;154(4):497-501.
25. Tariot PN, Podgorski CA, Blazina L, Leibovici A. Mental disorders in the nursing home: another perspective. *Am J Psychiatry*. 1993;150:1063-9.
26. Rovner BW, German PS, Brant LJ, Clark R, Burton L, Folstein MF. Depression and mortality in nursing homes. *JAMA*. 1991;265:993-6.
27. Parmelee PA, Katz IR, Lawton MP. Incidence of depression in long-term care settings. *J Gerontol*. 1992;47:M189-M196.

28. Wu LR, Parkerson GRJ, Doraiswamy PM. Health perception, pain and disability as correlates of anxiety and depression symptoms in primary care patients. *J Am Board Fam Pract*. 2002;15:183-90.
29. Parkerson GRJ, Broadhead WE. Screening for anxiety and depression in primary care with the Duke Anxiety-Depression scale. *Fam Med*. 1997;29:177-81.
30. Regier DA, Myers JK, Kramer M, et al. The NIMH Epidemiologic Catchment Area program: historical context, major objectives, and study population characteristics. *Arch Gen Psychiatry*. 1984;41:934-41.
31. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289:3106-16.
32. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701-9.
33. Swenson JR, O'Connor CM, Barton D, et al. Influence of depression and effect of treatment with sertraline on quality of life after hospitalization for acute coronary syndrome. *Am J Cardiol*. 2003;92:1271-6.
34. Serebruany VL, Glassman AH, Malinin AI, et al. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation*. 2003;108:939-44.
35. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation*. 2003;108:1682-7.
36. Carney RM, Freedland KE, Rich MW, Jaffe AS. Depression as a risk factor for cardiac events in established coronary heart disease: A review of possible mechanisms. *Ann Behav Med*. 1995;17:142-9.
37. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol*. 1995;14:88-90.
38. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160:2101-7.
39. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Arch Gen Psychiatry*. 1998;55:580-92.
40. Jiang W, Krishnan KR, O'Connor CM. Depression and heart disease: evidence of a link, and its therapeutic implications. *CNS Drugs*. 2002;16:111-27.
41. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *Am J Cardiol*. 1995;76:562-4.
42. Carney RM, Freedland KE, Stein PK, et al. Effects of depression on QT interval variability after myocardial infarction. *Psychosom Med*. 2003;65:177-80.
43. Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and B-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry*. 1997;42:290-5.
44. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. *Am J Psychiatry*. 1996;153:1313-7.
45. Appels A, Bar FW, Bar J, Bruggeman C, de Baets M. Inflammation, depressive symptomatology, and coronary artery disease. *Psychosom Med*. 2000;62:601-5.
46. Schneider LS, Nelson JC, Clary CM, et al. An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. *Am J Psychiatry*. 2003; 60:1277-85.
47. Tollefson GD, Bosomworth JC, Heiligenstein JH, Potvin JH, Holman S. A double-blind, placebo-controlled dinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. *Int Psychogeriatr*. 1995;7:89-104.
48. Posternak MA, Zimmerman M, Keitner GI, Miller IW. A reevaluation of the exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry*. 2002;159:191-200.