

Treatment of Depression and Anxiety with Medical Co-Morbidity

Charles DeBattista, DMH, MD
Associate Professor of Psychiatry
Director: Depression Research Clinic
Stanford University

Comorbidity of Anxiety and Depression

85% of Patients With Depression Experience Significant Symptoms of Anxiety

Comorbid Depression Symptoms or MDD Occur in up to 90% of Patients With Anxiety Disorders

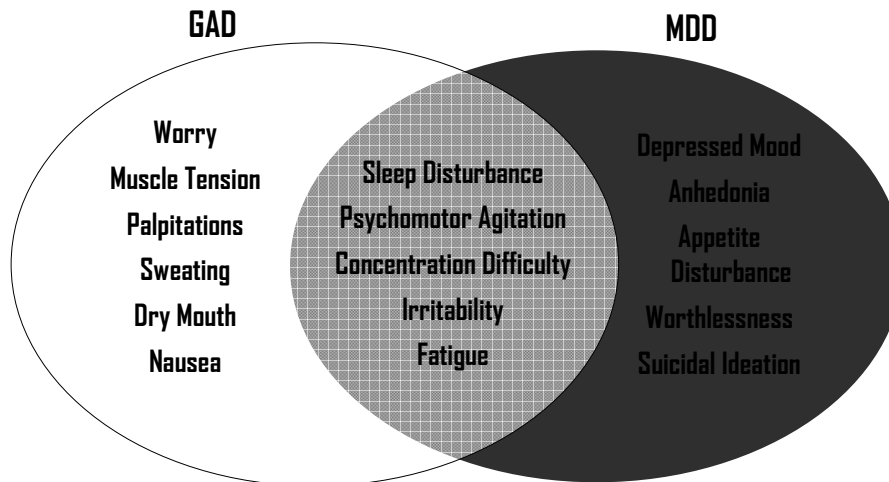
Coexisting Anxiety in Depressed Patients Is Associated With:

- Increased symptom severity
- More chronic course
- Greater medical co-morbidity
- Poorer outcome

Gorman JM (1996), *Depress Anxiety* 4(4):160-168

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Depression and GAD Symptoms Overlap



Balenger JC et al. (2001), Prim Care Companion J Clin Psychiatry 3(2):44-52; Lydiard RB (1991), J Clin Psychiatry 52(suppl):48-54; APA (2000), Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision. Washington, D.C.: American Psychiatric Publishing, Inc.; Liebowitz MR et al. (1990), J Clin Psychopharmacol 10(3 suppl):61S-66S

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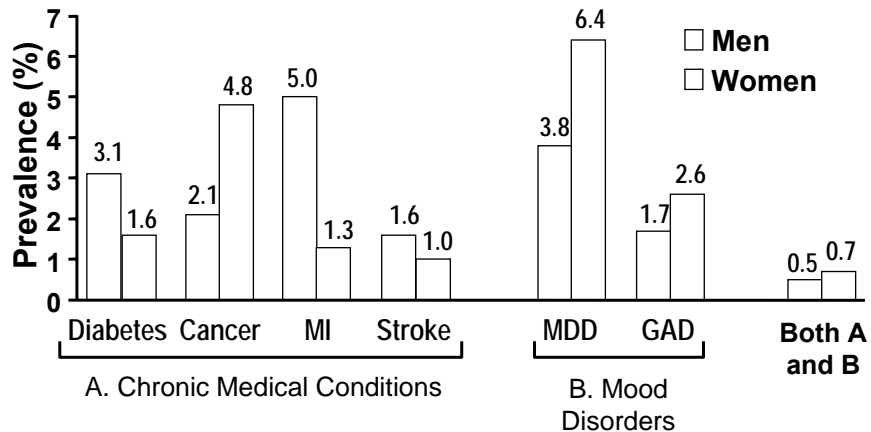
Functional Impact of Chronic Medical Conditions and Mood Disorders

- Depressive and anxiety disorders have a profound impact on functional health that is independent of chronic medical illness
- The degree of physical functional impairment associated with mood disorders was of equivalent magnitude to that associated with the presence of chronic medical conditions or with being some **12 years older**
- Chronic anxiety is associated with physical health limitations in excess of those associated with chronic depression or any of the physical health conditions considered except for stroke

Norfolk cohort of the European Prospective Investigation into Cancer (Epic-Norfolk, N=20,921) who completed the Health and Life Experiences Questionnaire; Surtees PG et al. (2003), Br J Psychiatry 183:299-303

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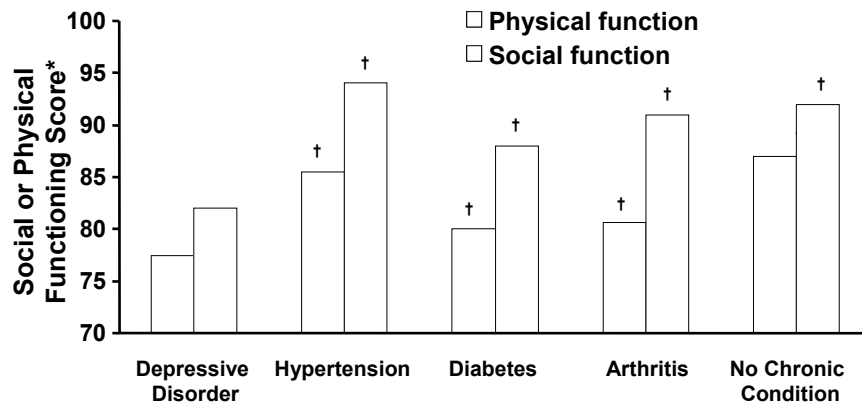
U.K. Functional Impact of Chronic Medical Conditions and Mood Disorders



Norfolk cohort of the European Prospective Investigation into Cancer (Epic-Norfolk, N=20,921) who completed the Health and Life Experiences Questionnaire; Surtees PG et al. (2003), Br J Psychiatry 183:299-303

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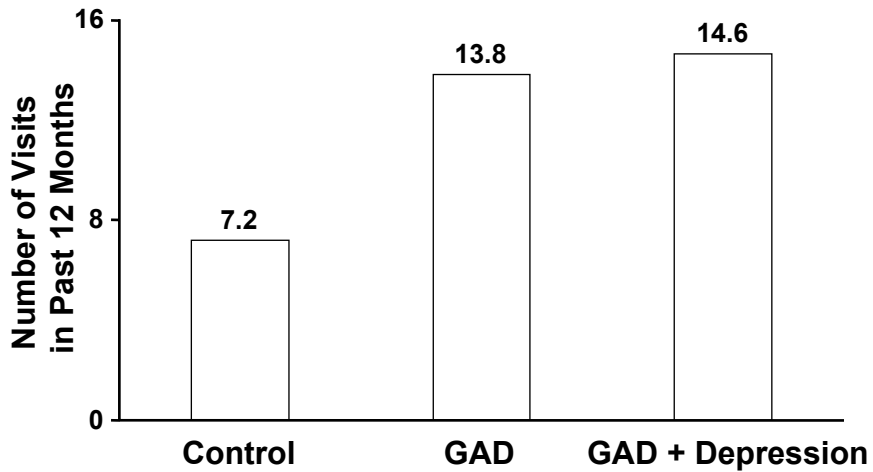
Physical and Social Functioning in Patients With Depressive Disorders



*Score of 100 = perfect functioning; [†]p<0.05 vs. depressive disorder; Wells KB et al. (1989), JAMA 262(7):914-919

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Increased Utilization of Primary Care in GAD

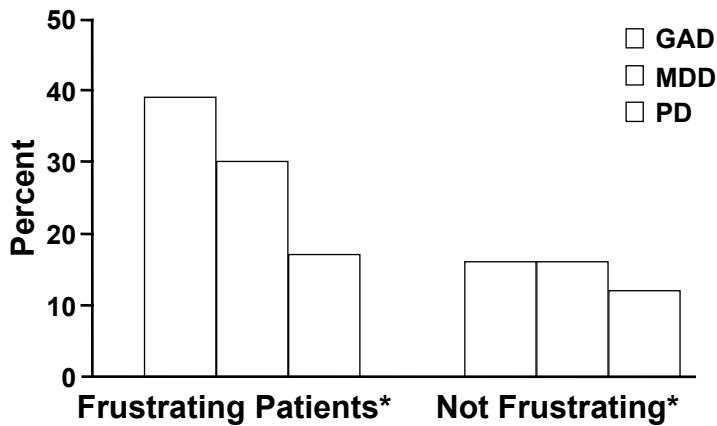


Wittchen HU (2002), *Depress Anxiety* 16(4):162-171

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MDD and GAD Among High Utilizers of Primary Care (ERD)

Frustrating Patients Had Higher Rates of Somatization and GAD



*As viewed by physicians; Lin EH et al. (1991), *J Gen Intern Med* 6(3):241-246

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How Depression and Anxiety May Be Mismatched Treating the Symptoms, Not the Syndrome

- 66% undiagnosed anxious and depressed patients made >6 visits/year to primary care physicians for somatic complaints
- Multiple agents used to treat symptoms, not syndrome, unnecessary consultations and hospitalizations
- Overuse of anxiolytics/hypnotics/analgesics/ narcotics

Katon W et al. (1997), Manag Care Interface 10(11):88-94; Pearson SD et al. (1999), J Gen Intern Med 14(8):461-468; Katon W, Sullivan MD (1990), J Clin Psychiatry 51(suppl):3-11

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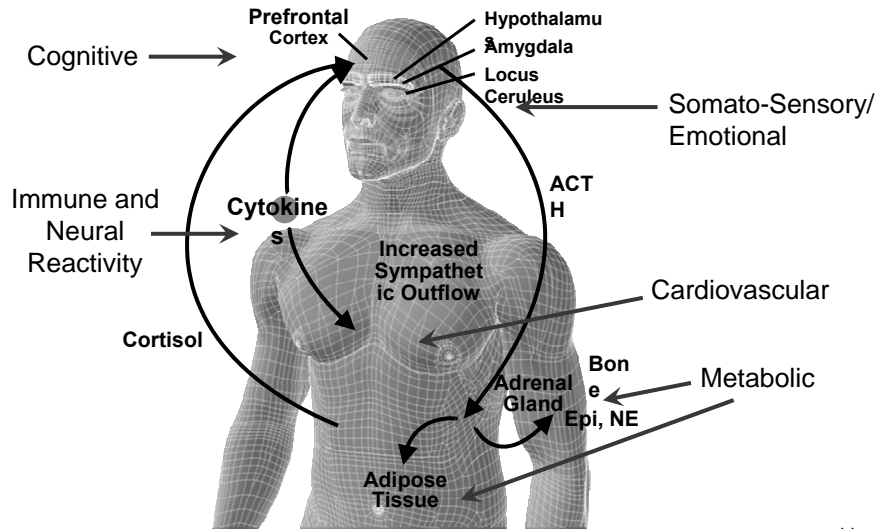
Consequences of Depression/Anxiety Comorbidity

- More severe/chronic anxiety disorders
- Greater social and vocational impairment
- Higher rates of alcohol/substance abuse
- Increased risk of suicide
- Poorer response to acute and long-term treatment

Lydiard RB, Brawman-Mintzer O (1998), J Clin Psychiatry 59(suppl 18):10-17

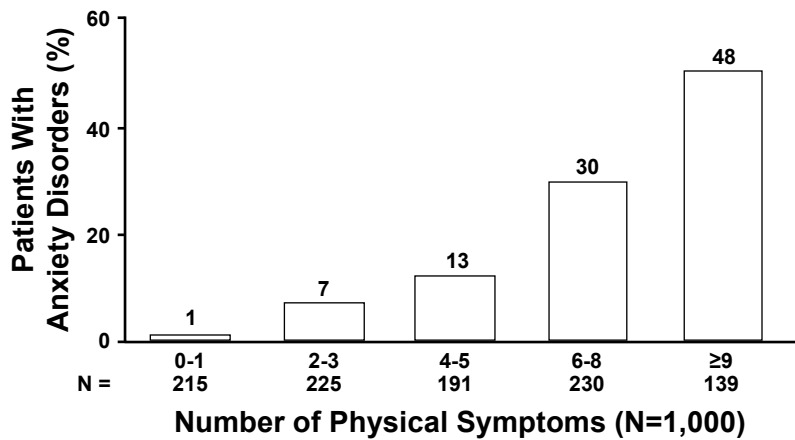
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Anxiety, Depression and Stress: Brain and Body Affected



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Number of Unexplained Physical Symptoms vs. Prevalence of Anxiety Disorders

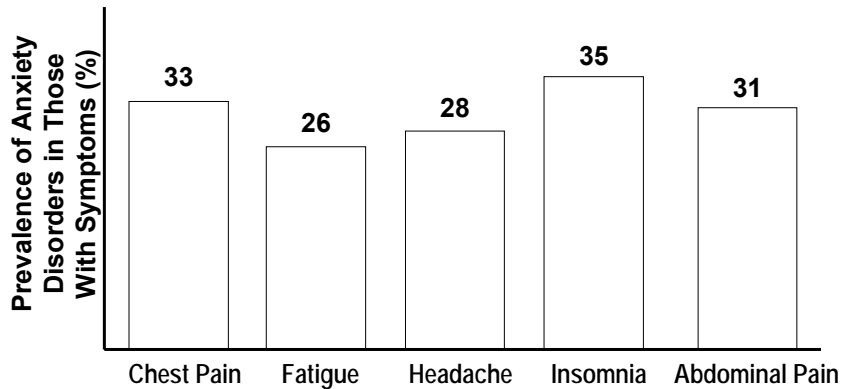


Kroenke K et al. (1994), Arch Fam Med 3(9):774-779

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Somatic Presentation of Anxiety Disorders

1,000 Patients at 4 Primary Care Clinics

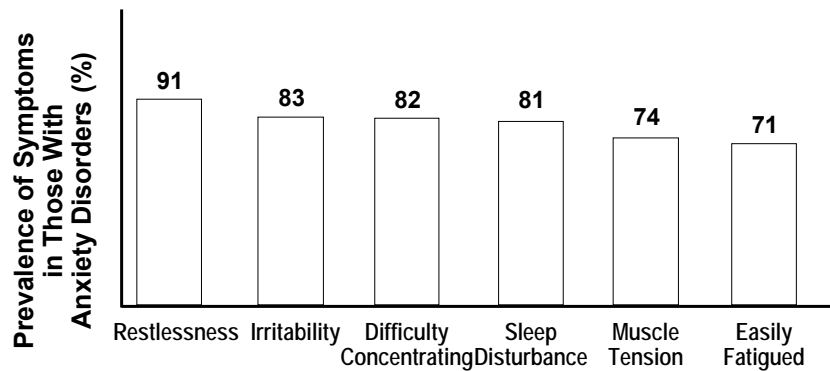


Kroenke K et al. (1994), Arch Fam Med 3(9):774-779; Weisberg R et al. (2004), Presented at the 24th Annual Meeting of the Anxiety Disorders Association of America. Miami; March 11-14

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Somatic Presentation of Anxiety Disorders (Cont.)

Primary Care Anxiety Project



Kroenke K et al. (1994), Arch Fam Med 3(9):774-779; Weisberg R et al. (2004), Presented at the 24th Annual Meeting of the Anxiety Disorders Association of America. Miami; March 11-14

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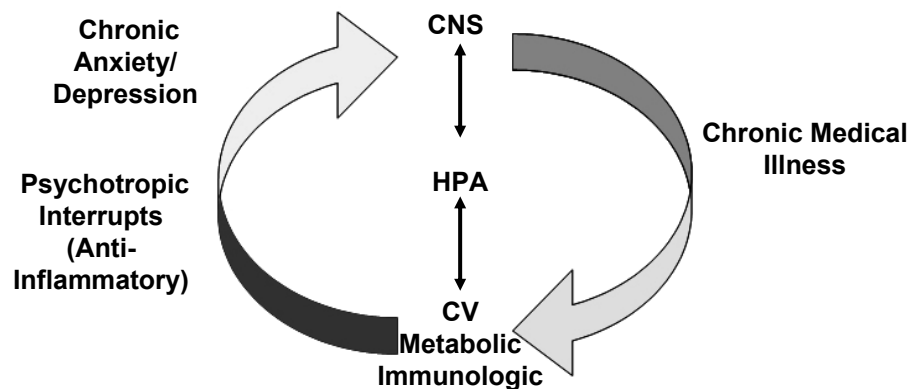
Depression and Comorbid Medical Illness

- Depression presents frequently in association with a chronic medical illness in the general population
- Presence of comorbid depression is predictive of worse outcomes of medical illness and increased mortality

Goodnick PJ, Hernandez M (2000), *Expert Opin Pharmacother* 1(17):1367-1384; Iosifescu DV et al. (2004), *Curr Psychiatry Rep* 6(3):193-201

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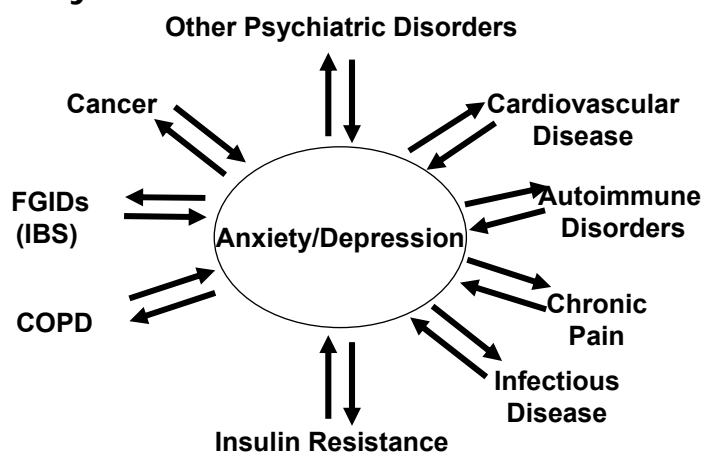
Medical Illness ↔ Anxiety/Depression Proinflammatory Chronicity Cycle



Kiecolt-Glaser JK et al. (2002), *Psychosom Med* 64(1):15-28; Kenis G, Maes M (2002), *Int J Neuropsychopharmacol* 5(4):401-412

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Anxiety/Depression: Comorbidity with Psychiatric and Medical Disorders



FGID = functional GI disorders; IBS = irritable bowel syndrome; Kroenke K (2003), *Int J Methods Psychiatr Res* 12(1):34-43; Folks DG (2004), *Curr Psychiatry Rep* 6(3):210-215; Mikkelsen RL et al. (2004), *Nord J Psychiatry* 58(1):65-70; Krueger RF et al. (2004), *Adv Psychosom Med* 25:63-77; Cruess DG et al. (2003), *CNS Spectr* 8(1):52-58; Iosifescu DV et al. (2004), *Curr Psychiatry Rep* 6(3):193-201; Parker JC, Wright GE (1995), *Arthritis Care Res* 8(4):279-283

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Medical Comorbidity

- 262 DSM-III-R-diagnosed probands with panic or GAD
- After controlling for gender, comorbid substance abuse/dependence and/or depression, patients with a lifetime anxiety disorder reported higher rates of:
 - Cardiac disorders (OR=4.6)
 - Hypertension (OR=2.4)
 - Gastrointestinal problems (OR=2.4)
 - Genitourinary disorders (OR=3.5)
 - Migraine (OR=5.0)
- Individuals presenting with anxiety disorders or medical illness need therefore to be evaluated carefully for comorbidity

Harter MC et al. (2003), *Eur Arch Psychiatry Clin Neurosci* 253(6):313-20

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Common Physical Conditions and Association of GAD

	% of Population With Condition	Impairment Days in Millions	Odds Ratio (GAD)
Hypertension	8.1	109	1.8*
Arthritis	6.5	142	2.0*
Asthma	5.3	107	2.7*
Ulcers	2.3	93	4.2*
Other GI	3.1	4.0	2.3*

*p=0.05; National Comorbidity Survey (unpublished data)

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GAD Dyslipidemia

- 40 patients with both GAD and MDD, 27 with MDD only, 26 with GAD only and 24 healthy control participants
 - Patients with both GAD and MDD have increased serum cholesterol, triglycerides and LDL-C, and reduced HDL-C levels
 - These patients may have a greater risk of mortality from coronary artery disease (CAD)

Sevincok L et al. (2001), Can J Psychiatry 46(1):68-71

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Anxiety/Depression Predicts CAD

- French nationwide power company: men aged 31-55 who developed ischemic heart disease from 1993 through 1997 (N=660 matched by age to 10 controls per case)
- Conclusion: depressive and anxiety disorders that lead to absenteeism were associated with an increased risk of ischemic heart disease in the 3 years thereafter, especially when depression and anxiety were severe and chronic (this association is independent of socioeconomic status)

Allonier C et al. (2004), Int J Epidemiol 33(4):779-786

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Depression and MI

- 1,551 individuals **without** heart trouble at baseline were studied from 1981-1994
- 444 individuals had a history of major depression or dysthymia at baseline
- Patients with a history of depressive disorders had a **5-fold** increased risk of cardiac mortality independent of other coronary risk factors

Pratt LA et al. (1996), Circulation 94(12):3123-3129

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Depression Worsened Many General Medical Conditions

Population	Increased Morbidity	Increased Mortality
General population ¹	✓	✓
Diabetes mellitus ^{2,3}	✓	-
Post-MI ^{4,5}	✓	✓
Congestive heart failure ^{6,7}	✓	✓
Poststroke ^{8,9}	✓	✓
Nursing home patients ^{10,11}	✓	✓

¹Murphy JM et al. (1987), Arch Gen Psychiatry 44(5):473-480; ²Lustman PJ et al. (2000), Diabetes Care 23(7):934-942; ³de Groot M et al. (2001), Psychosom Med 63(4):619-630; ⁴Frasure-Smith N et al. (1993), JAMA 270(15):1819-1825; ⁵Penninx BW et al. (2001), Arch Gen Psychiatry 58(3):221-227; ⁶Jiang W et al. (2001), Arch Intern Med 161(15):1849-1856; ⁷Vaccarino V et al. (2001), J Am Coll Cardiol 38(1):199-205; ⁸Pohjasvaara T et al. (2001), Eur J Neurol 8(4):315-319; ⁹Everson SA et al. (1998), Arch Intern Med 158(10):1133-1138; ¹⁰Parmelee PA et al. (1992), J Gerontol 47(6):M189-M196; ¹¹Rovner BW et al. (1991), JAMA 265(8):993-996

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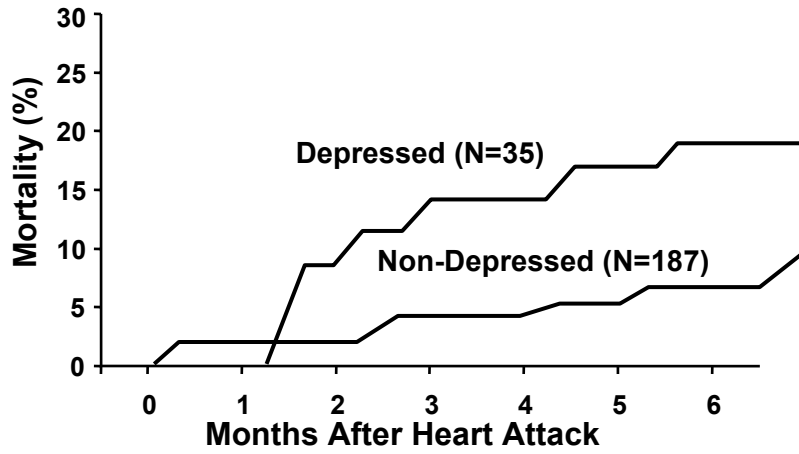
Major Depression and Cardiac Disease

- Prevalence: about 1/3 of acute post-MI patients are depressed
- Depression is a strong independent predictor of negative outcome in patients with CAD

¹Frasure-Smith N et al. (1993), JAMA 270(15):1819-1825; ²Penninx BW et al. (2001), Arch Gen Psychiatry 58(3):221-227; ³Jiang W et al. (2001), Arch Intern Med 161(15):1849-1856; ⁴Vaccarino V et al. (2001), J Am Coll Cardiol 38(1):199-205

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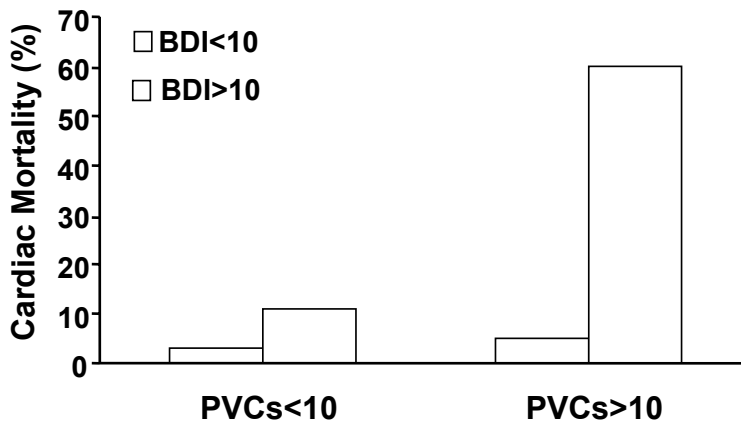
Cumulative Mortality for Patients with and without Depression After Heart Attack



Frasure-Smith N et al. (1993), JAMA 270(15):1819-1825

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PVCs and 18-Month Mortality

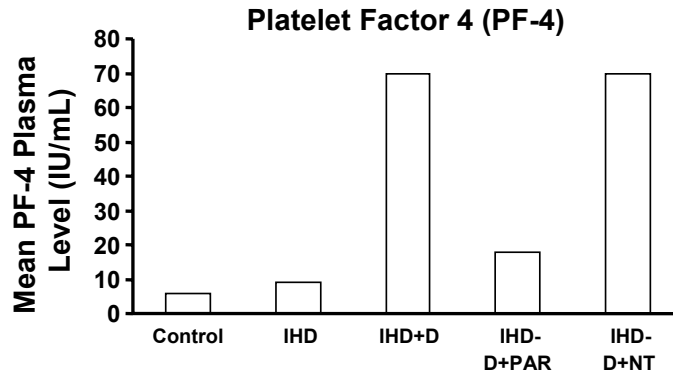


PVC = premature ventricular contraction; Frasure-Smith N et al. (1993), JAMA 270(15):1819-1825

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Platelet Activation

Ischemic Heart Disease and Depression

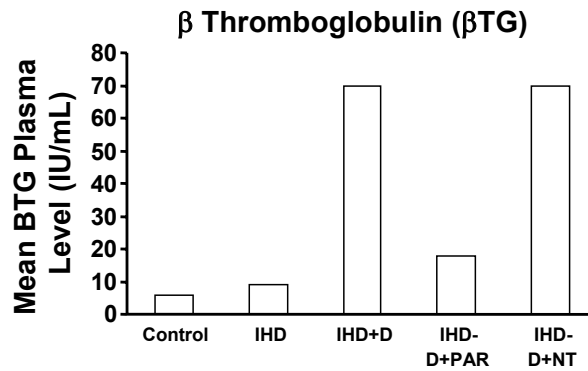


IHD = ischemic heart disease; D = depression; NT = nortriptyline (Aventyl, Pamelor); PAR = paroxetine (Paxil); Laghrissi-Thode F et al. (1997), *Biol Psychiatry* 42(4):290-295; Pollock BG et al. (2000), *J Clin Psychopharmacol* 20(2):137-140

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Platelet Activation (Cont.)

Ischemic Heart Disease and Depression



Laghrissi-Thode F et al. (1997), *Biol Psychiatry* 42(4):290-295; Pollock BG et al. (2000), *J Clin Psychopharmacol* 20(2):137-40

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Depression/Anxiety-Enhancing Risk Post-MI

- Increased risk of arrhythmias/sudden cardiac death
- Increased platelet aggregation
- Alterations in lipid metabolism
- Decreased adherence to lifestyle changes
 - E.g., cigarette cessation
- Decreased adherence to medical regimen

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Association Between Anxiety Disorder and Cerebrovascular Disease

- Saskatchewan health databases
 - Annual incidence of specified medical conditions in patients with anxiety disorders and in control subjects over a 10-year period
 - The anxiety cohort had a 2x higher relative risk of cerebrovascular disease as well as significantly higher rates of:
 - Atherosclerosis
 - Ischemic heart disease
 - Gastrointestinal disorders
 - Hypertension
 - Respiratory diseases

Bowen RC et al. (2000), Can J Psychiatry 45(5):459-464

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Depression as a Predictor of Stroke

- 2,812 noninstitutionalized elderly people
- Elevated Center for Epidemiologic Studies Depression (CES-D) scale scores were a significant predictor of stroke
- Depression may be related to other predictors of stroke

Colantonia A et al. (1992), Am J Epidemiol 136(7):884-894

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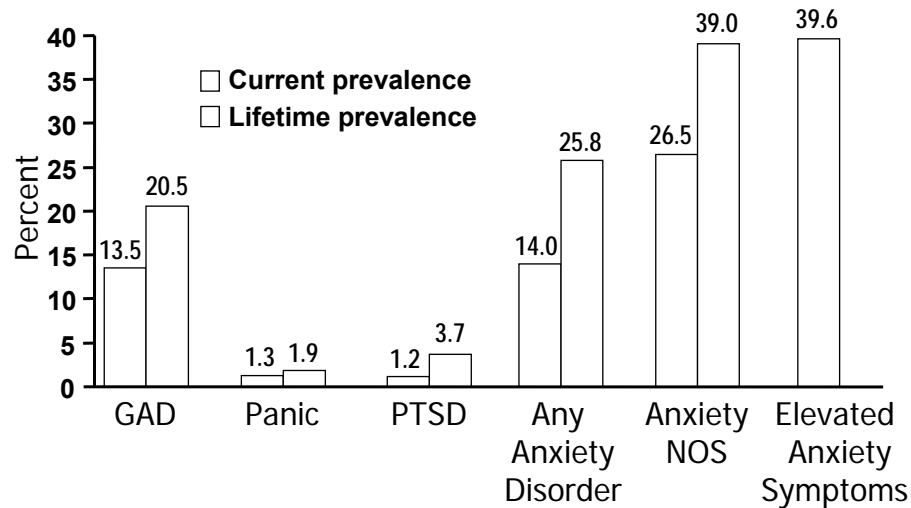
Post-Stroke GAD

- 277 patients with ischemic stroke aged 55-85
 - Comprehensive psychiatric evaluation 3-4 months post-stroke
- GAD in 20.6% (N=57)
 - Associated with poorer psychosocial functioning
- GAD is common in patients with ischemic stroke and may hamper their rehabilitation

Leppavuori A et al. (2003), Cerebrovasc Dis 16(3):257-264

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Prevalence of Anxiety in Adults with Diabetes



Grigsby AB et al. (2002), J Psychosom Res 53(6):1053-1060

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Depression/Anxiety and Diabetes

- GAD is twice as prevalent among people with diabetes than those without diabetes
 - MDD: 3-5x greater in people with diabetes
 - Associated with diabetic complications, lower adherence to diet and medications, and poor glycemic control compared to people with diabetes without depression
- Total health expenditures for persons with diabetes and depression are 4.5x higher than for people with diabetes without depression

Anderson RJ et al. (2001), Diabetes Care 24(6):1069-1078; de Groot M et al. (2001), Psychosom Med 63(4):619-630; Lin EH et al. (2004), Diabetes Care 27(9):2154-2160; Egede LE et al. (2002), 25(3):464-470; Egede LE (2004), Diabetes Care 27(2):421-428; Lustman PJ, Clouse RE (2002), J Psychosom Res 53(4):917-924; Katon WJ et al. (2004), Arch Gen Psychiatry 61(10):1042-1049; Gavard JA et al. (1993), Diabetes Care 16(8):1167-1178

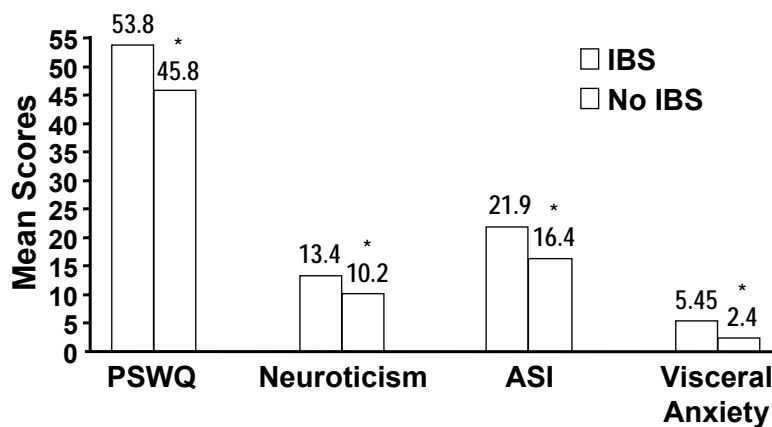
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Depression/GAD and Diabetes

- Decreased adherence to treatment plan
- Worse glucose control
- Increased complications
- Decreased overall functional well-being

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Relationship Between GAD and IBS

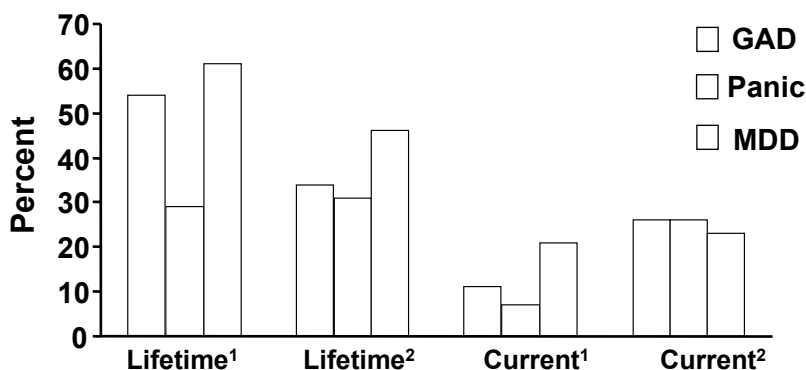


MEM of self-report measures; PSWQ = Penn State Worry Questionnaire; *p<0.001; Hazlett-Stevens H et al. (2003), J Psychosom Res 55(6):501-505

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GAD and Irritable Bowel Syndrome

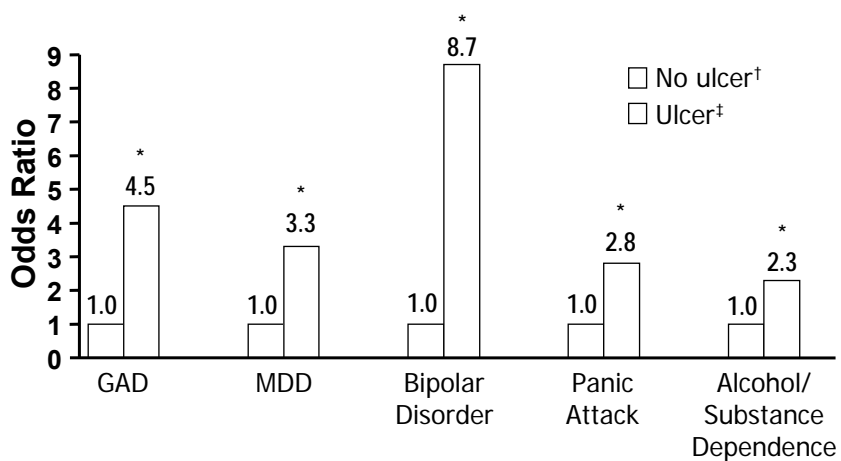
Most Had Suffered From Psychiatric Disorders, Particularly Anxiety Disorders, Before The Onset of Their Irritable Bowel Symptoms



¹Walker EA et al. (1990), Am J Psychiatry 147(12):1656-1661; ²Lydiard RB et al. (1993), Psychosomatics 34(3):229-234

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Psychiatric Comorbidity (12-Month) and Self-Reported Peptic Ulcer Disease in Adults



*p<0.05; [†]Reference group; [‡]OR (with 95% CI) computed with multiple logistic regression analyses adjusted per gender, race, marital status, education and income; Goodwin RD, Stein MB (2002), Psychosom Med 64(6):862-866

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Cancer and Chronic Major Depression

- Prospective, epidemiological survey (N=4,825)
- Cohort ages ≥ 71
- Screened for MDD at 6 and 3 years prior to study and at baseline
- Results: **88%** \uparrow in cancer risk over 3.8 years' follow-up for chronic major depression

Penninx BW (1998), J Natl Cancer Inst 90(24):1888-1893

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Depression and Parkinson's Disease

- 40% of patients with Parkinson's disease have comorbid depression
 - Diagnosis is difficult due to overlap in symptoms between Parkinson's disease and depression
 - May be "reactive" and due to psychosocial stress; alternatively, may be caused by neurodegeneration

McDonald WM et al. (2003), Biol Psychiatry 54(3):363-375; Menza M, Mark MH (1994), J Neuropsychiatry Clin Neurosci 6(2):165-169

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Fibromyalgia and Anxiety

- 115 patients with fibromyalgia syndrome (FMS) grouped into 3 psychosocial subgroups based on Multidimensional Pain Inventory (MPI)
 - Dysfunctional (DYS)
 - Interpersonally distressed (ID)
 - Adaptive copers (AC)
- Axis I diagnoses were present in 74.8%
- DYS subgroup mainly reported anxiety, and the ID group, mood disorders
 - The AC group showed little comorbidity
- Conclusion: FMS is not a homogeneous diagnosis, but shows varying proportions of comorbid anxiety (DYS) and depression (ID), depending on psychosocial characteristics of the patients

Comorbid depression and anxiety in FMS: relationship to somatic psychosocial variables;
Thieme K et al. (2004), *Psychosom Med* 66(6):837-844

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Fibromyalgia and Anxiety

- 50 participants with FMS and 20 with rheumatoid arthritis (RA) were assessed with respect to anxiety, depression, pain intensity and disability compared to 42 healthy controls
- Results: anxiety scores were the most important covariate determining the likelihood of having FMS, whereas depression scores increased the chances of being an RA patient
 - Age and disability scores did not differ between FMS and RA
- Conclusions: affective distress is not specific to FMS patients, but FMS seems to be associated with anxiety rather than depression

Sayar K et al. (2004), *Swiss Med Wkly* 134(17-18):248-253

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Treatment of Depression and GAD: Primary Care Implications

- Depressed/anxious patients often present with somatic complaints
- Comorbid medical illness is often clustered with GAD and MDD, which worsens outcomes
- Increased recognition and appropriate treatment reduce the significant morbidity and mortality related to these concomitant conditions