Managing Medical Comorbidities in Patients With Depression to Improve Prognosis

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Medical comorbidities contribute to poor antidepressant response, treatment resistance, and poor outcomes in many patients with depression. Depression can co-occur with thyroid conditions, chronic pain conditions, central nervous system disorders, and more. Inflammatory conditions such as diabetes and obesity are also associated with depression, and the connection between inflammation and depression may lead to testing that could better match patients to specific antidepressant treatment. Interventions for patients with depression and a comorbid medical condition include careful selection of antidepressant therapy as well as psychotherapy and adjunctive agents.

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Comorbid medical conditions can pose significant challenges to the successful treatment of major depressive disorder (MDD). One challenge is that chronic medical illnesses can hinder clinicians from recognizing and treating depression, due to overlapping symptoms.[1] Another challenge is that patients with depression and medical illnesses tend to have lower MDD recovery rates, poorer function, and higher rates of depressive relapse than patients with just depression.[1,2] Treatment resistance or nonresponse to MDD treatment is often explained by nonadherence, somatic symptoms or pain, or unrecognized diagnoses (eg, thyroid disease).[1,3]

Depression is a systemic illness that affects not only the brain but also the body. It has been associated with a proinflammatory state, including elevation of cytokines and suppression of neurotrophic or resilience factors, such as brain-derived neurotrophic factor (BDNF).[4,5] Depression increases the overall illness burden in those with chronic medical conditions, resulting in decreased quality of life and increased health care costs.[6] Clinicians must evaluate patients with MDD for comorbid conditions and select appropriate interventions to address depression along with any co-occurring conditions.

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RECOGNITION OF MEDICAL CONDITIONS WITH DEPRESSION

Depression not only is common among patients with medical illnesses but also is a risk factor for medical illnesses.[1,4] Patients may not recognize that their depressed mood can be treated because they think it is normal to feel "down" after being diagnosed with a serious medical condition such as cancer or human immunodeficiency virus (HIV). Because of this, clinicians should screen patients with known medical illnesses for MDD and, conversely, take a careful medical history in patients with depression to catch any undiagnosed medical condition, such as hypothyroidism.[1] Medications and family history are other factors that must be considered when evaluating patients for depression and comorbid conditions.[1]

Prevalence of Comorbidity

The large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[7] revealed that over 50% of patients with MDD had a comorbid medical condition. Conversely, depression is prevalent in patients with a variety of medical illnesses including central nervous system disorders (eg, Parkinson's disease, multiple sclerosis), thyroid conditions, and chronic illnesses such as HIV, heart disease, and diabetes (Table 1).[1,6] Rates of depression in the general community are between 3% and 8% for current MDD and about 16% for lifetime MDD.[8,9] Among patients who had experienced acute myocardial infarction, MDD was found in 20%,[10] while over 30% of patients with Parkinson's disease had a lifetime history of MDD.[11] A meta-analysis[12] of controlled studies of adults with diabetes found that the aggregate lifetime prevalence of MDD in those with diabetes was 29%.

The presence of depression can prove detrimental to the course and outcome of chronic conditions including arthritis, asthma, cardiovascular disease, cancer, diabetes, and obesity.[13] For example, in patients who survived a myocardial infarction, the greatest predictor of cardiac death over 5 years was an elevated depression score at hospitalization.[14] The more significant the depressive symptoms, the greater the impact was on subsequent longevity in these patients.[14]

Table 1. Medical Conditions Associated With a High Rate of Depression[a]

Alzheimer's dementia	HIV/AIDS
Cancer	Hyperprolactemia
Cardiac disease	Hypertension
Chronic fatigue syndrome	Hyperthyroidism
Chronic obstructive pulmonary disease	Hypoadrenalism
Chronic pain	Hypothyroidism
Cushing's disease	Illness related to medication
Deficiency of B_{12}, folate, iron, or minerals	Multiple sclerosis
Diabetes mellitus	Neurological illnesses
End-stage renal disease	Parkinson's disease
Fibromyalgia	Rheumatoid arthritis
Gastrointestinal diseases	Stroke

[a]Reprinted with permission from Fava et al.[1]

Clinical Points

- Depression co-occurs with a variety of medical conditions, some of which may have overlapping symptoms that make diagnosis a challenge.
- Clinicians should screen for depression, take a careful medical history, and conduct appropriate testing to assess for comorbid conditions such as thyroid dysfunction and chronic pain.
- Interventions for patients with depression and comorbid conditions may include antidepressant therapy, psychotherapy, and adjunctive agents, all of which should be selected, dosed, and monitored carefully.

Depression and Inflammation

Two key relationships have been identified between depression and inflammation: (1) depression promotes inflammation by elevating C-reactive protein (CRP) and cytokines (eg, interleukin-6 [IL-6],[5] tumor necrosis factor-α [TNF-α]), and (2) depression inhibits BDNF, one of the neurotrophic factors associated with neuronal resilience.[4,5] In a study[5] comparing patients with treatment-refractory depression with healthy controls, the plasma levels of IL-6 and TNF-α were higher in patients with depression, while their plasma BDNF levels were significantly lower than those of healthy controls. This study indicates that when depressive symptoms increase, so does inflammation. Conversely, when depressive symptoms are severe, BDNF is decreased.[5] These 2 consequences of depression may complicate or even cause comorbid medical illnesses.

Because of the connection between depression and inflammation, conditions associated with proinflammatory states, such as diabetes and obesity, are common in patients with depression.[13] The National Center for Health Statistics[15] reported that, from 2005 to 2010, 35% of US adults aged 20 years and older were obese, and individuals with depression were more likely to be obese than those without depression (43% vs 33%). Obesity and depression are both associated with increased risk of cardiovascular disease and diabetes.[15] Not only are individuals with diabetes twice as likely to have depression compared with the general US population without diabetes,[16] but also depression appears to be a risk factor for type 2 diabetes mellitus.[17] However, effective depression treatment can improve insulin levels. One study[17] of 80 nondiabetic patients with MDD found that successful treatment with either a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant (TCA) increased insulin sensitivity. The greatest benefit was found in patients who achieved remission, regardless of antidepressant type (Figure 1).[17]

Just as successful antidepressant treatment can improve insulin levels, it can also restore disturbances between the TNF-α system and hypothalamo-pituitary-adrenocortical (HPA) axis. The results of one study[18] in severely depressed hospitalized patients showed that elevated HPA axis activity in acute depression suppressed TNF-α activity. After remission, when HPA axis activity had normalized, the TNF-α system regained influence on the HPA system.[18] Alterations in the HPA system are common in patients with depression, but the effects of inflammatory cytokines can be improved with antidepressant therapy.

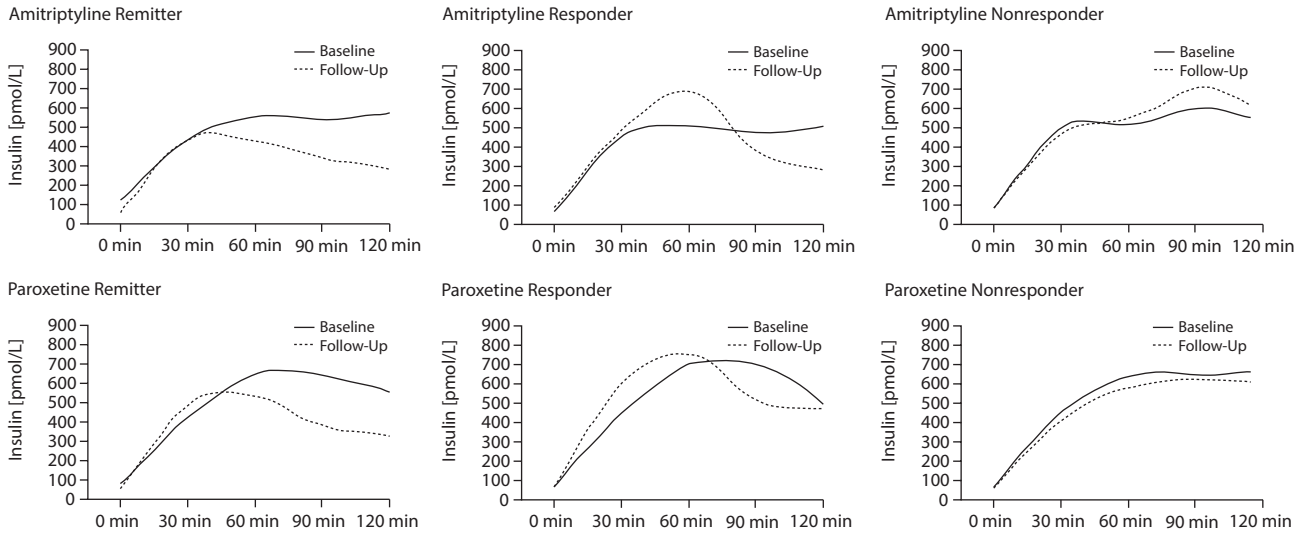
To further explore the connection between inflammation and antidepressant response, researchers in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study[19] tested whether baseline CRP levels would predict response to escitalopram (an SSRI) and nortriptyline (a serotonin-norepinephrine reuptake inhibitor [SNRI]). By measuring CRP in 241 adults with MDD, the researchers found that patients with low levels of CRP (< 1 mg/L) who were taking escitalopram showed a 3-point advantage on the Montgomery-Asberg Depression Rating Scale (MADRS) compared with those taking nortriptyline. For patients with higher baseline CRP levels, MADRS scores were 3 points higher for patients taking nortriptyline than escitalopram. Although the 2 antidepressants were comparable overall, these findings may explain why SSRIs seem to have poorer results in patients with proinflammatory status, such as chronic pain syndrome.[19] Findings such as these may eventually be used for clinicians to better match specific antidepressants with particular patients.

Another possibility from these findings is that a subset of patients with depression may respond to anti-inflammatory drugs. When Raison and colleagues[20] randomly assigned 60 patients with treatment-resistant MDD to take the TNF antagonist infliximab (3 infusions of 5 mg/kg) or placebo, no overall difference was found between groups on Hamilton Depression Rating Scale (HDRS) scores, but a strong moderating effect from TNF antagonism was found among the patients with elevated levels of CRP at baseline (Figure 2).[20] Thus, the subset of depressed patients who may benefit from anti-inflammatory treatment may be those with high baseline levels of inflammatory biomarkers. As with the GENDEP study findings, further prospective data are needed.

INTERVENTIONS FOR DEPRESSION AND COMORBID CONDITIONS

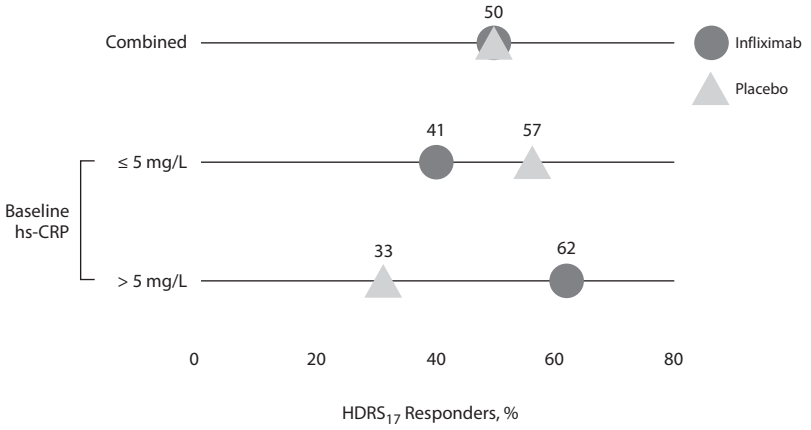
Interventions for patients with depression and medical conditions require careful selection of antidepressant treatment, especially for comorbidities such as cancer,

Figure 1. Insulin Concentrations During Oral Glucose Tolerance Test at Baseline and After Antidepressive Treatment (N = 80)[a]



[a]Reprinted with permission from Weber-Hamann et al.[17]

Figure 2. Treatment Responders in Infliximab vs Placebo in Patients With Treatment-Resistant Depression (N = 60)[a]



[a]Data from Raison et al.[20]
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, hs-CRP = high-sensitivity C-reactive protein.

HIV, and cardiovascular disease.[1] Clinicians must consider factors such as side effects and impairments that may already be present due to the condition or other medications. Drug interactions and metabolism are also important considerations when managing treatment, especially for patients with renal or hepatic impairment.[1] Clinicians may use antidepressant medications, psychosocial therapies, and adjunctive agents to reduce depressive symptoms and to target specific conditions such as thyroid dysfunction, chronic pain, and low folate levels.

Thyroid Dysfunction

Depression can be caused by both excess and insufficient thyroid hormones, conditions that are typically reversible with appropriate thyroid treatment, or depression may be accompanied by thyroid dysfunction.[21] Subclinical hypothyroidism is associated with antidepressant nonresponse, which makes it an important treatment target.[22] In addition, a relationship has been recognized between thyroid-stimulating hormone (TSH) levels in hypothyroidism and depression severity.[21] Because many patients with depression do not have thyroid dysfunction, clinicians do not need to test TSH in every patient who presents with depression, but thyroid testing should be included with a second level of medical screening when patients are nonresponsive to treatment, with any patient with a history of thyroid disease, and with any patient with signs and symptoms of thyroid dysfunction.

One reason that augmenting antidepressant treatment with thyroid hormone has some likelihood of a positive effect is because up to 40% of patients have unrecognized subclinical hypothyroidism.[21] For these patients who may be less responsive to antidepressants, the routine prescription of thyroid hormone in modest levels is a safe and easy remedy. However, the results of thyroid augmentation in patients with depression and normal thyroid function are questionable.

When thyroid hormone augmentation is used, triiodothyronine (T_3) is typically preferred over thyroxine (T_4),[23] possibly because T_3 is the biologically active form of the hormone in the brain.[24] The preferred dosing range for T_3 is 25 to 50 µg/d because it is typically well tolerated,[25] but this strategy is not indicated for patients with coronary artery disease or chronic heart failure and must be monitored carefully in patients with diabetes.[24] In my clinical practice, this strategy seems to be effective in patients with marginally elevated or borderline TSH levels, and it is the treatment of choice for patients with clearly elevated TSH.

In addition, T_3 augmentation may improve response in patients with resistance to some antidepressants, such as TCAs and SSRIs.[23,26] However, results from T_3 augmentation of antidepressants are inconsistent and often based on small studies or studies with other limitations.[24] A meta-analysis[27] based on 8 studies of T_3 augmentation of TCAs found that patients receiving T_3 were twice as likely to respond as controls ($P = .002$), but, among the 4 randomized, double-blind studies, pooled effects were not significant ($P = .29$).[27] In a small study[28] (N = 12) of T_3 augmentation of SSRI treatment, one patient withdrew due to side effects, but the other patients tolerated T_3 very well. T_3 significantly improved HDRS scores at 3 weeks ($P < .003$), and the response rate of 42% is similar to response rates reported for T_3 or lithium augmentation of TCAs or other combination strategies used for treatment-resistant depression.[28] The STAR*D trial[29] found that T_3 augmentation provided equivalent efficacy in treatment-resistant depression compared with lithium augmentation (remission rates were 24.7% and 15.9%, respectively) but with fewer side effects and less discontinuation. While both T_3 and lithium augmentation of TCAs have the most evidence for improvement in treatment-resistant depression,[30] one review[31] found that the efficacy of T_3 augmentation of TCAs was more likely in women than men. This finding may stem from the fact that thyroid disease itself is more common in women than in men.[32]

Another subgroup of patients who may benefit from T_3 augmentation was found in a study by Cooper-Kazaz and colleagues,[33] who examined acceleration of sertraline response with T_3 versus placebo augmentation in patients with the inherited DIO1-C785T polymorphism, which is involved in the conversion of T_4 to T_3. Patients with the polymorphism (ie, lower conversion activity) were more likely to respond to T_3 than to placebo.[33] This finding indicates that patients with low inherent conversion of T_4 to T_3 may benefit from T_3 augmentation.

Chronic Pain Conditions

Another complicating factor in people with depression is comorbid chronic pain, such as arthritis, musculoskeletal conditions, and migraine and other chronic headache conditions. These conditions may overlap with the physical symptoms associated with MDD, such as headache, neck and back pain, abdominal pain, and musculoskeletal pain.[34] A review[35] noted that the presence of pain negatively influences the recognition and treatment of depression.

Data analyzed from A Randomized Trial Investigating SSRI Treatment (ARTIST),[36] which had a naturalistic follow-up, showed that pain was present in more than two-thirds of depressed primary care patients at baseline. The presence of pain increased the odds of poor treatment response at 3 months, and greater pain severity was associated with greater odds of poor response.[36] A large international telephone survey[37] (N = 18,980) found that a chronic painful physical condition was present in almost half of respondents with MDD. These conditions negatively affected the duration, severity, and recurrence of depressive episodes.

Because both depression and pain share biological pathways and neurotransmitters, they must be treated concurrently for better outcomes.[35] Data from a study[38] examining the longitudinal relationship between pain and depression in older adults (aged 55–85 years) found a strong association between the 2 conditions, with no effect of age on the relationship. The challenge for clinicians treating comorbid pain with depression is that, with SSRI treatment, nonsomatic depressive symptoms are more likely to continue to respond over time than are painful somatic symptoms.[39]

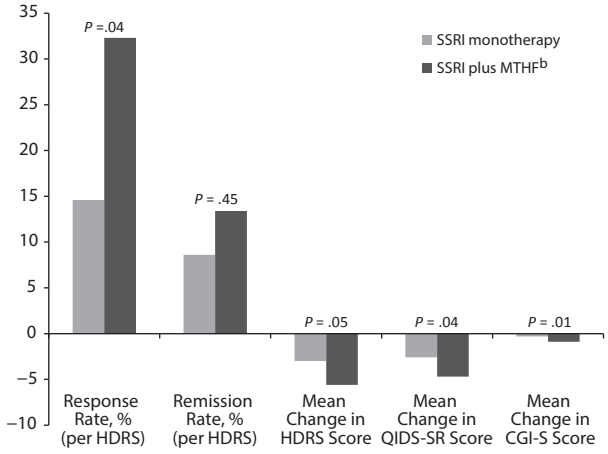
While SSRIs lack evidence for alleviating painful symptoms, antidepressant agents including SNRIs (eg, duloxetine, milnacipran, venlafaxine) and some TCAs (eg, amitriptyline, nortriptyline, desipramine) have shown effectiveness for relieving physical pain in depression or fibromyalgia and neuropathic pain associated with diabetes or other conditions.[1,34] Clinicians may also need to address somatic symptoms with specifically targeted pharmacologic interventions to improve outcomes.[1]

Inadequate L-Methylfolate Levels

Since low folate levels have been connected with depression, one promising adjunctive strategy is the prescription of the medical food L-methylfolate, a necessary cofactor in the synthesis of monoamine neurotransmitters associated with mood regulation (eg, serotonin, norepinephrine, dopamine).[40] About 70% of people with depression have a polymorphism of the C677T methyltetrahydrofolate reductase (*MTHFR*) gene, which results in inadequate L-methylfolate levels and therefore, decreased monoamine levels.[40]

Prescription L-methylfolate, an active form of folate (an essential B vitamin), is a safe augmentation therapy for patients with the C677T polymorphism.[40] The results of 2 randomized, double-blind trials[41] of L-methylfolate as adjunctive treatment for SSRI-resistant depression

Figure 3. Treatment Outcomes for SSRI Monotherapy Versus SSRI Plus L-Methylfolate (N = 75)[a]



[a]Data from Papakostas et al.[41]
[b]15 mg/d of L-methylfolate (MTHF) for 60 days.
Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, HDRS = Hamilton Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–self-rated, SSRI = selective serotonin reuptake inhibitor.

showed no significant difference in outcomes between SSRI treatment and adjunctive 7.5 mg/d of L-methylfolate versus SSRI monotherapy in the first study, but 15 mg/d of adjunctive L-methylfolate in the second study significantly improved response rates over those with placebo (Figure 3).[41] Adjunctive L-methylfolate was also well tolerated, with rates of adverse effects similar to those with placebo.[41] Another study[42] found that, among patients with inadequate SSRI response, those with a body mass index of 30 or more and those with inflammatory biomarkers (eg, high CRP levels) responded significantly better to adjunctive L-methylfolate than to placebo ($P \leq .05$). These findings suggest that risk factors for depression include a triangulation of inflammatory markers, hazards such as obesity, and inherited abnormality or difficulty converting dietary folic acid into L-methylfolate. In a naturalistic study,[43] patients taking L-methylfolate with their antidepressant or alone reported improvements in depressive symptoms and functioning as well as satisfaction with their treatment.

CONCLUSION

When treating patients for MDD, managing the whole person is important. A review of physical symptoms should occur not only at the outset of treatment but also at each subsequent decision point because medical comorbidities contribute to poor antidepressant response and poor outcomes in many patients with depression. Depression can commonly co-occur with endocrine conditions (eg, hypothyroidism), chronic conditions (eg, arthritis, HIV), and central nervous system disorders (eg, Parkinson's disease, multiple sclerosis). Inflammatory conditions such as diabetes and obesity are also associated with depression, and specific markers of inflammation (eg, IL-6, CRP) may one day help clinicians select targeted antidepressant treatment. Anti-inflammatory agents may be effective for patients with specific polymorphisms, while T_3 augmentation is warranted in patients with comorbid thyroid dysfunction. Chronic pain conditions may require antidepressants with analgesic properties in addition to adjunctive agents for specific somatic symptoms. Other adjunctive strategies, such as L-methylfolate, provide safe and tolerable options for patients with depression. Management of treatment-resistant depression should include a careful medical history, appropriate testing, and targeted interventions to help patients achieve recovery.

Drug names: desipramine (Norpramin and others), duloxetine (Cymbalta and others), escitalopram (Lexapro and others), lithium (Lithobid and others), milnacipran (Savella), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: Dr Thase has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

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