

VII. Comorbidity

Murray W Enns, MD, FRCPC¹, J Robert Swenson, MD, FRCPC², Roger S McIntyre, MD, FRCPC³,
Richard P Swinson, MD, FRCPC, FRCPsych⁴, Sidney H Kennedy, MD, FRCPC⁵,
and the CANMAT Depression Work Group⁶

Background: The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments partnered to produce clinical guidelines for psychiatrists for the treatment of depressive disorders.

Methods: A standard guidelines development process was followed. Relevant literature was identified using a computerized Medline search supplemented by review of bibliographies. Operational criteria were used to rate the quality of scientific evidence, and the line of treatment recommendations included consensus clinical opinion. This section, on Axis I, Axis II, and Axis III comorbidity, is 1 of 7 articles that were drafted and reviewed by clinicians. Revised drafts underwent national and international expert peer review.

Results: Comorbid depression on Axis I is particularly prevalent in patients with anxiety disorders, substance use disorders, and eating disorders, but it also occurs in patients with schizophrenia, attention-deficit hyperactivity disorder (ADHD), and dementia. Depressive comorbidity has implications for assessment, management, and outcome. The relation between depression and personality disorders is complex. Patients with this comorbidity often require longer, more intense, and multimodal therapies. Depression is also prevalent in medical illnesses, requires careful diagnosis, and responds to standard antidepressant treatments.

Conclusions: Comorbidity can influence the course and outcome of both associated conditions. Depression-specific psychotherapy and/or pharmacotherapy should be considered when comorbid depression is diagnosed.

INTRODUCTION

Comorbidity refers to the occurrence of 2 or more distinct disorders at the same time. Lifetime comorbidity refers to the occurrence of 2 or more distinct disorders over an individual's lifetime. In the US National Comorbidity Survey, most lifetime psychiatric disorders (79%) were comorbid disorders (1). Psychiatric disorders are common among the general population, but most functional impairment is accounted for by individuals with multiple comorbidities. It is not clear whether psychiatric comorbidity is the result of 2 or more distinct disorders, a measure of severity of a disorder, or at times an artifact of current diagnostic nosology, where similar symptoms may reflect the expression of 1 or more diagnostic categories.

The purpose of this section is to provide guidelines for the management of comorbid depression in the context of other Axis I, Axis II, or Axis III disorders. There are, however, very few treatment studies that specifically address comorbid major depressive disorder (MDD) and other conditions. Most of the available evidence is with open or naturalistic studies. Hence, there is insufficient evidence to give specific recommendations for each comorbid condition. Instead, this section will focus on the challenges of diagnosing depression when other diseases or disorders are present and will review the current evidence for treatment of MDD and comorbid disorders, including expert clinical opinion.

AXIS I COMORBIDITY

Anxiety Disorders

1. What are the clinical implications of comorbid depressive and anxiety disorders?

Epidemiological, family, and clinical studies support a model that links anxiety and depression. Approximately 50% of those in community samples who met criteria for lifetime MDD also met criteria for a comorbid anxiety disorder (2,3). The most common types of anxiety disorders in those with MDD were simple (specific) phobia, followed by agoraphobia, social phobia, panic disorder, and obsessive-compulsive disorder (OCD) (4). Patients with a primary diagnosis of

¹Associate Professor, Department of Psychiatry, University of Manitoba, Winnipeg, Manitoba.

²Associate Professor, Department of Psychiatry, University of Ottawa, Ottawa, Ontario.

³Assistant Professor, Department of Psychiatry, University of Toronto, Toronto, Ontario.

⁴Professor and Head, Department of Psychiatry, McMaster University, Hamilton, Ontario.

⁵Professor and Cameron Parker Holcombe Wilson Chair in Depression Studies, Department of Psychiatry, University of Toronto, Toronto, Ontario.

⁶The members of the CANMAT Depression Work Group include Sidney H Kennedy (co-chair), Raymond W Lam (co-chair), Murray W Enns, Stanley P Kutcher, Sagar V Parikh, Arun V Ravindran, Robin T Reesal, Zindel V Segal, Lilian Thorpe, Pierre Vincent, and Diane K Whitney.

generalized anxiety disorder (GAD) have rates of comorbidity with MDD ranging from 29% to 46% (5–7). Comorbidity rates among adolescents with anxiety disorders in the community vary from 20% to 60% (8), and the rates are significantly increased in treatment samples.

Primary care providers may overrecognize anxiety and underrecognize depression in individuals with mixed anxiety and depression (9). Attempts to differentiate depressive and anxiety syndromes over 3 decades (10–12) need to be contrasted with emerging evidence of overlapping neurobiological findings. Symptom overlap, including changes in sleep and concentration, feelings of tension, excessive worrying, panic attacks, and fear is common between depressive and anxiety disorders (13). By convention, unless the anxiety symptoms occur independently of the depressive episodes, an anxiety disorder diagnosis is not warranted (10). Nevertheless, many clinicians diagnose both anxiety and depressive disorders in circumstances where they are not clearly independent.

There is evidence that comorbid syndromes of depression and anxiety are associated with increased symptom severity, chronicity, and greater functional impairment, along with a decreased response to antidepressant monotherapy and a higher incidence of suicide (3,14,15). Failure to recover after treatment for major depression can be predicted by high baseline symptomatic anxiety, high trait anxiety, and a lifetime history of anxiety disorder (16).

2. How effective are pharmacotherapy and psychotherapy for comorbid depressive and anxiety disorders?

Common underlying neurobiological substrates for depression and anxiety provide a scientific rationale to prescribe antidepressants for patients with both syndromes. The efficacy of various antidepressant classes has been established for disparate anxiety syndromes and for anxiety-related symptoms in patients with depression (3,17) (see Section IV). The benzodiazepines, when combined with selective serotonin reuptake inhibitors (SSRIs) from the outset, may reduce dropout rates and improve treatment response (18). Randomized controlled trial (RCT) data describing the efficacy of antidepressants in persons with concurrent MDD and an anxiety disorder are, however, extremely limited. Until such studies are conducted and replicated, only open and naturalistic studies are available to inform the clinician.

The third-generation antidepressants (that is, SSRIs, serotonin norepinephrine reuptake inhibitors [SNRIs], serotonin antagonist and reuptake inhibitors [SARIs], noradrenergic and specific serotonergic antidepressants [NaSSAs], and reversible inhibitors of monoamine oxidase-A [RIMAs]) are rational choices for patients with both a depressive and an anxiety disorder. These agents offer an improved therapeutic

ratio and lower risk of suicide by overdose (19) when compared with the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (3,20). Optimal dosing schedules in the acute and maintenance treatment of comorbid depression and anxiety, and optimal duration of therapy, have not been scientifically established.

The efficacy of cognitive-behavioural therapy (CBT) in treating MDD with comorbid anxiety disorders is equivocal. Preliminary data for CBT suggests efficacy in concurrent major depressive and anxiety disorders (21,22). Although the efficacy of this approach awaits replication, CBT may be an appropriate alternative for patients who prefer not to take medication or who have a history of medication intolerance.

Substance Use Disorders

3. What are the clinical implications of comorbid depressive and substance use disorders?

Estimates for comorbidity of mood and anxiety disorders in substance-abuse populations range from 30% to 60%, and about one-third of mood-disorder patients have a lifetime history of substance-abuse (23,24). This might be because substance use induces social, psychological, and physical changes culminating in depression, or because the substance use is an attempt at self-medication for an underlying mood disorder, or because there is a shared underlying factor inducing both a mood disorder and a substance use disorder. There is evidence to suggest that the increased prevalence of MDD among substance-abusers is largely secondary (25), in contrast to bipolar disorder, which more often precedes the development of substance-abuse. About 20% of persons with alcohol problems and 26% of those with alcohol dependence have a lifetime history of a mood disorder, while 35% of those with drug dependence have a lifetime mood disorder (26).

Diagnosing MDD can be difficult in the presence of substance use because of the difficulty in differentiating between depressive symptoms that occur secondary to the substance use from preexisting mood disorders. Substance-induced depression can be expected to improve significantly during a period of sustained abstinence (DSM-IV suggests 4 weeks). This contrasts with a primary MDD, which is characterized by onset prior to substance-abuse, persistence beyond detoxification and periods of remission in addictive behaviour, family history of MDD, and increased severity of depressive symptoms. In addition, there has been a traditional separation of substance-abuse treatment centres and mental health treatment centres, with the result that people who present for treatment of a substance-abuse disorder may not be adequately screened for comorbid psychiatric illness (27). The Inventory to Diagnose Depression (IDD) can be used to reliably assess

the presence of MDD, particularly in abstinent alcoholics (28), but the issue of separating alcohol-induced depression from an independent MDD remains problematic in those who are still drinking to excess.

Comorbid substance use may also decrease case identification, diminish treatment responsiveness, decrease compliance, alter pharmacokinetics, and increase chronicity of the mood disorder. Help-seeking behaviour may be decreased: while 65% of people with depression sought treatment, only 15% of those with alcohol-use disorders and 6% of those with drug-use disorders sought treatment for their depressive symptoms (29).

The index of suspicion for comorbid substance use in patients with mood or anxiety disorders should be increased in heavy smokers. Despite attempts to control for comorbidity, 62% of heavy smokers treated with fluoxetine and behavioural treatment for their nicotine addiction were found to have lifetime mood, anxiety, or substance use disorders (30). Further clarification is necessary to examine whether smoking cessation increases the risk for either a relapse or recurrence of MDD (31,32). Suicide occurs more frequently in those who have comorbid depression and substance use disorders (33).

4. How effective are psychotherapy and pharmacotherapy for comorbid depressive and substance use disorders?

There is insufficient empirical evidence to determine which treatment modalities are best suited to acute symptom reduction of depression, acute reduction of substance or alcohol use, and maintenance of remission for both depressive symptoms and substance or alcohol use.

Both the depressive and substance use symptoms represent independent and valid therapeutic targets. Motivational Interviewing, which incorporates cognitive and behavioural principles, is effective in reducing alcohol or other substance-use and promoting abstinence in various comorbid populations (34–36).

In the only RCT involving an SSRI, fluoxetine was effective in reducing both depressive symptoms and alcohol consumption (37). Imipramine did not influence drinking patterns but did reduce depressive symptoms (38), while desipramine showed efficacy in treating depression and preventing alcohol relapse (39). In general, benzodiazepines are not recommended because of their abuse potential (35).

There are additional pharmacodynamic and pharmacokinetic implications associated with the use of antidepressants in patients with comorbid substance abuse. For example, the

concurrent administration of an SSRI and MDMA (Ecstasy), or an MAOI and opiate might increase the risk for serotonin syndrome (40). Tobacco and cannabis smoking induce cytochrome P450 (CYP) isoenzymes that may reduce antidepressant levels. Fluoxetine and paroxetine are potent inhibitors of CYP2D6, which could reduce the conversion of the prodrug codeine to its pharmacologically active metabolite, morphine, resulting in acute opiate withdrawal. Individual safety profiles of the antidepressants also need to be considered. For example, the risk of seizure with bupropion SR may be increased in substance-abusing patients.

Eating Disorders

5. What are the clinical implications of comorbid depressive and eating disorders?

Approximately 80% of young women with eating disorders (anorexia nervosa [AN] and bulimia nervosa [BN]) have comorbidity with mood disorders, anxiety disorders, and substance dependence (41). In a clinical sample of women with either AN or BN, 43% met criteria for MDD (42). In a 10-year follow-up of patients with AN, 84% of the sample had a lifetime diagnosis of affective disorder (43). In fact, both AN and BN have been considered atypical expressions of a mood disorder (44–46).

Overlapping symptoms in eating and mood disorders complicate diagnosis. Starvation may cause symptoms of depression, and conversely, depressive disorders can exacerbate eating behaviours. Cognitive symptoms, including discouragement, expectation of punishment, and indecisiveness, predicted depression in BN. Similarly, loss of interest in others, expectation of punishment, weight loss, and inability to work predicted depression in AN (42).

Mortality and suicide rates in AN are significantly elevated (47), with suicide being the most common cause of death (48). Rates of suicide attempts in women with AN are comparable with rates in women with MDD (49).

6. How effective are psychotherapy and pharmacotherapy for patients with comorbid depressive and eating disorders?

In general, TCAs and SSRIs have been moderately effective in small samples of AN patients with and without depressive symptoms (50,51), but they have not been systematically studied in large populations with comorbid depression. Patients with comorbid BN and MDD showed improvement in both eating behaviour and depressive symptoms following treatment with fluoxetine (52,53). Although limited by safety

and tolerability concerns, MAOIs have a positive effect on both eating behaviour and mood (54,55). Patients with comorbid BN and MDD may not respond as well to antidepressant treatment as do BN patients who do not have MDD (56).

Schizophrenia

7. What are the clinical implications for patients with comorbid depression and schizophrenia?

Depressive symptoms frequently occur in schizophrenia and can worsen course and outcome, increase risk of suicide, and lower quality of life. The incidence of depression in patients with schizophrenia is between 22% and 60% (modal prevalence 25%), depending on diagnostic criteria and patient sampling (57,58). The diagnosis of depression in patients with schizophrenia is problematic since negative symptoms may mimic depression, as may demoralization and extrapyramidal side effects from antipsychotic medications. Depressive symptoms may occur prodromally, be part of a psychotic episode, or follow the psychosis (59). The Calgary Depression Scale can be used to evaluate the severity of depressive symptoms in schizophrenia (60). In a 10-year follow-up of patients with schizophrenia, depressive symptoms followed an independent course from other clusters of schizophrenic symptoms (61).

There may be a correlation between the level of depression in chronic schizophrenia and social maladjustment (62). Patients with schizophrenia who are depressed are more likely to have experienced early parental loss, prior depressive episodes, more psychiatric admissions, and low self-esteem, and they are more likely to live alone (63). Between 9% and 13% of patients with schizophrenia commit suicide, and 40% to 60% will attempt suicide during their lifetime (64). Those with comorbid depression and schizophrenia also have more psychotic symptoms, poorer overall outcome, more unemployment, less satisfaction with nonwork activities and social functioning, and more suicidal ideation, compared with those with schizophrenia who do not have depression. (65). "First-episode" patients are significantly more likely to have comorbid depression than those who have multiple psychotic episodes (66). Vigilance for comorbid mood disorders in early schizophrenia is warranted to reduce the potential for suicide.

8. How effective are psychotherapy and pharmacotherapy for comorbid depression and schizophrenia?

Although there is an impressive literature to support the use of CBT or social-skills training combined with pharmacotherapy to improve both negative and positive symptoms and social functioning in schizophrenia (67,68), these findings cannot yet be generalized to comorbid schizophrenia and MDD. CBT is under investigation as a promising adjunctive or alternative therapy in persons with depression who suffer from schizophrenia (69).

Imipramine was effective in treating postpsychotic depression (70). Other reports support the use of SSRIs in the treatment of depressive symptoms in those with schizophrenia (58). Emerging data suggest that SSRIs may effectively attenuate negative symptoms (71,72).

Resolution of the acute psychotic episode and optimal use of the index antipsychotic are encouraged prior to adjunctive antidepressant administration. There are no available studies that guide the clinician on the optimal selection and duration of an antidepressant strategy for depression in schizophrenia. However, important pharmacokinetic interactions (for example, fluvoxamine, which raises levels of clozapine and its metabolites [73]), synergism of side effects, including SSRI-induced extrapyramidal side effects (74), and potential cumulative toxicities (for example, increased seizure risk with bupropion SR and clozapine) need to be considered when using antidepressants with antipsychotic drugs.

Attention-Deficit Hyperactivity Disorder (ADHD)

9. What are the clinical implications for comorbid depression and ADHD?

ADHD has a high rate of comorbidity in several psychiatric disorders. For example, the co-occurrence of ADHD and MDD, dysthymia, and bipolar disorder in clinical adult samples ranges from 15% to 70% (75,76). ADHD in childhood or adolescence is a common antecedent to adult MDD and bipolar disorder, although the impact of comorbid ADHD on MDD phenomenology, course, and outcome awaits further elucidation. ADHD is a risk factor for a spectrum of comorbidities (including anxiety disorders, substance abuse, and personality disorders) that are known to adversely influence the course and outcome of MDD.

10. How effective are psychotherapy and pharmacotherapy for comorbid depression and ADHD?

The stimulant medications (for example, methylphenidate) remain the paradigmatic treatments of choice for ADHD in childhood, and there is preliminary support for efficacy in adulthood ADHD (77). Monotherapy with antidepressant medication and adjunctive CBT have also been effective in the symptomatic suppression of adult ADHD (78). There are, however, no trials evaluating CBT or other psychotherapies in the population with comorbid ADHD and MDD.

There are no placebo-controlled studies of antidepressants in comorbid ADHD and MDD. Open-trial data suggest that bupropion SR may attenuate both depressive and ADHD symptoms (79), but sertraline and fluoxetine were only effective in treating the depressive symptoms, and the addition of methylphenidate was required to reduce symptoms of ADHD (80).

The Dementias

11. What are the clinical implications for patients with comorbid depression and dementia?

Depressive symptoms may represent a prodrome to dementia, be a risk factor, or complicate the dementia (81). High rates of comorbid MDD (22%) and minor depression (27%) have been reported in outpatients with Alzheimer's disease (82). There is substantial symptom overlap between MDD and various types of dementia, including Alzheimer's disease (83). Subcortical dementias are especially prone to present with depressive symptoms (84,85). Mood symptoms commonly found in dementia are recurrent but short-lived and shallow, with fragmentary and transient depressive ideation (86). Symptoms such as apathy, passivity, and decreased initiative, or memory and concentration disturbance, do not distinguish between dementia and a mood disorder. In patients with mild-to-moderate dementia, these depressive symptoms should be considered primarily as part of a mood disorder rather than of the dementia (86). The diagnosis of MDD should focus on symptoms that include consistently depressed mood, decreased self-esteem, hopelessness, preoccupation with death and dying, and suicidal ideation (87).

12. How effective are psychotherapy and pharmacotherapy for comorbid depression and dementia?

Treatment of comorbid depression in patients with dementia may not improve cognitive function but may improve quality of life and functional status. Behavioural treatment

interventions in patients with Alzheimer's disease and MDD or minor depression improved depressive symptoms in both patients and their caregivers (88). In placebo-controlled trials of patients with comorbid MDD and dementia, clomipramine significantly improved depressive symptoms (89), but imipramine did not (90). Among the SSRIs, citalopram (91) and sertraline (92) were superior to placebo for reducing depressive symptoms. In one comparative trial, fluoxetine and amitriptyline both improved depression ratings (93). The presence of dementia in patients with depression, however, has been associated with a lower rate of response to SSRIs, compared with patients who have depression without dementia (94,95). Finally, electroconvulsive therapy (ECT) has also been found to reduce depressive symptoms in patients with comorbid MDD and dementia (96).

AXIS II COMORBIDITY

Depression and comorbid personality disorders (PDs) may relate to one another in several different ways. First, personality dysfunction may precede depression and act as a vulnerability factor, conveying increased risk for the subsequent development of depression. Second, depression, particularly when chronic, may cause maladaptive changes in personality traits, thereby increasing the likelihood of a PD diagnosis. Third, PDs may modify the presentation, treatment response, or longitudinal course of depressive illness. Each of these possible interrelations has important implications for the treatment of patients with MDD.

13. What is the prevalence of comorbid MDD and personality disorders?

The estimated prevalence of PDs in patients with MDD varies considerably across practice settings (for example, community, outpatient, or inpatient; primary, secondary, or tertiary care), measurement methodology and study criterion (for example, diagnostic criteria used, depressive subtypes included, and interview type).

Currently used structured diagnostic instruments rely primarily on direct questions to elicit DSM criteria for Axis II disorders. In contrast, clinicians infrequently use such methods in making PD diagnoses. Instead, clinicians tend to rely on observations of patients' attitudes and behaviour and descriptions of their interpersonal interactions (97). Further, structured interviews for PDs typically assign patients with PDs 3 to 6 Axis II diagnoses (98), whereas clinicians tend to prioritize a single PD diagnosis (99).

Given the above considerations, it is not surprising that a wide range (6% to 87%) of prevalence estimates for PDs have been obtained in studies of patients with MDD (100). PD estimates in clinical samples are approximately 30% to 40%, with a

predominance of cluster B (dramatic, emotional, or erratic) and cluster C (anxious or fearful) PDs. The relatively high prevalence (47%) of PDs in a community sample of individuals with depression not seeking treatment suggests that the observed high rate of comorbidity is not simply an artifact related to treatment-seeking behaviour (101). There may be a particularly high prevalence of PDs in patients with early-onset MDD (102) and in patients with chronic depression, including dysthymia and double depression (103).

When personality dysfunction is assessed dimensionally (that is, using a range of scores on a rating instrument) rather than categorically (as in DSM-IV), a parallel pattern of results emerges. Patients with depression show elevations of several indices of personality dysfunction. Some of the most robust and well-replicated findings include elevated levels of neuroticism, self-criticism, dependency, and obsessiveness, as well as lower levels of extraversion (104).

14. Are personality assessments valid during major depressive episodes (MDEs)?

The apparent prevalence of PDs in patients with depression declines when patients are reassessed after treatment for depression (105–107). Elevated scores on personality trait measures, including neuroticism, harm avoidance, self-criticism, and dependency significantly decline (108–111), while (low) extraversion scores increase (110) after treatment for depression. Although absolute scores on various proposed personality vulnerability factors for depression change with treatment for depression, recent studies have also demonstrated the considerable relative stability of these traits over time (112,113). These observations indicate that the distinction between personality and depression cannot be seen as an absolute distinction of trait and state (114).

15. Are comorbid PDs a risk factor for suicidal behaviour in patients with depression?

Comorbidity of PDs with MDD has been associated with an increased frequency of suicidal ideation and attempts (115), as well as completed suicide (116). Much of this association is related to comorbidity between depression and the impulsive/erratic spectrum of PDs, including DSM-IV cluster B PDs, especially borderline PD (BPD), or ICD-10 emotionally unstable PD (116–118).

Patients with depression and a comorbid PD who are at increased risk for suicidal behaviour may require special precautions in treatment. For example, it may be appropriate to avoid the use of medications that are potentially lethal in overdose or to supply only limited quantities of such agents (for example, TCAs or lithium). The suicidal risk in patients with MDD and a comorbid PD may be more effectively managed by combining antidepressant strategies with other

therapeutic modalities targeting the underlying PD. Various forms of psychotherapeutic treatment have shown promise in the treatment of suicidal behaviour in patients with PDs, including dialectical behaviour therapy (119), partial hospitalization (120), and psychoanalytically oriented therapy (121). There is also preliminary evidence of the value of pharmacologic treatments for reducing important target symptoms in patients with PDs. For example, SSRIs (122,123) and anti-convulsants (124,125) may be of value in reducing suicidal behaviour and/or impulsivity in patients with PDs.

16. What is the impact of comorbid PDs on the treatment outcome for depression?

Many studies examining the outcome of treatment for depression exclude patients with severe PDs, particularly BPD (126). Despite this, there is evidence that PDs (or maladaptive personality dimensions) adversely affect the outcome of brief psychotherapy (127–129), pharmacotherapy (130–134), and ECT (135–137). These adverse effects have included lower rates of response or remission, slower response to treatment, increased likelihood of chronicity, and increased likelihood of relapse or recurrence. There has, however, been little consistency in the kinds of outcome measures used in the various reports, although one large study failed to find the expected association between PD diagnoses and the rate of response to pharmacotherapy for chronic depression (138,139).

17. What are the specific effects of antidepressants on comorbid depression and PDs?

The SSRIs have shown efficacy in reducing impulsive, aggressive, and self-destructive behaviour in BPD (17). Open-trial data suggest the utility of fluoxetine in the treatment of patients with BPD and depression (140–142). In a recent study of chronic depression in which most of the patients had coexisting PD, pharmacotherapy was effective in this patient population, with enhanced outcomes using pluralistic treatments that included pharmacotherapy and psychotherapy (143). Moreover, interpersonal therapy (IPT) may be a viable alternative therapy in the treatment of major depression and PD. As one of its focal points, interpersonal deficits are specifically targeted and modulated with the goal of reducing symptoms of major depression.

Further, open-trial data support the utility of some novel antipsychotics (olanzapine) against affective symptoms, anger, and interpersonal sensitivity (144). Although safety and tolerability concerns limit the use of MAOIs, there is evidence that phenelzine and tranylcypromine are effective in this population as antidepressants and in reducing hostility and anger (145–147).

Table 7.1 Medications with potential to induce depression^aMedications with a **probable** association:

Anabolic steroids
 Interferons
 Isotretinoin
 Systemic corticosteroids
 Substances of abuse: alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, hallucinogens, narcotics
 Oral contraceptives
 Certain anticonvulsant drugs (vigabatrin, clobazam, phenobarbital)

Medications with a **possible** association:

Cardiovascular
 Captopril (and other angiotensin-converting enzyme [ACE] inhibitors)
 Clonidine (Catapres)
 Digoxin
 Methyldopa (Aldomet)
 Propranolol (and other beta blockers)
 Verapamil (and other calcium channel blockers)

Other
 Various anticonvulsants
 Baclofen (and other muscular relaxants)
 Bromocriptine (Parlodel)
 Cimetidine (and other histamine H2 antagonists)
 Disulfiram (Antabuse)
 Indomethacin (and other nonsteroidal anti-inflammatory drugs [NSAIDs])
 Levodopa
 Reserpine
 Zidovudine (AZT and other anti-retroviral medications for HIV infection)

^aAdapted from Rundell and Wise (228) and Stoudemire and Fogel (229,230).**AXIS III COMORBIDITY**

Depression and medical disorders frequently co-occur. The lifetime prevalence of depressive and anxiety disorders in individuals with a medical disorder is 42% (148,149). Reported rates of depression vary considerably across medical disorders (150). Neurological, endocrine, and cardiovascular disorders, as well as cancer are frequently complicated by depressive disorders. The presence of concurrent depression may predispose an individual to medical symptom amplification, poor adaptation to illness, diminished adherence to medical regimens, and functional impairment. Further, comorbid depression increases health care use and mortality (151–153).

Depressive symptoms such as fatigue, anorexia, insomnia, and weight loss are often obscured by the overt disability imparted by the physical disease. Given this symptomatic overlap, careful attention should be paid to the cognitive and affective symptoms of depression, including pervasive anhedonia, hopelessness, crying, guilt, feelings of worthlessness, and suicidal ideation. Unless it can be unequivocally established that the somatic symptoms are due to the underlying medical disorder, they should be attributed to the comorbid major depression. It is also important to consider the potential for other medications to induce depression (see Table 7.1).

Importantly, the treatment of some medical disorders may be independently associated with the onset of depression. For example, alpha-interferon therapy, commonly employed in the treatment of hepatitis and certain forms of cancer, is associated with substance-induced depression. In circumstances such as this, where discontinuation is not an option, the initiation of antidepressant therapy is effective (154).

18. How effective is psychotherapy in the treatment of comorbid depression in various medical disorders?

Patient preference, clinical judgment, and the availability of treatment options will usually suggest an appropriate management strategy. Psychoeducation often includes a discussion about the influence of depression on physical illness (for example, exacerbation of pain, sleep difficulty, and fatigue). Spiegel (155) suggests that there are 4 basic components of psychotherapy for medically ill patients: social support, emotional expression, cognitive restructuring, and training in coping skills. Specific types of psychotherapy, such as CBT and IPT may be appropriate for treatment of depression in certain patients with medical illness, alone or in combination with antidepressant medication. There have only been a few RCTs for these therapies in patients with various types of comorbid physical illness. Trials of psychotherapeutic

interventions in patients with depression who have cardiac disease, HIV infection, cancer, and other common medical conditions will be reviewed.

Cardiac Disease. Despite evidence that the relation between depression and cardiac mortality decreases with increasing social support (156,157), an attempt to modify post myocardial infarction (post-MI) survival rates with a home-based psychosocial nursing intervention was ineffective (158). CBT is under investigation for the treatment of depression or social isolation in cardiac patients (159).

HIV Infection and AIDS. Group CBT, group supportive psychotherapy (SP), and individual psychotherapies have all been shown with RCTs to be effective in reducing symptoms of distress or depression among HIV-positive patients (160–164). Following encouraging results from an open trial of IPT for HIV-positive patients with moderate-to-severe depression (161), a subsequent RCT was conducted. IPT or imipramine plus SP were significantly better than either CBT or SP alone in alleviating symptoms of depression (163).

Cancer. Many psychosocial interventions in patients with cancer have often been directed toward treatment of psychosocial distress and not targeted specifically for patients with depressive disorders. Health education, stress management, behavioural training, problem-solving techniques, and psychosocial group support are beneficial for newly diagnosed patients or those in the early stages of treatment (165). Women with metastatic breast cancer showed improvement not only in mood but also in duration of survival following group psychotherapy (166,167). For patients with advanced metastatic disease, weekly group-support programs focused on daily coping, pain management, and dealing with existential issues related to death and dying were recommended. The National Comprehensive Cancer Network has developed practice guidelines for the management of psychosocial distress, which is considered to range from normal reactions to the stress of coping with cancer to full-fledged psychiatric disorders such as MDD, substance use disorders, and PDs (168). In a review of 10 RCTs of psychological counselling interventions for depression in cancer patients, tailored individual counselling strategies were as effective as structured cognitive-behavioural counselling, and drug therapy in combination with BT was also highly effective in the treatment of depression in patients with cancer (169).

Other Conditions. There is RCT support for CBT in patients with Type II diabetes (170) and for patients with multiple sclerosis (171). There is also evidence from open trials for the effectiveness of CBT in treating patients with poststroke depression (172).

19. How effective is pharmacotherapy for MDD in various medical disorders?

A metaanalysis of trials for depressive disorders in patients with medical illness provides evidence that antidepressants, including SSRIs, TCAs, and other antidepressants, significantly improve symptoms of depression in patients with a wide range of physical diseases (173). Nevertheless, certain markers of medical illness may confer decreased response to antidepressant treatment.

Cardiac Disease. In an RCT, both paroxetine and nortriptyline were efficacious, and paroxetine produced fewer cardiovascular side effects (174). Other open-label trials involving sertraline in post-MI patients with depression (175), as well as fluoxetine (176) or other SSRIs (177) and bupropion (178) in patients with MDD and cardiac conduction disease and/or congestive heart disease, suggested safety, tolerability, and effectiveness. Postural hypotension may occur in patients with preexisting orthostatic hypotension or congestive heart failure, or it may occur in elderly patients with osteoporosis, causing increased risk of falls and consequent bone fractures. TCAs have effects on cardiac conduction similar to those seen with type IA antiarrhythmic medications, which were demonstrated to be associated with excess mortality when given to patients with ischemic heart disease in a large RCT. Thus, there is evidence not to recommend the use of TCAs as first choice in patients with depression and cardiac disease (179).

HIV Infection and AIDS. Most RCTs in the HIV/AIDS population involved TCAs. Imipramine was superior to placebo (180) and comparable with paroxetine (181), while desipramine and methylphenidate were also equivalent (182). In trials of patients with HIV infection or AIDS, severity of immunosuppression was not associated with response to antidepressant medication (180,181,183). Data from open trials using SSRIs (184) and nefazodone also support effectiveness and tolerability. The effect of adding fluoxetine to structured group psychotherapy in HIV-positive men with mild-to-moderate depression produced additional benefit in one trial (185) but not in another (186).

Cancer. In 2 RCTs, mianserin (not available in the US or Canada) was efficacious in women with depression and cancer (187,188).

Acute Stroke Disease. In a placebo-controlled RCT in patients with major or minor depression and acute stroke disease, nortriptyline was significantly more efficacious than fluoxetine or placebo (189), confirming favourable findings from a previous placebo-controlled nortriptyline trial (190). Citalopram (191), but not trazodone (192), demonstrated efficacy in a placebo-controlled trial.

Other Conditions. In separate RCTs, both nortriptyline (193) and fluoxetine (194) were efficacious as antidepressants in diabetic patients, although benefits to glycemic control were

inconsistent. In Parkinson's disease, nortriptyline was superior to placebo in relieving depressive symptoms but had little effect on the movement symptoms (195), while open-label data support the use of sertraline (196) or paroxetine (197). Desipramine was superior to placebo in treating depression associated with multiple sclerosis (198). Limited data from open-label trials also support the use of desipramine (199) and fluoxetine (200) in patients receiving renal dialysis.

20. What are the added cautions to consider when using antidepressants in treating the medically ill patient?

Antidepressant pharmacokinetics are altered in medically ill patients. Drug interactions and the presence of gastrointestinal, hepatic, and renal disease affect drug absorption, metabolism, and excretion, respectively (201). Delay of gastric emptying by drugs such as metoclopramide and slowing of gastrointestinal motility by drugs with anticholinergic properties will change the rate of antidepressant absorption. Disease of the proximal ileum, where most psychotropic drugs are absorbed, may diminish drug absorption and cause poor response. TCAs and their metabolites are poorly dialyzable and can cause toxicity in patients with renal failure, despite normal laboratory-measured plasma levels of the drugs and their desmethylated metabolites. Pharmacokinetic data for SSRIs in patients with renal failure are limited; however, studies suggest fluoxetine and citalopram kinetics are not affected, and the same is likely true for the other SSRIs (201–203). Venlafaxine and mirtazapine clearance is decreased in renal failure, and as such, the dosages of these antidepressants should be reduced along with slower titration regimens. In renal failure, it is recommended to reduce the dosage of antidepressant at least initially, or in some cases increase the dosing interval, particularly with TCAs (201). Significant hepatic disease will alter protein-binding and decrease the metabolism of all antidepressants. Although there is limited clinical evidence guiding the use of antidepressants in patients with hepatic dysfunction, a reduced dose of one of the shorter half-life SSRIs, such as sertraline, fluvoxamine, or citalopram, would be logical for these patients (201,203). Because of concern about cognitive impairment due to subclinical hepatic encephalopathy, the choice of a non-sedating antidepressant is also suggested, along with careful follow-up of cognitive function (201).

The presence of neurologic disease poses a particular challenge with respect to minimizing the chance of adverse effects due to antidepressant medication. In patients with Parkinson's disease, SSRIs given to patients with depression have been reported to cause worsening in motor performance, which improved after withdrawal of the antidepressant (204,205). Nevertheless, reports suggest this occurs infrequently (205–207). Compared with TCAs, SSRIs have better

tolerability and comparable efficacy in patients who have depression with Parkinson's disease (208).

At therapeutic doses of different antidepressants, seizures are rare but have been reported in up to 4% of patients (209). Some TCAs and heterocyclics (for example, maprotiline) and bupropion SR may have a higher seizure risk, mainly in overdoses or with high plasma levels in patients who are slow metabolizers (210). With therapeutic doses of antidepressants, both patient factors (for example, history of previous seizures, brain damage, dementia, or alcohol abuse) and drug-related factors (for example, dosage of antidepressant and concurrent drugs which lower the seizure threshold or inhibit metabolism of the antidepressant) may predispose to seizures (211). All antidepressants have the potential to cause hyponatremia by inducing inappropriate secretion of antidiuretic hormone, which sometimes causes seizures, particularly in elderly patients who are also taking diuretics. When patient-related risk factors and medical therapies for depression were controlled for, major depression itself was found to be associated with a 6-fold increased risk for new-onset, idiopathic seizures in patients age 55 years or older (212). The SSRIs, moclobemide, nefazodone, and venlafaxine are believed to have low seizure-inducing properties and, because of this, are considered by some clinicians as first-line treatment in patients with depression and epilepsy (211,213).

21. What are the drug–drug interactions for antidepressants with drugs prescribed to the medically ill?

The potential for the SSRIs and novel antidepressants to interact with other medications prescribed to medically ill patients should be evaluated, but this should not prevent their use in these patients. If drug–drug interactions are a major concern, selection of citalopram, mirtazapine, or venlafaxine could be considered, because these medications have mild or no CYP-inhibition properties (201,214). In addition to consideration of an individual antidepressant's potential to inhibit CYP isoenzymes, it must be kept in mind that the genetic variability of CYP enzyme metabolism among patients of the same race, and among those from different races, limits our ability to predict drug interactions (215). Thus, a high level of clinical vigilance is warranted for drug interactions in medically ill patients treated for depression with the newer antidepressants.

The degree of CYP inhibition by newer antidepressants and the clinically significant substrates for antidepressant-inhibited isoenzymes are reviewed in Section IV. Although there is concern about potential drug–drug interactions in all patients treated with multiple medications, those at particular risk include patients on cardiac medications, antiretroviral medications, or antiepileptic medications who are treated with the new antidepressants.

Antidepressants that inhibit the CYP2D6 liver isoenzyme, such as paroxetine, fluoxetine, and sertraline should not be used in combination with type IC antiarrhythmics, such as encainide, flecainide, mexiletine, and propafenone. Also, if beta blockers are given with these antidepressants, there should be closer monitoring of patients' heart rates and electrocardiograms because of the potential for increased beta-blockade effects. Nefazodone, fluvoxamine, and fluoxetine all inhibit the CYP3A4 isoenzyme, which is responsible for metabolism of several cardiac medications: calcium channel blockers; "statin" medications (with the exception of pravastatin) given to lower blood lipids; some antiarrhythmics such as amiodarone, lidocaine, quinidine, and propafenone; and the antirejection drug, cyclosporin. Combination of nefazodone, fluvoxamine, and fluoxetine with these cardiac medications should be avoided if possible.

Medications given to patients with HIV infection, including protease inhibitors, other antiretroviral medications, and medications used to treat opportunistic infections (for example, ketoconazole) are substrates, inhibitors, or inducers of the CYP isoenzymes. Such medications have the potential to interact with the newer antidepressants (216). In patients with HIV infection who take protease inhibitors (particularly ritonavir, which strongly inhibits multiple CYP isoenzymes), antidepressants which inhibit CYP isoenzymes, such as nefazodone, paroxetine, and fluoxetine, should be avoided (217,218). Protease inhibitors also have the potential to increase levels of TCAs, causing increased risk of TCA side effects or toxicity.

Antiepileptic drugs such as phenytoin, carbamazepine, phenobarbital, and primidone can induce CYP isoenzymes, thereby decreasing levels of the antidepressant drugs that are metabolized by the same enzyme systems (213). The newer antiepileptic drugs, such as gabapentine, lamotrigine, and topiramate, appear to cause minimal liver CYP isoenzyme induction (213). Antidepressants that inhibit CYP isoenzymes, such as fluoxetine, paroxetine, nefazodone, fluvoxamine, and sertraline may increase levels of antiepileptic drugs metabolized by the same enzyme system. This inhibition has the potential to cause side effects or toxicity of some antiepileptic drugs; phenytoin and carbamazepine may be especially vulnerable (211).

St John's wort (*Hypericum perforatum*), a herbal product taken by some patients to reduce depressive symptoms, has the potential to induce certain cytochrome enzymes and thereby reduce levels of the following medications: protease inhibitors, cyclosporin (with potential to lead to transplant rejection), digoxin, warfarin, oral contraceptives, theophylline, amitriptyline, and possibly, other TCAs (219).

Interactions between warfarin and SSRIs, novel antidepressants, or TCAs can occur in anticoagulated patients. Changes in warfarin protein binding due to antidepressant

displacement, as well as CYP isoenzyme inhibition from newer antidepressants, can cause increased prothrombin times. As such, careful monitoring of anticoagulation is necessary if warfarin is combined with antidepressants.

Serotonin syndrome is a drug–drug interaction that is commonly the result of the interaction between serotonergic agents and MAOIs (220). Clinical features include confusion, agitation, hyperreflexia, sweating, and tremor. Combining other antidepressants (particularly SSRIs), meperidine, dextromethorphan, pentazocine, or L-dopa with the irreversible MAOIs (phenelzine and tranylcypromine) is contraindicated, and combining SSRIs or TCAs with moclobemide should be done with great caution (221). There has also been concern about the potential for serotonin syndrome occurring in patients with Parkinson's disease given SSRIs in combination with selegiline. The combination should be avoided, and it is also recommended waiting 2 weeks after stopping selegiline before starting an SSRI (221,222). Serotonin syndrome has also been reported with the combination of fluoxetine and carbamazepine (223).

22. Is there evidence to support the use of ECT in patients with depression and comorbid medical illness?

The use of ECT with appropriate medical preassessment, stabilization, and follow-up is almost never contraindicated and may be a safe alternative, especially in frail, elderly, or ill patients who cannot tolerate fast medication increases or who suffer from long periods of unremitting depressive illness (224). Early consideration of ECT has been recommended for patients with severe depression and cancer who do not respond to antidepressant medication or cannot tolerate side effects (225). Patients with Parkinson's disease and other movement disorders have been shown to benefit not only from alleviation of depression but also from improvement in their motor symptoms (226). ECT is the treatment of choice for "lethal catatonia," a syndrome of delirium, fever, rigidity, autonomic instability, dehydration, mutism, and posturing associated with schizophrenia, mood disorders, and organic illnesses such as encephalitis (227). Patients with neuroleptic malignant syndrome may benefit from ECT if they do not respond to standard pharmacologic treatment (224).

Medical conditions that may increase the risk of morbidity associated with ECT include the following: 1) conditions associated with increased intracranial pressure, such as brain tumours, subdural hematoma, meningitis, or acute stroke; 2) conditions associated with risk of serious hemorrhage, such as intracranial bleeding and unstable vascular aneurysms; and 3) cardiac instability, such as recent MI or unstable cardiac arrhythmia. To reduce cognitive impairment associated with ECT when it is given to patients with cognitive impairment or dementia, the treatment frequency can be

reduced to once or twice weekly and nondominant-unilateral electrode placement used.

ACKNOWLEDGEMENTS

The authors thank the following for their contributions: Dr Raymond W Lam, Dr Juan C Negrete, Dr Blenos AT Pedersen, and Dr Lilian Thorpe contributed to earlier drafts of this paper; Dr Scott B Patten and Dr Michael Rosenbluth provided peer review prior to publication.

REFERENCES

- Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 1993;29:85–96.
- Regier DA, Rae DS, Narrow WE, Kaelber CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. *Br J Psychiatry* 1998; Suppl: 24–28.
- Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depress Anxiety* 2000;12 (Suppl 1):69–76.
- Judd LL, Kessler RC, Paulus MP, Zeller PV, Wittchen HU, Kunovac JL. Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). *Acta Psychiatr Scand* 1998;393 (Suppl 1):6–11.
- Brown TA, Barlow DH. Comorbidity among anxiety disorders: implications for treatment and DSM-IV. *J Consult Clin Psychol* 1992;60:835–44.
- Massion AO, Warshaw MG, Keller MB. Quality of life and psychiatric morbidity in panic disorder and generalized anxiety disorder. *Am J Psychiatry* 1993;150:600–7.
- Noyes R Jr, Woodman C, Garvey MJ, Cook BL, Suelzer M, Clancy J, and others. Generalized anxiety disorder vs. panic disorder. Distinguishing characteristics and patterns of comorbidity. *J Nerv Ment Dis* 1992;180:369–79.
- Kendall PC, Kortlander E, Chansky TE, Brady EU. Comorbidity of anxiety and depression in youth: treatment implications. *J Consult Clin Psychol* 1992;60:869–80.
- Leclercq Y. Is depression under-recognised and undertreated? *Int Clin Psychopharmacol* 1998;13 (Suppl 5):S3–S6.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): American Psychiatric Association; 1994.
- Gurney C, Roth M, Garside RF, Kerr TA, Schapira K. Studies in the classification of affective disorders. The relationship between anxiety states and depressive illnesses. II. *Br J Psychiatry* 1972;121:162–6.
- Roth M, Gurney C, Garside RF, Kerr TA. Studies in the classification of affective disorders. The relationship between anxiety states and depressive illnesses. I. *Br J Psychiatry* 1972;121:147–61.
- Keller MB, Hanks DL. Anxiety symptom relief in depression treatment outcomes. *J Clin Psychiatry* 1995;56 (Suppl 6):22–9.
- Bakish D. The patient with comorbid depression and anxiety: the unmet need. *J Clin Psychiatry* 1999;60 (Suppl 6):20–4.
- Goldney RD, Fisher LJ, Wilson DH, Cheok F. Major depression and its associated morbidity and quality of life in a random, representative Australian community sample. *Aust N Z J Psychiatry* 2000;34:1022–9.
- Parker G, Wilhelm K, Mitchell P, Gladstone G. Predictors of 1-year outcome in depression. *Aust N Z J Psychiatry* 2000;34:56–64.
- Schatzberg AF. New indications for antidepressants. *J Clin Psychiatry* 2000;61 (Suppl) 11:9–17.
- Furukawa T, Streiner DL, Young LT. Antidepressant plus benzodiazepine for major depression (Cochrane Review). *Cochrane Database Syst Rev* 2000;CD001026.
- Hoehn-Saric R, Ninan P, Black DW, Stahl S, Greist JH, Lydiard B, and others. Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Arch Gen Psychiatry* 2000;57:76–82.
- Goodnick PJ, Puig A, DeVane CL, Freund BV. Mirtazapine in major depression with comorbid generalized anxiety disorder. *J Clin Psychiatry* 1999;60:446–8.
- King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, Byford S. Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care. *Health Technol Assess* 2000;4:1–83.
- Rief W, Trenkamp S, Auer C, Fichter MM. Cognitive behavior therapy in panic disorder and comorbid major depression. A naturalistic study. *Psychother Psychosom* 2000;69:70–8.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, and others. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8–19.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, and others. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264:2511–8.
- Raimo EB, Schuckit MA. Alcohol dependence and mood disorders. *Addict Behav* 1998;23:933–46.
- Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, and others. Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addict Behav* 1998;23:893–907.
- Ross HE, Swinson R, Larkin EJ, Doumani S. Diagnosing comorbidity in substance abusers. Computer assessment and clinical validation. *J Nerv Ment Dis* 1994;182:556–63.
- Hodgins DC, Dufour M, Armstrong S. The reliability and validity of the inventory to diagnose depression in alcohol-dependent men and women. *J Subst Abuse* 2000;11:369–78.
- Galbaud du FG, Newman SC, Boothroyd LJ, Bland RC. Treatment seeking for depression: role of depressive symptoms and comorbid psychiatric diagnoses. *J Affect Disord* 1999;52:31–40.
- Keuthen NJ, Naura RS, Borrelli B, Goldstein M, DePue J, Murphy C, and others. Comorbidity, smoking behavior and treatment outcome. *Psychother Psychosom* 2000;69:244–50.
- Covey LS, Glassman AH, Stetner F. Major depression following smoking cessation. *Am J Psychiatry* 1997;154:263–5.
- Thorsteinsson HS, Gillin JC, Patten CA, Golshan S, Sutton LD, Drummond S, and others. The effects of transdermal nicotine therapy for smoking cessation on depressive symptoms in patients with major depression. *Neuropsychopharmacology* 2001;24:350–8.
- Statistical report on the health of Canadians. Statistical report on the health of Canadians prepared by the federal, provincial and territorial advisory committee on population health for the meeting of ministers of health, Charlottetown, PEI: September 16–17, 1999. Ottawa: Minister of Public Works and Government Services Canada; 1999.
- Martino S, Carroll KM, O'Malley SS, Rounsaville BJ. Motivational interviewing with psychiatrically ill substance abusing patients. *Am J Addict* 2000;9:88–91.
- Scott J, Gilvarry E, Farrell M. Managing anxiety and depression in alcohol and drug dependence. *Addict Behav* 1998;23:919–31.
- Swanson AJ, Pantalon MV, Cohen KR. Motivational interviewing and treatment adherence among psychiatric and dually diagnosed patients. *J Nerv Ment Dis* 1999;187:630–5.
- Cornelius JR, Salloum IM, Ehler JG, Jarrett PJ, Cornelius MD, Perel JM, and others. Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1997;54:700–5.
- McGrath PJ, Nunes EV, Stewart JW, Goldman D, Agosti V, O'Cepek-Welickson K, and others. Imipramine treatment of alcoholics with primary depression: A placebo-controlled clinical trial. *Arch Gen Psychiatry* 1996;53:232–40.
- Mason BJ, Kocsis JH, Ritvo EC, Cutler RB. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *JAMA* 1996;275:761–7.
- Mueller PD, Korey WS. Death by "ecstasy": the serotonin syndrome? *Ann Emerg Med* 1998;32:377–80.
- Braun DL, Sunday SR, Halmi KA. Psychiatric comorbidity in patients with eating disorders. *Psychol Med* 1994;24:859–67.
- Kennedy SH, Kaplan AS, Garfinkel PE, Rockert W, Toner B, Abbey SE. Depression in anorexia nervosa and bulimia nervosa: discriminating depressive symptoms and episodes. *J Psychosom Res* 1994;38:773–82.
- Halmi KA, Eckert E, Marchi P, Sampugnaro V, Apple R, Cohen J. Comorbidity of psychiatric diagnoses in anorexia nervosa. *Arch Gen Psychiatry* 1991;48:712–8.
- Cantwell DP, Sturzenberger S, Burroughs J, Salkin B, Green JK. Anorexia nervosa. An affective disorder? *Arch Gen Psychiatry* 1977;34:1087–93.
- Hatsukami DK, Mitchell JE, Eckert ED. Eating disorders: a variant of mood disorders? *Psychiatr Clin North Am* 1984;7:349–65.
- Fava M, Abraham M, Clancy-Colecchi K, Pava JA, Matthews J, Rosenbaum JF. Eating disorder symptomatology in major depression. *J Nerv Ment Dis* 1997;185:140–4.
- Herzog DB, Greenwood DN, Dorer DJ, Flores AT, Ekeblad ER, Blais MA, and others. Mortality in eating disorders: a descriptive study. *Int J Eat Disord* 2000;28:20–6.
- Patel DR, Phillips EL, Pratt HD. Eating disorders. *Indian J Pediatr* 1998;65:487–94.
- Bulik CM, Sullivan PF, Joyce PR. Temperament, character and suicide attempts in anorexia nervosa, bulimia nervosa and major depression. *Acta Psychiatr Scand* 1999;100:27–32.
- Kaye WH, Weltzin TE, Hsu LK, Bulik CM. An open trial of fluoxetine in patients with anorexia nervosa. *J Clin Psychiatry* 1991;52:464–71.
- Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? *Am J Psychiatry* 1998;155:548–51.
- Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo-controlled, double-blind trial. *Arch Gen Psychiatry* 1992;49:139–47.

53. Goldstein DJ, Wilson MG, Ascroft RC, al Banna M. Effectiveness of fluoxetine therapy in bulimia nervosa regardless of comorbid depression. *Int J Eat Disord* 1999;25:19–27.
54. Rothschild R, Quitkin HM, Quitkin FM, Stewart JW, Ocepek-Welickson K, McGrath PJ, and others. A double-blind placebo-controlled comparison of phenelzine and imipramine in the treatment of bulimia in atypical depressives. *Int J Eat Disord* 1994;15:1–9.
55. Kruger S, Kennedy SH. Psychopharmacotherapy of anorexia nervosa, bulimia nervosa and binge-eating disorder. *J Psychiatry Neurosci* 2000;25:497–508.
56. Wold PN. Eating disorder symptoms in affective disorder. *J Psychiatry Neurosci* 1991;16:204–8.
57. Lindenmayer JP, Grochowski S, Kay SR. Schizophrenic patients with depression: psychopathological profiles and relationship with negative symptoms. *Compr Psychiatry* 1991;32:528–33.
58. Siris SG. Depression in schizophrenia: perspective in the era of “Atypical” antipsychotic agents. *Am J Psychiatry* 2000;157:1379–89.
59. Korean AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. Depression in first-episode schizophrenia. *Am J Psychiatry* 1993;150:1643–8.
60. Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res* 1992;6:201–8.
61. Marengo J, Harrow M, Herbener ES, Sands J. A prospective longitudinal 10-year study of schizophrenia’s 3 major factors and depression. *Psychiatry Res* 2000;97:61–77.
62. Glazer W, Prusoff B, John K, Williams D. Depression and social adjustment among chronic schizophrenic outpatients. *J Nerv Ment Dis* 1981;169:712–7.
63. Roy A, Thompson R, Kennedy S. Depression in chronic schizophrenia. *Br J Psychiatry* 1983;142:465–70.
64. Meltzer HY. Suicide and schizophrenia: clozapine and the InterSePT study. International Clozaril/Leponex Suicide Prevention Trial. *J Clin Psychiatry* 1999;60 (Suppl 12):47–50.
65. Sands JR, Harrow M. Depression during the longitudinal course of schizophrenia. *Schizophr Bull* 1999;25:157–71.
66. Addington D, Addington J, Patten S. Depression in people with first-episode schizophrenia. *Br J Psychiatry* 1998;172 (Suppl):90–2.
67. Sensky T, Turkington D, Kingdon D, Scott JL, Scott J, Siddle R, and others. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry* 2000;57:165–72.
68. Tarrier N, Kinney C, McCarthy E, Humphreys L, Wittkowski A, Morris J. Two-year follow-up of cognitive-behavioral therapy and supportive counseling in the treatment of persistent symptoms in chronic schizophrenia. *J Consult Clin Psychol* 2000;68:917–22.
69. Inoue K, Kawabata S. Cognitive therapy for a major depressive episode in residual schizophrenia. *Psychiatry Clin Neurosci* 1999;53:563–7.
70. Siris SG, Morgan V, Fagerstrom R, Rifkin A, Cooper TB. Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Arch Gen Psychiatry* 1987;44:533–9.
71. Silver H, Nassar A. Fluvoxamine improves negative symptoms in treated chronic schizophrenia: an add-on double-blind, placebo-controlled study. *Biol Psychiatry* 1992;31:698–704.
72. Spina E, De Domenico P, Ruello C, Longobardo N, Gitto C, Ancione M, and others. Adjunctive fluoxetine in the treatment of negative symptoms in chronic schizophrenic patients. *Int Clin Psychopharmacol* 1994;9:281–5.
73. Heeringa M, Beurskens R, Schouten W, Verduijn MM. Elevated plasma levels of clozapine after concomitant use of fluvoxamine. *Pharm World Sci* 1999;21:243–4.
74. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998;12:192–214.
75. Alpert JE, Maddocks A, Nierenberg AA, O’Sullivan R, Pava JA, Worthington JJ III, and others. Attention deficit hyperactivity disorder in childhood among adults with major depression. *Psychiatry Res* 1996;62:213–9.
76. Carlson GA. Mania and ADHD: comorbidity or confusion. *J Affect Disord* 1998;51:177–87.
77. Santosh PJ, Taylor E. Stimulant drugs. *Eur Child Adolesc Psychiatry* 2000;9 (Suppl 1):127–43.
78. Searight HR, Burke JM, Rottnek F. Adult ADHD: evaluation and treatment in family medicine. *Am Fam Physician* 2000;62:2077–2.
79. Daviss WB, Bentivoglio P, Racusin R, Brown KM, Bostic JQ, Wiley L. Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. *J Am Acad Child Adolesc Psychiatry* 2001;40:307–14.
80. Findling RL. Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents, and adults: a case series. *J Child Adolesc Psychopharmacol* 1996;6:165–75.
81. Raskind MA. The clinical interface of depression and dementia. *J Clin Psychiatry* 1998;59 (Suppl 10):9–12.
82. Lyketsos CG, Steele C, Baker L, Galik E, Kopunek S, Steinberg M, and others. Major and minor depression in Alzheimer’s disease: prevalence and impact. *J Neuropsychiatry Clin Neurosci* 1997;9:556–61.
83. Heun R, Papassotiropoulos A, Jessen F, Maier W, Breitner JC. A family study of Alzheimer disease and early- and late-onset depression in elderly patients. *Arch Gen Psychiatry* 2001;58:190–6.
84. Cummings JL. Vascular subcortical dementias: clinical aspects. *Dementia* 1994;5:177–80.
85. Cummings JL, Benson DF. Psychological dysfunction accompanying subcortical dementias. *Annu Rev Med* 1988;39:53–61.
86. Katz IR. Diagnosis and treatment of depression in patients with Alzheimer’s disease and other dementias. *J Clin Psychiatry* 1998;59 (Suppl 9):38–44.
87. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. *J Clin Psychiatry* 1999;60 (Suppl 20):9–15.
88. Teri L, Logsdon RG, Uomoto J, McCurry SM. Behavioral treatment of depression in dementia patients: a controlled clinical trial. *J Gerontol B Psychol Sci Soc Sci* 1997;52:159–66.
89. Petracca G, Teson A, Chemerinski E, Leiguarda R, Starkstein SE. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer’s disease. *J Neuropsychiatry Clin Neurosci* 1996;8:270–5.
90. Reifler BV, Teri L, Raskind M, Veith R, Barnes R, White E, and others. Double-blind trial of imipramine in Alzheimer’s disease patients with and without depression. *Am J Psychiatry* 1989;146:45–9.
91. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. *Br J Psychiatry* 1990;157:894–901.
92. Lyketsos CG, Sheppard JM, Steele CD, Kopunek S, Steinberg M, Baker AS, and others. Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer’s disease: initial results from the depression in Alzheimer’s disease study. *Am J Psychiatry* 2000;157:1686–9.
93. Taragano FE, Lyketsos CG, Mangone CA, Allegri RF, Comesana-Diaz E. A double-blind, randomized, fixed-dose trial of fluoxetine vs. amitriptyline in the treatment of major depression complicating Alzheimer’s disease. *Psychosomatics* 1997;38:246–52.
94. Trappler B, Cohen CI. Use of SSRIs in “very old” depressed nursing home residents. *Am J Geriatr Psychiatry* 1998;6:83–9.
95. Karlsson I, Godderis J, Augusto De Mendonca LC, Nygaard H, Simanyi M, Taal M, and others. A randomised, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. *Int J Geriatr Psychiatry* 2000;15:295–305.
96. Rao V, Lyketsos CG. The benefits and risks of ECT for patients with primary dementia who also suffer from depression. *Int J Geriatr Psychiatry* 2000;15:729–35.
97. Westen D. Divergences between clinical and research methods for assessing personality disorders: implications for research and the evolution of axis II. *Am J Psychiatry* 1997;154:895–903.
98. Skodol AE, Rosnick L, Kellman D, Oldham JM, Hyler SE. Validating structured DSM-III-R personality disorder assessments with longitudinal data. *Am J Psychiatry* 1988;145:1297–9.
99. Widiger T, Frances A. Towards a dimensional model for the personality disorders. In: Costa P, Widiger T, editors. *Personality disorders and the five-factor model*. Washington (DC): American Psychological Association;1994. p 19–36.
100. Corruble E, Ginestet D, Gueffi JD. Comorbidity of personality disorders and unipolar major depression: a review. *J Affect Disord* 1996;37:157–70.
101. Zimmerman M, Coryell W. DSM-III personality disorder diagnoses in a nonpatient sample. Demographic correlates and comorbidity. *Arch Gen Psychiatry* 1989;46:682–9.
102. Fava M, Alpert JE, Borus JS, Nierenberg AA, Pava JA, Rosenbaum JF. Patterns of personality disorder comorbidity in early-onset versus late-onset major depression. *Am J Psychiatry* 1996;153:1308–12.
103. Pepper CM, Klein DN, Anderson RL, Riso LP, Ouimette PC, Lizardi H. DSM-III-R axis II comorbidity in dysthymia and major depression. *Am J Psychiatry* 1995;152:239–47.
104. Enns MW, Cox BJ. Personality dimensions and depression: review and commentary. *Can J Psychiatry* 1997;42:274–84.
105. Joffe RT, Regan JJ. Personality and depression. *J Psychiatr Res* 1988;22:279–86.
106. Peselow ED, Sanfilippo MP, Fieve RR, Gulbenkian G. Personality traits during depression and after clinical recovery. *Br J Psychiatry* 1994;164:349–54.
107. Stuart S, Simons AD, Thase ME, Pilkonis P. Are personality assessments valid in acute major depression? *J Affect Disord* 1992;24:281–9.
108. Brody AL, Saxena S, Fairbanks LA, Alborzian S, Demaree HA, Maidment KM, and others. Personality changes in adult subjects with major depressive disorder or obsessive-compulsive disorder treated with paroxetine. *J Clin Psychiatry* 2000;61:349–55.
109. Hellerstein DJ, Kocsis JH, Chapman D, Stewart JW, Harrison W. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: effects on personality. *Am J Psychiatry* 2000;157:1436–44.
110. Hirschfeld RM, Klerman GL, Clayton PJ, Keller MB, McDonald-Scott P, Larkin BH. Assessing personality: effects of the depressive state on trait measurement. *Am J Psychiatry* 1983;140:695–9.
111. Joffe RT, Bagby RM, Levitt AJ, Regan JJ, Parker JD. The tridimensional personality questionnaire in major depression. *Am J Psychiatry* 1993;150:959–60.
112. Santor DA, Bagby RM, Joffe RT. Evaluating stability and change in personality and depression. *J Pers Soc Psychol* 1997;73:1354–62.
113. Zuroff DC, Blatt SJ, Sanislow CA III, Bondi CM, Pilkonis PA. Vulnerability to depression: reexamining state dependence and relative stability. *J Abnorm Psychol* 1999;108:76–89.

114. Widiger TA. Issues in the validation of the personality disorders. *Prog Exp Pers Psychopathol Res* 1993;16:117-36.
115. Van Gastel A, Schotte C, Maes M. The prediction of suicidal intent in depressed patients. *Acta Psychiatr Scand* 1997;96:254-9.
116. Cheng AT, Mann AH, Chan KA. Personality disorder and suicide. A case-control study. *Br J Psychiatry* 1997;170:441-6.
117. Lesage AD, Boyer R, Grunberg F, Vanier C, Morissette R, Menard-Buteau C, and others. Suicide and mental disorders: a case-control study of young men. *Am J Psychiatry* 1994;151:1063-8.
118. Corbitt EM, Malone KM, Haas GL, Mann JJ. Suicidal behavior in patients with major depression and comorbid personality disorders. *J Affect Disord* 1996;39:61-72.
119. Koerner K, Linehan MM. Research on dialectical behavior therapy for patients with borderline personality disorder. *Psychiatr Clin North Am* 2000;23:151-67.
120. Simpson EB, Pistorello J, Begin A, Costello E, Levinson J, Mulberry S, and others. Use of dialectical behavior therapy in a partial hospital program for women with borderline personality disorder. *Psychiatr Serv* 1998;49:669-73.
121. Bateman A, Fonagy P. Effectiveness of partial hospitalization in the treatment of borderline personality disorder: a randomized controlled trial. *Am J Psychiatry* 1999;156:1563-9.
122. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry* 1997;54:1081-8.
123. Verkes RJ, Van der Mast RC, Hengeveld MW, Tuyl JP, Zwinderman AH, Van Kempen GM. Reduction by paroxetine of suicidal behavior in patients with repeated suicide attempts but not major depression. *Am J Psychiatry* 1998;155:543-7.
124. Stein DJ, Simeon D, Frenkel M, Islam MN, Hollander E. An open trial of valproate in borderline personality disorder. *J Clin Psychiatry* 1995;56:506-10.
125. Kavoussi RJ, Coccaro EF. Divalproex sodium for impulsive aggressive behavior in patients with personality disorder. *J Clin Psychiatry* 1998;59:676-80.
126. Sullivan PF, Joyce PR. Effects of exclusion criteria in depression treatment studies. *J Affect Disord* 1994;32:21-6.
127. Pilkonis PA, Frank E. Personality pathology in recurrent depression: nature, prevalence, and relationship to treatment response. *Am J Psychiatry* 1988;145:435-41.
128. Shea MT, Pilkonis PA, Beckham E, Collins JF, Elkin I, Sotsky SM, and others. Personality disorders and treatment outcome in the NIMH treatment of depression collaborative research program. *Am J Psychiatry* 1990;147:711-8.
129. Hardy GE, Barkham M, Shapiro DA, Stiles WB, Rees A, Reynolds S. Impact of cluster C personality disorders on outcomes of contrasting brief psychotherapies for depression. *J Consult Clin Psychol* 1995;63:997-1004.
130. Ezquiaga E, Garcia A, Bravo F, Pallares T. Factors associated with outcome in major depression: a 6-month prospective study. *Soc Psychiatry Psychiatr Epidemiol* 1998;33:552-7.
131. O'Leary D, Costello F. Personality and outcome in depression: an 18-month prospective follow-up study. *J Affect Disord* 2001;63:67-78.
132. Patience DA, McGuire RJ, Scott AI, Freeman CP. The Edinburgh Primary Care Depression Study: personality disorder and outcome. *Br J Psychiatry* 1995;167:324-30.
133. Peselow ED, Robins CJ, Sanfilippo MP, Block P, Fieve RR. Sociotropy and autonomy: relationship to antidepressant drug treatment response and endogenous-nonendogenous dichotomy. *J Abnorm Psychol* 1992;101:479-86.
134. Sato T, Sakado K, Sato S, Morikawa T. Cluster A personality disorder: a marker of worse treatment outcome of major depression? *Psychiatry Res* 1994;53:153-9.
135. Casey P, Meagher D, Butler E. Personality, functioning, and recovery from major depression. *J Nerv Ment Dis* 1996;184:240-5.
136. Sareen J, Enns MW, Guertin JE. The impact of clinically diagnosed personality disorders on acute and 1-year outcomes of electroconvulsive therapy. *J ECT* 2000;16:43-51.
137. Zimmerman M, Coryell W, Pfohl B, Corenthal C, Stangl D. ECT response in depressed patients with and without a DSM-III personality disorder. *Am J Psychiatry* 1986;143:1030-2.
138. Duggan CF, Lee AS, Murray RM. Does personality predict long-term outcome in depression? *Br J Psychiatry* 1990;157:19-24.
139. Surtees PG, Wainwright NW. Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. *Br J Psychiatry* 1996;169:338-47.
140. Norden MJ. Fluoxetine in borderline personality disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 1989;13:885-93.
141. Cornelius JR, Soloff PH, Perel JM, Ulrich RF. Fluoxetine trial in borderline personality disorder. *Psychopharmacol Bull* 1990;26:151-4.
142. Markowitz JC. Combined therapy for a 30-year-old woman with early-onset dysthymia. *Hosp Community Psychiatry* 1991;42:1103-4, 1107.
143. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, and others. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342:1462-70.
144. Schulz SC, Camlin KL, Berry SA, Jesberger JA. Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. *Biol Psychiatry* 1999;46:1429-35.
145. Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. *Arch Gen Psychiatry* 1993;50:377-85.
146. Parsons B, Quitkin FM, McGrath PJ, Stewart JW, Tricamo E, Ocepek-Welickson K, and others. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. *Psychopharmacol Bull* 1989;25:524-34.
147. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch Gen Psychiatry* 1988;45:111-9.
148. Patten SB. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *J Affect Disord* 2001;63:35-41.
149. Wells KB, Golding JM, Burnam MA. Psychiatric disorder and limitations in physical functioning in a sample of the Los Angeles general population. *Am J Psychiatry* 1988;145:712-7.
150. Rodin G, Craven J, Littlefield C. Depression in the Medically III: an Integrated Approach. New York: Brunner/Mazel; 1991.
151. Wells JE, Bushnell JA, Hornblow AR, Joyce PR, Oakley-Browne MA. Christchurch Psychiatric Epidemiology Study, Part I: Methodology and lifetime prevalence for specific psychiatric disorders. *Aust N Z J Psychiatry* 1989;23:315-26.
152. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. *Psychosom Med* 1999;61:6-17.
153. von Ammon CS, Furlanetto LM, Creech SD, Powell LH. Medical illness, past depression, and present depression: a predictive triad for in-hospital mortality. *Am J Psychiatry* 2001;158:43-8.
154. Musselman DL, Lawson DH, Gummick JF, Manatunga AK, Penna S, Goodkin RS, and others. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001;344:961-6.
155. Spiegel D. Cancer and depression. *Br J Psychiatry* 1996; Suppl:109-16.
156. Frasure-Smith N, Lesperance F, Gravel G, Masson A, Juneau M, Talajic M, and others. Social support, depression, and mortality during the first year after myocardial infarction. *Circulation* 2000;101:1919-24.
157. Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *Eur Heart J* 2000;21:1072-80.
158. Frasure-Smith N, Lesperance F, Prince RH, Verrier P, Garber RA, Juneau M, and others. Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. *Lancet* 1997;350:473-9.
159. The ENRICH investigators. Enhancing recovery in coronary heart disease patients (ENRICH): study design and methods. *Am Heart J* 2000;139:1-9.
160. Kelly JA, Murphy DA, Bahr GR, Kalichman SC, Morgan MG, Stevenson LY, and others. Outcome of cognitive-behavioral and support group brief therapies for depressed, HIV-infected persons. *Am J Psychiatry* 1993;150:1679-86.
161. Markowitz JC, Klerman GL, Clougherty KF, Spielman LA, Jacobsberg LB, Fishman B, and others. Individual psychotherapies for depressed HIV-positive patients. *Am J Psychiatry* 1995;152:1504-9.
162. Lutgendorf SK, Antoni MH, Ironson G, Starr K, Costello N, Zuckerman M, and others. Changes in cognitive coping skills and social support during cognitive behavioral stress management intervention and distress outcomes in symptomatic human immunodeficiency virus (HIV)-seropositive gay men. *Psychosom Med* 1998;60:204-14.
163. Markowitz JC, Kocsis JH, Fishman B, Spielman LA, Jacobsberg LB, Frances AJ, and others. Treatment of depressive symptoms in human immunodeficiency virus-positive patients. *Arch Gen Psychiatry* 1998;55:452-7.
164. Lee MR, Cohen L, Hadley SW, Goodwin FK. Cognitive-behavioral group therapy with medication for depressed gay men with AIDS or symptomatic HIV infection. *Psychiatr Serv* 1999;50:948-52.
165. Fawzy FI, Fawzy NW, Arndt LA, Pasnau RO. Critical review of psychosocial interventions in cancer care. *Arch Gen Psychiatry* 1995;52:100-13.
166. Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. *Arch Gen Psychiatry* 1981;38:527-33.
167. Spiegel D, Bloom JR, Kraemer HC, Gotthel E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989;2:888-91.
168. National Comprehensive Cancer Network. NCCN practice guidelines for the management of psychosocial distress. *Oncology (Huntingt)* 1999;13:113-47.
169. Sellick SM, Crooks DL. Depression and cancer: an appraisal of the literature for prevalence, detection, and practice guideline development for psychological interventions. *Psychooncology* 1999;8:315-33.
170. Lustman PJ, Griffith LS, Freedland KE, Kissel SS, Clouse RE. Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med* 1998;129:613-21.
171. Larcombe NA, Wilson PH. An evaluation of cognitive-behaviour therapy for depression in patients with multiple sclerosis. *Br J Psychiatry* 1984;145:366-71.
172. Gordon WA, Hibbard MR. Poststroke depression: an examination of the literature. *Arch phys med rehabil* 1997;78:658-63.
173. Gill D, Hatcher S. Antidepressants for depression in people with physical illness (Cochrane Review). *Cochrane Database Syst Rev* 2000;4:CD001312.
174. Nelson JC, Kennedy JS, Pollock BG, Laghrissi-Thode F, Narayan M, Nobler MS, and others. Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. *Am J Psychiatry* 1999;156:1024-8.

175. Shapiro PA, Lesperance F, Frasure-Smith N, O'Connor CM, Baker B, Jiang JW, and others. An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHAT Trial). Sertraline antidepressant heart attack trial. *Am Heart J* 1999;137:1100-6.
176. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT, Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry* 1998;155:660-5.
177. Askinazi C. SSRI treatment of depression with comorbid cardiac disease. *Am J Psychiatry* 1996;153:135-6.
178. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry* 1991;148:512-6.
179. Glassman AH, Roose SP, Bigger JT, Jr. The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. *JAMA* 1993;269:2673-5.
180. Rabkin JG, Rabkin R, Harrison W, Wagner G. Effect of imipramine on mood and enumerative measures of immune status in depressed patients with HIV illness. *Am J Psychiatry* 1994;151:516-23.
181. Elliott AJ, Uldall KK, Bergam K, Russo J, Claypoole K, Roy-Byrne PP. Randomized, placebo-controlled trial of paroxetine versus imipramine in depressed HIV-positive outpatients. *Am J Psychiatry* 1998;155:367-72.
182. Fernandez F, Levy JK, Samley HR, Pirozzolo FJ, Lachar D, Crowley J, and others. Effects of methylphenidate in HIV-related depression: a comparative trial with desipramine. *Int J Psychiatry Med* 1995;25:53-67.
183. Rabkin JG, Wagner GJ, Rabkin R. Fluoxetine treatment for depression in patients with HIV and AIDS: a randomized, placebo-controlled trial. *Am J Psychiatry* 1999;156:101-7.
184. Ferrando SJ, Goldman JD, Charness WE. Selective serotonin reuptake inhibitor treatment of depression in symptomatic HIV infection and AIDS. Improvements in affective and somatic symptoms. *Gen Hosp Psychiatry* 1997;19:89-97.
185. Zisook S, Peterkin J, Goggin KJ, Sledge P, Atkinson JH, Grant I. Treatment of major depression in HIV-seropositive men. HIV Neurobehavioral Research Center Group. *J Clin Psychiatry* 1998;59:217-24.
186. Targ EF, Karasic DH, Diefenbach PN, Anderson DA, Bystritsky A, Fawzy FI. Structured group therapy and fluoxetine to treat depression in HIV-positive persons. *Psychosomatics* 1994;35:132-7.
187. Costa D, Mogos I, Toma T. Efficacy and safety of mianserin in the treatment of depression of women with cancer. *Acta Psychiatr Scand* 1985;320(Suppl):85-92.
188. van Heeringen K, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. *Br J Psychiatry* 1996;169:440-3.
189. Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, and others. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. *Am J Psychiatry* 2000;157:351-9.
190. Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR. Nortriptyline treatment of post-stroke depression: a double-blind study. *Lancet* 1984;1:297-300.
191. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. *Stroke* 1994;25:1099-1104.
192. Reding MJ, Orto LA, Winter SW, Fortuna IM, Di Ponte P, McDowell FH. Antidepressant therapy after stroke. A double-blind trial. *Arch Neurol* 1986;43:763-5.
193. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, and others. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom Med* 1997;59:241-50.
194. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000;23:618-23.
195. Andersen J, Aabro E, Gulmann N, Hjeltnest A, Pedersen HE. Anti-depressive treatment in Parkinson's disease. A controlled trial of the effect of nortriptyline in patients with Parkinson's disease treated with L-DOPA. *Acta Neurol Scand* 1980;62:210-9.
196. Hauser RA, Zesiewicz TA. Sertraline for the treatment of depression in Parkinson's disease. *Mov Disord* 1997;12:756-9.
197. Tesi S, Antonini A, Canesi M, Zecchinelli A, Mariani CB, Pezzoli G. Tolerability of paroxetine in Parkinson's disease: a prospective study. *Mov Disord* 2000;15:986-9.
198. Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *Am J Psychiatry* 1990;147:1493-7.
199. Kennedy SH, Craven JL, Rodin GM, Roin GM. Major depression in renal dialysis patients: an open trial of antidepressant therapy. *J Clin Psychiatry* 1989;50:60-3.
200. Levy NB, Blumenfeld M, Beasley CM Jr, Dubey AK, Solomon RJ, Todd R, and others. Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function. *Gen Hosp Psychiatry* 1996;18:8-13.
201. Beliles K, Stoudemire A. Psychopharmacologic treatment of depression in the medically ill. *Psychosomatics* 1998;39 (Suppl):S2-S19.
202. Bergstrom RF, Beasley CM, Jr., Levy NB, Blumenfeld M, Lemberger L. The effects of renal and hepatic disease on the pharmacokinetics, renal tolerance, and risk-benefit profile of fluoxetine. *Int Clin Psychopharmacol* 1993;8:261-6.
203. Joffe P, Larsen FS, Pedersen V, Ring-Larsen H, Aaes-Jorgensen T, Sidhu J. Single-dose pharmacokinetics of citalopram in patients with moderate renal insufficiency or hepatic cirrhosis compared with healthy subjects. *Eur J Clin Pharmacol* 1998;54:237-42.
204. Steur EN. Increase of Parkinson disability after fluoxetine medication. *Neurology* 1993;43:211-3.
205. Richard IH, Maughn A, Kurlan R. Do serotonin reuptake inhibitor antidepressants worsen Parkinson's disease? A retrospective case series. *Mov Disord* 1999;14:155-7.
206. Caley CF, Friedman JH. Does fluoxetine exacerbate Parkinson's disease? *J Clin Psychiatry* 1992;53:278-82.
207. Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. *J Clin Psychiatry* 1996;57:449-54.
208. Cummings JL, Masterman DL. Depression in patients with Parkinson's disease. *Int J Geriatr Psychiatry* 1999;14:711-8.
209. Rosenstein DL, Nelson JC, Jacobs SC. Seizures associated with antidepressants: a review. *J Clin Psychiatry* 1993;54:289-99.
210. Preskorn SH, Fast GA. Tricyclic antidepressant-induced seizures and plasma drug concentration. *J Clin Psychiatry* 1992;53:160-2.
211. Lambert MV, Robertson MM. Depression in epilepsy: etiology, phenomenology, and treatment. *Epilepsia* 1999;40 (Suppl 10):S21-S47.
212. Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. *Ann Neurol* 2000;47:246-9.
213. Kanner AM, Nieto JC. Depressive disorders in epilepsy. *Neurology* 1999;53:S26-S32.
214. Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Drug interactions with newer antidepressants: role of human cytochromes P450. *J Clin Psychiatry* 1998;59 (Suppl 15):19-27.
215. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996;153:311-20.
216. Tseng AL, Foisy MM. Significant interactions with new antiretrovirals and psychotropic drugs. *Ann Pharmacother* 1999;33:461-73.
217. Elliott AJ, Russo J, Bergam K, Claypoole K, Uldall KK, Roy-Byrne PP. Antidepressant efficacy in HIV-seropositive outpatients with major depressive disorder: an open trial of nefazodone. *J Clin Psychiatry* 1999;60:226-31.
218. Penzak SR, Reddy YS, Grimsley SR. Depression in patients with HIV infection. *Am J Health Syst Pharm* 2000;57:376-86.
219. Boullata JI, Nace AM. Safety issues with herbal medicine. *Pharmacotherapy* 2000;20:257-69.
220. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991;148:705-13.
221. Shulman RW. The serotonin syndrome: a tabular guide. *Can J Clin Pharmacol* 1995;2:139-44.
222. Lieberman A. Managing the neuropsychiatric symptoms of Parkinson's disease. *Neurology* 1998;50 (Suppl):S33-S38.
223. Dursun SM, Mathew VM, Reveley MA. Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993;342:442-3.
224. Beale MD, Kellner CH. Electroconvulsive therapy: an overview. In: Rundell JR, Wise MG, editors. *The American psychiatric press textbook of consultation-liaison psychiatry*. 1st ed. Washington (DC): American Psychiatric Press; 1996. p 1039-50.
225. Beale MD, Kellner CH, Parsons PJ. ECT for the treatment of mood disorders in cancer patients. *Convuls Ther* 1997;13:222-6.
226. Faber R, Trimble MR. Electroconvulsive therapy in Parkinson's disease and other movement disorders. *Mov Disord* 1991;6:293-303.
227. Mann SC, Caroff SN, Bleier HR, Welz WK, Kling MA, Hayashida M. Lethal catatonia. *Am J Psychiatry* 1986;143:1374-81.
228. Rundell JR, Wise MG, editors. *The American psychiatric textbook of consultation-liaison psychiatry*. 1st ed. Washington (DC): American Psychiatric Press; 1996.
229. Stoudemire A, Fogel BS. Organization and development of combined medical-psychiatric units: Part 1. *Psychosomatics* 1986;27:341-5.
230. Stoudemire GA, Fogel BS. The emergence of medical psychiatry: a provocative viewpoint. *Psychosomatics* 1988;29:207-13.