Diagnosis and Treatment of Depression in Patients With Congestive Heart Failure: A Review of the Literature

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ABSTRACT

Context: Major depressive disorder (MDD) can be challenging to diagnose in patients with congestive heart failure, who often suffer from fatigue, insomnia, weight changes, and other neurovegetative symptoms that overlap with those of depression. Pathophysiologic mechanisms (eg, inflammation, autonomic nervous system dysfunction, cardiac arrhythmias, and altered platelet function) connect depression and congestive heart failure.

Objective: We sought to review the prevalence, diagnosis, neurobiology, and treatment of depression associated with congestive heart failure.

Data Sources: A PubMed search of all English-language articles between January 2003 and January 2013 was conducted using the search terms *congestive heart failure* and *depression*.

Study Selection: We found 1,498 article abstracts and 19 articles (meta-analyses, systematic reviews, and original research articles) that were selected for inclusion, as they contained information about our focus on diagnosis, treatment, and pathophysiology of depression associated with congestive heart failure. The search was augmented with manual review of reference lists of articles from the initial search. Articles selected for review were determined by author consensus.

Data Extraction: The prevalence, diagnosis, neurobiology, and treatment of depression associated with congestive heart failure were reviewed. Particular attention was paid to the safety, efficacy, and tolerability of antidepressant medications commonly used to treat depression and how their side-effect profiles impact the pathophysiology of congestive heart failure. Drug-drug interactions between antidepressant medications and medications used to treat congestive heart failure were examined.

Results: MDD is highly prevalent in patients with congestive heart failure. Moreover, the prevalence and severity of depression correlate with the degree of cardiac dysfunction and development of congestive heart failure. Depression increases the risk of congestive heart failure, particularly in those patients with coronary artery disease , and is associated with a poorer quality of life, increased use of health care resources, more frequent adverse clinical events and hospitalizations, and twice the risk of mortality.

Conclusions: At present, limited empirical data exist with regard to treatment of depression in the increasingly large population of patients with congestive heart failure. Evidence reveals that both psychotherapeutic treatment (eg, cognitive-behavioral therapy) and pharmacologic treatment (eg, use of the selective serotonin reuptake inhibitor sertraline) are safe and effective in reducing depression severity in patients with cardiovascular disease. Collaborative care programs featuring interventions that work to improve adherence to medical and psychiatric treatments improve both cardiovascular disease and depression outcomes. Depression rating scales such as the 9-item Patient Health Questionnaire should be used to monitor therapeutic efficacy.

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Major depressive disorder (MDD), a condition characterized by ≥2 weeks of depressed mood or loss of pleasure and ≥4 neurovegetative symptoms (ie, abnormalities in sleep, energy, concentration, appetite, and/or psychomotor functioning), as well as affective and cognitive symptoms (eg, abnormalities in interest, concentration, feelings of guilt, suicidal ideation),[1] has a 12-month prevalence in men and women of 4.9% and 8.6%,[2] respectively, and a lifetime prevalence of 13.2% in men compared with 20.2% in women.[3]

Patients with coronary artery disease who suffer a myocardial infarction (MI) or undergo coronary artery bypass grafting often develop depression (16%–20%),[4–7] and those with comorbid depression and coronary artery disease have a diminished quality of life, an increased rate of cardiac-related morbidity, and premature mortality.[8] Coronary artery disease is thought to be the cause of congestive heart failure (CHF) in nearly 65% of patients.[9]

Indeed, CHF afflicts an estimated 6.6 million Americans ≥18 years of age[10] and another 15 million patients in the 51 countries represented by the European Society of Cardiology.[11] In addition, depression impairs patient self-care of CHF,[12] diminishes quality of life,[13] increases use of health care resources,[14] leads to more patient hospitalizations,[15] and is associated with a higher mortality rate.[16]

Studies of patients with CHF[17,18] indicate that they also suffer from an increased prevalence of depression, as is the case with other cardiovascular conditions and procedures (eg, MI,[4–6] cardiac catheterization,[19–21] unstable angina,[22] coronary artery bypass grafting[7]) (Table 1).

METHOD

We conducted a PubMed search of all English-language articles between January 2003 and January 2013 using the search terms *congestive heart failure* and *depression*. We found 1,498 article abstracts and 19 articles (meta-analyses, systematic reviews, and original research articles) that were selected for inclusion, as they contained information about our focus on diagnosis, treatment, and pathophysiology of

Clinical Points

- Patients with congestive heart failure (CHF) have clinically significant depression at a rate 2- to 3-times higher than those of the general population, and depression creates barriers to successful CHF treatment (eg, more frequent adverse clinical events and hospitalizations, twice the risk of mortality).
- Depression increases the risk of CHF, particularly in those with risk factors for CHF, such as systolic hypertension.
- Depression is underrecognized and undertreated in patients with CHF, and clinicians can use screening tools to improve diagnosis and potentially improve morbidity and mortality in these patients.

Table 1. Prevalence of Depression in Various Patient Populations With Cardiovascular Disease

Patient Population	Prevalence	Reference
Post–myocardial infarction	16%–20% (MDD)	Frasure-Smith et al, 1993[4] Schleifer et al, 1989[5] Thombs et al, 2006[6]
Cardiac catheterization	17%–23% (MDD)	Carney et al, 1988[19] Hance et al, 1996[20] Gonzalez et al, 1996[21]
Unstable angina	15% (MDD)	Lespérance et al, 2000[22]
Post–coronary artery bypass surgery	20% (MDD)	Connerney et al, 2001[7]
Congestive heart failure	21.6% (clinically significant depression)	Jiang et al, 2001[17] Freedland et al, 2003[18] Rutledge et al, 2006[16]

Abbreviation: MDD = major depressive disorder.

depression associated with CHF. The search was augmented with a manual review of reference lists of articles from the initial search. Articles selected for review were determined by author consensus. We reviewed the prevalence, diagnosis, neurobiology, and treatment of depression associated with CHF. Particular attention was paid to the safety, efficacy, and tolerability of antidepressant medications commonly used to treat depression and how their side-effect profiles impacted the pathophysiology of CHF. Drug-drug interactions between antidepressant medications and medications used to treat CHF were examined.

RESULTS

Neurobiology of Depression and Its Potential Contribution to CHF

Multiple pathophysiologic processes link MDD and cardiovascular disease.[23,24] In particular, depression and CHF share many potential biopsychological mechanisms.[24–41] Table 2 reviews the pathophysiology of depression and its proposed role in CHF.

Prevalence and Impact of Depression on Quality of Life in Patients With CHF: Cross-Sectional Studies

A meta-analysis by Rutledge and colleagues[16] of patients with CHF calculated an overall aggregated point prevalence rate of clinically significant depression of 21.5%, a rate 2 to 3 times higher than that of the general population[42] (based on clinical interviews, review of the patient's medical record, or depression symptom inventories, eg, the Beck Depression Inventory [BDI][43] or Zung Self-Rating Depression Scale[44]). The mean overall prevalence rate of minor depression (defined as a BDI score ≤ 10), on the basis of 13 studies with 5,376 participants, was even greater (35.5%).[16]

Whether the quality or severity of depression symptoms varies among those with subclasses of CHF (eg, systolic or diastolic CHF or CHF with preserved vs diminished ejection fraction) remains to be determined.[16] In the Depression After Myocardial Infarction Study,[45] those with new-onset post-MI depression had a trend toward a lower ejection fraction, and it stands to reason that patients with a decreased ejection fraction may experience more somatic symptoms (eg, fatigue) due to diminished cardiac output. However, Evangelista and colleagues[46] examined the correlates of fatigue in patients with heart failure and did not find an association between fatigue and ejection fraction. The authors[46] explained the lack of association by noting that all patients with CHF, regardless of ejection fraction, are expected to have symptoms such as fatigue, and symptom status has never been well correlated with ejection fraction. They commented that symptom improvement is a major indicator in CHF guidelines rather than ejection fraction when determining efficacy of drug therapy.[46]

Few studies have examined the influence of selected patient characteristics (eg, gender, race) on the prevalence of depression in patients with CHF.[47] In a study with a substantial proportion of participants with CHF and an ejection fraction < 40%, nearly half scored as depressed (as measured by the BDI[43]), and of those patients, more than half were women.[47] Moreover, in comparison to nondepressed patients with CHF, depressed patients reported a significantly worse quality of life,[47] as characterized by the Medical Outcomes Study 36-item Short Form Health Survey (SF-36)[48] and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).[49]

Results of a cross-sectional study by Evangelista and colleagues[50] of 241 patients with advanced systolic heart failure (7% non-Latino black patients, 22.8% Latino patients, and 60.7% non-Latino white patients) showed that non-Latino blacks had higher levels of depression ($P = .026$) compared to the Latino patients, as measured by the self-administered, 9-item Patient Health Questionnaire (PHQ-9).[51] This study[50] defined a positive depression screen as ≥ 2 of the 9 depressive symptoms answered at least "more than half the days" and endorsement of at least 1 of the 2 main MDD diagnostic symptoms (depressed mood or loss of interest) by the patient. Each of the 9 items on the PHQ-9 describes 1 symptom corresponding to 1 of the 9 *DSM-IV* diagnostic criteria.[1] A similar trend of higher levels of depression was noted when

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Table 2. Pathophysiology of Depression and Potential Contribution to Heart Failure

Pathophysiologic Alterations of Depression	Impact on Congestive Heart Failure Disease Process
Increased activity of the hypothalamic-pituitary-adrenal axis, leading to increased secretion of corticotropin-releasing hormone activation, adrenocorticotropic hormone, and cortisol	Cortisol may play an important role in the progression of heart failure due to mineralocorticoid receptor agonism (under conditions of oxidative stress and/or tissue damage) and has been shown to be an independent predictor of cardiac events (ie, death or hospitalization)[27]; another study[28] showed that higher serum levels of both cortisol and aldosterone were independent predictors of increased mortality risk in chronic heart failure
Increased sympathoadrenomedullary activity (resulting in increased levels of circulating catecholamines)	Norepinephrine has significant predictive power for adverse heart failure prognosis[29–35]
Altered autonomic nervous system activity, which contributes to reduced heart rate variability; imbalance between sympathetic and parasympathetic systems	May increase the risk for several types of adverse cardiac events, including ventricular fibrillation,[36] arrhythmias,[37] and sudden death[38]
Increases in inflammation and circulating tumor necrosis factor, interleukin-6, and C-reactive protein levels	Inflammation[39,40] and a shift in the type 1/type 2 helper T cell ratio[41] may induce not only depressive symptoms, but also congestive heart failure progression
Increases in platelet activation and aggregation	May result in an increased risk of thrombus formation[24]

comparing non-Latino blacks and non-Latino whites, but the differences were not statistically significant.[50] In another cross-sectional study of 241 urban, low-income, minority patients in a CHF management program, roughly half had prominent depression symptoms (K.A.H., unpublished data, 2012), as measured by a PHQ-9[51] score > 9. One limitation of this study was that there were an insufficient number of white patients in the analysis.

Negative Impact of Depression on Cardiac Outcomes in Patients With CHF: Longitudinal Studies

Depression increases the risk of CHF,[52] particularly in those already at risk for CHF (eg, patients with systolic hypertension).[53] Indeed, one study[54] analyzed the medical records of 7,719 patients who, at the time of diagnosis of coronary artery disease (with ≥ 70% stenosis), failed to meet criteria for depression or CHF. Depression was associated with an increased risk for development of CHF (adjusted hazard ratio [HR] = 1.50; 95% CI, 1.38–1.63; $P < .0001$).[54]

The Myocardial Infarction and Depression-Intervention Trial (MIND-IT)[55] showed that, after an index myocardial infarction, the prevalence and severity of depression are interrelated with the degree of cardiac dysfunction and the development of CHF. Levels of left ventricular ejection fraction (LVEF) were inversely correlated with BDI[56] scores 3 months post-myocardial infarction. An inverse relationship was also found between LVEF and *ICD-10* depressive disorder, ie, a lower LVEF was associated with a higher rate of depression 3–12 months post–myocardial infarction ($P < .01$).[55] Unadjusted logistic regression analysis showed that patients with severe left ventricular dysfunction (LVEF < 30%) after myocardial infarction had 4.46 times the odds (95% CI, 2.91–6.83) of being depressed compared with those with preserved left ventricular function (LVEF > 60%).[55]

In another longitudinal study, DeWolfe and colleagues[13] quantified the relationship between PHQ-9[30] and MLHFQ[49] scores for patients enrolled in an outpatient study. The MLHFQ assessed the burden of disease on an individual's overall quality of life. Even when controlling for other factors (eg, age, gender, LVEF, body mass index, ischemic etiology of CHF, diabetes, hypertension, New York Heart Association class), which could potentially affect the relationship between the 2 scales, depression was associated with a worse quality of life.[13]

Clinically significant depression often complicates the management of CHF (eg, increases the tendency to use health care resources,[14] to be admitted to a hospital,[15] and to develop adverse clinical events).[16] Rutledge and colleagues'[16] meta-analysis of depression and CHF reviewed 8 independent cohort studies,[17,18,57–62] ranging from 6 months to > 4 years, and tracked the incidence of mortality and associated cardiac events (eg, heart transplantation) in association with depression. The aggregated risk estimate revealed a > 2-fold risk of death and associated clinical events for patients with CHF and depressive symptoms or a depressive disorder (relative risk = 2.1, 95% CI, 1.7–2.6). The combined evidence did not indicate that the relationship between depression and CHF outcomes differed by length of follow-up (eg, graded association between depression mortality over time). However, the results of individual studies[58,59] indicated that this is an area that requires further study.[16]

More recent research has confirmed and extended the association of depression and CHF.[63,64] A study[65] of 974 participants (of whom 85% were men) followed for > 3 years showed that increased depression symptoms (as measured by BDI-II[66] score ≥ 14) in patients included in the Atrial Fibrillation and Congestive Heart Failure trial[67] with comorbid atrial fibrillation, with electrocardiogram documentation within the past 6 months, an LVEF ≤ 35% within the past 6 months, and a history of symptomatic CHF (and eligibility for rhythm and rate control treatment strategies) were associated with increased cardiovascular mortality (adjusted HR = 1.57; 95% CI, 1.20–2.07; $P < .001$), arrhythmic death (adjusted HR = 1.69; 95% CI, 1.13–2.53; $P = .01$), and all-cause mortality (adjusted HR = 1.38; 95% CI, 1.07–1.77; $P = .01$).[65]

Screening Tests for the Diagnosis of Depression in Patients With CHF

Unfortunately, depression often goes unrecognized in patients with CHF,[68] most likely due to the overlap of CHF symptoms (eg, fatigue, weight changes, poor sleep) with the neurovegetative symptoms of depression (eg, diminished

energy and concentration, insomnia, decreased appetite, psychomotor retardation).[69] A systematic review[70] of the accuracy of depression screening of patients receiving cardiovascular care demonstrated that screening instruments with a priori–defined cutoff scores, irrespective of the depressive symptoms endorsed, had a sensitivity ranging from 39%–100% (median of 84%) and a specificity ranging from 58%–94% (median of 79%). The inclusive approach (ie, including somatic symptoms used to make a diagnosis of depression) has led to an almost 2-fold difference in the estimates of depression (in medically ill elderly hospitalized patients).[71] The exclusive (ie, eliminating somatic items to provide more specificity) diagnostic approach missed 49% of patients with MDD identified by the inclusive approach.[71] Exclusive approaches to the diagnosis of depression in the medically ill may also lead to the noninclusion of patients with subsyndromal depression.[69] Higher mortality rates have been observed in patients after acute myocardial infarction who have levels of depressive symptoms not generally considered clinically significant (ie, BDI score of 4–9, below the usual cutoff of < 10 for identifying mild depression) and lower than the levels usually considered predictive of mortality post–myocardial infarction, compared to those without depression.[72] Lesperance and colleagues[73] also observed an increase in cardiac mortality with BDI scores < 10 and showed a dose-dependent association between the level of depression during an admission for myocardial infarction and a long-term cardiac mortality independent of established prognostic factors; most of the impact was explained by improvement in depressive symptoms. Similar to low-density lipoprotein cholesterol levels, depressive symptoms within the normal range for a healthy population may represent a cardiac risk factor in patients with coronary artery disease.[73]

The American Heart Association[74] recommends screening for depression with either of 2 brief screening tools for depression (ie, the 2-item[75] or 9-item[51] PHQ). If the answer is "yes" to either or both questions on the PHQ-2, then all PHQ-9 items should be asked. The PHQ-9 is efficient and easily administered; the PHQ-9 has been used successfully on inpatient cardiac units with good acceptance by staff and patients.[76]

One study[77] that used cutoffs on the PHQ-2 (≥ 3) and PHQ-9 (≥ 10) resulted in excellent specificity (92% and 90%, respectively) but poor sensitivity (39% and 54%, respectively) in patients with coronary artery disease. However, another study[78] utilizing sample-specific receiver operating characteristic curve analysis demonstrated that a lower threshold on the PHQ-9 (≥ 6) optimized sensitivity (83%) and specificity (78%) among outpatients with coronary artery disease.

Screening tools are not designed to establish a diagnosis, as they do not rely on having all (or even the majority of) relevant symptoms. The most effective tools (eg, the PHQ-9) are easy to administer and interpret. Thus, screening tools are used to take "shortcuts" to identify who needs a more in-depth assessment (ie, mental health referral). For example, the PHQ-9 can screen positive with only 3 items being scored. However, 3 symptoms, even if severe, would not qualify a patient for a diagnosis of MDD per the *DSM-IV*.[1] Ongoing controversy continues as to whether or not to "score as positive" somatic items consistent with CHF (eg, fatigue, sleep disruption [associated with cough, orthopnea, paroxysmal nocturnal dyspnea, and nocturia][79]). Sleep disturbances may increase the risk of comorbid depression,[79] but depression will not be diagnosed if depressed mood or anhedonia is absent, even in a patient with 5 or more neurovegetative symptoms. The criteria for depression are predicated on having the symptoms, including depressed mood or anhedonia (the loss of pleasure).

After an initial screening, patients with significant depression should be assessed for suicide risk by asking, "Have the symptoms or feelings we've been talking about led you to think you might be better off dead?" "Recently, have you had any thoughts that life is not worth living or that you'd be better off dead?" and "Have you had thoughts about hurting or killing yourself?" (If yes, ask, "Do you have a plan to hurt or kill yourself? Have you actually done anything to hurt or kill yourself?")[80] Indications for an immediate referral to psychiatry include recent self-harm or thoughts of suicide, expressed intent and/or a plan for suicide, and psychotic symptoms (eg, hallucinations, delusions, and/or paranoia).

Other indications for psychiatric consultation/referral include hopelessness or extreme feelings of guilt/shame, a significant decline in social or occupational functioning, and prominent agitation or volatility, as well as complicated psychiatric comorbidity (eg, obsessive-compulsive disorder, posttraumatic stress disorder, substance abuse), a complex psychopharmacologic regimen, and an inadequate response to 3 or more antidepressants.[81] In one prospective study of 158 elderly patients with CHF,[68] the use of a primary care–based depression screening measure (the 15-item Geriatric Depression Scale)[82] was related to patients receiving subsequent mental health treatment. Patients who screened positive for depression (during an 18-month medical record review period), as measured by the Geriatric Depression Scale, were more than 3 times as likely to either receive psychotropic medications or to use mental health services.[68]

Psychotherapeutic Treatments of Depression in CHF

Treatment of depression in the setting of CHF involves talking therapies (eg, psychotherapy), somatic interventions (eg, medications or electroconvulsive therapy [ECT]), or a combination of both. Practitioners of cognitive-behavioral therapy (CBT) encourage their patients to monitor thoughts about their condition and/or life events that lead to depression; patients are instructed to formulate alternative ways to view the situation and then to take appropriate action.[83] Treatment with CBT may lead to improved patient self-efficacy, elicit better adherence, and lead to a more positive approach to health and life in patients with depression and CHF.[83]

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Table 3. Selective Serotonin Reuptake Inhibitor and Atypical Antidepressants Approved for the Treatment of Major Depressive Disorder

Medication	Usual Target Dose to Achieve During Wk 1–3	Usual Higher Dose During Wk 4–8 If No Improvement on Initial Therapeutic Dose	Other Information
Fluoxetine	20 mg/d	40–80 mg/d	Active metabolite (norfluoxetine) has half-life of 2 wk; strong inhibitor of CYP450 2D6 and inhibitor of 3A4
Paroxetine	20 mg/d	30–60 mg/d	Strong inhibitor of CYP450 2D6
Sertraline	50 mg/d	100–200 mg/d	Inhibits 2D6 and 3A4 (weakly at low doses)
Citalopram	20 mg/d	30–40 mg/d	Inactive *R* enantiomer may interfere with therapeutic actions of active *S* enantiomer at serotonin reuptake pump
Escitalopram	10 mg/d	20 mg/d	Steady-state plasma concentrations achieved within 1 wk; efficacy of this *S* enantiomer comparable in efficacy to 40 mg of citalopram with fewer side effects
Fluvoxamine	50 mg/d; increase by 50 mg/d in 4–7 d	Usually wait a few weeks to assess drug effects but can increase by 50 mg/d until desired efficacy reached; maximum dose: 300 mg/d; doses below 100 mg/d usually given as a single dose at bedtime; doses above 100 mg/d can be divided into 2 doses to enhance tolerability, with the larger dose administered at night	Potent inhibitor of multiple CYP enzymes (CYP450 3A4, 1A2, and 2C9/2C19); often a preferred treatment for anxious depression as well as depression comorbid with anxiety disorders (eg, obsessive-compulsive disorder)
Bupropion	75 mg twice daily, then to 100 mg 3 times daily (immediate release)	Maximum dose: 450 mg/d	Norepinephrine dopamine reuptake inhibitor; strong inhibitor of CYP450 2D6; may lower seizure threshold; also used as nicotine cessation aid
Mirtazapine	15 mg at bedtime	Maximum dose: 45 mg/d	α_2 antagonist (norepinephrine and specific serotonergic agent); side effects: increased appetite and sedation

Abbreviation: CYP = cytochrome.

Gary and colleagues[84] compared the effectiveness of a combined 12-week home-based exercise/CBT program (n = 18) with CBT alone (n = 19), exercise alone (n = 20), and usual care (n = 17) in stable New York Heart Association Class II to III CHF patients diagnosed with depression (per the Hamilton Depression Rating Scale [HDRS]).[85,86] The combined CBT/exercise group exhibited a significant increase in 6-minute walk distance after 24 weeks ($F = 13.5$, $P < .001$). Among all groups with moderate-to-major depression (HDRS score ≥ 15), only those in CBT/exercise had sustained lower HDRS scores at 12 and 24 weeks and showed the greatest improvement in health-related quality of life, as measured by the SF-36. Thus, interventions designed to improve both physical and depressive symptoms may prove best for optimizing function and enhancing quality of life in patients with CHF.[84]

A multicenter, randomized controlled trial (Effects of Exercise Training on Depressive Symptoms in Patients With Chronic Heart Failure: The HF-ACTION Randomized Trial)[87] found that those in the exercise training group had lower mean BDI-II scores at 3 months (aerobic exercise: 8.95 [95% CI, 8.61–9.29] vs usual care: 9.70 [95% CI, 9.34–10.06]; difference: −0.076 [95% CI, −1.22 to −0.29] $P = .002$) and at 12 months (aerobic exercise: 8.86 [95% CI, 8.67–9.24] vs usual care: 9.54 [95% CI, 9.15–9.92]; difference: −0.68 [95% CI, −1.20 to −0.16] $P = .01$).

Positive psychology interventions help focus patients on targeted activities (eg, performing acts of kindness), gratitude (eg, systematically recalling positive life events), optimism (eg, imagining positive future outcomes), and using one's personal strengths in a deliberate manner.[88] A meta-analysis[89] of over 50 trials of positive psychology interventions in more than 4,000 generally healthy subjects found that these interventions consistently led to increases in happiness, reductions in depression, and improvements in overall well-being. Huffman and colleagues[88] developed an 8-week, phone-based positive psychology intervention based on empirically validated exercises for patients hospitalized with acute cardiac disease (acute coronary syndrome or decompensated CHF). This study achieved its primary aim of successfully creating and delivering a positive psychology intervention and delivering it to cardiac inpatients.[88] In addition, primary outcome measures showed that the positive psychology intervention proved to be feasible and effective (eg, overall helpful, improved optimism) relative to the other interventions, although subjects in the "relaxation response" group were slightly more likely to report that they would continue the exercises in the study relative to the other groups.[88] Furthermore, the subjects in the positive psychology intervention experienced greater improvement in secondary outcome measures of depressive symptoms, anxiety, happiness (Center for Epidemiologic Studies Depression subscale),[90] and health-related quality of life relative to the subjects in the other 2 groups.[88]

Somatic Treatments of Depression in CHF

Psychopharmacologic treatments of depression include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine, duloxetine), a norepinephrine dopamine reuptake inhibitor (bupropion), an α_2 antagonist (mirtazapine), and a serotonin antagonist/reuptake inhibitor (trazodone) (Table 3).[91]

Electroconvulsive therapy is the most efficacious somatic treatment for depression, effective in up to 80% of patients with

either unipolar or bipolar depression.[92] Treatment with ECT provides a response rate (a decrease in depressive symptoms by 50%) nearly 4 times greater than that of antidepressant drugs (odds ratio = 3.72; 95% CI, 2.60–5.32).[93]

Although ECT is generally considered to be safe, cardiac complications can occur even with a "cardiac-modified" ECT protocol (which should be used for elderly patients and those with cardiac disease).[94] A retrospective review[95] of the medical records of patients (with a median age of 77 years) with CHF and a mean LVEF of 30% (range, 15%–40%) who underwent ECT revealed no deaths or episodes of decompensated CHF, myocardial ischemia, or myocardial infarction within 24 hours following an ECT session.

The TCAs routinely increase heart rate by 11% (secondary to their anticholinergic effects).[96] Tertiary amine TCAs (eg, amitriptyline, clomipramine, trimipramine, doxepin, imipramine) are more anticholinergic than are secondary amines (eg, nortriptyline, desipramine), with the exception of the secondary amine protriptyline, which is second only to amitriptyline among the TCAs with regard to muscarinic receptor binding affinity.[97] Increases in heart rate shift the Starling curve to the right, dropping cardiac output; such effects must be considered when selecting an antidepressant for a depressed patient with CHF. Due to their blockade of α_1 receptors, TCAs induce orthostatic hypotension, which can be problematic for those with CHF. An early double-blind, placebo-controlled study[98] (n = 39) showed that pretreatment systolic orthostatic hypotension in geriatric patients with depression may be a predictor of response to TCAs (imipramine and doxepin). Other TCA-associated anticholinergic side effects include urinary hesistancy, dry mouth, constipation, and blurred vision[97]; dry mouth may lead to increased thirst and to subsequent fluid overload in those with CHF.

Slowing of cardiac conduction by TCAs can result in 2:1 atrioventricular block in patients with preexisting bundle branch block.[96] Indeed, fatalities induced by TCA overdose via ventricular fibrillation are thought to be due to their class 1A antiarrhythmic effects and their impact on the initial sodium current of Purkinje fibers and the reduction of intraventricular conduction velocity. Furthermore, TCAs are known to decrease heart rate variability, to prolong the QTc interval, and to increase QT variability, which may precipitate ventricular fibrillation and sudden cardiac death.[96] The TCA medications should not be prescribed for patients with bifascicular and left fascicular block.[99]

Like TCAs, MAOIs are also avoided in patients with CHF, as this class of antidepressants is notorious for causing cardiovascular side effects, including hypertensive crisis (caused by dietary interactions with tyramine and drug-drug interactions, eg, nasal decongestants) and orthostatic hypotension.[100] Thus, patients taking MAOIs must follow a tyramine-free diet to avoid hypertensive crises. Interestingly, one MAOI, the selegiline transdermal system at a dose of 6 mg/24 h, allows patients to avoid the usual dietary restrictions of other MAOIs.[101,102] The SNRIs, such as, venlafaxine, duloxetine, and milnacipran, have not been formally studied for depression in patients with cardiovascular disease; however, given the tendency of venlafaxine to increase blood pressure, SNRIs should not be considered unless SSRIs were ineffective in treating a patient's symptoms.[8] Oslin and coworkers[103] reported increased levels of side effects and serious adverse events (including cardiac arrhythmias) in a small (N = 52) 10-week randomized, double-blind, controlled trial of venlafaxine (in doses up to 150 mg/d) versus sertraline (in doses up to 100 mg/d) in depressed elderly patients with mild-to-moderate dementia. Moreover, after venlafaxine overdose, drug-induced pneumonitis and CHF, tachycardia, hypotension, angina pectoris, extrasystoles, and (rarely) myocardial infarction may occur.[104,105] Venlafaxine has been shown to decrease heart rate variability, the degree of which correlates with the magnitude of norepinephrine transporter inhibition.[106]

The SSRIs are nearly free of cardiovascular effects. Clinically insignificant slowing of heart rate by a few beats per minute may occur in patients treated with SSRIs. Nevertheless, with other agents that slow heart rate and lower perfusion, the potential for interaction by SSRIs, either through additive effects or effects on metabolism of these other agents, should be considered, especially in patients with CHF treated with chronotropic medications (eg, β-adrenergic blockers).[100] Severe sinus node slowing has been reported in only a few cases following SSRI treatment.[107] Although SSRI-induced bleeding is infrequent, clinicians should be aware of the potential for bleeding both inside and outside of the gastrointestinal tract in association with use of SSRIs, especially in those who have heightened risk of bleeding (eg, with peptic ulcer disease or liver disease, those undergoing surgical or dental procedures, and those also receiving NSAIDs, anticoagulant drugs, or antiplatelet drugs).[108]

Only a limited number of clinical trials of SSRIs for treatment of patients with CHF have been conducted. An early small, open-treatment, nonrandomized study by Roose and colleagues[109] examined the blood pressure, heart rate and rhythm and cardiac conduction intervals (measured by 24-hour electrocardiogram recordings), and ejection fraction determined by radionuclide angiography before and after 2 and 7 weeks of treatment with the SSRI fluoxetine (doses ranging up to 60 mg/d) of 27 depressed psychiatric inpatients with CHF, conduction disease, and/or ventricular arrhythmia (20 males, mean age of 73.3 years, 14 of whom had an ejection fraction < 50% with a mean [SD] of 36.3% [10.7%]). The same cardiovascular variables were also studied in 60 patients (mean age of 69.5 years, with a mean ejection fraction of 32.4%) at baseline and after 3 weeks of treatment with nortriptyline.[109] In this study,[109] fluoxetine decreased heart rate (by 6%), while nortriptyline increased heart rate (by 10%). With respect to LVEF, fluoxetine had a small but statistically significant beneficial effect, whereas nortriptyline caused a small but statistically significant negative effect.[109]

In a subsequent 6-week, double-blind, randomized controlled trial, Roose and coworkers[110] assessed the efficacy,

cardiovascular effects, and safety of the SSRI paroxetine compared to the TCA nortriptyline (dosage titrated to achieve therapeutic plasma concentrations of 50 to 150 ng/mL) in 81 patients with depression and ischemic heart disease. There was a significantly greater rate of dropout due to adverse cardiovascular events in the nortriptyline group (eg, sinus tachycardia, severe angina, proarrhythmic effect) as compared with the paroxetine group (2-tailed Fisher exact test, $P < .03$). By intent-to-treat analysis, 25 of 41 patients (61%) improved (decline in HRSD score of 50% and final score of ≤ 8) during treatment with paroxetine, and 22 of 40 (55%) improved with nortriptyline.[110]

A much larger randomized, double-blind, placebo-controlled study of 469 patients with CHF, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure trial,[111] was designed to test the hypothesis that patients treated with the SSRI sertraline (n = 234, mean [SD] age of 62.9 [10.5], 133 men, mean [SD] LVEF of 31.3% [9.5%]) would have lower HDRS scores and fewer cardiovascular events compared with the placebo group (n = 235, mean [SD] age of 61.4 [11.1], 146 men, mean [SD] LVEF of 29.5% [10.1%]) after 12 weeks of treatment. Patients in the treatment group received sertraline 50–200 mg/d for 12 weeks, along with nurse-facilitated telephone contact or in-person visits every 2 weeks during the first 12 weeks. This regimen did not improve psychiatric or cardiac outcomes (eg, acute myocardial infarction, arrhythmia, CHF exacerbation) in patients with CHF when compared to placebo combined with nurse-facilitated support only. Relevant in this regard is the 6-month, double-blind, randomized Sertraline Antidepressant Heart Attack Randomized Trial[112] of patients with unstable angina or following acute myocardial infarction comparing placebo (n = 183) and sertraline (n = 186). This study documented that patients with more severe depression experienced a significant improvement in their HDRS score (mean [SD] change of −12.3 [0.88] compared to −8.9 [0.98] for placebo) and Clinical Global Impressions–Improvement of illness[113] scores in comparison with those who received placebo treatment.[112]

No study has demonstrated the beneficial effects of a depression intervention in patients with CHF on clinical outcomes, such as cardiac events (eg, myocardial infarction) or survival.[16] However, the Morbidity, Mortality, and Mood in Depressed Heart Failure patients study,[114] a prospective, randomized, double-blind, placebo-controlled, 2-armed, parallel-group, multicenter trial investigating the effects of treatment with the SSRI escitalopram in 700 patients with symptomatic systolic CHF and MDD (diagnosed by structured clinical interview), is underway.

Drug-Drug Interactions in the Treatment of Depressive Symptoms in Patients With CHF

The central tenet of medical management of CHF involves termination of renin-angiotensin system hyperactivity to prevent the long-term complications (eg, cardiac remodeling) of the cascade.[115] Pharmacologic treatments for CHF often focus on a combination of afterload reduction with angiotensin-converting-enzyme (ACE) inhibitors, reduction of catecholamine surges and sympathetic hyperactivity with β-blockers, and reduction of preload with diuretics. Although β-blockers were thought to induce depressive symptoms in patients with CHF, there have been few empirical data to support the notion of the "β-blocker blues."[25]

Certain antidepressants can lead to potentially harmful drug interactions with medications used in the treatment of CHF. Cardiovascular drugs may be subject to clinically significant increase (with risk of toxicity) or decrease (with risk of ineffectiveness) in concentrations by coadministration of cytochrome (CYP) P450 inhibitors or inducers, respectively. Conversely, they may inhibit or induce CYP450 and cause significant changes in the concentrations of other drugs.[116] Fluoxetine and paroxetine are strong 2D6 inhibitors in comparison to other SSRIs, and they can impact the metabolism of commonly used cardiovascular medications (eg, β-blockers).[91] Furthermore, the active metabolite of fluoxetine (norfluoxetine) has a half-life of 2 weeks and thus may cause drug-drug interactions with cardiovascular medications as long as 2 to 3 months after it is discontinued. Of note, agents that are renally excreted, eg, diuretics and ACE inhibitors, may have lower potential for drug-drug interactions with other medications metabolized by liver CYP enzymes. Nevertheless, the potential still exists for adverse drug-drug interactions of these renally excreted drugs with other medications excreted by the kidney.

Unfortunately, the extent to which antidepressant pharmacokinetics may be altered in patients with acute CHF remains unknown. In patients with a recent or current episode of decompensated CHF, higher doses of antidepressant (eg, sertraline) may be needed to overcome the lower absorption that may occur in states of significant volume overload or reduced cardiac output (and decreased gastrointestinal perfusion) states.[111] (See Table 4 for pharmacokinetic interactions[105,117] and Table 5 for pharmacodynamic interactions[91,100,105,118] between medications commonly used for patients with CHF and antidepressant medications.)

Treatment Response Monitoring/Outcome Measures/ Indications for Mental Health Referral

The HDRS has been the criterion standard outcome measure in clinical trials; however, it can require 15–30 minutes of clinician time to administer. The Montgomery-Asberg Depression Rating Scale is approximately half as long as the HDRS and just as sensitive to change,[119,120] but it must be administered by a clinician with special training and is also fairly time intensive. Self-administered scales, such as the BDI, have been used as outcome measures but may be somewhat less sensitive to change than the HDRS.[121]

The self-administered PHQ-9 is well-validated as a diagnostic measure, and it has also been proven to be a responsive and reliable measure of depression treatment outcome.[122] In a study[122] that included 434 subjects (63% female, mean age of 71 years) from the Improving Mood–Promoting Access to Collaborative Treatment study,[123] a multisite treatment trial of patients with late-

Table 4. Potential Pharmacokinetic Interactions Between Medications Commonly Used for Patients With Congestive Heart Failure and Oral Antidepressant Agents

Medication	Proposed Mechanism	Psychotropic Agent	Clinical Outcome
Warfarin	Inhibition of multiple CYP 450 enzymes by psychotropic agent(s) causing decreased hepatic metabolism of warfarin	Fluvoxamine, fluoxetine, sertraline	Warfarin toxicity, bleeding
Angiotensin II blockers (losartan and irbesartan)	CYP450 2C9 enzyme inhibition by psychotropic agent	Sertraline	Increased levels of angiotensin II blockers
β-blockers (carvedilol, S-metoprolol, propafenone, timolol, propranolol), type 1C antiarrhythmics (flecainide, mexiletine, propafenone)	CYP450 2D6 inhibition by psychotropic agent	Bupropion, fluoxetine, and paroxetine (strong inhibitors), as well as duloxetine, sertraline, citalopram, and escitalopram	Increased levels of β-blocker, type 1C antiarrhythmics
Calcium channel blockers	CYP450 3A4 inhibition by psychotropic agent	Fluvoxamine, fluoxetine, sertraline	Increased plasma concentrations of calcium channel blocker

Abbreviation: CYP = cytochrome.

Table 5. Pharmacodynamic Effects of Antidepressant Medications Relevant to Patients With Congestive Heart Failure

Medication	Effect
Fluoxetine, paroxetine, sertraline	May displace highly protein-bound drugs such as warfarin, potentially leading to warfarin toxicity; altered hemostasis by selective serotonin reuptake inhibitors may also contribute to bleeding
Mirtazapine	Association with weight gain and hyperlipidemia
Citalopram	Citalopram should no longer be used at doses greater than 40 mg/d because it can cause abnormal changes in the electrical activity of the heart; the US Food and Drug Administration, in a QT interval study,[118] has determined that citalopram causes dose-dependent QT interval prolongation
Tricyclic antidepressants	Anticholinergic effects, which may lead to tachycardia and reduced cardiac output (note: paroxetine has mild anticholinergic effects); due to their blockade of α_1 receptors, tricyclic antidepressants induce orthostatic hypotension
Venlafaxine	Propensity to increase heart rate and diastolic blood pressure, arrhythmia, or cardiac block in overdose; decreased heart rate variability
Trazodone	Propensity to cause orthostatic hypotension
Selective serotonin reuptake inhibitors	Slowing of heart rate by, at most, a few beats per min may occur in patients treated with selective serotonin reuptake inhibitors; potential for interaction with other agents that slow heart rate and lower perfusion, through either additive effects or effects on metabolism of other agents, should be considered, especially in patients with congestive heart failure likely to be taking drugs with chronotropic effects (eg, β-adrenergic blockers)

life depression in primary care settings, changes in PHQ-9 scores over a 6-month period were evaluated with respect to change scores of the Hopkins Symptom Checklist 20-item depression scale (SCL-20),[124,125] as well as by 2 independent structured diagnostic interviews for depression. The PHQ-9 responsiveness, as measured by effect size, was significantly greater than the SCL-20 at 3 months and equivalent at 6 months.[122]

Monitoring the treatment response of depressive symptoms requires clinical evaluation of the individual patient. As a rule of thumb, a decline in the PHQ-9 score of at least 5 points is necessary to qualify as a clinically significant response to depression treatment[126] on the basis of the fact that every 5-point change on the PHQ-9 corresponds with a moderate effect size on multiple domains of functional status and health-related quality of life.[50] Furthermore, an absolute PHQ-9 score < 10 qualifies as a partial response and a score < 5 as a remission.

Tapering of SSRIs to avoid potential withdrawal reactions is generally prudent; many patients tolerate a 50% dose reduction for 3 days, then another 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation.[91] If withdrawal symptoms emerge during discontinuation, the SSRI dose may be temporarily increased back to the previous dosage to stop the discontinuation symptoms, and then the taper can be restarted and conducted more slowly. Due to its active metabolite (norfluoxetine, which has a half-life of 2 weeks), fluoxetine does not require extended tapering. SSRI discontinuation symptoms (eg, dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias) can be more common or severe with paroxetine than with other SSRIs. Withdrawal effects of paroxetine may be related to the self-inhibition of its own metabolism.[91] It is possible that withdrawal effects could represent a danger to patients with CHF due to sympathetic activation. For patients who experience severe problems when discontinuing paroxetine, dosing may need to be tapered over many months in small increments (eg, 1%–5%).[91]

Eight weeks of antidepressant treatment at a sufficient dosage is considered an adequate trial of an antidepressant (ie, the acute phase of treatment). If there is positive response/remission of depressive symptoms, antidepressant treatment should continue for another 16–20 weeks (ie, the continuation phase of treatment). Given the nearly 100% risk/odds of suffering a recurrent, disabling episode of MDD, maintenance treatment for ≥ 1 year should be considered for those patients with ≥ 2 disabling episodes of MDD.[80] If the patient is clearly better or is continuing to improve (as shown by a partial response, eg, PHQ-9 score < 10), the antidepressant should be continued until complete remission (PHQ-9 score < 5) has been achieved.[80] If there is only some improvement, but the antidepressant is well-tolerated, the

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initial antidepressant should be titrated to its maximal dosage. If there is no clinically significant response of depressive symptoms (eg, a decline in the PHQ-9 score of 5 points) to the antidepressant by 4–8 weeks, alternative strategies should be employed. Advantages of switching to a different antidepressant agent (such as sertraline or mirtazapine, as opposed to a combination of antidepressants or augmentation with other agents) include improved adherence, reduced medication cost, and fewer drug interactions.[127]

Medical care providers may choose to refer to mental health treatment providers for complex cases of mood disorders and/or management of "treatment-resistant" depression, ie, depression that does not initially respond well to treatment (Nelson[127] and Nemeroff[128]), which involves antidepressant combinations (such as an SSRI with an antidepressant from another class, eg, the norepinephrine dopamine reuptake inhibitor bupropion) or augmentation (adding a second pharmacologic agent generally not used as an antidepressant, such as atypical antipsychotics [eg, aripiprazole, quetiapine, olanzapine] or stimulants). The advantages of these treatment strategies include rapid response and maintenance of initial improvements from the first medication.[127] Atypical antipsychotic administration has been associated with weight gain, diabetes (including diabetic ketoacidosis), and increased low-density lipoprotein cholesterol and triglycerides (in addition to lowered high-density lipoprotein cholesterol).[129] Stimulants have sympathomimetic effects and may elevate heart rate and blood pressure and increase risk of ventricular tachyarrhythmias; however, methylphenidate in doses of 5–30 mg/d has been shown in generally healthy adult patients (diagnosed with attention-deficit/hyperactivity disorder) to have minimal effects on heart rate or blood pressure and small absolute risk of adverse cardiac events.[130] To date, however, there are no studies specifically addressing stimulant use or augmentation for treatment of depression in patients with CHF.[100]

There are many factors to consider in patients who do not respond to their first trial of antidepressant (including comorbid medical and psychiatric conditions; diagnostic inaccuracy; inadequate drug therapy, dose, or duration; alcohol or substance abuse; severity and complexity of the depression; and/or treatment nonadherence).[128] At 8 weeks, if there is minimal response to treatment, the best choice may be to refer or consult with a psychiatrist or another mental health professional. However, in underserved areas with limited access to mental health professionals, further adjustment of the psychotropic regimen may be required by the primary care physician or cardiologist. Telemedicine interventions (eg, videoconference, self-help Internet programs) may be helpful in these instances.[131]

Future Directions in Research and Treatment of Depression in Patients With CHF

Congestive heart failure leads to staggering economic, social, and psychological costs worldwide. In the United States alone, the direct (medical) costs of CHF are projected to be $46.8 billion by the year 2015.[10] Given that costs of care for patients hospitalized with a primary diagnosis of CHF are significantly higher for patients with evidence of depression (29% higher according to a 3-year retrospective cohort study of a staff-model health-maintenance organization),[132] depression in patients with CHF merits further research.

Evidence-based treatment algorithms, supported by well-conducted clinical trials, are an initial step by which practitioners can identify and treat depression in patients with CHF. Optimal treatment pathways for patients with CHF and comorbid depression, be they psychotherapeutic, psychopharmacologic, or exercise based, could be identified by sequential, multiple-arm, randomized trials, as is done in other patient populations.[84]

Culturally specific interventions tailored to patients from diverse cultural and racial minority groups and creative outreach to those patients are essential so that such studies may generate results applicable to populations most at risk for depression or those with limited resources and/or access to care.[114] Prospective studies are needed to delineate cluster categories associated with certain CHF subtypes (ie, systolic vs diastolic heart failure) and investigate relationships between symptom clusters and longitudinal profiles of patients with CHF.

Collaborative care, based on Wagner's Chronic Care model,[133,134] involves active follow-up by a nonphysician "care manager" who adheres to a structured, evidence-based treatment protocol.[135] The care manager, in collaboration with primary care physicians and specialists (when indicated), contacts patients, educates them about their illness, and proactively monitors their response to treatment. Katon and colleagues[136] conducted a single-blinded, randomized, controlled trial in 14 primary care clinics in an integrated health care system in Washington State and found that an intervention involving proactive follow-up by nurse care managers (working closely with physicians), integrating the management of medical and psychological illnesses, and using individualized treatment regimens guided by treat-to-target principles improved both depression and medical outcomes in depressed patients with coronary heart disease, diabetes, or both. One pioneering prospective, randomized trial[137] of the effect of a nurse-directed, multidisciplinary intervention (which included comprehensive education of the patient and family, a prescribed diet, social service consultation, medication review, and intensive follow-up) demonstrated improved quality of life, decreased hospital readmissions, and reduced medical costs for elderly patients with CHF. More recently, organizations that participated in a disease-targeted collaborative provider interaction significantly improved counseling and education rates and, less dramatically, improved rates for appropriate ACE-I and lipid-lowering therapy for CHF patients.[138]

The "patient-centered medical home" is a team-based care delivery model that coordinates the clinical and social services of a patient, led by a personal physician.[139] This model focuses on the development of electronic medical records to facilitate improved access to clinical information obtained at multiple sites (eg, physician's offices, hospitals),

payment reforms that would provide support for inadequately reimbursed services (eg, telephone contact with patients), and routine assessment of functional outcomes, such as quality of life and health.[139] One such program is the White River model of colocated collaborative care, a platform for mental and behavioral health care in the medical home (implemented in 2004).[140] The primary mental health care clinic located in Vermont is staffed by a therapist and a psychiatrist or advanced practice nurse (complemented by care management and health psychology) and offers a full spectrum of mental health care that allows 75% of referred patients to receive all of their care within the primary care clinic and conserves specialty services for the most complex patients. Integration of mental health care into primary care and medical settings may offer improved quality of care for patients with chronic illnesses (such as CHF), and better adherence to the principles that guided its development may be useful in any health system.[140]

CONCLUSIONS/RECOMMENDATIONS

Major depressive disorder is highly prevalent in patients with CHF and has been associated with a variety of poor medical outcomes, including increased risk of mortality. Assessment and intervention for depression associated with cardiovascular diseases such as CHF are complicated, as these patients often feel fatigued for weeks and lack energy to conduct routine activities.[141] Physicians' competing demands when treating patients with CHF create further challenges in the diagnosis and treatment of depression.[70]

At present, limited empirical data exist with regard to treatment of depression[100] in this increasingly large population of patients with cardiovascular disease.[10] Evidence reveals that both psychotherapeutic treatment (eg, CBT) and pharmacologic treatment (eg, use of the SSRI sertraline) are safe and effective in reducing depression severity in patients with cardiovascular disease.[100] Depression and CHF should be treated together rather than managed as isolated conditions. Rating scales, such as the PHQ-9, should be used to monitor therapeutic efficacy, just as blood pressure is measured after the initiation of antihypertensive agents to monitor treatment response. Patients with depression in medical settings require follow-up and follow-through.[142] The assertion that "the type of treatment matters less than ensuring it is done properly and followed up"[143] is particularly salient to treatment of depression in patients with CHF. It is important to avoid clinical inertia (failure of health care providers to initiate or intensify therapy when indicated), which is caused by at least 3 problems: lack of education and training and practice organization aimed at achieving therapeutic goals, overestimation of care provided, and use of "soft" reasons to avoid intensification of therapy.[144] Coordinated care programs featuring interventions that work to improve adherence to cardiac and psychiatric treatments should be employed in cardiac settings.[8]

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), methylphenidate (Focalin, Daytrana, and others), metoprolol (Toprol, Lopressor, and others), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), propranolol (Inderal, InnoPran, and others), protriptyline (Vivactil and others), quetiapine (Seroquel), selegiline transdermal system (EMSAM), sertraline (Zoloft and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others), warfarin (Coumadin, Jantoven, and others).

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