Evaluation of Mood Disorder Patients in a Primary Care Practice: Measures of Affective Temperament, Mental Health Risk Factors, and Functional Health in a Retrospective, Descriptive Study of 35 Patients

Patricia D. Cunningham, D.N.Sc., APRN-BC; Pamela D. Connor, Ph.D.; J. Sloan Manning, M.D.; Cheryl Cummings Stegbauer, Ph.D., APRN-BC; and Sarah L. Mynatt, Ed.D., APRN-BC

Objective: The purpose of this retrospective, descriptive study was to evaluate primary care patients diagnosed with a mood disorder on the basis of the following: (1) comorbid medical illnesses, (2) risk factors for mood disorders and longitudinal presence of symptoms, (3) presence of affective temperament, and (4) functional status and quality of life.

Method: Patients (N = 35) were a convenience sample diagnosed in the Mood Disorder Clinic (MDC), a family practice site–based mental health treatment consultation service. All study patients were assessed using a semistructured interview and diagnosed according to DSM-IV-TR criteria. Data were collected using both chart review and secondary analysis of a computerized touch-screen mood disorders database that included the 36-item Short-Form Medical Outcomes Study Health Survey (SF-36) and an affective temperament survey. The study was conducted from January 2000 through August 2000.

Results: A total of 62 comorbid medical illnesses were present in this group of patients; only 2 patients had no comorbid illnesses. Psychiatric diagnoses included 25 cases (78.1%) of bipolar depression, 5 cases (15.6%) of unipolar or dysthymic depression, and 2 cases (6.3%) of nonmood or anxiety disorders. All patients (100%) had a positive family history for mood disorders or substance abuse. Twenty-four patients (70.6%) had onset of their depressive symptoms prior to age 21, and 11 patients (35.5%) had a positive history of sexual abuse. Affective temperaments were positive in the 30 patients who completed this section. SF-36 scale scores were predominantly below national norms.

Conclusion: The medical comorbidities in our study were expected; the positive family and individual histories for risk along with low SF-36 scores reflect the severity and chronicity of mood disorders in this population.

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Corresponding author and reprints: Patricia Cunningham, D.N.Sc., University of Tennessee Health Science Center, College of Nursing, 877 Madison Ave., Ste 612, Memphis, TN 38163 (e-mail: pcunningham@utmem.edu).

R esearch endeavors have exposed the hidden nature of mental health needs and their effect on health care utilization.¹⁻⁵ It is generally accepted that 30% of general primary care patients have disturbances of mood,⁶ which encompass dysthymia, bipolar spectrum disorders, major and so-called "minor" depression, and anxiety disorders. Higher prevalence rates of 51% have been reported for the poor, uninsured primary care population.⁷ Assessments of patients' "chief complaint" are often from a traditional, cross-sectional, single-illness perspective versus a longitudinal, temperamental perspective.⁸ Often missed is the subtle, evolving, subsyndromal presentation of mood disruptions, hindering opportunities for early detection, treatment, and patient education.^{9,10}

The prevalence of undetected mental health problems in communities has led to the examination of the limitations of diagnostic criteria and assessment tools.^{8,11-13} The traditional multiaxis diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition (DSM-IV)¹⁴ emphasize presenting symptoms and cross-sectional assessments, with prior illness episodes and psychosocial history de-emphasized, contributing to knowledge gaps in patient care. Depressive illnesses are best understood in terms of a multiple-risk strategy involving temperament, psychosocial and biological stressors, mediating demographic factors, developmental influences, character traits, and familialhereditary information.¹⁵

Table 1. Temperamental Profiles			
Temperament	Profile		
Dysthymic	Gloomy, pessimistic, hypercritical, passive, worrying, and conscientious with tendency to oversleep (> 10 hours/night)		
Hyperthymic	Cheerful, overconscientious, impulsive, vigorous, meddlesome, uninhibited, and stimulus-seeking with tendency to undersleep (< 6 hours/night)		
Cyclothymic	Cycling of moods from hypersomnic and introverted with psychomotor inertia to uninhibited and people-seeking with restless pursuit of activity		
Irritable	Moody with angry, unprovoked outbursts; dysphoric restlessness; and intermittent insomnia		

Temperament

Wells et al.⁴ found temperament measures to be more effective for understanding the course of depressive illness than examination of psychiatric comorbidities such as anxiety and alcohol use. Temperament in children is defined as relatively stable, primarily biologically based, individual differences in emotional reactivity and self-regulation.¹⁶ Rothbart et al.¹⁷ view temperament as the characteristic phenomena of an individual's emotional nature that include susceptibility to emotional stimulation, customary strength and speed of response, and the quality of prevailing mood.

Temperament's effects on health and illness are described in a longitudinal study of a cohort of medical students.¹⁸ Differences in 2 behaviors, loss of appetite and difficulty sleeping, suggested distinct and separate pathways in reactivity when under pressure of stress. These 2 behaviors are also notable symptoms of mood disorders. In another study by Joyce et al.,¹⁹ temperament explained 35% to 50% of clinical variance in patient antidepressant response. Temperament was a much greater predictor than other clinical variables that explained less than 5% of the variance in treatment outcomes.¹⁹

The hypothesis that the presence of affective temperaments (mood disturbances) in adults predicts the clinical course of mood disorders has been presented in a seminal paper by Akiskal and Mallya,²⁰ and temperamental factors were a better predictor than the DSM definition of hypomania for a switch to a bipolar diagnosis in an influential National Institute of Mental Health prospective study.²¹ Subsequently, the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A) has been validated as a measure of affective temperaments.²² In the Family Practice Mood Clinic, where this study was completed, the TEMPS-A was used to operationalize affective temperamental constructs psychometrically.^{23,24}

In addition to patient self-report, patients' shared stories helped capture their "affective temperament essence" (Table 1). Persons with a dysthymic temperament had lists of life disappointments, shared with the clinician as if they had just recently occurred. Persons with hyperthy-

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mic temperament shared stories of improvident, driven activities expressed within the context of their life, from a homemaker constantly changing her home décor to a young executive, uninhibited and sexually driven. Those with cyclothymic temperament were perceived by significant others as unreliable, planning weekend activities on Tuesday and frequently cancelling by Friday due to an unrecognized or undisclosed shift in moods. Last, persons with irritable temperament were experienced by significant others as interpersonally difficult. These partners felt that they were always "walking on egg shells" when with the person with irritable temperament.

Health Status

Because primary care patients with mood disturbances present with complaints about their everyday functions in activities of daily living (ADL) versus their mood, alternative ways to assess patients are being explored. Kroenke²⁵ recommends adding measures of health status, quality of life, and patient functioning to complement symptom-specific scales to permit the comparison of impairment and symptomatology.²⁶

Longitudinal studies in depression demonstrate that many patients retain significant subclinical symptoms that impair ADL, as well as social and vocational functioning, between episodes of depression.^{27,28} This retention is especially significant for patients with bipolar disorder, who spend most of their lives struggling with the depressive pole of the illness.²⁹ Ware and Sherbourne³⁰ found that functional status and well-being, as measured by the 36item Short-Form Medical Outcomes Study Health Survey (SF-36), were a more powerful predictor of outcomes than current psychiatric diagnostic classification schemes. In the Medical Outcomes Study,⁴ depressive symptoms and functional status were a more powerful predictor of treatment outcomes than the current depressive disorder classification schemes, particularly for primary care.³¹

Risk Factors

Certain risk factors increase acquired vulnerability to mood disorders, for example, exposure to adverse childhood experiences, such as sexual abuse or living in a home with an alcoholic parent.^{32,33} A history of life events with past and present activities of daily living, including risk behaviors, was solicited on the intake questionnaire.^{33,34} Three generations of family history, with a focus on mental health disorders as well as physical disorders, were explored to detect inherited vulnerability related to family history.^{35,36}

Our purpose was to explore unconventional aspects of patients assessed and treated for mood disorders. We describe study participants diagnosed and treated for mood disorders, mostly bipolar disorders, in a family practice. All of the study participants had medical comorbidities, and the mood disorders described are of advanced complexity. All participants were assessed for (1) comorbid illnesses, (2) risk factors for mood disorders and longitudinal presence of symptoms, (3) presence of affective temperament, and (4) functional status and quality of life. We discuss considerations relevant for accurate appraisal of mood disorders in primary care.

METHOD

Study Design

The study was a retrospective, descriptive study of mood disorder patients (N = 35) in a family practice Mood Disorders Clinic (MDC).¹⁰ Data were collected using both chart review and secondary analysis of a computerized touch-screen mood disorders database. The study was approved by the University of Tennessee Health Science Center Institutional Review Board, and all participants gave written informed consent.

Patient Selection

Patients in the study were from the Department of Family Medicine at the University of Tennessee Health Science Center in Memphis. A convenience sample of consecutive mood disorder patients was approached by the research staff on their appointment day to participate in the touch-screen project for collecting data on patients with mood disorders. Less than 5% of patients approached who met the study criteria declined. The study was conducted from January 2000 through August 2000.

All participants were diagnosed with a mood disorder and followed in the MDC, a family practice site–based mental health treatment consultation service.¹ All patients included in the study were assessed using a semistructured assessment process and diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria.¹⁴ Exclusion criteria included patients under age 18, no informed consent, or incomplete medical record data.

Data and Instruments

Data were collected using both chart review and secondary analysis of a computerized touch-screen mood disorders database. The mood disorders database uses a patient-driven, touch-screen program designed for the study site by Assist Technologies Outcomes Suite version 5.2 software (Assist Technologies, Inc., Phoenix, Ariz.). Besides decreased error rates and ease of data use, one study has shown a high degree of patient acceptability of electronic questionnaires.³⁷ The questionnaire used to collect data has been tested on 3000 primary care patients, with revisions based on statistical analysis as well as patient and clinician feedback. It included information on demographics; patient and family neurologic, mental, and substance use history; comorbid medical illnesses; and risk factors. *The SF-36.* The SF-36 and the temperament survey were part of the touch-screen data collection. The SF-36 is a multi-item scale that assesses 8 health concepts: physical functioning (PF), role limitations due to physical problems (RP), social functioning (SF), bodily pain (BP), general mental health (MH), role limitations due to emotional problems (RE), vitality (VT), and general health perceptions (GH). The SF-36 identifies functional presentations coexisting with mood disorder symptoms and other common health problems in primary care patients. Psychometric properties are well documented in the literature.³⁸

Affective Temperament Survey. The temperament scale²² used was one of the pilots for the TEMPS-A. The version used is an 84-item questionnaire containing the 4 subscales of affective temperaments: hyperthymic, dys-thymic, cyclothymic, and irritable. Presence of affective temperament is indicative of risk for affective illness as well as premorbid traits. Affective temperaments are indicators for mood lability, lifestyle risks, energy levels, and biopsychosocial treatment approaches.

Charts were reviewed for demographic data; clinical information included psychiatric and medical diagnoses, nature of presenting symptoms, and comorbid diagnoses.

Analysis

The SF-36 was evaluated using mean subscale scores. The SF-36 subscales served as comparison conditions for temperament subscales and the computerized questionnaire. Other data were examined through descriptive statistics. JMP Statistical Discovery Software, version 4.0, by Statistical Analysis Software (SAS Inc., Cary, N.C.) was used for additional scoring.

RESULTS

Of the 35 people in the study, 31 were female (89%) and 4 (11%) were male. The mean age was 39.2 years (SD = 13.0 years). Ages ranged from 18 to 66 years, with 86% over the age of 21 years, and distribution in each 5-year age period. All but 8 participants were high school graduates, and 10 had some college education. Of the 35 participants, 9 (26%) were single, 13 (37%) were married, 10 (29%) were divorced, and 2 (6%) indicated "other." Racial/ethnic background included 29 (83%) white and 3 (9%) African American.

The number of participants with private insurance was 12 (34%) and with public-funded insurance was 23 (66%). Race/ethnicity was significant (p = .04) by site, accounted for by the low number (N = 3) of African Americans in the study.

Of the 35 patients treated in the MDC, all but 2 had comorbid medical diagnoses: the predominant comorbid symptoms and illnesses were related to the gastrointestinal and neurologic body systems (Table 2). Nineteen pa-

Туре	Treated Comorbid Illness, N (%)
Cardiovascular	9 (14.5)
Muscular-skeletal	7 (11.3)
Endocrine	4 (6.4)
Neurological	12 (19.4)
Gynecological	7 (11.3)
Gastrointestinal	12 (19.4)
Respiratory	2 (3.2)
Metabolic	9 (14.5)

Table 2 Comorbid Medical Illnesses of Mood Disorde

Table 3. Three-Generation Family History of 34 Patients	
With Positive Family History for Mood Disorders	

	Patient	Maternal	Paternal
	Family	Family	Family
Family History Item, N (%)	History	History	History
Alcohol/drug use	N = 21	N = 15	N = 15
Father	12 (57.1)	7 (46.7)	10 (66.7)
Mother	5 (23.8)	3 (20.0)	0(0)
Sibling	17 (80.9)	12 (80.0)	11 (73.3)
Children	5 (23.8)	1 (6.7)	0 (0)
Depression, "nerves"	N = 26	N = 16	N = 9
Father	10 (38.5)	3 (18.8)	2 (22.2)
Mother	21 (80.8)	10 (62.5)	3 (33.3)
Sibling	14 (53.8)	12 (75.0)	8 (88.9)
Children	9 (34.6)	0 (0)	0 (0)
Hospitalized for depression, "nerves"	N = 13	N = 6	N = 6
Father	4 (30.8)	0 (0)	1 (16.7)
Mother	9 (69.2)	3 (50.0)	0(0))
Sibling	5 (38.5)	4 (66.7)	5 (83.3)
Children	2 (15.4)	0 (0)	0 (0)
Suicide attempts/completions	N = 9	N = 4	N = 3
Father	2 (22.2)	0 (0)	1 (33.3)
Mother	3 (33.3)	2 (50.0)	1 (33.3)
Sibling	6 (66.7)	2 (50.0)	3 (100)
Children	1 (11.1)	0 (0)	1 (33.3)
Migraines, headaches	N = 18	N = 11	N = 7
Father	5 (27.8)	0 (0)	0 (0)
Mother	12 (66.7)	7 (63.6)	3 (42.9)
Sibling	10 (55.6)	7 (63.6)	6 (85.7)
Children	7 (38.9)	0 (0)	1 (14.3)
Seizures	N = 7	N = 2	N = 1
Father	0 (0)	0 (0)	0 (0)
Mother	2 (28.6)	0 (0)	0 (0)
Sibling	2 (28.6)	2 (100)	1 (100)
Children	3 (42.9)	0 (0)	0 (0)

tients had 3 or more comorbid illnesses; 6 were diagnosed with 2 or more; and 8 patients had 1 comorbid illness.

All patients had positive family histories (N = 34; one patient did not complete the family history section of the questionnaire); some with positive histories of drug and/ or alcohol use, depression, hospitalization, suicide, migraines, and/or seizures in their family of origin. Maternal and paternal histories were also revealed (Table 3).

There were 24 patients (70.6%) with onset of depression prior to age 21 years; and 11 patients (35.5%) had a history of sexual abuse. Three patients did not answer the sexual abuse question (Table 4).

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Table 4. Risk Factors for Mood Disorders in 34 Patients

Variable	Ν	%
Loaded family history		
Yes	34	100
No	0	
Onset of depression prior to 21 years of age		
Yes	24	70.6
No	10	29.4
History of sexual abuse ^a		
Yes	11	35.5
No	20	64.5
^a Three patients did not answer this question.		

Table 5. SF-36 Analysis of Study Population Below National Norms (N = 33)

	G	Below	SF-36 National
	Group	National	Norm Scale,
SF-36 Scale	Mean Value	Norm, % (N)	% Value
Physical Functioning (PF)	60.0	78.8 (26)	90
Role Physical (RP)	42.1	69.7 (23)	85
Bodily Pain (BP)	57.9	87.9 (29)	82
General Health (GH)	50.7	87.9 (29)	78
Vitality (VT)	25.5	93.9 (31)	59
Social Functioning (SF)	38.8	93.9 (31)	82
Role Emotional (RE)	23.9	90.9 (30)	78
Mental Health (MH)	40.3	93.9 (31)	72
Abbreviation: SF-36 = 36-i Health Survey.	tem Short-For	m Medical Outc	omes Study

Affective temperaments were positive in the 30 patients who completed this part of the study. Affective temperaments endorsed were 10 (33.3%) hyperthymic, 16 (53.3%) dysthymic, 2 (6.7%) cyclothymic, and 2 (6.7%) irritable. There were also some affective temperament blends, with 7 patients endorsing items for more than 1 affective temperament. Psychiatric diagnoses included 25 cases (78.1%) of bipolar depression, 5 cases (15.6%) of unipolar or dysthymic depression, and 2 cases of (6.3%) nonmood or anxiety disorder.

The SF-36 scale scores for the 33 respondents completing this section were compared to the SF-36 normative scale scores. Most patients scored below the national norms on all SF-36 subscales (Table 5).

DISCUSSION

Psychosomatic presentations of mental distress and illness are common. According to Ehlert and Straub,³⁹ patients with depression or anxiety disorders seem to show exaggerated physiologic reactions to psychological stressors, mediated in part through an exaggerated adrenocortical response. This sample reports neurologic and gastrointestinal conditions most frequently, with each category having a 19.4% prevalence (Table 2). Unexplained somatic symptoms and high utilization of medical resources should increase a clinician's level of suspicion for mood and anxiety disorders.⁴⁰

All study participants reported positive family histories for impairing mood disorders (Table 3). Most (61.8%) indicated substance abuse problems in close family members, including siblings. More fathers than mothers (57.1%, 23.8%, respectively) were reported as having alcohol/drug problems. Over three quarters (76.5%) reported positive family histories for "depression/nerves." Substance abuse affects family life; environmental and stress-related exposures are other risk factor considerations. A positive family history of mood disorders and alcoholism is an important indicator for increased risk of mood disorders for the offspring.^{36,41}

Study participants endorsed dysthymic (depressive) temperamental attributes most frequently (53.3%). The hyperthymic (manic) temperament was the second most frequently endorsed affective temperament (33.3%). Cyclothymic temperament, with nonimpairing moods that cycle from a hypersomnic and introverted to uninhibited people-seeking activities was endorsed by 6.7% of our study population, percentages consistent with the findings of Akiskal et al.²² and Henry et al.⁴² Affective temperaments may be viewed as phenotypical expressions of inherited vulnerability to mood disorders. Recognizing these temperaments offers the potential for earlier interventions. Our patients responded positively to discussions about their temperament, and such discussions fostered their collaboration with clinicians to think through temperament behavioral inclinations. These psychoeducational interventions increased the potential for selfprotection and protection of others from detrimental behaviors such as excesses in spending, negative expressed emotion, and/or tendencies toward unhealthy passivity.

Future studies are needed to discriminate critical differences in primary care patients with mood disorders who are likely to improve quickly and completely from those at greater risk for chronicity or partial recovery.⁴³ Our investigation suggests that in-depth evaluations of patient and family histories will strengthen these studies. Furthermore, learning about our patients' temperamental inclinations will aid an understanding that life biographies are significantly influenced by temperament, with its profound effect on emotional intensity, reactivity, stability of behavior over time, and the emotional/behavioral responses provoked in others.⁴⁴

Neuroticism has been defined as an enduring tendency to experience negative perceptions, resulting in distressing emotions.⁴³ Our measurement of the presence of the dysthymic or cyclothymic temperament, 53.3% and 6.7%, respectively, correlates with the above definition of neuroticism. Persons classified with these temperaments are more likely to interpret ordinary life stressors as threatening or overly difficult. They are often guilt ridden, shy, and sensitive, but they may have difficulty controlling impulsivity and delaying gratification. They have limited capacity to balance thinking to override their emotionally driven interpretations. High levels of neuroticism have been shown to be predictive of persistence of depression in primary care.⁴³

High neuroticism is hypothesized to interact with adverse stimuli, resulting in heightened reactivity of the autonomic nervous system, leading to acute adverse emotional and physical symptoms. Certain temperaments (e.g., dysthymic and cyclothymic) seem to predispose to onset of depression at an early age, with higher rates of positive family history of mood disorders, higher rates of recurrence, greater suicidality, and even more severe depression, with greater episode severity.⁴⁴ Others view temperamental expressions of mood, psychomotor energy, cognitive, and vegetative state functions and their behavioral expressions as manifestations of a mood spectrum disorder that includes prodromal, typical, residual, and trait-like symptoms.45 Clarification of the similarities and differences in these constructs, moving toward consensual concepts and definitions, may help clinicians with early identification and interventions with potential for prevention of the adverse life-long morbidity related to unrecognized and untreated mood disorders.

The large number of patients in the study below national norms on SF-36 scales describes a group of patients seeking care in primary care with enduring disruptions in everyday function (Table 5). As Benazzi⁴⁶ found in his study on depressive mixed states, none of the currently available structured clinical interview guides encouraged the type of clinical exploration also found in this study. As previously noted, ceiling and floor effects of the SF-36 limit the tool's ability to detect differences, depending on populations studied. Reasonable attempts to document function are needed; reliable and expedient measurements are desired.

This study was limited by small sample size and retrospective design. Further studies using a larger primary care population and a prospective design are recommended.

CONCLUSION

Our methodology used an integration of recent theoretical concepts and research findings to describe a small but significant subset of patients receiving mental health care in a primary care setting. The findings suggest that clinicians consider alternative ways to understand and explore the type and effects of mood disorders on patients' lives, especially the significance of a longitudinal history with in-depth life stories and family histories.

Our findings highlight the intricacies of these primary care patients with mood disorders. Data reflect the complexity of the task at hand and resonate with the growing body of literature that describes the limitations of current detection and treatment approaches to mental health care. Primary care patients present with a combination of physiologic and psychological responses to altered physiology: a biopsychosocial approach is essential to effective care for these patients. We point out the value of documenting patient and family histories, with emphasis on mood disturbances and substance abuse. Our findings, when combined with the work of many others, should close the door of mind-body dualism in the delivery of primary health care.

REFERENCES

- Manning JS, Zylstra RG, Connor PD. Teaching family physicians about mood disorders: a procedure suite for behavioral medicine. Prim Care Companion J Clin Psychiatry 1999;1(1):18–23
- Regier DA, Narrow WE, Rae DS, et al. The de facto US mental and addictive disorders service system: epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50(2):85–94
- Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Controlled Clinical Trials 2004;25(1):119–142
- Wells KB, Burnam MA, Rogers W, et al. The course of depression in adult outpatients: results from the Medical Outcomes Study. Arch Gen Psychiatry 1992;49(10):788–794
- Wittchen HU, Zhao S, Kessler RC, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1994;51(5):355–364
- DHHS. Mental health: a report of the surgeon general. Available at: http://www.surgeongeneral.gov/library/mentalhealth/home.html. Accessed May 23, 2006
- Mauksch LB, Tucker SM, Katon WJ, et al. Mental illness, functional impairment, and patient preferences for collaborative care in an uninsured, primary care population. J Fam Pract 2001;50(1):41–47
- Cloninger CR. A new conceptual paradigm from genetics and psychobiology for the science of mental health. Aust N Z J Psychiatry 1999; 33(2):174–186
- Judd LL, Rapaport MH, Paulus MP, et al. Subsyndromal symptomatic depression: a new mood disorder? J Clin Psychiatry 1994;55(suppl): 18–28
- Manning JS, Haykal RF, Akiskal HS. The role of bipolarity in depression in the family practice setting. Psychiatr Clinics North Am 1999; 22(3):689–703
- Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatric Clinics North Am 1999;22(3):517–534
- Goodwin FK, Jamison JR. Manic depressive illness. New York, NY: Oxford University Press; 1990
- Regier DA, Kaelber CT, Rae DS, et al. Limitations of diagnostic criteria and assessment instruments for mental disorders: implications for research and policy. Arch Gen Psychiatry 1998;55(2):109–115
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM IV), Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
- Akiskal HS. Interaction of biologic and psychologic factors in the origin of depressive disorders. Acta Psychiatr Scand Suppl 1985; 319:131–139
- 16. Goldsmith HH, Buss AH, Plomin R, et al. Roundtable: what is temperament? four approaches. Child Dev 1987;58(2):505–529
- Rothbart MK, Ahadi SA, Evans DE. Temperament and personality: origins and outcomes. J Pers Soc Psychol 2000;78(1):122–135
- Graves PL, Mead LA, Wang NY, et al. Temperament as a potential predictor of mortality: evidence from a 41-year prospective study. J Behav Med 1994;17(2):111–126
- Joyce PR, Mulder RT, Cloninger CR. Temperament predicts clomipramine and desipramine response in major depression [see comment]. J Affect Disord 1994;30(1):35–46
- 20. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull 1987;23(1):68–73
- 21. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from 'unipolar' to bipolar II: an 11-year prospective study of clinical and temperamental

predictors in 559 patients. Arch Gen Psychiatry 1995;52(2):114-123

- Akiskal HS, Akiskal KK, Haykal RF, et al. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J Affect Disord 2005;85(1–2):3–16
- 23. Cassano GB, Akiskal HS, Savino M, et al. Proposed subtypes of bipolar II and related disorders: with hypomanic episodes (or cyclothymia) and with hyperthymic temperament. J Affect Disord 1992;26(2):127–140
- Placidi GF, Signoretta S, Liguori A, et al. The semi-structured affective temperament interview (TEMPS-I): reliability and psychometric properties in 1010 14–26-year old students. J Affect Disord 1998;47(1–3):1–10
- Kroenke K. Studying symptoms: sampling and measurement issues. Ann Intern Med 2001;134(9 pt 2):844–853
- Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. Psychiatr Ann 2002;32(9):509–515
- Judd L, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatr Clin North Am 2002;25(4):685–698
- Wells KB. Caring for depression in primary care: defining and illustrating the policy context. J Clin Psychiatry 1997;58(suppl 1):24–27
- Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, doubleblind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162(7):1351–1360
- Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1992;30:473–483
- Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. JAMA 1989;262(7):914–919
- 32. Edwards VJ, Holden GW, Felitti VJ, et al. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the Adverse Childhood Experiences Study. Am J Psychiatry 2003;160(8):1453–1460
- 33. Felitti VJ, Anda RF, Nordenber^A D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14(4):245–258
- McEwen BS, Seeman T. Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. Ann N Y Acad Sci 1999;896:30–47
- Andreasen NC, Endicott J, Spitzer RL, et al. The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 1977;34(10):1229–1235
- Weissman MM, Wickramantne P, Nomura Y, et al. Families at high and low risk for depression: a 3-generation study. Arch Gen Psychiatry 2005; 62(1):29–36
- Drummond HE, Ghosh S, Ferguson A, et al. Electronic quality of life questionnaires: a comparison of pen-based electronic questionnaires with conventional paper in a gastrointestinal study. Qual Life Res 1995;4:21–26
- Ware JE. SF-36 Health Survey: Manual and Interpretation Guide. Boston, Mass: The Health Institute, New England Medical Center; 1997
- Ehlert U, Straub R. Physiological and emotional response to psychological stressors in psychiatric and psychosomatic disorders. Ann N Y Acad Sci 1998;851:477–486
- Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. Ann Intern Med 2001;134:917–925
- Preisig M, Fenton BT, Stevens DE, et al. Familial relationship between mood disorders and alcoholism. Compr Psychiatry 2001;42(2):87–95
- 42. Henry C, Lacoste J, Bellivier F, et al. Temperament in bipolar illness: impact on prognosis. J Affect Disord 1999;56(2–3):103–108
- Katon W, Lin E, von Korff M, et al. The predictors of persistence of depression in primary care. J Affect Disord 1994;31(2):81–90
- Akiskal HS. Temperament, personality, and depression. In: Hippius H, Stefanis C, eds. Research in Mood Disorders: An Update. Seattle, Wash: Hogrefe & Huber; 1994:44–57
- Cassano GB, Frank E, Miniati M, et al. Conceptual underpinning and empirical support for the mood spectrum. Psychiatr Clin North Am 2002; 25(4):699–712
- Benazzi F. Major depressive episodes with hypomanic symptoms are common among depressed outpatients. Compr Psychiatry 2001; 42(2):139–143